The Artificial Cardiac Pacemaker : its history, development and clinical apllication

THALEN, HJT

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ITS HISTORY, DEVELOPMENT AND CLINICAL APPLICATION

H. J. Th. THALEN

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Stellingen

1. Bij de beoordeling van de prikkelbaarheid van het hart door middel van een hartelectrode, dient te worden uitgegaan van de prikkeldrempel voor de stroom en niet van de prikkeldrempel voor de spanning of de energie.

2. Gezien de thans bereikte graad van betrouwbaarheid van de electrische gangmaker van het hart en de ontwikkelde controlemogelijkheden, behoeft dit electro-therapeuticum thans geen contra-indicatie meer te vormen voor het verkrijgen van een rijbewijs.

3. Indien men bij stimulatie van weefsel een electrode gebruikt, die zo klein is dat de gradient van de stroomdichtheid in het omringende weefsel sterk varieert over een afstand, die kleiner is dan de karakteristieke lengte van het betreffende weefsel, kan men verwachten, dat het verband tussen impulsduur, τ, en prikkeldrempel, i, niet door de gebruikelijke chronaxie-rheobase curve gegeven wordt.

   Lale, P. G. - Med. Biol. Eng. 4, 319, 1966.

4. Door een drukgenerator aan de ingang van hun stethoscopen te gebruiken, komen Ertel et al. tot geheel verkeerde waarderingen van verschillende typen stethoscopen. Door de objectieve meetwijze vormt hun artikel toch een belangrijke bijdrage tot kennis van de geluidsoverdracht van stethoscopen.

   Ertel, P. Y. et al. - Circulation, 34, 889, 1966.

5. Bij toenemende stijfheid van de arteriewanden neemt aanvankelijk de perifere polsdruk niet of nauwelijks toe, maar wordt het hart in toenemende mate ineffectief belast.

O'Rourke, M. F. et al. - Circ. Res. 23, 567, 1968.

6. De 'thrombose par effort' wordt ten onrechte aan surmenage van de musculatuur van de bovenarm geweten.

Wouda, A. A. en Holla, A. T. J. - Ned. T. Gen. 112-5, 240, 1968.

7. Het onderzoek van patiënten met een vermeend myocardinfarct is onvoldoende, als niet ook een vectorcardiogram wordt gemaakt.

Gunnar, R. M. et al. - Circulation, 35, 158, 1967.

8. Uitbreiding van de responsies op stroboscopische lichtflitsprikkeling naar temporaal en centraal kan een aanwijzing zijn voor een corticale irritatie.

9. Voor de operatieve reconstructie van een megacolon congenitum (Morbus Hirschsprung) verdient de techniek volgens Rehbein de voorkeur.

Koop, C. E. - J. Ped. Surg. 1-6, 523, 1966.
Rehbein, F. et al. - J. Ped. Surg. 1-6, 526, 1966.

10. Daar men bij jongens met enuresis bedacht moet zijn op de aanwezigheid van urethrakleppen, is observatie van de mictie zelf noodzakelijk.

Burrows, E. H. - Urethral lesions in infancy and childhood, Charles C. Thomas Springfield, 1965.

11. In discussies onder artsen over het uitvoeren van de abortus arte provocatus wordt meer geworsteld met de gewetensnood van de arts, dan met de gewetensnood van de patiënte.

12. De veronderstelling van Vernadakis en Woodbury, dat de intracellulaire Cl-concentratie van gliacellen in het centrale zenuwstelsel te berekenen zou zijn met behulp van de bekend veronderstelde extracellulaire Cl-concentratie en de door anderen gevonden membraanpotentiaal van gliacellen, is aan bedenkingen onderhevig.

Vernadakis, A. and Woodbury, D. M. - Am. J. Physiol. 203-4, 748, 1962.

13. De waarnemingen van Ducommun et al. betreffende de door 'stress' bij ratten teweeggebrachte daling van het gehalte aan schildklierstimulerend hormoon in het bloed, zijn van groot belang voor de interpretatie van de bepalingen van dit hormoon in het bloed.

Ducommun, P. et al. - Proc. Soc. exp. Biol. Med. 121, 921, 1966.

14. De aan Van Eyck toegeschreven uitvinding van het olieverfschilderen berust niet op het verwrijven van pigment met een drogende olie, maar op het als bindmiddel gebruiken van een omgekeerde emulsie, waarin olie de gesloten phase is.

Coremans, P. et Thissen, J. - Bull. Inst. Royal Patr. Artist. 2, 41, 1959.

15. De dood van de aan aanvallen van Adams-Stokes lijdende mevrouw Eveline Jave-le Guéree behoeft niet aan digitalis toegeschreven te worden. De door Prof. Loireau en Dr. Pardon verkeerd voorgelichte commissaris Maigret dient derhalve het onderzoek te heropenen.

Simenon, G.: Maigret s'amuse. Presses de la Cité-Paris, 1957.

Stellingen behorende bij H. J. Th. Thalen, The Artificial Cardiac Pacemaker.
Groningen, februari 1969

RIJKSUNIVERSITEIT TE GRONINGEN

The Artificial Cardiac Pacemaker

ITS HISTORY, DEVELOPMENT AND CLINICAL APPLICATION

PROEFSCHRIFT

ter verkrijging van het doctoraat in de geneeskunde
aan de Rijksuniversiteit te Groningen
op gezag van de Rector Magnificus Dr. J. Th. Snijders,
hoogleraar in de faculteit der sociale wetenschappen,
in het openbaar te verdedigen
op woensdag 26 februari 1969 des namiddags te 4 uur
door

HILBERT JAN THOMAS THALEN

geboren te Beilen

te Assen bij
Van Gorcum & Comp. N.V. - Dr. H. J. Prakke & H. M. G. Prakke

PROMOTOR : PROF. DR. JW. VAN DEN BERG

CO-PROMOTOREN : PROF. DR. J. N. HOMAN VAN DER HEIDE
PROF. DR. J. NIEVEEN

De uitgave van dit proefschrift werd mede mogelijk gemaakt door financiële steun van de ,,Jan Dekkerstichting'' en de ,,Dr. Ludgardine Bouwmanstichting''.

Aan mijn moeder
Aan de nagedachtenis van mijn vader

Contents

Introduction

CHAPTER I

Omni custodia serva cor tuum quia ex ipso vita procedit

Proverbs IV-23

Electrical stimulation of various organs of the human body was already practiced more than one and a half centuries ago. Applications however did not pass beyond the experimental stage. Only in recent decennia one aspect emerged from this stage, to develop into a new therapy, the electrical stimulation of the heart.

Development of the artificial cardiac pacemaker was made possible by advances in the physical and medical fields. Groningen too contributed to this development. The first pacemaker developed here was implanted in a patient March 21, 1962 (VAN DEN BERG, HOMAN VAN DER HEIDE, NIEVEEN *et al.* 1963). In April 1963 I became engaged in the further development of this pacemaker.

The experimental part of the development took place under the leadership of PROF. DR. JW. VAN DEN BERG, who designed the electronic circuits, in the Laboratory of Medical Physics, where the physical and animal research was carried out.

Clinical research took place under leadership of PROF. DR. J. NIEVEEN together with the staff of the Cardiology Department of the Clinic for Internal Medicine, while the surgical operations were carried out by PROF. DR. J. N. HOMAN VAN DER HEIDE and the staff of the Department of Thoracic Surgery of the Clinic of Surgery, in collaboration with DR. J. C. DORLAS of the Anaesthesia Department.

The manuscript was translated with the help of MR. A. N. R. WRIGHT, University of Groningen, DR. E. G. SOWTON, Institute of Cardiology, London and DR. R. SUTTON, St. George's Hospital, London.

The author owes a great deal of gratitude to many people of these groups, who all have contributed, sometimes quite unawares, by inspiration and by practical help, to the teamwork, to which this thesis owes its existence.

Although the results of artificial stimulation of the heart appeared theoretically attractive compared with the usual pharmacological therapy, we observed, as did other authors, many complications in the first clinical applications. Initial complications centred upon the electrodes, and so research was concentrated upon this point, but attempts were also made to perfect the stimulation unit itself (fig. I-1). This led to the development of stimulation units based on completely new principles.

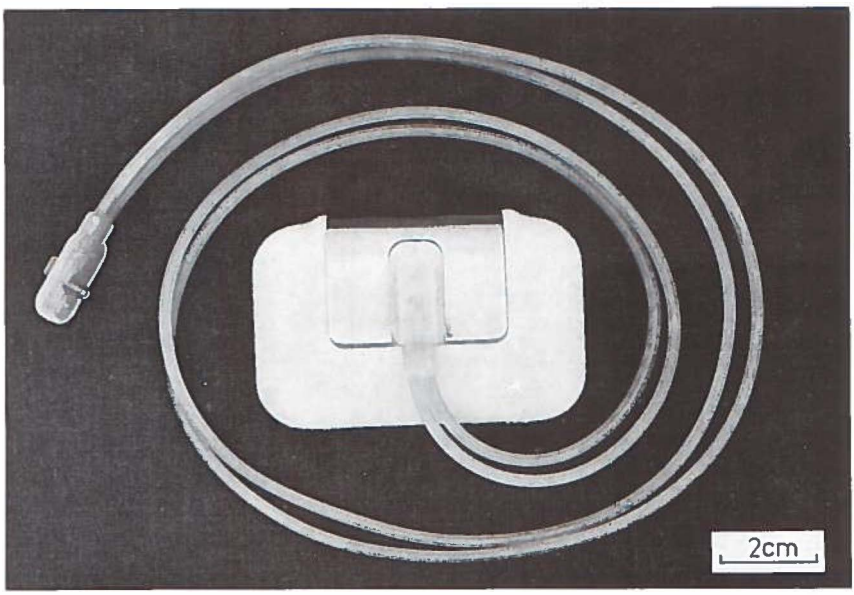


Fig. I-1. Latest version (1967) of the Groningen asynchronous pacemaker in combination with the intramural loop electrode.

The original purpose of this thesis was exclusively to describe this research. During a study of the literature however, it became clear that there was a serious gap despite the abundance of publications on the subject of cardiac stimulation. This omission was the absence of a systematic survey of literature, and so the lay-out of this thesis was altered into its present form, such a systematic survey being included in the first chapters. In subsequent chapters our own research is described and the results are used to provide a framework for the above-mentioned survey and a basis for a general discussion of all aspects of the problem.
The subject has been dealt with from a medical-physical viewpoint, and no research was carried out in the field of physiology, e.g. bloodpressure

and cardiac output. Where these factors play a role, use is made of research done by others.

In Chapter II the conduction system of the heart is discussed from this viewpoint, together with the defects to which it is subject, their causes, and the therapeutic possibilities.

Chapter III gives an historical outline of early and recent developments in the field of the stimulation of the heart.

In Chapter IV the now well-known methods of electrical stimulation are dealt with, the principle of each method, animal research and clinical applications being discussed. After the description of each method of stimulation a synopsis is given of the specific advantages and disadvantages.

Then, in Chapter V, the aims and achievements of the Groningen research are discussed. At the same time the various auxiliary apparatus is dealt with. Subsequently the three parts of a stimulation unit are analysed.

Chapter VI is devoted to the various types of electrodes and includes a discussion of the reactions in the surrounding cardiac muscle. Special attention is given to the fundamentals of electrical stimulation.

Chapter VII reviews the transmission of the stimulation impulse from the stimulator to the electrode in the heart.

Finally, Chapter VIII is concerned with the stimulator itself. The basic unit is dealt with initially and the discussion then includes the different kinds of stimulators which have been developed from it.

After the latter three chapters, which together give an insight into the complete stimulation unit, Chapter IX is devoted to the monitoring of the pacemaker patient, with the emphasis being laid on a new method of analysing the implanted stimulator.

The survey of the present state of affairs in artificial stimulation of the heart is concluded in Chapter X, with some observations on future possibilities.

It will be apparent that this thesis is not intended to be a report in which large numbers of patients are analysed in detail. Rather, its purpose is to give an outline of the principles of heart stimulation and the possibilities which exist in this field.

The conduction system of the heart

CHAPTER II

The heart is a complicated network of muscle fibres, which contains four cavities. In order to bring about a good circulation these muscle fibres must contract in a definite sequence. The necessary co-ordination between all portions of the heart muscle is achieved by special heartcells, which form the conduction system of the heart.

When defects of this conduction system are present, therapeutic possibilities are offered by electrical stimulation of the heart.

Before dealing with this electrotherapy, it is necessary to give first an outline of the normally functioning conduction system of the heart, defects of the conduction system and possible causes of these defects.

I. ANATOMY AND PHYSIOLOGY OF THE CONDUCTION SYSTEM

A. Anatomy (fig. II-1)

1. Morphology and localization

Morphologically the conduction system of the heart consists of: a. the sino-auricular node – b. the atrio-ventricular node – c. the atrio-ventricular bundle with – d. the left and the right branches which finally divide into – e. the Purkinje cells.

The S-A node does not in fact conduct stimuli but forms the stimuli. Nevertheless we are discussing this node with the conduction system of the heart since it is both functionally and anatomically closely related with this system.

The A-V node and the A-V bundle with both branches together form the atrio-ventricular conduction system of the heart. This could be considered to include the Purkinje cells.

a. Sino-auricular node. In 1907 Keith and Flack found cells in the sulcus terminalis situated by the recess of the vena cava superior in the right atrial appendage, which showed resemblance to the cells of the atrio-ventricular conduction system. These cells form the sino-auricular node (node of KEITH-FLACK).

The node has a prolonged shape and extends caudally to the right from the angle between the recess of the vena cava superior and the right atrial appendage to approximately the middle of the sulcus terminalis (KOCH 1922, JAMES 1961). The cross-section is 2 × 3 mm, the length varies from 15-30 mm, while the shape also varies (i.e. tuberous horseshoe). The node contains much connective tissue and is difficult to distinguish microscopically from the surrounding cardiac muscle tissue. It is capable

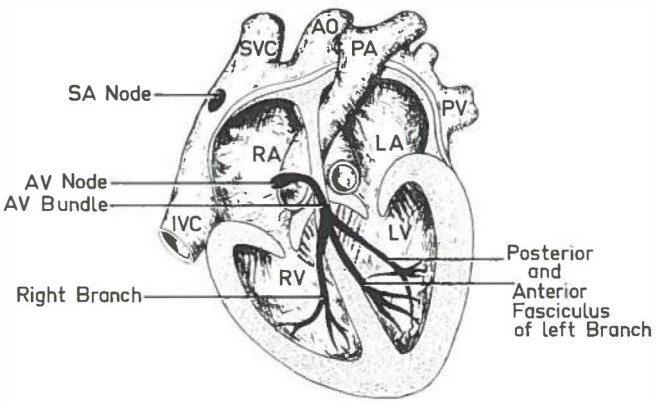


Fig. II-1.
The conduction system of the heart.

of generating by itself depolarisation waves which propagate throughout the cardiac muscle and cause contractions. For this reason the S-A node is called the 'pacemaker'.

These contraction waves diverge over the atria, but whether the conduction occurs by special conduction tissue is not yet clear. Some researchers believe they have proved the existence of special conduction bundles to the left atrium (TANDLER 1913, BACHMAN 1916) and the A-V node (THOREL 1910). The 'specific' tissue however is difficult to distinguish from its surroundings. Other investigators therefore believe that these bundles do not exist, but do not exclude the possibility of physiological pathways (LEV 1964).

The depolarisation wave diverging over the atria cannot reach the ventricles directly because of the annalus fibrosus between the atria and the ventricles. The transition to the ventricles occurs by means of the

atrio-ventricular conduction system. The 'musculous connection' between the atria and the ventricles, which forms a part of this system was demonstrated in human beings in 1893 by HIS.

b. Atrio-ventricular node. This specific group of heart cells was found by ASCHOFF and TAWARA in 1905. The atrio-ventricular node (node of ASCHOFF-TAWARA) is situated in the septum on the boundary between the atrium and ventricle, just superiorly to the pars membranacea septi and inferiorly to the base of the septal leaflet of the tricuspid valve. The proximal end of the node lies a few millimeters ($\pm$ 6 mm) medioventrally to the recess of the coronary sinus, the distal end perforates the trigonum fibrosum dexter, where the node passes into the crus commune of the atrio-ventricular bundle. The node is situated against the tissue of the annulus fibrosis (VERDUYN LUNEL 1964).

In adults the flat, ovoid A-V node is approximately 3 mm wide, and 6 mm long. It consists of a loose network of fibres, imbedded in connective tissue, and is clearly distinct from the other cardiac muscle cells.

c. Atrio-ventricular bundle. The crus commune of the atrio-ventricular conduction bundle (bundle of HIS, after the discoverer, who in 1893 called the bundle a musculous connection) passes from the A-V node and begins where the conduction system perforates the trigonum fibrosum dextrum. From here the bundle passes along the dorsal and inferior section of the pars membranacea septi ventriculorum. The crus commune is situated subendocardially on the right side of the septum and extends to the left apically in the septum, whereupon it bifurcates into a right branch (crus dexter) and a left branch (crus sinister).

From the A-V node to the ventral boundary of the crus sinister the band-shaped crus commune is approximatively 8-10 mm long and 2-4 mm wide in adult. The bundle is constructed compactly from specific conducting cells and is surrounded by connective tissue.

d. Right and left branch. The *right branch* first extends on a line from the crus commune towards the apex. The bundle, which is round and surrounded by connective tissue, lies deeper in the muscle of the septum ventriculorum than the crus sinister. Apically to the base of the musc. Lancisii the crus dexter approaches closer to the surface, after which it leads sub-endocardially to the trabecula septomarginalis where arborisation occurs. The final transmission of the impulse to the cardiac muscle cells takes place by means of small branches.

The *left branch* bends to the left dorsally from the origin of the crus dexter. The bundle reaches the left part of the septum ventriculorum via the inferior section of the septum membraneceum under the attachment of the valvula semilunaris posterior aortae. The flattened bundle, surrounded by connective tissue, extends sub-endocardially and divides in a fanlike manner in the superior third part of the septum into anterior and posterior fasciculi which pass apically into smaller branches near the trabeculae at the anterior and posterior papillary muscle.

e. Purkinje cells. These cells, which were discovered in 1845 by PURKINJE, are distinguished from the other heart cells by their larger size, by having one or more nuclei with clear cytoplasm, by showing a halo around the nucleus and by containing few myofibrils, situated in the periphery of the cell (LEV 1964). Although Purkinje cells also occur in other parts of the conduction system, the crus dexter and sinister are composed entirely of Purkinje cells. Via the small branches of these bundles and the subendocardial network, the Purkinje cells form the last transition between the conduction system and the myocardial cells and effect the depolarization and subsequent contraction of the heart.

2. Vascularisation

The conduction system shows a wide variation in the vascularisation of the different parts (fig. II-2), especially with regard to the origin of the vessels supplying blood. The S-A node receives its blood in most cases – 70% according to LEV (1964) – via the atrial branches of the right coronary artery which reach the node ventrally and laterally. In the other cases the S-A node is vascularized by branches originating from the left or even both coronary arteries.

The A-V node is supplied with blood by an artery branch to the fibrous septum. This branch originates in most cases from the right coronary artery, just before this forms the posterior descending branch. In the remaining 10-20% of the cases (JAMES and BURCH 1958, LUMB and SINGLETARY 1962, LEV 1964) the septal branch originates from the circumflex branch of the left coronary artery or from both coronary arteries. The septal branch forms anastomoses with the anterior descending branch of the left coronary artery.

The crus commune and the first parts of the crus dexter and sinister are likewise supplied with blood by the septal branch, while they also receive blood from the anterior descending branch of the left coronary

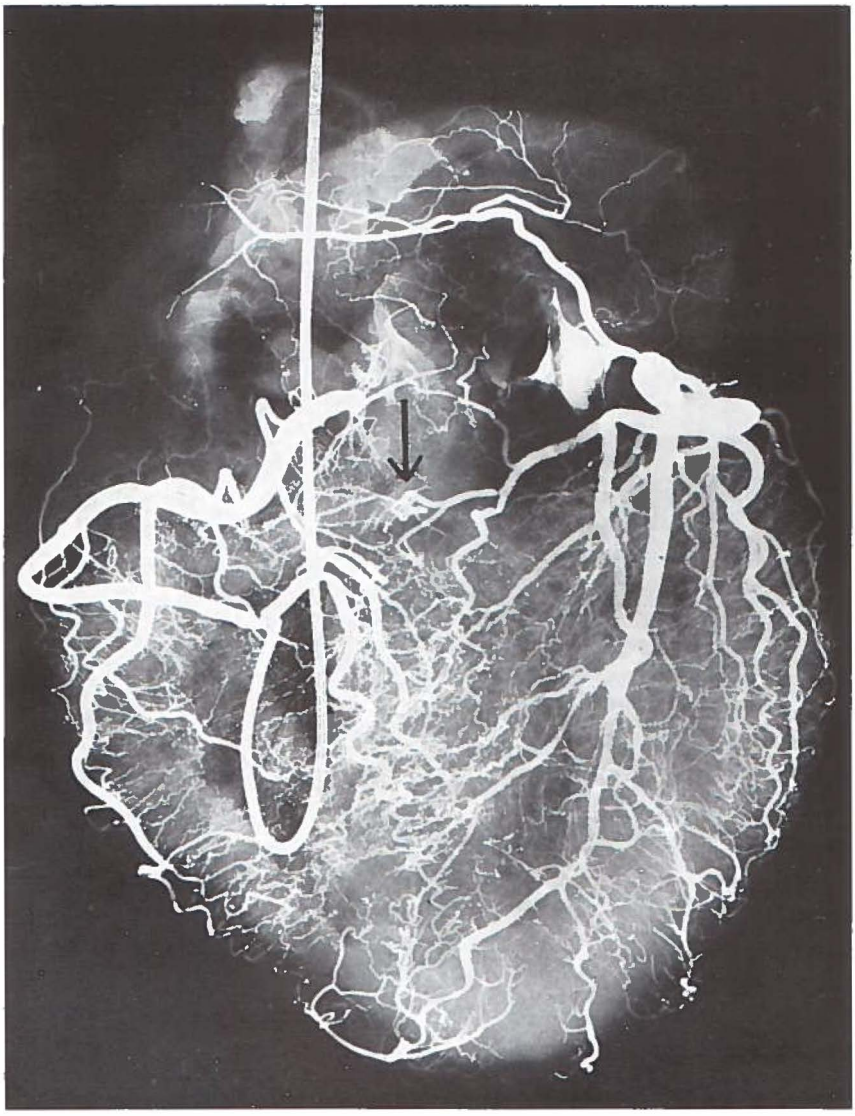


Fig. II-2. X-ray picture of coronary artery tree.
The vessels supplying the A-V node are arrowed. A bipolar catheter-electrode in the right ventricle is also shown. (By courtesy of DR. E. G. SOWTON.)

artery and the posterior descending branch of the right coronary artery, branches of which penetrate the ventricular septum.

In its further course the crus dexter receives blood especially from the vessels originating from the second perforating branch of the anterior descending branch.

In its further course the crus sinister receives blood from the anterior descending branch for the fasciculus anterior and the posterior descending branch for the fasculus posterior.

Of importance to the supply of blood to the atrio-ventricular conduction system are therefore the branches to the fibrous septum, which originate mostly from the right coronary artery and the perforating branches of the anterior and posterior descending branch, the branches of the anterior descending branch of the left coronary artery being of particular importance (JAMES and BURCH 1958).

B. Physiology

1. Pacemaker mechanism

The sequence in which the cardiac muscle fibres contract depends upon the point where the depolarization begins. This point must be the location of the pacemaker. Although many myocardial areas are capable of spontaneous activity, the pacemaker may be defined as that region of the heart possessing the highest rate of spontaneous rhythmicity (BULLARD 1963).

Investigations showed that the S-A node has the highest idio-frequency and normal sinus rhythm in man is approximately 70-80 beats per minute. Next to the S-A node the A-V node has the highest idio-frequency, so if the S-A node is eliminated atrio-ventricular rhythm of 50-60 beats per minute originates. The slowest rhythm is idio-ventricular rhythm, which is approximately 25-45 beats per minute. Continuous heart activity is guaranteed by the many automatic stimulus centres, situated especially in the normal conduction system of the heart; the frequency of contraction is slower as the site of origin of the impulse moves further towards the terminal branches.

The mechanism of the automatic depolarization is not yet completely know. An advance towards the explanation of this phenomenon was made when it became possible to deduce the potentials of a single cell by means of glass capillary micro-electrodes with a diameter smaller than 1 micron. Using this method it proved possible to demonstrate differences between the pacemaker cells and the other cardiac cells (fig.

II-3). The pacemaker cells and latent pacemaker cells were found to depolarize slowly by themselves during diastole. This self-depolarization, the prepotential, was not found in the muscle cells (HOFFMAN 1959).

There are various explanations for the origin of the prepotential. Probably a change in permeability of the cell membrane to potassium ions plays a role. It is assumed that after the repolarization of an unspecialized depolarized cell a balance is reached with a constant permeability of the cell membrane for sodium and potassium ions. In the pacemaker cells on the contrary a decrease in the permeability of the cell

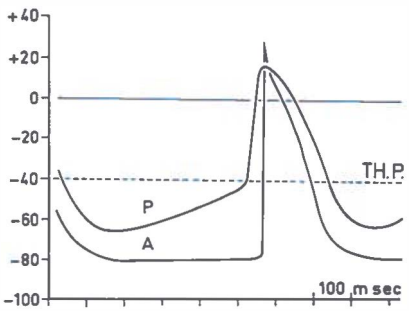


Fig. II-3. Record of membrane-potentials obtained from an atrial (A) – and a pacemaker (P) – cell. Note the progressive self-depolarization of the pacemaker cell.

membrane to potassium ions is assumed during diastole. Therefore there is a relative increase in the influx of sodium ions through the membrane of the pacemaker cells, resulting in a progressive development of the prepotential. Finally the potential is reduced so much that the threshold voltage is reached, whereupon the cell depolarizes and a depolarization wave to the other cells results (BULLARD 1963, BOUMAN 1965).

2. Course of the activation wave

In a normally functioning heart the S-A node is the pacemaker, as it has the highest idio-rhythm. The depolarization wave moves at a speed of 0.1-0.2 m/sec. through the S-A node and diverges from there over both the atria, where the activation wave has a speed of 0.8-1 m/sec. After approximately 70 msec the A-V node is reached, by which time the atrium is not yet completely depolarized. Due to this factor, and also to the slow conduction in the A-V node (0.05-0.1 m/sec) atrial systole can be completed, before the ventricular contraction begins. Finally the depolarization wave reaches the Purkinje fibres at a speed of 0.8-1 m/sec by way of the bundle of His. The endocardium is quickly reached via the Purkinje fibres (2-5 m/sec) whereupon the activation takes place

at a speed of 0.3 m/sec from the endocardium outwards through the heart muscle.

On the outside of the heart the depolarizations of the ventricles first appear paraseptally in the thin walled right ventricle in the so-called area trabecularis, approximately 20 msec after the beginning of the ventricular depolarization (ROOS 1964). The complete ventricular myocardium is activated in approximately 100 msec.

3. *Influence of the autonomic nervous system*

The human heart is influenced by the sympathetic and the parasympathetic nervous system.

a. Sympathetic nervous system. The preganglionic sympathetic fibres of the five superior thoracic ventral roots have their synapses in the corresponding five thoracic ganglia, the stellate ganglion and, in some cases, the medial and superior cervical ganglion. Postganglionic axones reach the heart as the superior, medial and inferior cardiac nerves via the superficial and deep cardiac plexus where they radiate to the S-A node, the atrio-ventricular conduction system, the myocardium of atrium and ventricle and the coronary vessels.

This nervous system is called 'cardiac accelerator', as the depolarization frequency of the S-A node increases, probably as a result of an increase of the slope of the prepotential, while the conduction of the activation wave is accelerated by the sympathetic effect. The sympathetic system has a vasodilatory effect on the coronary vessels.

b. Parasympathetic nervous system. Preganglionic parasympathetic fibres reach the ganglia of the heart in the left and right vagus nerves via the superficial and deep cardiac plexuses. Postganglionic axones go to the S-A node and the A-V node as well as the coronary arteries. There is as yet no unanimous opinion about the way the parasympathetic system influences the A-V conduction system and the myocardium, although an influence upon the atrio-ventricular bundle is assumed by some authors (TRUEX 1960).

The parasympathetic nervous system has an inhibiting effect on heart activity and for that reason is called 'cardiac inhibitor system'. The frequency of the S-A node depolarization is decreased by a reduction of the slope of the prepotential, while conduction of the activation wave is delayed. The parasympathetic system has a vasoconstrictory effect upon the coronary vessels.

The conduction system of the normally functioning heart has been discussed above. In the second part of this chapter the defects, which may occur in this system will be considered.

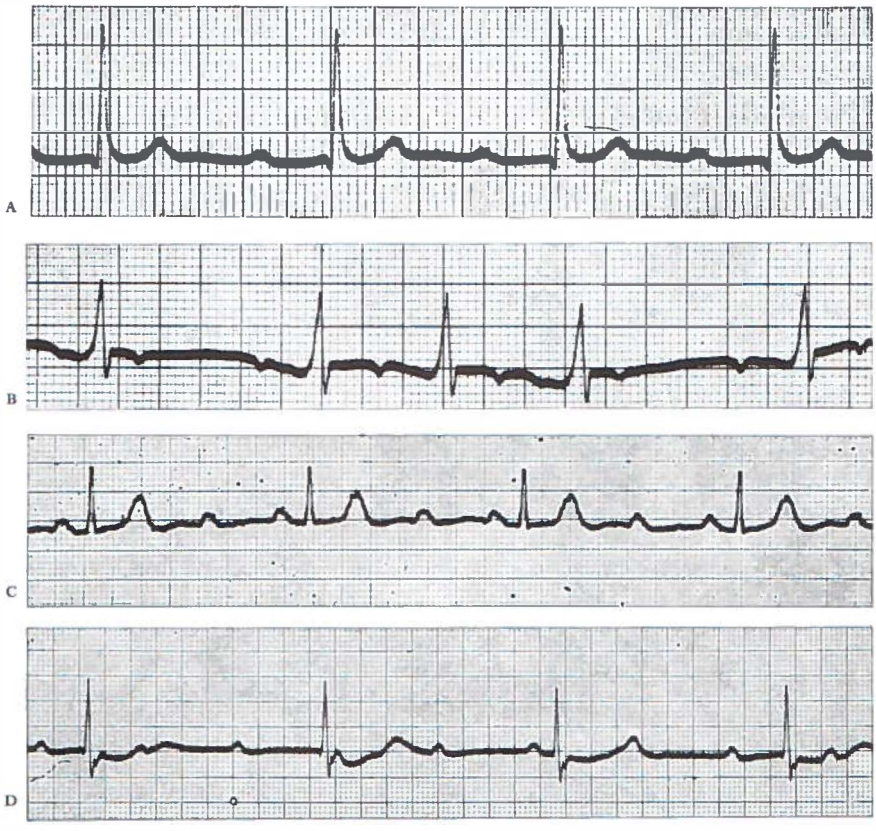
II. DEFECTS IN THE CONDUCTION SYSTEM

The defects of the conduction system can be classified according to their temporal character into permanent and temporary defects.

Furthermore the lesions can be classified according to their localization in the conduction system, a distinction being made between com-

Fig. II-4. Different degrees of A-V block.

A. First degree or latent heartblock.
B. Second degree or partial heartblock with Wenckebach phenomenon.
C. Second degree or partial heartblock. (3 : 1).
D. Third degree or complete heartblock.



plete or incomplete sino-atrial and atrio-ventricular block (Fig. II-4), in addition to intra-atrial and intra-ventricular block.

This discussion of defects of the conduction system is limited to those defects, which are of importance within the framework of the present subject, viz. complete atrio-ventricular block and to a lesser degree the more serious forms of incomplete atrio-ventricular block, where failure of an idio-ventricular pacemaker or severe bradycardia results in potentially fatal cardiac arrest or intractable heart failure.

By complete A-V block is meant that form of conduction disturbance in which the conduction system is completely defective, so that no atrial impulse can reach the ventricles. Other types of high degree heart block include those forms in which only a small number of atrial impulses reach the ventricles by way of the conduction system, so that severe bradycardia results. Incomplete A-V heart block with Wenckebachs periods or other incidental incomplete conduction disturbances do not belong to this group.

Within the framework of this investigation the most important conduction disturbance is complete A-V block. This can be caused by lesions in the converging fibres of the A-V node, the A-V node itself, the crus commune of the A-V bundle, both the bundle branches of the conducting bundle or a combination of these lesions.

A. Occurence of complete A-V block

Accurate details on the occurence of complete A-V block do not exist, as many patients with a heart block experience no trouble at first and therefore do not seek medical attention. Analysing 50,000 electrocardiograms WRIGHT *et al.* (1922) found complete A-V block in 0.2% of the cases. An identical percentage was found by ROWE and WHITE (1958) in 160,000 electrocardiograms. VAN ERVEN (1965) saw A-V block in 0.6% in a total of 17,000 recordings, while KATZ and PICK (1956) were able to show complete A-V block in 0.5% of a total of 50,000 patients with rhythm disturbances.

These surveys are concerned with patients who for some reason came into contact with a medical centre. Conclusions about the occurrence of heart block in the whole population may not therefore be drawn unreservedly from these figures.

B. Etiology of A-V block

Following the classification of LANDEGREN and BIÖRCK (1963) it is possible to divide the causes of the defects of the conduction system into four main groups:

1 Structural lesions of the heart
2 Abnormal parasympathetic influence
3 Electrolyte disorders
4 Intoxication

1. *Structural lesions of the heart*

This group is the most important of the four groups mentioned. It contains a large number of structural changes which may cause total heart block.

a. Ischaemia

I. *Arteriosclerosis oblitterans.* Arteriosclerosis oblitterans has been quoted as the chief cause of total atrio-ventricular block. According to ZANCHI and LENÈGRE (1955) arteriosclerosis dominates the vascular pathology of the conduction system of the human being.

In a survey totalling 849 patients with complete heart block FRIEDBERG (1964) found that 37% had coronary heart disease. At first it was thought that there was a causal connection between the coronary sclerosis and the heart block. However, later histopathological investigations by LENÈGRE (1962) and others have demonstrated that this connection between lesions of the conduction system and coronary arterial disease is far from being universally present. Lesions of the conduction system as a result of prolonged stress and a secondary fibrosis (GILCHRIST 1958) or a bacterial or allergic myocarditis resulting in fibrosis (LENÈGRE 1962, ZOOB 1963), are now thought to be possible causes of heart block in many cases.

II. *Acute myocardial infarction.* This ischaemic myocardial lesion is accompanied in 3-5% of the cases by a total A-V block, although some investigators have found higher values (COURTER 1963, 9.6%). These differences are explained by the heart block being reversible in approximately 90% of the cases (COHEN 1958) and having disappeared within one or two weeks. The probable cause of the heart block is temporary ischaemia with possible oedema formation and inflammation. Thirteen percent of the patients with complete heart block in FRIEDBERG's survey (1964) had an etiology of acute myocardial infarction. A-V block occurs

particularly with a posterior wall infarction resulting from an occlusion of the right coronary artery, which supplies the A-V node and a part of the conducting bundle with its septal branches, (MAHAIM 1931, PENTON *et al.* 1956). In these cases septal infarction is mostly present as well.

III. *Diffuse lesions due to anaemia.* Diffuse lesions due to anaemia of the entire heart are also known. The causes here are necrotic areas which affect the A-V system (TROFINOV 1955), and may cause conduction disturbances.

b. Inflammations

Inflammatory processes are not often accompanied by A-V block. In cases where this combination does occur the block mostly disappears after recovery from the primary disease. The primary diseases which may give rise to a total A-V block are:

I. *Acute articular rheumatism.* In acute articular rheumatism complete A-V block does not occur frequently, although in approximately 50% of the cases an increased A-V conduction-time is observed. (LANDEGREN and BIÖRCK 1963). Eight per cent of the group of patients with complete heart block observed by Friedberg had an etiology of acute articular rheumatism. It is supposed that the atrio-ventricular conducting system is interrupted by Asschoff's tubercles or the expansion of the fibrous part of the cardiac skeleton (GROSS and FRIED 1936).

II. *Other collagen diseases.* Complete atrio-ventricular heart block also occurs in other collagen diseases, although less frequently than in acute articular rheumatism. Quite a large relationship was found to exist between ankylosing spondylitis (BERNSTEIN and BROCH 1949) and uro-polyarthritis (= Reiter's disease) (OLHAGEN 1960), while polyarteritis (DOERR 1961) and lupus erythematosis have also been observed as causes of heart block.

III. *Diphtheria.* Diphtheria occurs more frequently in the past medical history of patients with complete heart block than in an unselected group (BUTLER and LEVINE 1929). The cardiac lesions caused by a toxin appear mostly in the second week of the disease, but heart block may even manifest itself years later (HOEL 1958). It is advisable to consider this possibility in cases of heart block of unknown etiology.

IV. *Lues.* In lues the formation of gummata in the course of the conduction system may cause complete A-V block (MAJOR 1923). This etiology occupied an important place especially in the first decade of the 20th Century. Even now, although less frequently, lues with A-V block is still observed (PENTON *et al.* 1956, WRIGHT *et al.* 1956). Investigations by DOERR (1955) demonstrated however that the gummata have become less frequent in lues, due to a 'Gestaltwandel der Krankheiten', but that complicating atrio-ventricular conduction defects are now often caused by circulatory diseases originating at the coronary ostia as a result of syphilitic arteritis.

V. *Sarcoidosis.* Although primary cardiac affections are rarely observed clinically in this disease, cardiac lesions are found in 20% of the autopsies. A-V block will frequently be found in those patients who develop clinical cardiac lesions (PORTER 1960). This disease should be included in the diagnosis as a possible cause particularly in cases of heart block appearing between the ages of 20 and 40 years.

VI. *Chagas disease.* This disease, caused by the Trypanosoma cruzi is, particularly in South-American countries, a very common etiology of complete A-V block. This is the result of secondary myocarditis associated with this disease (ROSENBAUM and ALVAREZ 1955, KÖBERLE 1957).

VII. *Myocarditis of unknown etiology.* Myocarditis of unknown etiology as a cause of complete A-V block is described by CLARK (1955) and NIEVEEN (1964), among others.

VIII. *Other forms of infections.* Of the remaining infectious diseases in which complete A-V block is described, VAN ERVEN (1965) mentioned further: thyphus, rubeola, mononucleosis infectiosa, morbilli, parotitis epidemica, pneumonia and scarlatina.

Appearance of an atrio-ventricular conduction disturbance in these diseases is however extremely rare.

c. Defect in the development of the conduction system

Congenital heart block may arise as a result of a defect in the development of the conduction system. Intra-uterine myocarditis may also be a cause of congenital heart block. Heart block may occur by itself, or in combination with other cardiac defects. In the latter case the associated heart defect is the important determining factor in the prognosis of the child.

With an isolated heart block the prognosis is good, and the heart compensates under stress by an increase in frequency and cardiac output better than hearts with a conduction disturbance of other etiology (HOLMGREN *et al.* 1959, IKKOS *et al.* 1960).

d. Valvular diseases

Acquired valvular diseases occur in approximately 10% of the cases of patients with A-V block (PENTON *et al.* 1956, ROWE *et al.* 1958). This combination may be explained by:

- the valve disease and the myocardial disease having the same cause,
- valve calcification extending into the heart skeleton and damaging the bundle of His,
- the valvular disease causing secondary changes in the myocardium resulting in conduction disturbances.

Only in the last of these three combinations is there any question of heart block resulting from the valvular disease. In the first two combinations the valvular disease and conduction disturbance are both the results of other diseases, and the valvular disease cannot be included amongst the etiologies of heart block.

e. Tumors

Primary tumors of the heart are rare. BENJAMIN (1939), STRAUSS and MERLISS (1945) and SAPHIR (1960) discovered only 14 primary tumors in a total of 80,000 autopsies. A search of the literature has failed to identify any reports of primary tumors of the conduction system causing A-V block. The tumors causing conduction disturbances are metastases of malignant melanomas, of bronchial, intestinal, liver or prostate carcinomata, leukaemia and lymphogranulomata (MAHAIM 1945).

f. Traumata

An A-V block resulting from thoracic trauma does indeed occur (PAULIN and RUBIN 1956), but in this group iatrogenic lesions of the conduction system during intracardiac interventions are of especial importance. Block may be caused directly by instruments or sutures or indirectly by the formation of oedema, haematomata or infarctions. This complication occurs particularly during surgical treatment of the tetralogy of Fallot, ostium primum, atrio-ventricular canal, resections of the aortic valve, resections of subvalvular stenoses and repair of ventricular septal defects.

Attempts have been made to plot the conduction system by means of

special techniques such as colouring (ALLEN *et al.* 1959, IWA *et al.* 1961), and impedance measurement (BERNHARD and GRASZ 1961). The improved anatomical knowledge gained in investigations by TRUEX (1958), LEV (1960, 1963), VERDUYN LUNEL (1964) and others are of greater importance. This improved knowledge and the improved surgical techniques resulted in a drop in the percentage of patients at the Mayo Clinic encountering heart block as a complication during operations for ventricular septal defects. Block occurred in 10% of patients during 1960 (LAUER *et al.* 1963), but only in 0.9% in later years (MCGOON 1964) without special techniques being used to trace the conduction system.

A permanent heart block caused by catheterisation (GAULT *et al.* 1966), should also be mentioned in this section.

g. Deposits of foreign substances in the cardiac tissue

1. *Calcific deposits.* Calcific deposits may occur in the myocardium as dystrophic calcification resulting from necrosis. This was observed by MAHAIM (1931) and LUMB and SHACKLET (1960). This calcification may occur both in the conduction system and around the nerve fibres, in which case the conduction is interrupted by the pressure caused by the calcific deposit.

Likewise, in metastatic calcification from such causes as osteitis deformans (HARRISON and LENNOX 1948) an interruption in the conduction system of the heart may be observed, particularly when the deposit appears in the annulus fibrosis or the cardiac valves. The heart block resulting from calcification in the aortic valves observed by YATER and CORNELL (1935) was of this type.

II. *Ferrous deposits.* Haemosiderin pigment is sometimes stored in the interstitium of the heart (DOERR 1955) and may cause heart block as in haemochromatosis (PETIT 1945).

III. *Amyloid deposits.* Amyloid deposits in the myocardium may cause disorders in the form of an A-V block (ROWE and WHITE 1958).

h. Degenerative diseases

1. *Progressive neuromuscular diseases.* Diseases, such as muscular dystrophies, muscular atrophies and Friedreich's ataxia may be accompanied by heart block.

II. *Degenerative, non-ischaemic disorders.* Although extremely rare, gly-

cogen storage disease (WARTMAN and HIL 1960) and endomyocardial fibroelastosis, may cause cardiac block.

2. Abnormal parasympathetic influence

Besides a local interruption of the conduction system as described in the survey above, hyperactivity of the 'cardiac inhibitor system' i.e. the parasympathetic system, which stimulates the heart via the vagus nerves may also cause heart block. Hyperactivity of the parasympathetic system is mostly a reaction to influence elsewhere in the body.

In their survey LANDEGREN and BIÖRCK distinguish hyperactivity of the vagus nerves in

a. Stimulation of the carotid sinus. Even in healthy persons it is possible to inhibit the conduction of the atrio-ventricular system by pressure on the carotid sinus (LOWN and LEVINE 1961).

b Reactions resulting from lesions of the gastro-intestinal and respiratory tracts. As a result of lesions of the abdominal organs, such as cholecystitis (JOHANSSON 1960) or an esophageal diverticulum (WEISS and FERRIS 1934), vagal reflexes are sometimes provoked, which depress the conduction system of the heart and may cause an A-V conduction disorder.

c. Carotid sinus syndrome. Pressure on the carotid sinus due to disorders such as tumors (WEISS and BAKER 1933), may provoke a carotid sinus reflex causing conduction disorders, which may sometimes be accompanied by syncope. Syncopes with this etiology are grouped together as the carotid sinus syndrome.

d. Glossopharyngeal neuralgia. This syndrome rarely occurs. It is characterised by an unilateral pain in the sensory area of the nerve and is sometimes accompanied by hypersecretion of the parotid gland and sometimes also by cardiac arrest (KJELLIN *et al.* 1959).

Heart block due to abnormal parasympathetic influences summarised above, is not of particular clinical importance, but cannot be omitted from a survey of the etiology.

3. Electrolyte disorders

a. Hyper potassaemia. The potassium ion is important to the conduction

and the excitability of the heart, since an increase in the concentration of potassium has an unfavourable effect on the depolarization of the cell membranes. With high concentrations of potassium ions block may arise, particularly at the atrial rim of the A-V node (HOFFMAN 1960). These conduction disorders may occur at a concentration as low as 7-8 mEq/L, twice the normal concentration (BELLET *et al.* 1959, ANTONI 1963). Hyperpotassaemia may arise in kidney disorders and serious tissue damage (crush syndrome).

b. Hypo- and extreme hypercalcaemia. In hypocalcaemia suppression of the conduction and the excitability of the heart is seen. A high degree of hypercalcaemia may cause bradycardia to change into tachycardia, ventricular fibrillation or cardiac arrest.

c. Acidosis. Suppression of the conduction and excitability is also observed in acidosis.

For the sake of completeness, it should be remarked here that hypercalcaemia, alkalosis and hypersodiaemia promote the conduction and excitability of the heart (ROTHE 1963, BROOKS *et al.* 1955).

4. *Intoxication.*

a. Digitalis. An important cause of heart block is digitalis intoxication. In FRIEDBERG's survey (1964) the number of cases having this etiology is exceeded only by those with ischaemic heart disease; it occurred in 86 of the 849 patients. The effect of digitalis on the atrio-ventricular conduction system is due to an indirect influence via the parasympathetic system, by the carotid sinus (HEYMANS) or an increase in the sensitivity to vagal impulses and also to a direct effect on the conducting tissue (FRIEDBERG 1960).

Digitalis results in both an extension of the P-R time and a decrease in frequency. An incomplete heart block may become complete following administration of digitalis.

b. Quinidine and procainamide. These medicaments suppress the excitability, the spontaneous impulse formation, the conduction velocity, and the contracting power of the myocardium. This may result in complete heart block.

III. CLINICAL SYMPTOMS OF A-V BLOCK

If the atrio-ventricular conduction is interrupted the ventricles are activated from a new centre somewhere in the ventricles. The new pacemaker centre originates independently of the location of the lesion, and usually has a lower frequency than the sinus node. This causes bradycardia, resulting in smaller cardiac output and a decreased oxygenation. In many cases however this is compensated primarily by an increased stroke volume and secondarily by a higher arterio-venous oxygen ratio. A higher systolic and a lower diastolic blood pressure is found in these patients. The patients are able to lead a more or less normal life within limits which are dependent on the degree of bradycardia.

If the heart does not adapt or if the cardiac disorders reduce the effect of adaptation, the patient may complain of weariness, drowsiness and dizziness. Symptoms of congestive heart failure such as oedema and dyspnoea on effort may also arise. In older people, such as those above 70 years of age, low cardiac output often results in brain or kidney damage.

Under stress these complaints are often aggravated, as the heart is not able to respond with a normal increase in frequency. In most cases there is no increase or only a slight increase, but in patients with congenital heart block a greater increase may be seen.

Extreme bradycardia may often lead to syncope, a symptom «signalé d'abord par ADAMS des 1827 en suite par STOKES, d'ou le nom de maladie d'Adams ou de Stokes-Adams que je propose de lui donner» (HUCHARD 1899).* These Adams-Stokes attacks arise due to cerebral anoxia, caused by a sudden decrease in the cardiac output by changes in the ventricular frequency. The decrease in the cardiac output may be due to extreme bradycardia or even cardiac standstill but also to ventricular tachycardia or ventricular fibrillation. It has recently become evident that a low frequency during total block predisposes to rapid ectopic impulse-formation (SCHWARTZ *et al.* 1949, ROBERTSON 1952).

The Adams-Stokes attack is characterized by its sudden appearance and the rapid loss of consciousness. The patient becomes pale, and exhibits convulsive muscular contractions. During the attack, which rarely lasts for more than one or two minutes, no pulse is noticeable. At the end of the attack the patient rapidly regains consciousness. The paleness, which

* In 1719 two cases of syncopes with total absence of the pulse already had been observed by MORGAGNI in Venice. The attacks are therefore also referred to as Morgagni-Adams-Stokes attacks.

may become cyanosis in longer attacks, changes into a flush when the attack is over, while respiration, which has continued normally during the attack, is interrupted. This apnoea is explained by the fact that the blood in the lungs contains very little carbon dioxide, due to hyperventilation as a result of the circulatory arrest and normally continued respiration. When circulation is restored the respiratory centre is no longer stimulated by the hypocarbonized blood and apnoea results (FORMIJNE 1938). After circulation has been restored for some time the blood becomes recarbonized to such an extent that the respiratory centre is stimulated again and respiration is restored. These Adams-Stokes attacks occur sooner or later in most patients with A-V block. In patients with a damaged conduction system the Adams-Stokes attacks may be evoked by such factors (BELLET 1964) as:

- increase in heart activity during emotion or excitement (in Groningen we ourselves frequently saw attacks occur during transport of the patients to the hospital),
- transition of incomplete to complete A-V block,
- sudden increase in cardiac frequency such as ventricular tachycardia and flutter.

The Adams-Stokes attacks entail the danger of cerebral damage while immediate death is also possible. Traumatic lesions may be caused by the patient falling during the attack. Because of these dangers atrio-ventricular block requires immediate therapy, especially when the block is accompanied by Adams-Stokes attacks.

IV. *Therapy*

The therapy of A-V block should be directed at preventing cardiac arrest and ventricular tachycardia and restoring ventricular rhythm with an adequate circulation.

Therapy should be directed in the first place towards treatment of the lesion causing heart block. Since this is frequently not possible, symptomatic and preventive treatment, having direct effect on the atrio-ventricular conduction system and the myocardium, assumes great importance. The therapeutic methods can best be divided into:
A. Medicamental therapy – B. Surgical therapy – C. Physical therapy.

A. Medicamental therapy

The following drugs are most frequently used.

1. Sympathomimetics

– In patients with heart block sympathomimetic drugs result in:
– improvement of atrio-ventricular conduction
– increase of idio-ventricular frequency
– increase of pacemaker activity, thus terminating possible cardiac arrest more rapidly
– increase of myocardial contractility, resulting in a greater stroke-volume.

The following sympathomimetic drugs are used:

Epinephrine. The disadvantage of Epinephrine is the risk of precipitating ventricular fibrillation. In ventricular arrhythmia administration is therefore contra-indicated.

Epinephrine may be administered by subcutaneous, intramuscular, intravenous or intracardiac injection. The dose depends upon the method of administration.

Norepinephrine. Norepinephrine has less effect upon the heart than Epinephrine, but is used particularly in cases of heart block with hypotension, because of its peripheral vasoconstrictive effect. It may be administered subcutaneously or intravenously.

Ephedrine. Ephedrine acts like Epinephrine, but may also be administered orally.

Isoproterenol. Isoproterenol is one of the most important medicaments in the treatment of A-V block. It increases the frequency and the force of myocardial contraction, resulting in an increase of the cardiac output. At the same time it reduces the peripheral vascular resistance, causing a lowering of the blood pressure. In contrast to epinephrine it is thought less likely to precipitate ventricular fibrillation. It may be administered sublingually, subcutaneously or intravenously.

2. Parasympatholytics

The effect of parasympatholytics on patients with complete A-V block depends on the influence and the distribution of the vagal nerve-endings in the heart. The parasympatholytics do not promote heart activity, but counteract the inhibiting effects of acetylcholine on the conduction system and the myocardium. These medicaments are therefore effective in heart block resulting from exaggerated parasympathetic influence.

Atropine. Atropine is a parasympatholytic which is sometimes administered to patients whose heart block results from abnormal parasympathetic influence.

Methantheline bromide. Instead of Atropine, Methanteline bromide is also used (BELLET 1964). Both parasympatholytics may be administered subcutaneously.

3. *Molar sodium lactate*

Molar sodium lactate lowers the plasma potassium and causes alkalosis. In addition lactate is utilized for metabolism by the myocardium (BELLET 1960). Molar sodium lactate seldom causes ventricular fibrillation. The solution is administered by transfusion and is particularly effective in cases of ventricular activity being disturbed by acidosis or hyperpotassaemia.

Since Molar sodium lactate acts by different routes from sympathomimetics or parasympatholytics, it may be used in combination with these medicaments.

4. *Chlorothiazide*

Chlorothiazide is a diuretic and has the effect of reducing the potassium concentration in plasma, although the intracellular potassium remains unchanged. Its action causes an increased resting potential of the cell-membrane. This increased potential enables more rapid development of the action-potential, which becomes larger and spreads faster.

These mechanisms have a favourable effect upon the ventricular activity in A-V block (TOBIAN 1964).

As not all patients respond to Chlorothiazide (BELLET 1964), TOBIAN states that in those cases where Chlorothiazide has achieved no permanent result within 8 weeks, the therapy may be abandoned.

As the beneficial effects are due to lowering the potassium concentration in the plasma, Hydrochlorothiazide could theoretically also be administered. Clinical experience with this drug has not yet been described.

5. *Corticosteroids*

Good results in the treatment of A-V block have been reported following the use of corticosteroids (FRIEDBERG 1960, ABER 1960, TORRESANI

1962). These drugs are of great importance in cases of heart block caused by myocardial infarction or infections. The exact mechanism of action is not known, although a number of possibilities have been suggested, such as:

a anti-inflammatory effect, acting favourably on myocarditis or ischaemic cardiac diseases which often show secondary inflammation, so that reactions around the conducting tissue diminish (PRINZMETAL and KENNAMER 1960).
b promotion of alkalosis and hypopotassaemia (PERRY and JAECK 1960).
c increase in sensitivity of the heart to epinephrine and norepinephrine in the region of the sympathetic fibres (RAMY *et al.* 1951).
d direct effect on the conducting system (LOWN *et al.* 1955).

The corticosteroids used most frequently are Cortisone and Prednisone. These preparations may be administered by many routes, but are usually given orally.

The effect of the corticoids may also be achieved by administering the adrenocorticotropic hormone (ACTH). PRINZMETAL and KENNAMER (1953) succeeded in correcting atrio-ventricular conduction disorders by this indirect way of increasing the corticoidsteroid concentration. ACTH is mostly given intramuscularly, but for more rapid effect may also be administered by transfusion.

Prognosis of A-V block with medicamental therapy

It is difficult to give an accurate prognosis for patients with A-V block treated medically. Prognosis depends upon both the etiology and the complications of the primary disease. The choice of therapy should be determined by the etiology of the block, but the implementation of the various possibilities may vary greatly.

These factors have led to various opinions concerning the prognosis for A-V block, but it is generally agreed that the prognosis becomes less favorable if the conduction disturbances are accompanied by Adams-Stokes attacks.

FRIEDBERG (1964) reported on 100 patients with complete heart block and Adams-Stokes attacks, in whom the etiologies of myocardial infarction, digitalis intoxication or congenital heart disease were not included. Of these 100 patients treated medically, 30 died within the first 6 months after hospitalization and 50 patients were still alive after one year. Five years after their first hospitalization 56 patients had died,

24 were still alive and information on the remaining 20 patients was not available.

Prognosis is also poor in the case of combined myocardial infarction and A-V block, particularly when the infarction is extensive. PENTON *et al.* (1956) found a mean survival time of 5.5 months in 49 patients with acute myocardial infarction combined with heart block and ROWE and WHITE (1958) found a survival time of 13 months in a similar group. The same authors calculated an average survival time of 28 months in patients with combined heart block and chronic coronary heart disease (angina pectoris, old infarction) and this corresponds to the 29.4 months which PENTON *et al.* (1956) found in 58 similar patients.

Congenital heart block has the most favourable prognosis, providing the congenital heart disease does not also affect the heart in other ways, as in this case the associated lesion is frequently the determining factor for survival. Adams-Stokes attacks are seen less frequently in congenital heart block while the haemodynamic capacity of such patients often makes a normal and long life possible, owing to the relatively rapid idioventricular rhythm. CAMPBELL and THORNE (1956) studied 7 patients with congenital heart block for 25 years and found none with cardiac symptoms apart from one Adams-Stokes attack. Although the prognosis can be said to be favourable with a congenital etiology, this does not apply to patients with heart block of other origins, nor does drug therapy have wholly favourable results. Symptoms can often be temporarily corrected, but the actual conduction disturbance is not removed by the administration of, for instance, sympathomimetics, so that a patient with heart block and Adams-Stokes attacks treated in this way runs the risk that in course of time the therapy will fail.

B. Surgical therapy

In order to obtain permanent improvement in conduction disturbances attempts have been made to increase ventricular activity by surgical means.

1. Vagotomy

Because medicamental treatment with parasympatholitics did not always produce the desired effect in cases of heart block resulting from abnormal parasympathetic influence, attempts have been made to eliminate the parasympathetic influences in these cases by vagotomy, with limited results however (GREENWOOD 1960).

2. Transplantation of the sino-auricular node

In A-V block caused by interruption in the atrio-ventricular conduction system, transplantation of the S-A node would seem to be an ideal solution. This therapeutic possibility has been investigated by carrying out homotransplantations and autotransplantations in a number of dogs.

a. Homotransplantation of the sino-auricular node. The possibility of restoring ventricular activity by means of homotransplantation of the S-A node in a heart with conduction disturbances was suggested as early as 1927 by RYLANT. Although he reports good results, recent investigations give another picture.

COHN (1962) transplanted 2 cm^2 of atrial tissue in which part of the S-A node was represented in dogs, by inclusion of the medial base of the superior vena cava in the transplant. This tissue, which was transplanted to the corresponding site in the recipient, proved able to stimulate the ventricle immedicately after the operation. The effect of the transplant however was never observed longer than the second post-operative day. From microscopic investigation of the tissue it appeared that the transplant disintegrated and that round cell infiltrations were to be seen in the transplant from the fourth post-operative day. Investigations by PUECH *et al.* (1954) and HUDSON (1960) demonstrated that it is impossible to achieve lastingly effective ventricular stimulation in a heart with conduction disturbances by means of a homotransplant because of disintegration and encapsulating fibrosis around the transplant.

b. Autotransplantation of the sino-auricular node. Autotransplantation of the S-A node has also been investigated in animals. It proved possible to transplant the S-A node, which in dogs is supplied with blood by the right circumflex coronary artery, with a pedicle graft in which this nutrient artery is included, from the right atrium to the right ventricle (WIEBERDINK *et al.* 1961, ERNST *et al.* 1964). In the dogs in which these transplantations were performed and where no A-V block was created, normal sinus rhythm remained. In some dogs sinus rhythm persisted even after a second operation in which A-V block was created 2-4 months later. In these cases heart block occurred when the transplant was removed.

Microscopic investigations showed however that in many cases the transplant had been encapsulated by a layer of connective tissue preventing contact between the transplant and the intact ventricular myocardium. It was not possible to demonstrate relation between the amount

of connective tissue and the effect of the transplant. It is probable, however, that the formation of connective tissue will provide an impediment to long term effective stimulation. Application of this method in humans also encounters the difficulty that the blood supply to the human sinus node is not from one large branch, but by several smaller branches of the coronary arteries, making the blood supply to the pedicle graft less favourable.

Human applications of sinus node transplantations have not yet been described.

C. Physical therapy

Although surgical therapy has so far been unable to restore good ventricular activity, it was heart surgery that stimulated the development of a new therapeutic method. The unfavourable prognosis for surgical heart block, even with medicamental treatment provided the stimulus to research for a new therapy, which was finally found in electrical stimulation of the heart. Thanks to almost simultaneous progress in the electronic field, electrotherapy has experienced rapid growth, particularly since 1950. This development, and the extensive possibilities for the application of electrical stimulation of the heart with atrioventricular conduction disturbances, will be dealt with in the following chapters.

Historical survey of electrical stimulation of the heart

CHAPTER III

I. EARLY HISTORY (1774-1932)

«Avant mon départ d'Italie (1802) j'ai annoncé que j'avais excité par moyen de la pile (DE VOLTA) le mouvement du coeur dans les animaux à sang froid.» Thus one of the first successful experiments of electrical stimulation of the heart is mentioned in «Aldini essai théorique et expérimental pour le Galvanisme avec planches» published in Paris in 1804.

ALDINI, however, did not completely succeed, for he added «mais, j'ai avoué avec inguinité que je n'avais pas obtenu le même effet dans les animaux à sang chaud.» After experiments at Alfort's veterinary college he concludes from his twelfth experiment there: «De tous les organes musculaires, le coeur est le seul qui soit complétement demeuré impassible aux violentes commotions galvaniques, lors meme qu'il les recevait en l'armant d'un des arcs.»

Attempts to achieve contractions of human hearts by use of galvanic current failed at first as well. As Aldini reported, («Sur des expériences galvaniques faites sur un supplicié pendu a Londres le 17 janvier 1803») it was impossible to cause contractions of the heart muscle in executed criminals in Turin (hanged, guillotinated) and in London. His description stated «Je fis ensuite ouvrir la poitrine, pour appliquer le galvanisme au plus important de tous les muscles, au coeur. Le péricarde ayant été détaché, j'appliquai le conducteur sur le principal organe de la vie; de plus, je le fis ouvrir pour voir si, dans quelques-unes de ses parties, il existait quelque fibre capable d'oscillation; mais tous recherches furent vaines.» (fig. III-1).

Many other research workers apart from Aldini were occupied with galvanism and their investigations are described by him. In Paris, BICHAT investigated the influence of the brain – and when that failed that of the nerves – upon the heart by means of electrical stimulation. His experiments, unlike those of HUMBOLDT, failed, but he was able to

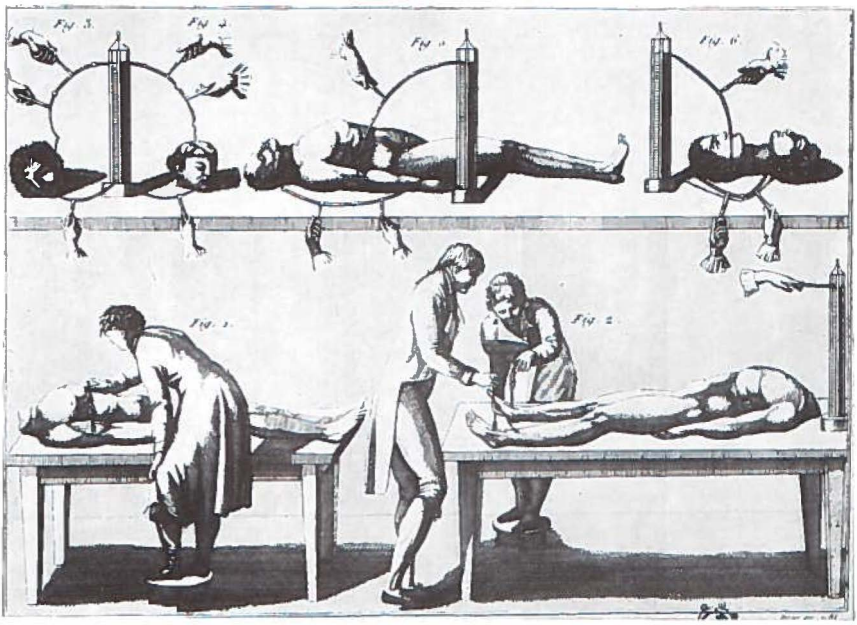


Fig. III-1. Illustration in «Aldini essai théorique et expérimental pour le Galvanism avec planches» (1804), showing the authors experiments with decapitated criminals.

cause heart contractions in both cold and warm blooded animals such as dogs by making a direct contact between the connecting wires and the heart muscle.

Effects to achieve the same results with guillotinated persons failed in his case also, as happened in Aldini's experiments, although other muscle groups did show contractions when stimulated in this way.

However, Aldini and Bichat could have forecasted their results. In 1791 LUIGI GALVANI had published his famous observations on the electrical stimulation of frog legs. In one of his experiments he placed the heart together with some other muscle groups of a frog on the back of an electric eel (gymnotus electricus); as long as the electric eel remained quiet he saw no contractions in the frog muscles, but when the electric eel moved and discharged – 'all the muscle groups including the heart contracted violently' –. In this experiment Galvani noticed that the heart was the first to become insensitive to electrical stimulation.

In the recordings of his experiments Aldini himself also comments: «Il est certain que cet organe (the heart) perd en très-peu de temps, et bien plustôt que les autres muscles, la faculté d'être agité par le Galvanisme.»

Since Bichat began his experiments on criminals 30-40 minutes after the execution and since the bodies of the executed remained on Newgate Square for one hour before Aldini could start his experiments, it will be clear why these efforts undertaken with human hearts were fruitless, whereas the gastrocnemius and biceps muscles did react, although weakly, to galvanic stimulation.

The first successful stimulation of a human heart post-mortem was carried out at the end of the 18th Century in Turin by VASSALI, GIULIO and ROSSI, but it is not known how soon after the execution they carried out this research. In a report to the Italian Society of Sciences on research with decapitated criminals cited by Aldini they described one of their methods: «En armant la moelle épinière par le moyen d'un cylindre de plomb enfoncé dans le canal des vertèbres cervicales, et en portant ensuite l'une des deux extrémités d'un arc d'argent sur la surface du coeur, et l'autre a l'armature de la moelle épinière. Le coeur, qui, dans l'individu soumis au galvanisme, jouissait encore d'une grande vitalité, présenta aussitôt des contractions très visibles et assez fortes.»

This result does not stand alone, since from even earlier times a case was known of therapeutic application of electric current. Aldini mentioned the successful reanimation of a three year old child, who had fallen downstairs, described in the records for 1774 of the Royal Human Society: 'Electric pulses applied to different places on the body had no success. When pulses were given through the thorax, a small pulsation was to be noticed.' The child recovered completely, according to the report. This single success was overshadowed however by many failures of attempts at galvanic reanimation of the heart. Electrotherapy had, as yet, found no acceptance as a method of combatting cardiac arrest.

After experiments in 1858 WALSHE suggested in 1862 the possible importance of faradic stimulation of the nervi sympatici of the heart in treatment of cardiac arrest.

Unfortunately Walshe did not give specific details of this suggestion, but DUCHENNE DE BOULOGNE in 1872 pronounced that – «l'excitation électrique rythmée de la région précordiale qui circonscrit la pointe du coeur est l'un des meilleurs moyens de combattre les syncopes par arrêt cardiaque.»

Duchenne de Boulogne elaborated this in his so-called 'main électrique» in which one electrode is placed somewhere on the skin of the patient, the other electrode being held in the physician's right hand; by then placing the back of the left hand rhythmically on the precordial area of the patient's thorax the physician should be able to produce contrac-

tions of the heart-muscle. Duchenne de Boulogne claims to have successfully stimulated in this way the heart of a diphteria patient with bradycardia.

Further experiments were carried out throughout the 19th Century. According to HYMAN by 1932 sixty-five publications on the electrical stimulation of the heart had appeared since Walshe's publication in 1862. Subsequently, many people have proceeded from a knowledge of the neuromuscular mechanisme of the heart to try to achieve reanimation by stimulation of the sympathetic nerves, although not all have followed Walshe's ideas.

JOHN A. MC. WILLIAM (1889) applied the current directly to the heart. He saw that the stimulation of the heart with faradic or galvanic current used by him often brought the ventricles to 'fibrillar contractions or heart delirium.' Mc.William conjectured on enhanced sensitivity to fibrillation of the arrested and therefore hypoxygenated heart. On the other hand hearts inhibited by stimulation of the vagus nerve responded to – 'a periodic series of single induction shocks, sent through the heart at approximately the normal rate of cardiac action (60-70/min).' The heart followed the pulses, which in animal experiments were applied directly on to the apex of the ventricles during thoracotomy, and the blood pressure rose. Mc.William recommended the above-mentioned method for reanimating hearts inhibited in such a way. He noted that to produce proper contractions of the whole heart large electrodes should be used (e.g. large sponge electrodes) one being applied on the anterior thoracic wall and the other on the back near the 4th thoracic vertebra.

Forty years later, in 1929, at a medical congress in Sydney, GOULD demonstrated an electrical apparatus for heart stimulation. This consisted of an indifferent plate and a positive needle-electrode, which was put in the heart and Gould reported the case of a baby reanimated by such stimulation.

The definitive foundation for electrical stimulation of the heart as it is applied today depended upon the development by Hyman of apparatus and methods which led to a sound experimental basis. In 1930 transthoracic intracardiac injections were the most important therapy for cardiac arrest, but mechanical stimulation of the heart by means of pressure on the precordium and diaphragm was also customary. In his analysis of these methods of therapy Hyman recorded 250 patients as having been treated in this way with positive results of the injection in 25% of cases. Epinephrine was usually the choice for intracardiac in-

jection, but eter (BOLTON 1926), caffein (BIANCHETTI 1926, WIECKOWSKI 1928), dextrose (IMERMAN 1927), sodiumthiosulfate (ZIMMAN 1928), campher, digitalis, strophanthine and many other preparations were also used. According to an investigation by VOGT they all proved more or less successful and Hyman concluded that 'the variety of the heart is probably not specific to any pharmacodynamic action, but that other factors are responsible for the resuscitation of the heart.'

Not only Hyman came to this conclusion. In 1928 KORBLER published his surmise, that 'ein geschädigtes Herz durch das einfache Anstechen zur Wiederaufnahme der Tätigkeit angeregt werden kann.' Correspondingly Hyman found that the wound in the heart resulting from his 4.5 inch long steel needle was 'a focus of increased sensitivity from which extrasystoles originated that changed into a normal sinus rhythm, if action was taken promptly after cardiac arrest.' This method was not optimal since damage was caused to the myocardium as a result of the repeated punctures and lesions of the coronary vessels were also a risk.

In 1932 HYMAN concluded: 'Since the entire phenomenon of stimulus production as the result of the mechanical irritation of the needleprick is dependant on the development of differences in electric potential, it would seem that a control of the latter factor might favourably affect the chances of myocardial contractions. The needle prick initiates only a single cardiac contraction', and 'if the electric difference of potential could be rhythmically developed during this period of cardiac standstill, it would appear a priori that regular contractions of the heart would follow, and under such artificial stimulus production an automatic activity of the entire heart might be maintained.'

In 1927 Hyman had already developed an apparatus that rhythmically stimulated a heart-lung preparation. The apparatus consisted of a Fiertz-Kaufman induction-coil stimulator with a rotating polyphasic interruptor, which permitted faradic current to be applied directly to the heart muscle, although this apparatus could not be used to resuscitate a stopped heart. To fulfil that function an apparatus was needed which provided an imitation of the impulse from the S-Anode and which passed this impulse to the heart in such a way as to produce a normal heart contraction. The latter condition was met by choosing a special needle-electrode having the positive and negative poles close together on the same needle.

In co-operation with the Electrophysical Department of New York University Hyman succeeded in 1932 in constructing an apparatus for stimulation (fig. III-2) which generated satisfactory impulses. Since

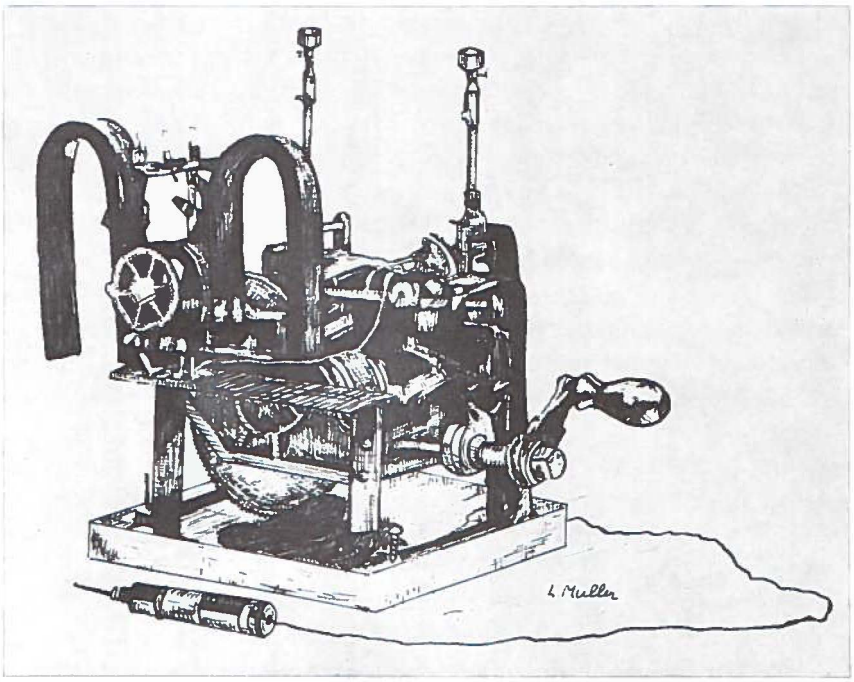


Fig. III-2. First 7,2 KG 'artificial pacemaker' after Hyman (1932). See text.

batteries were not very reliable at that time and had a useful life of only six months, a special magneto-generator was chosen for the power supply. A spring wound motor with a ballistic governor was used to spin the generator for a period of six minutes and a rotary two-phase interruptor disc controlled the duration and speed of the electric current delivered to the output terminals. In this way, Hyman was able to resuscitate the heart after a period of up to 14 minutes of ventricular standstill. He introduced the electrode into the right atrium to reduce the risk of ventricular fibrillation as much as possible.

Three years later the designer says of his apparatus: 'Since it was conceived as a substitute for a non-functioning normal sinus nodal pacemaker, it has been called the 'artificial pacemaker'. This was the first occasion on which an 'artificial pacemaker' was built, and the first use of the term.

A disadvantage of this first 7.2 kilo 'artificial pacemaker' was that the spring had to be wound up every 6 minutes, to keep the generator spinning, but this was of minor importance as the apparatus was not

meant for long-term application. The most significant point was that this apparatus laid the foundation for a whole new field of electrotherapy, so Hyman was completely justified in his remark that 'The use of the artificial pacemaker gave way to a full acceptance of its use, and although the number of patients successfully treated by this method is still very small, a more or less widespread adoption of the method would unquestionably show the validity of the procedure.'

Widespread use and further development of artificial pacemakers begin about 1950, and this development is the subject of the second part of this chapter.

II. DEVELOPMENT AFTER 1932

Most researchers focussed their investigations on the problem of reanimation in cases of cardiac arrest. Nowhere a clear description was given of the forms of circulatory arrest in which electrical stimulation of the heart would be an applicable therapy, although Hyman did give an indication in 1935 when he wrote: 'The normal healthy heart which stops from extracardiac causes is the type which is most susceptible to resuscitation by intracardial injection or by the use of the artificial pacemaker.'

By 'extracardiac causes' Hyman meant:

- neurogenic syndromes,
- hyperthyroidism, hyperadrenalism, hyperinsulinism,
- disturbances in the major neurologic control of S-A node area.

Other causes of cardiac arrest such as – 'cardiac standstill because of progressive conduction changes' – are mentioned by Hyman, but here he saw no therapeutic possibilities for the pacemaker.

After Hyman, other researchers also directed their attention to cardiac standstill resulting from extracardiac causes and one recent example is in the increasing development of heart surgery; especially heart surgery under hypothermia (1950 BOEREMA in Amsterdam and BIGELOW in Toronto) expands. In the early days of such operations cardiac arrest was rather frequent because of lack of experience of the many different causes.

Nevertheless, in this period just after 1950 when cardiac surgery developed, another possibility for the use of an artificial pacemaker was discovered, which later proved to be the most important application. At this time ZOLL was searching for means to deal with temporary ventricular standstill, starting from the considerations that 'in patients with

complete heartblock, the cardiac standstill may be transient, causing the Stokes-Adams syndrome' and noting that 'intravenous or intracardiac injections of epinephrine, myocardiac stimulation with a needle and direct cardiac massage after emergency thoracotomy have been employed successfully in some cases, but they are intrinsically hazardous and difficult'. In 1952 ZOLL published the successful use in 2 patients of 'a quick, simple, effective and safe method of arousing the heart from ventricular standstill by an artificial external, electric pacemaker.' He succeeded in counteracting Adams-Stokes attacks with intermittent pacemaker stimulation and in reanimating both patients to an idio-ventricular rhythm with sufficient circulation.

This was probably not the first application of a pacemaker on patients with complete heartblock and Adams-Stokes attacks. The successful application by DUCHENNE DE BOULOGNE in 1872 of the 'main électrique' on a patient with a slow pulse and diphteria was almost certainly the very first case. Zoll's success however gave rise to the great development of pacemakers which is still continuing.

This development is partly the result of experience gained, but also depends to an important extent on the widespread and rapid developments in the field of electronics, stimulated amongst other things by space-flight exploration.

In the two patients mentioned in his publication of 1952, ZOLL used a *completely external system with skin electrodes* upon the thoracic wall. This stimulation technique has many disadvantages, among which are the need for high voltages and the unpleasant muscular contractions experienced by the patient. These and other disadvantages, to be discussed later, persisted in spite of improvements made by ZOLL *et al.* (1954). Other workers also used Zoll's technique (DOUGLAS and WAGNER 1955, LEATHAM, COOK and DAVIES 1956) but were unable to introduce improvements sufficient to make long-term clinical application of this stimulation technique acceptable. For short-term stimulation this method is still used, among others, in the form of the pacemakermonitor (BOUVRAIN and ZACOUTO 1959, NICHOLSEN *et al.* 1959).

In 1957 SHAFIROFF and LINDER attempted stimulation of the heart by *electrodes in the oesophagus*. This technique had too many practical disadvantages however, and was not elaborated.

Throughout this period evolution of cardiac surgery continued. In 1954 LILLEHEI and VARCO closed the first ventricular septal defect and a year later the first cirrestor was constructed by DE WALL and LILLEHEI. Initially lesions of the atrio-ventricular conduction system and cardiac

arrest were frequent and in 1957 WEIRICH, GOTT and LILLEHEI for the first time placed electrodes directly on the ventricular wall for treatment of iatrogenic heartblock. In this way they were able to increase the heart rate and to restore sufficient circulation. The same *transthoracic method* was used by OLMSTEDT, KOLFF and ESSLER and by BROCKMAN, WEBB and BAHNSON in 1958, followed by many others. They placed one electrode in the heart, the so called *monopolar stimulation*, whilst in 1959 HUNTHER *et al.* implanted both the positive and the negative electrode in the heart, producing so-called *bipolar stimulation*.

Simultaneously with this transthoracic method, another direct stimulation technique for the heart was developed, *the transvenous method*. After experiments of BIGELOW, CALLAGHAN and HOPPS (1950, 1954) in 1959 FURMAN and SCHWEDEL succeeded in stimulating the hearts of patients via the right ventricular endocardium with a catheter electrode inserted through the jugular vein into the right ventricle.

All the above-mentioned electrodes had to be regularly supplied with energy from outside, and so were connected to large external pulse-forming apparatus. Success was later achieved in providing power-packs with a longer life-time, and in reducing the size of the apparatus so that it was easier to carry about, making the patient more mobile. One disadvantage of all these methods however, was the percutaneous lead connection from the external pulse-forming apparatus to the internal heart electrodes. At the perforation of the skin many breakages of the leads occurred whilst the leads themselves formed a point of entry for infections.

VERZEANO, WEBB and KELLY in 1958 avoided this disadvantage with the magnetic impulse transmission. In this technique a secondary coil, situated under the skin, was connected with myocardial electrode leads. The pulse-forming section of the apparatus was situated extra-corporally and stimulation pulses were induced in the subcutaneous coil from a primary coil placed in alignment with the subcutaneous coil. Skin perforation by the leads was thus avoided. ABRAMS, HUDSON and LIGHTWOOD (1960) and SUMA, FUJIMORI, MITSUI *et al.* (1965) used the same techniques.

GLENN (1959) and CAMMILLI, POZZI, DRAGO *et al.* (1961) attempted to apply the same principle by means of *electro-magnetic waves* (modulated radio-waves) emitted by a transmitting coil and detected by a receiving coil. In 1962 CAMMILLI, POZZI and DRAGO no longer had to make use of internal thoracic wires, as they placed a receiving coil directly on the myocardium, the electrodes being an integral part of this receiver.

The magnetically or electro-magnetically coupled pacemaker means a great burden for the patient who will have to live with a transmitter constantly attached to his chest. In view of this, most investigators believe in the idea: 'out of sight, out of mind'.

Technical advances enable ELMQVIST and SENNING to develop a *fully implantable pacemaker* in 1959. However the pacemaker batteries had to be recharged inductively from time to time, due to the small capacity of the powerpack. In 1960 they developed a pacemaker with a power supply providing sufficient energy for several years. In that year also ZOLL *et al.*, KANTROWITZ and CHARDACK, GAGE and GREATBATCH all achieved the same object.

The implantable pacemakers produced impulses with a fixed frequency, output and pulse-duration. Subsequently however, VAN DEN BERG, HOMAN VAN DER HEIDE, NIEVEEN *et al.* (1962); DAVIES (1962); RAILLARD (1962); KANTROWITZ *et al.* (1962); CHARDACK (1962) and GLASS, SHAW and SMITH (1963) constructed implantable pacemakers with limited *adjustable variations in the electronic circuit.*

Catheter electrodes were also connected with fully implanted pacemakers by LAGERGREN and JOHANSSON (1963), SIDDONS and DAVIES (1963) and others.

An attempt by FOLKMAN and EDMUNDS (1962) to construct a *drug pacemaker*, possibly in combination with an implantable pulse-forming apparatus, failed in longterm application.

The electronic possibilities expended rapidly since the early clinical application by ZOLL in 1952. These possibilities assisted FOLKMAN and WATKINS (1957) and STEPHENSON *et al.* (1959) in constructing a *P-wave triggered pacemaker*. Here the function of the atrio-ventricular node and the bundle of His was partly taken over by an electronic circuit. An epicardial atrial electrode detected the P-waves of the atrium, and passed these signals on to the pulse-forming apparatus, which after a delay, corresponding to the delay time of the conducting system, emitted an impulse to stimulate the ventricles. In 1963 NATHAN, CENTER *et al.* and also BONNABEAU, BILGUTAY, STERNS, WINGROVE and LILLEHEI succeeded in making implantable pacemakers of this type.

Two years later, in 1965, RODEWALD *et al.* succeeded in detecting the P-wave of the atrial endocardium with a catheter electrode which was connected to an implanted pulse-forming apparatus, which in its turn passed impulses to a second catheter electrode, thus stimulating the right ventricle.

The same idea is applied in the development of the '*on demand pace-*

maker'. The 'on demand' pacemaker is controlled by the R-waves of the QRS-complex, detected (in)directly from the ventricle and induces only ventricular contractions when the heart-frequency decreases below the fixed pacemaker frequency. The R-wave controlled pacemaker is known in two types. The one type, the R-wave triggered pacemaker, is a modification of the P-wave triggered pacemaker and functions continuously (DONATO and DENOTH 1966). In the other type, the R-wave blocked pacemaker, the pacemaker impulses are blocked by the ventricular contractions if the heartfrequency is higher than the fixed pacemaker frequency (LEMBERG *et al.* 1965, VAN DEN BERG and THALEN 1965, MEYER *et al.* 1966). The first clinical applications of implantable versions of both types were reported in 1966.

A survey is given above of the development of the 'artificial pacemaker', which is now employed especially in the treatment of atrio-ventricular block with Adams-Stokes attacks. In this overall picture it was not possible to specify the various stimulation methods especially with respect to their advantages and disadvantages. Such a specification is the subject of the next chapter.

Methods of stimulation

CHAPTER IV

The various designs of the stimulation apparatus, the impulse transmission and the electrodes are discussed in separate chapters. There is a great variety in the designs of these three components, so that several combinations are possible. A combination of stimulation apparatus, impulse transmission, and two or more electrodes constitutes an artificial pacemaker, which represents a method of stimulation.

In the accompanying diagram (fig. IV-1) an outline is given of all combinations which have been or are still being used for electrical stimulation of the heart. The various methods of stimulation are dealt with in chronological order of their development.

Whenever a change is made in either the stimulation apparatus, in the impulse transmission or in the electrode of a pacemaker, giving rise to a fundamentally different method of heart stimulation, then this is considered to provide a new method of stimulation. Applying this norm, ten methods of stimulation can be distinguished:

1. completely external system; indirect, diffuse impulse transmission,
2. external stimulation apparatus; semi-direct impulse transmission via oesophagal electrode,
3. external stimulation apparatus; direct impulse transmission by transthoracic leads and intramural or epicardial electrodes,
4. external stimulation apparatus; direct impulse transmission via transvenous leads and endocardial electrodes,
5. external stimulation apparatus; magnetic impulse transmission,
6. external stimulation apparatus; electro-magnetic impulse transmission,
7. internal asynchronous system,
8. drug pacemaker in combination with electrical pacemaker,
9. internal P-wave triggered synchronous system,
10. internal R-wave controlled on demand system.

After reviewing the principle and the development of each method, the advantages and disadvantages are examined insofar as they are related to the fundamental alterations, distinguishing the next method from those preceding. In discussion of any technique therefore reference is made to advantages or otherwise of preceding methods.

1. COMPLETELY EXTERNAL STIMULATION SYSTEM

Stimulation by the completely external stimulation system involves indirect and diffuse stimulation of the heart, either by disc electrodes on the thoracic wall, or by needle electrodes in the subcutaneous tissue of the chest, which are connected by leads to an external stimulation unit (fig. IV-2).

Animal research

The principle of the artificial pacemaker had already been applied by Hyman in patients with cardiac arrest resulting from extra-cardiac causes, as described in the preceding chapter.

ZOLL (1952) also applied this method in patients with complete heart block and Stokes-Adams attacks. In order to determine the optimal pacemaker frequency and impulse shape he stimulated dogs, in whom cardiac depression had been induced by administering Quinidine. The apparatus used was a thyratron physiologic stimulator which gave periodic, monophasic, rectangular D.C. impulses. These had a voltage adjustable up to 130 V and a duration adjustable between 2-20 msec. and proved to be effective for canine hearts.

Clinical application

ZOLL (1952) was the first to apply the method on 2 patients, using needle electrodes. Later, these were replaced by round metal discs with a diameter of 3 cm on the thoracic wall and fixed by means of an elastic strip around the thorax.

The electrodes may be placed anywhere on the thorax provided there is sufficient conduction of current through the heart. The negative electrode is usually attached near the apex (V_5-V_6) and the positive electrode on the right half of the thorax near V_3R–V_4R. The optimal location and polarity of the electrodes can be chosen according to the lowest stimulation threshold. To ensure good contact with the skin,

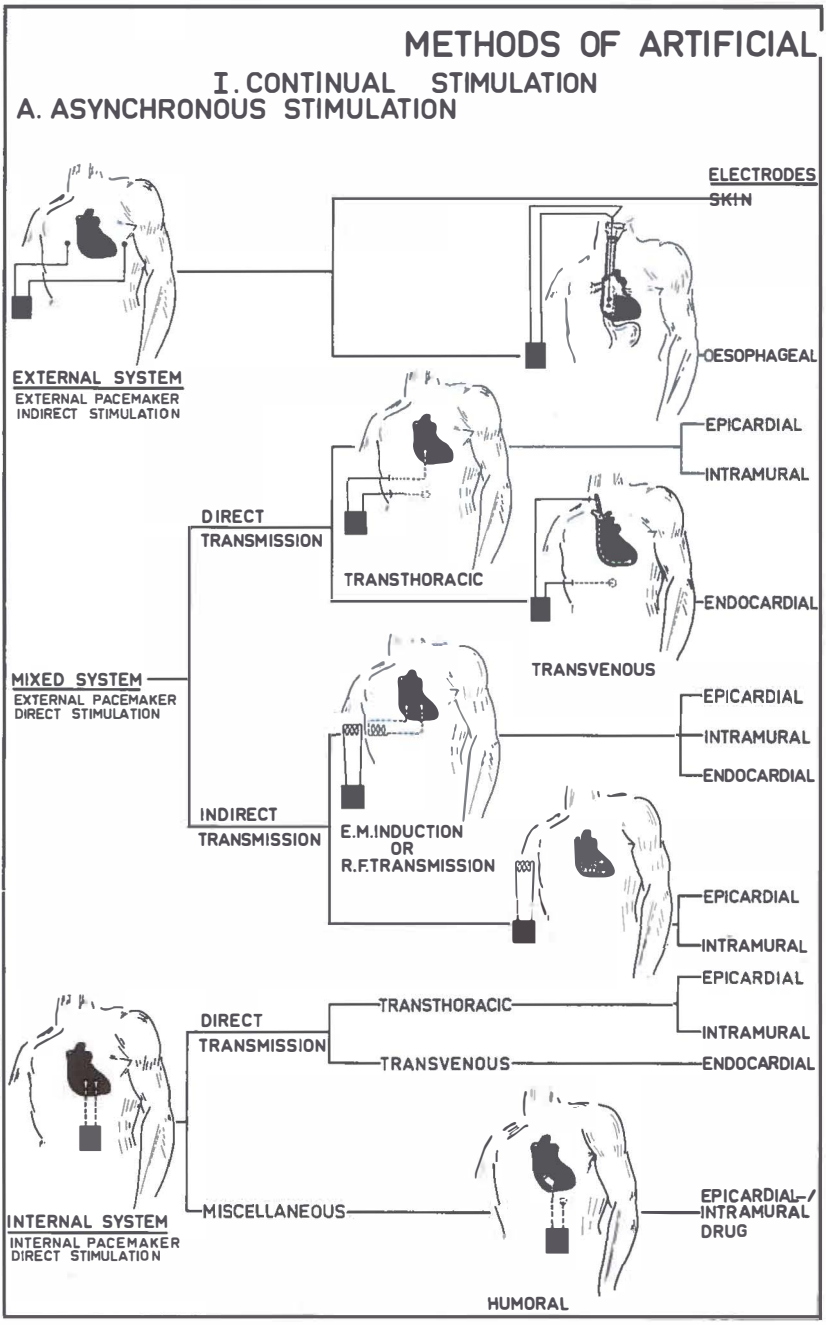
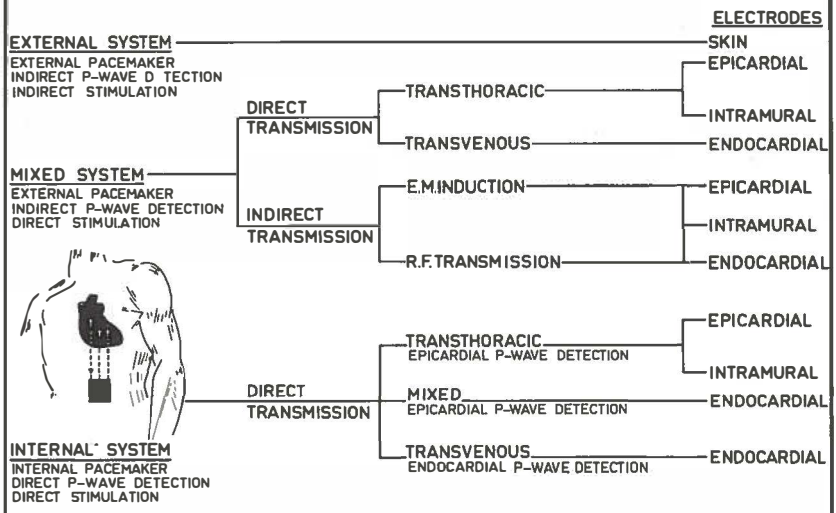


Fig. IV-1. Tableau of the various methods of artificial cardiac stimulation.

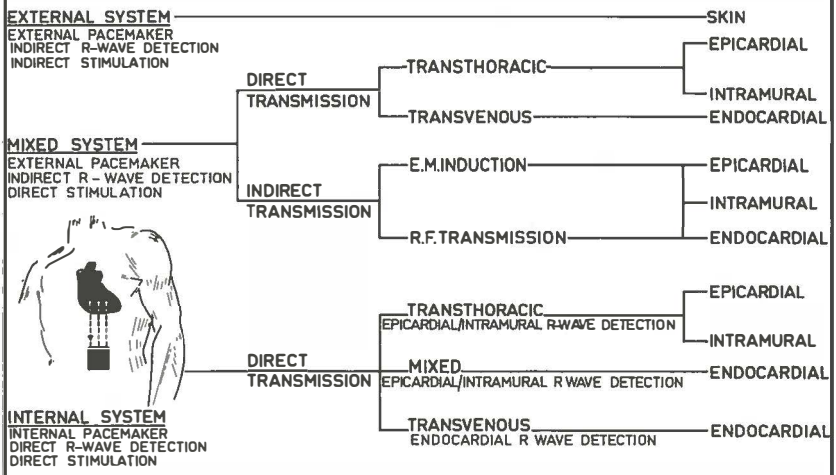
CARDIAC STIMULATION

B. SYNCHRONOUS STIMULATION
P-WAVE TRIGGERED STIMULATION



II ON DEMAND STIMULATION
R-WAVE CONTROLLED STIMULATION

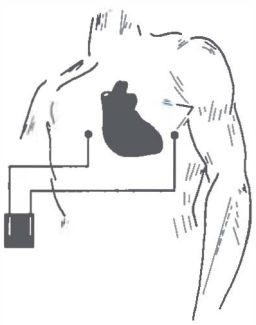
A. ASYNCHRONOUS STIMULATION



B. SYNCHRONOUS STIMULATION
P-WAVE TRIGGERED, R-WAVE CONTROLLED STIMULATION

electrode paste should be used and renewed frequently. In order to prevent a short-circuit occurring along the surface of the skin, the distance between the electrodes should be minimally 7-8 cm, and the skin between the electrodes should be dry.

Fig. IV-2. Scheme of completely external stimulation-system, diffuse impulse transmission.



Needle electrodes in the subcutaneous tissue pose less problems. They need no paste, and are simple to attach. For this reason they are preferable to disc electrodes, especially for control of the heart rate under anaesthesia (NICHOLSON, EVERSOLE *et al.* 1959).

After this clinical application in 1952, several researchers used this method. The stimulation values, as used for the first investigations are contained in Table IV-1.

TABLE IV-1. *Types of impulses used in early reports of external indirect stimulation*

	shape of impulse	duration	voltage	current
ZOLL 1952	rectangular	2-20 msec	130 V	not mentioned
ZOLL 1954	rounded	2-3 msec	0-15 V	75-150mA
DOUGLAS 1955	rectangular	2 msec	70 V	not mentioned
LEATHAM 1956a	rectangular	20 msec	40 V	25 mA
LEATHAM 1956b	rectangular	1-4 msec	40-200 V	not mentioned

The stimulation frequency used, varied from 50-90 impulses per minute. An impulse duration of 2-3 msec was chosen by Zoll in later models, on the grounds that impulses of less than 2 msec required far more voltage and current, while the voltage and current required for impulses of longer duration did not diminish appreciably. Also, long impulses involved the risk of multiple responses to one stimulus. LEATHAM (1956), in his second stimulation unit, developed by DAVIES, also reduced the

impulse duration since serious skin irritations had resulted when an impulse of 20 msec. was used.

The impulse shape is usually rectangular, although in Zoll's second stimulator (1954) a different shape (monophasic rounded) was used because a variety of other waveforms (monophasic and biphasic spike, monophasic and biphasic rectilinear and sinusoidal) were found to be less effective. Later ZOLL and LINENTHAL (1960) used a rectangular pulse again for implanted pacemakers. It appears that the threshold values for stimulation via electrodes on the skin of the chest vary from patient to patient and from measurement to measurement. The mean values vary from 45-100 volts, at a current of 75-150 mA (ZOLL *et al.* 1955).

The decision to discontinue stimulation is based upon satisfactory changes in the peripheral pulse, the ECG or blood pressure. Thereupon, the voltage of the pacemaker is slowly reduced until the heart is no longer being stimulated. Stimulation can be definitely discontinued when sinus rhythm or a sufficiently rapid idio-ventricular rhythm has returned, but this rhythm should then be monitored closely for 2 to 4 days. In order to promote the return of a sufficient idio-ventricular rhythm, pacemaker stimulation can be combined with the administration of drugs; Epinephrine, Norephinephrine, Ephedrine, Ephedrine Lactate (ZOLL) and Sodium Lactate (LEATHAM) have all been used successfully.

The period of stimulation may be short in cases of brief fainting attacks or in a series of brief attacks. Sometimes, however, the spontaneous idio-ventricular rhythm may be intermittent or too slow, or sometimes it may not appear at all. In these cases it is necessary to continue stimulation often for an extended period to maintain satisfactory circulation. Thus Zoll applied longterm stimulation to 20 of 27 patients reported in 1955, with a maximum uninterupted stimulation time of 109 hours, while others needed stimulation times of 7 days (DOUGLAS and WAGNER 1955), 16 days (PEARCE and NORDYKE 1957) and even 58 days (LEVOWITZ *et al.* 1960).

These experiences have shown that it is possible to keep a patient alive in this way during ventricular asystole lasting for hours to days. However, ventricular contractions cannot be aroused by this method of stimulation if circulatory arrest occurs due to tachycardia or ventricular fibrillation.

Advantages and disadvantages

The new electro-therapy made it possible to abolish ventricular stand-

still rapidly, simply, efficiently and safely, rendering intracardiac injections or direct heart massage after emergency thoracotomy no longer necessary. As is the case with each new therapy, the disadvantages were only brought to light clearly during general application on a wide scale in spite of all prior investigations.

Advantages

A. External stimulation apparatus

1. Adjustable stimulation. Because the stimulation unit is situated extracorporally, the stimulation can be adjusted for frequency, pulse-shape and pulse-amplitude. In order to maintain optimal stimulation the values may be adjusted during the long term stimulation.

2. Defects simple to trace and repair. Since the stimulation unit is situated extracorporally, defects in the apparatus can be rapidly traced and repaired.

3. Unlimited energy supply. External stimulation requires high voltages. The required energy may be obtained by connecting the apparatus to the mains so that stimulation can take place without the energy supply limiting the duration of use of the method.

Due to developments in the field of electronics and more efficient direct cardiac stimulation it became possible to stimulate the heart for long periods by small battery powered units, and in these cases it is easy to renew the powerpack by simply exchanging or recharging the batteries. WEIRICH *et al.* used such small stimulators as early as 1958, while THEVENET *et al.* treated 26 of their 55 patients by battery powered pacemakers in the same year.

4. Simple termination of stimulation. In case of a return to sinus rhythm, artificial stimulation can be simply terminated thus avoiding interference between the natural and artificial rhythms.

B. Diffuse impulse transmission

1. Location of the electrode variable. Since the method of diffuse stimulation transmission is concerned here, no particular electrode location is indicated, and the electrodes may be fixed in various places on the thorax.

C. Electrodes

1. *Electrodes rapidly fixed.* It is an advantage that the electrodes can be attached rapidly, particularly in emergencies. When disc-electrodes are used the skin however should first be well rubbed with electrode-paste. This is unnecessary when using needle-electrodes.

2. *Defects rapidly traced and repaired.* Regular inspection of the electrodes is essential. Defects can be detected rapidly and are simple to correct by replacing the electrode.

Disadvantages

A. External stimulation apparatus

1. *Restricted mobility.* To obtain the high voltages needed for this method of stimulation the apparatus is generally connected to the mains, which restricts the mobility of the patient. The small battery powered units which were developed later, could be carried by the patient in a special belt or bag and so did not suffer from this disadvantage. However, the batteries needed frequent recharging or renewing. More efficient stimulators (transistors) and more efficient methods of stimulation (direct) led to further extension of battery lifetimes.

2. *Mental stress.* The external stimulator puts a psychological stress on the patients, because it reminds him of his dependence on the vulnerable pacemaker (FAIVRE, GILGENKRANTZ and RENAUD, 1964).

3. *Difficulties and risks accompanying the use of the electrocardiograph.* Monitoring these patients by electrocardiograph is difficult. In cardiographs with A.C. input (with condensors in the input circuit), monitoring is difficult because the deviations caused by the relatively large stimulation impulses are too great. Electrocardiographs with D.C. input do not have this disadvantage.

Care should be taken in earthing the patient and the apparatus, because of the risk of electrocution, and both should be earthed by only one lead. This condition can be met by earthing the electrocardiograph and other apparatus via the pacemaker and by earthing one of the stimulation electrodes. The customary method of earthing the patient by the right leg may therefore not be employed here (see also Chapter IX).

B. Diffuse impulse transmission

1. Contractions of the thoracic muscles. The high currents through the thoracic electrodes not only stimulate the heart, but also cause contractions of the thoracic muscles, especially the pectoral muscles. These contractions may be reduced by administering muscle relaxent drugs.

2. Sensations of pain. The muscular contractions are accompanied by pain, which is not adequately relieved by local infiltration of Procaine hydrochloride. Somewhat better results are obtained by administering Meperidine hydrochloride or Paraldehyde and the pain also lessens as stimulation progresses. Both the muscular contractions and the painful sensations are particular disadvantages when applying this method to children.

3. Stimulation of the diaphragm. Occasionally the diaphragm muscles are stimulated. REIFF *et al.* (1957), LEVOWITZ *et al.* (1960) and DE VOS (1962) recorded a reaction by the disphragm muscles to the pacing stimulus and this was sometimes accompanied by contractions of the abdominal muscles. These contractions disappeared when the electrodes were moved. ZOLL (1954) once observed a case of apnoea, when the diaphragm muscles were stimulated via the electrodes (7-8th i.c.s.) and interference with the respiratory rhythm occurred. This symptom disappeared when the electrodes were moved to the 4-5th i.c.s.

4. Rise of the stimulation threshold. Some authors found that the longer the stimulation lasted, the higher the threshold current became. ROSENFELD and SEGALL (1955) were forced after some time to apply the maximum voltage of their stimulation unit (150 V) in two of their three patients. After 63 hours and 70 hours of continuous stimulation respectively, even 150 V was ineffective in these cases, the heart could no longer be stimulated, and the patients died.

LEVOWITZ (1959) too, reported having to increase the voltage in the first 3 days from 52 to 70 V for effective stimulation in one of his patients. In the following four weeks, the voltage had to be increased again. He thereupon decided to implant an intramural heart-electrode which had been developed in the meantime. DE VOS made a similar observation in 1962.

5. Pericardial and/or myocardial changes. The question as to whether pericardial and/or myocardial changes appear as result of the electrical stimu-

lation has still not been settled. ROSE and WARTONICK (1955) argued they could demonstrate such a connection; they stimulated a patient intermittently for 46 days, the longest period of continuous stimulation being 26 hours, until finally the heart no longer responded to stimulation. At the autopsy they found a hyperaemic pericardium with apparently inflammatory changes, which they ascribed as due to the electrical stimulation. REIFF *et al.* (1957) also observed pericardial lesions at an autopsy after 40 hours' stimulation. Sixteen hours before the patient died he developed a pericardial rub. On the other hand, others (LEATHAM, ROSENFELD and ZOLL) never found similar lesions. (see also Electrodes: skin irritations).

C. Electrodes

1. Skin irritations. The skin electrodes can cause irritation and skin lesions which resemble burns and may change into ulcerations after as little as one day's stimulation. By moving the electrodes several times a day and by cleaning and moistening the underlying skin these lesions may be minimised.

These skin irritations are not caused by pressure of the electrodes, but by electrical stimulation, as is shown in fig. IV-3, in which the stimula-

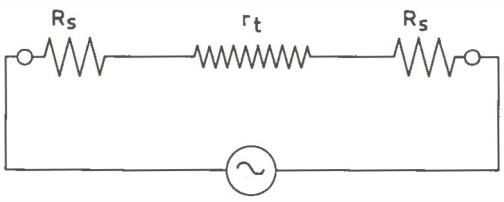


Fig. IV-3. Diagram to elucidate the occurrence of lesions near skinelectrodes. R_s: resistance of the skin; r_t: resistance of the (internal) tissues. See text.

tion circuit is shown schematically. The resistance in the circuit is composed of two parts, R_s, representing the skin below the corresponding electrodes, and r_t, representing the body tissues between these areas, with $R_s \gg r_t$.

The current in the circuit required for stimulation is determined by the required current through the heart. The latter current is only a small fraction of the total current and this means that the total current needs to be rather large. As heat is generated in proportion to the product of the square of the current, the resistance and the time ($W = ai^2Rt$ cal.), this means that most of the heat is generated in small volumes of skin below both electrodes. As the current assumes high

values during external stimulation skin lesions are caused after sometime in the form of burns. Heat generation may be counteracted by moistening the skin or using electrode-paste at the contact with the electrode, thus lowering the resistance (R_s). The use of electrodes with large surfaces is also helpful since this reduces current density.

When needle electrodes are used lesions occur less rapidly, because these electrodes pierce the skin, resulting in a contact point with a smaller resistance. Moreover, should heat be generated it is absorbed more easily by the subcutaneous tissue so that the risk of burns is slight.

It seems improbable that the explanation for pericardial and myocardial lesions is analogous to that for the skin irritations. As the current through the heart is small, little heat is produced. Because any heat generated can also be absorbed easily, it is not plausible that pericardial or myocardial lesions can be produced in this way.

2. *Vulnerable fixation of electrodes to skin.* As the electrodes are fixed to the skin, there is a danger that they will be moved or loosened by external causes, thus interrupting stimulation.

Conclusion

It may be concluded that completely external stimulation gives good results in cases of ventricular arrest and extreme bradycardia, and in the prevention of ventricular tachycardia and fibrillation.

The disadvantages of this method of stimulation, especially the high voltage and the concomitant muscular contractions and skin lesions, made it impracticable for long-term application. The solutions found for these problems are discussed with the following methods of stimulation.

Nevertheless, in spite of its disadvantages, completely external stimulation is still employed in cases of acute cardiac arrest, when emergency treatment is necessary.

A special device, the pacemaker monitor, is incorporated in the present day monitoring unit, and is discussed together with the R-wave pacemaker.

II. EXTERNAL STIMULATION UNIT, SEMI-DIRECT IMPULSE TRANSMISSION USING OESOPHAGAL ELECTRODES

In this method, the heart is stimulated semi-directly, through one or more electrodes in the oesophagus, sometimes in combination with a

skin electrode, connected by leads to an external stimulation unit (fig. IV-4).

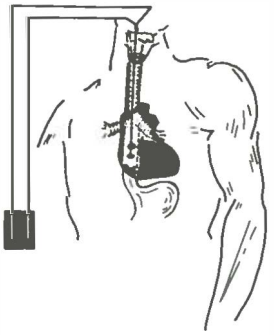


Fig. IV-4. Scheme of external stimulation apparatus with semi-direct impulse transmission via oesophagal electrodes.

Animal research

ZOLL (1952) reduced the heart rhythm in a number of dogs by administering Quinidine. The hearts were then stimulated by an insulated electrode with a metal tip, introduced into the oesophagus near the superior part of the ventricles. A skin electrode over the apex of the heart was used as a second electrode.

Although the heart could be stimulated via these electrodes by low current impulses, the disadvantages of this method which will be discussed below, proved to be greater than those of completely external stimulation. Therefore no extensive animal research was carried out.

Clinical application

In 1957 SHAFIROFF and LINDER applied this method in patients to evaluate in greater detail the effect of electrical stimulation of the human heart both under near normal conditions and during periods of operative stress. The electrodes they used consisted of a medium-sized stomach tube, around which 5 ring-electrodes were attached at 0.5 cm intervals. These rings were each 1 cm wide and were connected inside the tube by converging leads connected to the stimulator. A switch allowed stimulation by two or more rings. Using this combination of electrodes no external indifferent electrode was needed.

Stimulation was successfully attempted in two groups of patients with normal sinus rhythm. The first group (16 patients) received no sedation, and the heart followed the impulses during stimulation at a frequency

slightly above the sinus rhythm, by a monophasic rectangular 30-50 volt pulse with a duration of 20 msec. The stimulation threshold varied, but no heart could be stimulated by impulses below 10 volts, independent of the impulse duration.

The second group (19 patients) was stimulated under anaesthesia during appendectomy or herniorraphy. Stimulation was applied with a frequency of 100-120 imp./min, with a pulse duration of 30 msec and a potential of 4 volts. All the hearts followed the stimuli well. Further applications of this method have not been mentioned by these or other investigators.

Advantages and disadvantages

When discussing the advantages and disadvantages of this stimulation method in relation to stimulation by completely external means it must be borne in mind that the stimulation carried out by SHAFIROFF and LINDER was only applied for a few hours, and that the method has never been employed for long term stimulation.

Advantages

A. Semi-direct stimulation

1. Lower stimulation threshold. Semi-direct stimulation requires a lower voltage and a lower current than completely external stimulation so that side-effects in the form of muscular contractions and pain are less. It should be noted however, that stimulation was applied for short periods only.

Disadvantages

A. Semi-direct stimulation

1. Disadvantageous side-effects. Stimulation by oesophagal electrodes is possible at low stimulation thresholds, but even here the voltage needed is 30-50 volts, and this was sufficient to produce pain in the first group of patients. If the stimulation was carried out with an impulse voltage of more than 70 volts this pain became intolerable. In addition to the pain, diaphragmatic contractions occurred in 33% of the patients in the first group, although these were probably influenced by the location of the electrodes.

In view of the fact that the second group of patients was stimulated under general anaesthesia with artificial respiration, no observations could be made with regard to sensations of pain, and observations with regard to the diaphragm muscles were not conclusive.

B. Oesophagal electrodes

1. Long-term continuous stimulation impossible. Location of an electrode in the oesophagus prevents long term stimulation because of difficulties with nutrition.

2. Risk of damage to oesophagal tissue. No details are available concerning damage to oesophagal tissue resulting from the stimulation, because of the short duration and the absence of autopsies. The risk of tissue reactions similar to those which occur during external stimulation seems very real.

Conclusion

It may be concluded that it is possible to stimulate the heart in this way with impulses of suitable duration and amplitude, but that long term stimulation of the heart by this method is not possible. The method might be practicable for stimulation of the heart under anaesthesia, although difficulties during induction and termination of anaesthesia due to the location of electrodes and leads are likely to be considerable.

This stimulation method has never passed the experimental stage because of the great disadvantages, and due also to the simultaneous development of direct heart stimulation, which offered far wider perspectives.

III. STIMULATION WITH AN EXTERNAL STIMULATION UNIT AND DIRECT TRANSTHORACIC IMPULSE TRANSMISSION USING INTRAMURAL OR EPICARDIAL ELECTRODES

With direct transthoracic impulse transmission, the heart is directly stimulated via intramural or epicardial electrodes in or on the heart muscle; these electrodes perforate the thoracic wall and are connected to an extracorporal stimulation unit (fig. IV-5).

Introduction

The techniques of completely external stimulation had shown that application of an artificial pacemaker was an useful therapy in disturbances of the conduction system of the heart, but it's use suffered from the disadvantages discussed above. The advances in heart surgery formed the direct stimulus to the further development of electrical methods of stimulation.

During open correction of many intracardiac defects such as ASD, VSD or deformities of the aortic valves the bundle of His was damaged during intracardiac manipulations. ALLEN and LILLEHEI (1957) reported a post-operative heart block in 19 out of 165 patients in whom a ventricular septal defect had been corrected by use of the pump-oxygenator.

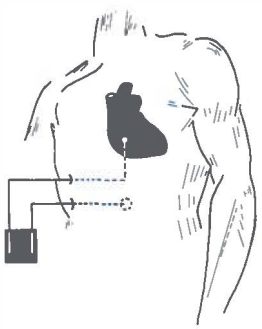


Fig. IV-5. Scheme of external stimulation apparatus with direct impulse transmission via a transthoracic electrode (monopolar).

This complication occurred frequently, especially during the early period of development of open heart surgery and gave rise to rapid advances in the treatment of iatrogenic heart block. The technique of stimulating the heart by means of electrodes attached directly on or in the heart during the operation was developed in the hope that this would be only a temporary measure. The electrode leads were extended out through the skin when the thorax was closed, in order to remain connected with the stimulator and it was found that the heart could be efficiently stimulated at low voltages in this way, even for long periods.

Although this method was in fact intended to bridge the post-operative heart block period, the method was finally also applied in patients with heart block due to other causes. In these cases a thoracotomy was performed with the aim of fixing the electrodes to the epicardial or intramural aspects of the heart, and this method thus developed to include patients with chronic heart block.

Animal research

Direct stimulation by transthoracic electrodes was developed by WEIRICH, GOTT, PANETH and LILLEHEI who began to study the treatment of iatrogenic heart block in 1957. Starting from the standard procedure for electrical stimulation of an animal heart for investigational or teaching purposes they initially created block in 5 dogs by ligating the bundle of His. They then passed a silverplated copper wire welded to a surgical needle through part of the anterior wall of the right ventricle and subsequently cut off the needle. The lead itself was insulated by teflon or polyethylene and passed through the thoracic wall, so that it could be easily extracted later. An indifferent electrode was attached to the skin or in the subcutaneous connective tissue. An attempt to stimulate the heart by electrodes in the left and/or right atrium was abandoned because of the high voltage required.

With ventricular wall electrodes it was found that the heart could be efficiently stimulated with a 2 msec. square wave impulse, with threshold values varying from 0.8-9 V (average 2,25 V) at currents of 5-45 mA (average 18 mA).

The good results of WEIRICH *et al.* led to an extensive study of direct electrical stimulation of the heart. In subsequent chapters concerning investigations into the problem of electrodes, impulse transmission and stimulation apparatus, various factors such as stimulation threshold, monopolar and bipolar stimulation and electrode site will be discussed in more detail.

A method of introducing the cardiac electrode without resorting to thoracotomy was investigated by THEVENET, HODGES and LILLEHEI (1958). Using the pump-oxygenator they created heart block in 15 dogs and then closed the thorax. They then inserted a trocar containing the electrode through the thoracic wall into the heart muscle; the trocar was then retracted leaving the electrode in position in the heart. In all cases the heart followed the stimulating impulses well with thresholds varying from 2.5 to 4,0 V. Stimulation was carried out in one case for 10 days and in the other cases for 6 hours. Postmortem investigation showed no mechanical damage of the heart by the wire, nor was damage found which could be attributed to the electric current.

This method of introducing the cardiac electrode was not investigated in animal research by others.

Clinical application

A. Post-operative iatrogenic heart block

This method was applied clinically for the first time on 30th of Januay 1957 by WEIRICH, GOTT and LILLEHEI and a year later Weirich described his experiences with 18 patients.

The method was especially intended for stimulation during iatrogenic temporary heart block until sinus rhythm or an idioventricular rhythm of sufficient frequency returned. When adequate cardiac activity returned the pacemaker was switched off for a trial period, but remained connected to the heart. If all was well, the electrode was later extracted.

This method was used by other surgeons such as CLARK, ROSS, TAYLOR and GEORGE (1959).

B. Trocar method

After their experiments on animals, THEVENET *et al.* investigated the correct manner of introducing the trocar in the bodies of seven dead patients. From these investigations they concluded that the trocar should be introduced near the 5th left intercostal space, 6-7 cm from the mid line (4-5 cm in children). The needle was then directed medially, dorsally and cephalically towards the 2nd right costo-chondral junction at an angle of 30° with the body-surface so that the right and anterior descending coronary arteries were avoided.

This operation can be performed under local anaesthesia, with the patient connected to an electrocardiograph. When the heart has been reached some extra systoles appear on the ECG and the needle is inserted a further 5 mm into the myocardium; the electrode is then pushed through the needle which is retracted, leaving the electrode in the myocardium. The electrode position can be checked by X-ray and should be situated approximately 2-3 cm superior to the inferior edge of the right ventricle. A second cardiac electrode or stainless steel subcutaneous electrode near the apex of the heart completes the circuit. The heart electrodes should be connected to the negative pole of the pacemaker.

THEVENET, HODGES and LILLEHEI stimulated 55 patients by this method, the longest period of stimulation being 57 days. Others also applied this method clinically, particularly ROSS and HARKINS (1959) and BELLET *et al.* (1960).

C. Thoracotomy

The trocar method was employed only in emergency cases and Thevenet *et al.* used another solution for patients requiring long term stimulation. They state 'should a thoracotomy incision provide a better means of establishing a permanent connection of these medical patients with a permanent block, we believe that the therapeutic gains would make such an operation entirely feasible, because of the mortality and morbidity of the Adams-Stokes syndrome in those more seriously afflicted.'

The introduction of a thoracotomy for transthoracic direct stimulation of the heart allowed a considerable increase in the application of electrotherapy for heart block. Later this method was also used in combination with implantable pacemakers.

Advantages

A. Direct impulse transmission

1. Low voltage and current. Direct stimulation of the heart is effective with weak electrical impulses, so that low voltages are sufficient, the stimulation threshold being minimal.

2. No pain or adverse muscular contractions. Due to the low voltage and current impulses, the electrodes can be positioned so that no painful sensations or adverse muscular contractions are caused. Thus stimulation of the diaphragm or abdominal muscles and respiratory effects need not occur. In the case of monopolar stimulation, temporary muscular reactions may occasionally occur around the indifferent electrode immediately after the implantation especially if the indifferent electrode is located in the neighbourhood of nerve fibres.

3. No skin irritations. Due to the location of the electrodes (and the low current and voltage) naturally no skin burns or ulcerations can occur.

B. Electrodes

1. Rapid insertion of electrodes by means of trocar. In emergencies, the trocar method offers the possibility of rapidly achieving direct stimulation. The localisation and fixation of the electrodes is not optimal in this case.

2. Optimal localisation and fixation of the electrodes by means of thoracotomy. When fixing the electrodes by thoracotomy, the surgeon has a part of

the heart under direct vision. He is then able to fix the electrode to the most favourable place and attach it as well as possible. The problems arising with this method have led to development of a large variety of leads and electrodes. This method of fixing heart electrodes is not suitable for emergencies.

Disadvantages

A. Direct impulse transmission

1. Infection entering through skin-perforation of leads. Because the lead has to connect the external stimulator with the heart electrodes the skin must be perforated. This perforation provides an entry route for infections, which may proceed along the lead to the heart (inter al. LEVOWITZ *et al.* 1960).

2. Lead fracture. A frequent complication is fracture of the leads. These occur particularly at the places where the leads perforate the skin, but intracorporal fractures also happen (BLUESTONE *et al.* 1965). This complication may necessitate rethoracotomy.

3. Rise in stimulation threshold. As is the case with the completely external indirect stimulation, the stimulation threshold occasionally rises during direct stimulation also. If the increase is so great that stimulation cannot be continued a further thoracotomy for attachment of new electrodes may be necessary.

The increase of the stimulation threshold may be caused, among other things, by an infection proceeding along the lead and myocardial tissue reaction.

4. Pheumo-thorax. The possibility exists of air passing directly along or through the lead to the thoracic cavity, resulting in a pneumo-thorax (LINDE and MULDER 1965).

B. Electrodes

1. Operation. The disadvantages associated with the electrodes in direct transthoracic stimulation are the consequences of the particular method employed, and both trocar and thoracotomy methods have their particular problems.

Trocar method

Even if the location and the angle of introduction of the trocar have been selected carefully, the method still entails a certain risk, as the following disadvantages show.

a. Myocardial lesions. Due to the insertion and retraction of the trocar and the electrode myocardial lesions may occur, accompanied by haemorrhages.

b. Lesion of coronary vessels. The possibility of damage to coronary vessels cannot be excluded in this 'blind' insertion method.

c. Perforations of the ventricular wall. Such perforations have occurred both during animal research (THEVENET *et al.* 1958) and during clinical applications (BELLET *et al.* 1960).

d. Poor fixation of the electrodes. The poor fixation of the electrodes in the heart is a great disadvantage of the trocar method. This may be obviated to some extent by leaving part of the lead in the thoracic cavity, which will absorb a great deal of external traction, but respiratory and other movements are nevertheless capable of shifting or even dislodging the electrode.

Thoracotomy method

Although even electrodes fixed in this way may become dislodged, the great disadvantage of this method is the thoracotomy itself, with its inherent potential complications.

a. Operational risk. Although the operational risk is rather slight, it should be borne in mind that a heart operation is concerned. Since the patients have an irregular heart rhythm, pre-operative control of this is desirable in order to bring the patient into optimum condition, while during the operation itself, control is likewise desirable in order that the heart may be immediately stimulated in case of complications. When the heart is exposed, cardiac arrest may also be treated by massage and direct electrical stimulation.

b. Pleuro-pulmonary complications. Post-operative pleuro-pulmonary complications like atelectasis and pneumonia may occur. Diaphragm paresis or unilateral hemiparesis may also arise due to damage of the phrenic nerve.

c. Post-pericardiotomy (Post-commissurotomy) syndrome. This syndrome was originally reported in relation to other heart operations (NIEVEEN 1962 inter al.) and was noted to follow introduction of pacemakers by DRESSLER in 1962. The syndrome may occur from 2-3 weeks to 6 months post-operatively, and is characterised by intermittent fever and precordial or retrosternal pain, together with accumulation of fluid within the pericardial cavity.

d. Post-operative thrombosis and embolism. The appearance of thrombosis (like thrombophlebitis) and/or embolism may form a serious complication.

2. *Complications occurring at electrode removal.* At the termination of temporary stimulation, complications such as myocardial lesions may occur, when the electrodes are being removed by traction.

Conclusion

This method of stimulation is now hardly used for its original purpose i.e. direct stimulation in post-operative heart block. Improved operational techniques and more detailed anatomical knowledge, together with improvements in extracorporal circulation have resulted in a considerable reduction of the number of patients with iatrogenic heart block. Even if block is produced, stimulation is frequently applied via a catheter electrode – a method to be discussed in the following chapter. Direct transthoracic stimulation, however, was an important improvement in spite of its many disadvantages and this method of fixing the electrodes is still used frequently in combination with an implanted stimulator.

The direct transthoracic trocar method, however, is now very rarely used as its most important advantage, the rapid insertion of an electrode, is also possible by use of a catheter electrode. This latter method is discussed in the following paragraph.

IV. STIMULATION WITH AN EXTERNAL STIMULATION UNIT AND DIRECT TRANSVENOUS IMPULSE TRANSMISSION

With transvenous impulse transmission, the heart is directly stimulated via a catheter electrode, of which one end lies in the right ventricle, while the other end is connected to an external stimulator (fig. IV-6).

FURMAN and ROBINSON (1958) sought a method of stimulating the heart directly without resorting to surgery. They concluded that 'the only portion of the heart available without resort to thoracotomy is the endocardial surface, which can be approached with a cardiac catheter.' Taking advantage of this possibility they succeeded in stimulating the heart directly by means of a conduction catheter.

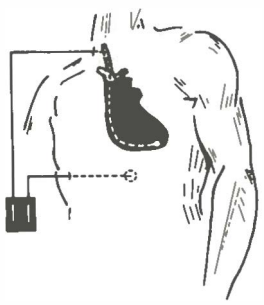


Fig. IV-6. Scheme of external stimulation apparatus with direct impulse transmission via an intravasal catheter electrode (monopolar).

Animal research

This method originated from investigations carried out by BIGELOW, CALLAGHAN and HOPPS (1950). During experimental heart surgery under hypothermia, they often saw normal cardiac function cease as a result of ventricular fibrillation or cardiac arrest. In 1954 they described how, after defibrillation, they controlled the heart action mechanically, or by means of a pacemaker. HOPPS and BIGELOW (1954) stimulated the S-A node of open chest dogs externally and with the thorax closed they also approached the area of the S-A node with ring electrodes at the end of a cardiac catheter, which was passed from a peripheral vein.
FURMAN and ROBINSON (1958) extended these animal and surgical results in the development of their stimulation method. It appeared from their investigations that stimulation of the canine heart can be undertaken as easily from the endocardial surface as from the myocardium directly. After creating heart block in dogs FURMAN and ROBINSON (1959) introduced a stimulation catheter into the right jugular vein and completed the electric circuit with an indifferent electrode in the subcutaneous tissue.

The lowest threshold value was obtained with the catheter electrode connected to the cathode, but even then the heart did not always respond to the stimuli. From X-ray inspection it appeared that contact between the electrode tip and endocardium was required for efficient stimulation.

At autopsies after stimulation for periods of 4-5 hours, no damage in

relation to the catheter was found either in the heart or vascular system.

A disadvantage of this method was the fixation of the electrode tip at the endocardium. ZUCKER, PARSONNET, GILBERT and NEWARK (1963) attempted to overcome this disadvantage by using a bipolar catheter. After creating heart block by ligation of the bundle of His in 12 dogs they investigated the possibilities of stimulation by means of a catheter with 5 ring electrodes 1 cm apart. The distance between the electrodes did not prove very important; what was important, however, was the location of the electrodes in the heart. The investigations by ZUCKER *et al*. gave the following results:

a. impulses through 2 electrodes in the pulmonary artery could not pace the heart even at 15 V.
b. stimulation by 1 electrode in the pulmonary artery and 1 electrode in the outflow tract of the right ventricle, required 6 V in all combinations to pace the heart.
c. stimulation by 2 electrodes in the right ventricle was possible in all combinations at 0.25 V.
d. stimulation by 1 electrode in the right ventricle and 1 electrode in the right atrium required 6 V in all combinations.
e. impulses through 2 electrodes in the right atrium did not activate the heart in any combination, even at 15 V.

Moving an electrode either to the atrium or to the pulmonary artery, therefore, often resulted in interruption of the stimulation, quite apart from the loss of contact between endocardium and electrode. These investigations proved that contact between the catheter tip and the ventricular endocardium is essential for optimal stimulation.

These results and especially the first investigations by FURMAN and SCHWEDEL (1958) resulted in general clinical application of the catheter electrode and since it proved possible to introduce the catheter electrode in human beings without any serious disadvantages, experiments on animals remained limited.

Clinical application

In 1959 FURMAN and SCHWEDEL described their experiences with the first 2 patients. They used a catheter containing a copper wire which protruded at the end. The catheter was introduced into the basilic vein and was passed to the right ventricle under X-ray monitoring. The indifferent electrode was a stainless steel wire, inserted into the subcutaneous tissue of the anterior wall of the right part of the thorax.

When the electrode tip and the endocardium were in direct contact threshold values were equal to those for a myocardial electrode. Furman and Schwedel argued that with direct contact the impulse was more effective than if it was transmitted through the blood, because the current density in the endocardium is lower in the latter case.

Others also applied the transvenous stimulation method. DAVIES, LEATHAM and ROBINSON (1959) confirmed clinically that stimulation of the right atrium needed far higher voltages than stimulation of the right ventricle and WEALE, DEUCHAR and NIGHTINGALE (1960) described investigations with several catheter electrodes in one patient. BOUVRAIN and ZACOUTO (1961) used a hollow catheter enabling simultaneous perfusion and reported stimulation periods up to 3 months.

BOUVRAIN and ZACOUTO considered transvenous stimulation to have a place midway between temporary completely external stimulation by skin electrodes and long-term transthoracic stimulation by myocardial electrodes. The development of improved catheter electrodes (LAGERGREN and JOHANSSON 1963) and improved technique of introduction, however, facilitated long term stimulation by this method. As early as 1961 FURMAN *et al.* described clinical stimulation of a patient for 16 months.

Interruption of stimulation caused by shifting of the catheter into the pulmonary artery or the right atrium was frequently a problem when the catheter was introduced into the basilic vein (FURMAN and SCHWEDEL 1959, PARSONNET *et al.* 1962). By introducing the catheter into the right external jugular vein above the clavicle and attaching it to subcutaneous tissue there, when the correct position in the ventricle has been obtained, these difficulties were largely overcome, but in spite of this improved technique dislocations continued to occur especially in cases of dilated and large hearts (FAIVRE *et al.* 1964, BLUESTONE *et al.* 1965). However the jugular vein route has proved very useful and is usually easily accessible even in children.

The catheter may also be introduced into the femoral vein. This does not provide a more stable position, but it is a quick and simple method. With this technique, which is also used in angiography (SELDINGER 1953, BROCKENBROUGH 1960), it is possible to introduce the catheter by means of a thin walled needle in approximately 10 minutes (SOLOMON 1963). This application, however, is only suitable in cases where short term stimulation has to be provided rapidly and where external indirect stimulation is contra-indicated.

Attempts were also made to prevent dislocation by changes in the

construction of the catheters. ABELSON *et al.* (1961) and DE VOS (1964) developed a catheter in which the electrode was positioned 15 cm and 10-12 cm respectively from the end of the catheter. By placing the catheter tip in the pulmonary artery or a branch, a stable position was obtained. This method is still used for short term stimulation but very rarely for long term stimulation, although EDMUNDOWICZ *et al.* (1965) have once more turned to a bipolar catheter of this type after experiencing three ventricular perforations by a normal bipolar catheter in 20 patients.

The shifting of the catheter is not only caused by external traction, but also by other factors such as breathing (GOETZ 1963) and by the action of the heart itself. For this reason PARSONNET *et al.* (1963) warned against a large loop of catheter in the ventricle, since this facilitates shifting to the pulmonary artery and others advocate placing the catheter tip between the trabecular muscles, because this provides stable fixation. Some others (ZUCKER *et al.* 1963, GOETZ 1963) argue that more stable stimulation is obtained with the bipolar catheter. Even with a bipolar catheter the most favourable stimulation is achieved when the negative electrode makes contact with the ventricular endocardium and activation of the heart via conduction of the impulse by the blood seems only possible at high voltages.

Advantages

A. Slight operational risk during introduction of the electrode

The introduction of the stimulation catheter is a minor operation, which can be carried out under local anaesthesia.

Disadvantages

A. Dislocation of the catheter

Dislocation of the catheter is a recurring problem in transvenous stimulation, especially in the early post-operative period, when the catheter has not yet become fixed.

In spite of catheter improvement and improved fixation of the electrode the risk of this complication remains, especially with large and dilated hearts. Regular X-ray inspection is therefore advisable in these patients especially during the first post-operative years.

B. Increase of the stimulation threshold

In direct endocardial stimulation high threshold values are sometimes found especially in case of large catheter electrodes. The stimulation threshold may in some cases exceed the operational value of the pacemaker with a resulting failure of stimulation. Small movements of the catheter tip may also be involved in causing threshold changes.

C. Breakage of the lead of the catheter

Breakage of the catheter lead is another disadvantage. FURMAN *et al.* (1961) reported this 3 times in their 18 patients. BLUESTONE *et al.* (1965) observed 80 breakages in 49 patients with implanted units and 'numerous' breakages of the lead near the skin perforation when the pacemakers were external. Due to improvements in the catheter (LAGERGREN and JOHANSSON 1963) this complication is now infrequent.

D. Extrasystoles

A fourth, less serious, disadvantage are extrasystoles, which frequently occur during introduction of the catheter. They are caused by mechanical stimulation from the tip of the catheter touching the tricuspid valves, the ventricular septum or the ventricular wall. The extra systoles mostly disappear as soon as the catheter is in place. In one case ZUCKER *et al.* (1963) saw these extrasystoles develop into ventricular fibrillation.

E. Infections

A disadvantage of transvenous stimulation in combination with an external stimulation unit is infection (SCHWEDEL and ESCHER 1964; BLUESTONE *et al.* 1965). The skin perforation, as mentioned above, provides an entry site for infections which tend to proceed along the catheter. In order not to have the skin perforation and the entrance into the vein too close to each other, the catheter is sometimes passed subcutaneously for a distance of about 10-15 cm.

The infection usually remains limited to a local, unimportant process, but occassionally complications such as an abscess, thrombophlebitis, bacteriaemia or sepsis may arise. BLUESTONE *et al.* (1965) noted endocarditis in one patient with rheumatic heart disease and for this reason

they deem the catheter method unsuitable for patients with rheumatic or congenital heart diseases.

It is recommended that antibiotics are administered if manipulation of the catheter is necessary, for instance in order to improve stimulation (SCHWEDEL and ESCHER 1964). If infection has occurred and cannot be overcome with antibiotics, the catheter should be replaced.

F. Thrombus formation

During transvenous stimulation, the risk of thrombosis is present. Opinion is divided on the question of whether this risk should be minimized by administering anticoagulants. All but one of the first 18 patients of Furman et al. received anticoagulants, and at the autopsy of this one patient, after 4 months of stimulation, a thrombus was found to have developed around the electrode tip. This thrombus had prevented further effective stimulation via the catheter as it was accompanied by a rise in stimulation threshold.

Both DE VOS (1964) and FAIVRE *et al.* (1964) reported thrombus formation in spite of anticoagulants and therefore questioned their use.

Due to improved implantation technique and improved catheters, thrombus formation now occurs less frequently, and the present trend in many clinics is not to administer anticoagulants. A statistical investigation of this subject however is not yet available.

Investigations on thrombus formation have also been carried out during bipolar stimulation. SCHWEDEL and ESCHER (1964), who did not administer anticoagulants, reported three cases of deposition of fibrin at the positive pole occurring in 36 patients, and other investigators also reported thrombus formation around the positive pole (ZUCKER *et al.* 1963). These findings, among others, decided LAGERGREN and JOHANSSON (1963) to apply monopolar transvenous stimulation with the negative pole in the heart. (See also Chapter VI)

G. Pulmonary embolism

The occurrence of pulmonary embolism has been described by several authors, including DE VOS (1962), PORTAL *et al.* (1963) and FAIVRE *et al.* (1964).

H. Perforation of the ventricular wall

The catheter electrode does not usually cause significant lesions of the

heart tissue and SCHWEDEL and ESCHER (1964) reported only a small patch of thickened endocardium at the place of contact between electrode and endocardium.

A rigid catheter however may penetrate into the myocardium and perforate the ventricular wall. FURMAN *et al.* (1961) found a haemopericardium as a result of a perforation in one of their first 18 patients, while BLUESTONE *et al.* (1965) NIEVEEN and HOMAN VAN DER HEIDE (1966, fig. VII-2) and SYKOSCH (1966) also diagnosed perforations. This complication occurs less frequently when the catheters are very flexible, but the introduction of such catheters is sometimes very difficult. The temporary use of a central stiff mandrin or an external stiff catheter has been helpful in manipulating very flexible electrodes. The mandrin or outer catheter is removed when the stimulating electrode is in place.

I. Various other complications

Other complications which may occur with this stimulation method are: location of the catheter in the coronary sinus (ZUCKER *et al.* 1963), resulting in a high stimulation threshold and the risk of perforation of the sinus; air embolism with the introduction of the catheter (DE VOS 1964); artificial tricuspid valve insufficiency (LANDEGREN and BIÖRCK 1963); contractions of the diaphragm (NIEVEEN and HOMAN VAN DER HEIDE 1966).

Conclusion

It might be concluded that the advantages of the direct transvenous stimulation method are accompanied by a agreat number of serious disadvantages. However, the advantages are such that the intravenous catheter nowadays is used widely. For short term stimulation it can be used with an external pacemaker carried by the patient in a way such as a leather-tape around the arm, or the catheter electrode may be used in combination with a pacemaker monitor. For long term stimulation the catheter electrode is usually combined with a fully implanted pacemaker, although long term stimulation by an external unit has been reported (BLUESTONE, HARRIS and DAVIES 1965).

V. STIMULATION WITH MAGNETIC IMPULSE TRANSMISSION

In stimulation with magnetic impulse transmission the heart is directly stimulated by electrodes connected with a subcutaneous secondary

coil in which impulses are induced by a primary external coil, connected with an external pulse forming apparatus (fig. IV-7).

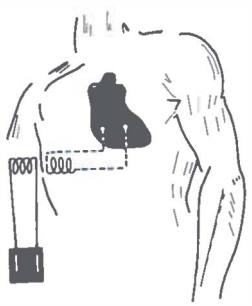


Fig. IV-7. Scheme of external stimulation apparatus with magnetic impulse transmission (bipolar).

Introduction

It is apparent from the previous discussion that direct stimulation of the heart has advantages over indirect stimulation. A disadvantage, however, is the need for the conduction lead to perforate the skin and transmit the impulse from the stimulation apparatus to the heart. In order to avoid this perforation and yet stimulate the heart directly a method was developed in which transmission through the skin was achieved by induction. In this case the impulses pass from a pulse forming apparatus outside the body to a primary coil placed on the skin. Subcutaneously and parallel to the primary coil a secondary coil is situated to which the heart electrodes are connected. Impulses are induced in the secondary coil from the primary coil, whereupon they stimulate the heart directly via the electrodes.

Animal research

A century after FARADAY's discovery of magnetic induction, a number of publications by LOUCKS (1933), LIGHT and CHAFFEE (1934) and FENDER (1936) appeared almost simultaneously. In these they described the application of induction in the transmission of energy for biological experiments. LIGHT and CHAFFEE (1934) used induction to stimulate nerves in a number of animals. The voltages induced in the secondary coil were conducted by electrodes to the nerves or areas of the brain to be stimulated and the investigators were able in this way to induce peristaltic contractions and attacks of Jacksonian epilepsy. The stimulation systems developed by LOUCKS (1933) and FENDER (1936) were

similar, and in 1948 HARRIS used this method to stimulate the hypophysis in rabbits.

Further animal research into this method of stimulating the heart was reported by HOLSWADE and LINARDOS in 1962, who stimulated 30 canine hearts in which heart block had been created. Initially, continuous stimulation was carried out, but 6-8 weeks post-operatively this was changed to intermittent stimulation; this change was accompanied by a high mortality rate from congestive cardiac failure. In 10 dogs, in which stimulation could be maintained for 7-16 weeks, it appeared that after an average of 8 weeks all secondary implanted coils had incurred defects, particularly wire fracture and leakage through the silastic coating. Accordingly, Holswade and Linardos reported that this method was 'not ready for human use until further refinement and testing has been done'. Nevertheless, ABRAMS, HUDSON, SHEFF and LIGHTWOOD (1960) were able to achieve satisfactory clinical results with a different design of induction stimulater.

Clinical application

In February 1960 ABRAMS *et al.* applied their first inductive-coupled pacemaker in a patient. This first pacemaker consisted of an external primary coil with a diameter of 5 cm, connected by flexible leads with a pulse generator. The pacing impulses had a duration of 1 msec. and were biphasic, thus limiting the effects of electrolysis at the electrodes. The amplitude and frequency were adjustable. The 3 cm. diameter internal, secondary coil consisted of 1,000 turns of copper wire encased in teflon, and with stainless-steel suture electrodes connected to both ends. Later versions incorporated some improvements to the coils (fig. IV-8), but the stimulation principle remained the same (ABRAMS and NORMAN 1964).

The pacemaker was applied to a patient in two stages, the heart being stimulated during the interval by direct transthoracic or transvenous electrodes. In the first stage the heart was approached through a left hemi-thoracotomy in the fourth i.c.s., the transthoracic stimulation electrodes being attached first and connected to an external pacemaker. If transvenous electrodes were employed, they were introduced prior to the operation. When the heart action was controlled in this way, the two stainless steel suture electrodes of the secondary coil were fixed on the heart and the coil was securely attached near the left 3rd i.c.s. For effective induction in stout patients the coil was placed before the

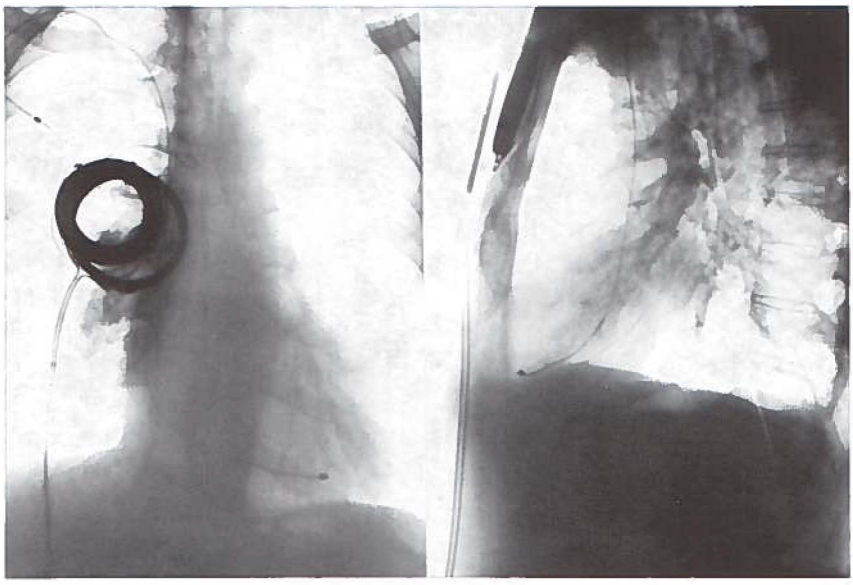


Fig. IV-8. X-ray pictures of a patient stimulated with magnetic impulse transmission, showing external transmitter coil, internal receiver coil and monopolar catheter electrode. (By courtesy of DR. L. D. ABRAMS).

sternum. In the second operation, after 1-2 weeks, when the wound was healed, the external primary coil was fixed over the secondary coil with adhesive plaster. The primary coil then took over the stimulation from the temporary external pacemaker, whereupon the latter and its electrodes were removed.

In 1964 ABRAMS had already treated 45 patients in this manner, of whom 12 had been paced for more than 2 years.

SUMA *et al.* (1965) also developed an inductively coupled pacemaker, but the impulse transmission differed from the Abrams type in that a ferrous core was placed in the primary and secondary coil, resulting in improved efficiency. Between March 1964 and April 1967 7 long term and 3 temporary patients were stimulated with this unit (TOGAWA *et al.* 1967).

Advantages and disadvantages

The advantages and disadvantages of stimulation by magnetic impulse transmission include those of direct electrodes on the heart with some of the features of an external stimulation unit.

Advantages

A. No skin perforation by leads

Since no leads perforate the skin in this method, there is no easy route for infections, so that sepsis and lead fractures due to perforation of the skin are no problem.

B. Simplicity of implanted section

The apparatus implanted in the body is extremely simple in this stimulation method. The implanted coil and electrodes consist of no more in fact than a length of wire with its two ends in the heart.

Disadvantages

A. Accurate fixation of the coils in relation to each other

Accurate fixation of the primary coil relative to the secondary coil is essential to maintain stimulation.

B. Skin irritations

Due to the continuous fixation of the primary coil skin irritations may appear. The skin beneath the coil should therefore be cleaned regularly.

C. Lead fracture

Lead fracture may also occur in this method. Although this fracture is more likely to affect the vulnerable external lead connecting the pulse forming circuit with the primary coil, the consequences of a fracture of the internal unit are far more serious.

D. Influence of external electromagnetic fields

Strong external electromagnetic fields may affect the stimulation. The strength and the nature of the external magnetic field determine the induction in the secondary coil.

E. Efficiency

Much energy is lost in impulse transmission by means of induction. The

modification using a coil with ferrous core of SUMA *et al.* (1965) is more efficient, but the yield of both types of transmission is small, thus necessitating frequent recharging of the batteries of the external stimulator.

Conclusion

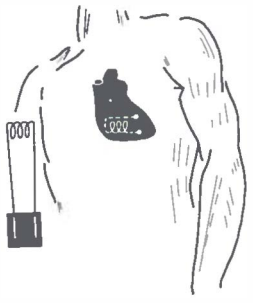
In conclusion it may be stated that stimulation with magnetic impulse transmission does not have the disadvantage of skin perforations, but this advantage does not outweigh the disadvantages. For this reason this stimulation method has not found general application.

VI. STIMULATION WITH ELECTRO-MAGNETIC IMPULSE TRANSMISSION

Principle

In stimulation using electro-magnetic impulse transmission, the heart is directly stimulated by electrodes connected to an implanted receiver, in which impulses are induced by an external transmitter (fig. IV-9).

Fig. IV-9. Scheme of external stimulation apparatus with electro-magnetic impulse transmission (bipolar).



Introduction

Stimulation by this method depends upon the fact that low frequency stimulation impulses can be transmitted over long distances by high frequency modulated radio waves. The transmitter broadcasts its signal by way of a pretuned external primary coil, which induces the high frequency signal in a secondary coil situated subcutaneously or on the heart and tuned to that frequency.

The modulated high frequency secondary signal is not itself capable of stimulating the heart because the duration of the cycle of the high frequency A.C. voltage is extremely short in relation to the chronaxie of the tissue, so that the current threshold is relatively large in relation

to the rheobase. After rectification by means of a diode and a buffer-condenser, D.C. impulses are produced having the rhythm and duration of the low frequency impulses modulating the carrier wave; these impulses are capable of stimulating the heart. In this method the heart is stimulated without perforation of the skin by leads.

Animal research

NEWMAN, FENDER and SAUNDERS (1937) applied the method for the first time in long term stimulation of the nerves of laboratory animals. They used a radio wave with a frequency of 450 KHz, and were able to obtain a current of 4 mA in a resistance of 2000 ohms situated in the middle of a cage. To generate this 32 mWatt in the secondary circuit, 450 Watt was needed in the transmittor, so that the efficiency was less than 0.01%. With this apparatus the splanchnic nerve in one animal was stimulated for 5.5. months.

Other investigators also employed this method for nerve stimulation in animals (GREIG and RITCHIE 1944; LAFFERTY and FARRELL 1949). VERZEANO, WEBB and KELLY (1958) applied the method for the first time to stimulate the hearts of animals (dogs). They employed a 200 Watt radio transmitter to broadcast the impulses through a primary coil in the bottom of a cage. Heart block was created in several dogs, who then had receivers fixed near the 3rd and 5th rib beneath the latissimus dorsi muscle. An electrode circuit consisting of a stainless steel suture electrode in the heart and an indifferent electrode in the muscle was connected to the receiver. With this unit, the impulses reaching the heart had a minimum voltage of 2.7 V, determined by the maximum distance between both coils (± 30 cm), and a maximum voltage of 3.7 V, determined by the rectifier (Zenerdiode) in the receiver.

In 1960 TOOLE, LONGO, MAURO and GLENN applied this method in 36 dogs. CAMMILLI *et al.* (1962) developed a receiver which is placed directly on the heart to supersede the implanted leads. The receiver had a diameter of 3 cm, a weight of 1.5 grams and consisted of a coil of 20 turns, a diode as rectifier, and a condenser.

The efficiency of stimulation by impulse transmission using radio waves is very small. STOECKLE and SCHUDER (1963) calculated an efficiency of 1% in canine experiments. i.e. one per cent of the energy input in the primary coil reaches the electrode circuit attached to the heart via the secondary coil. ANAGNOSTOPOULOS, HOLCOMB and GLENN (1965) reported a somewhat higher efficiency.

Although experiments are still being carried out with this method, a number of clinical applications have already been reported.

Clinical application

GLENN, MAURO, LONGO, LAVIETES and MACKAY (1959) applied this stimulation method for the first time clinically on 27th January, 1958. The transmittor used was a vacuum tube, line-powered radio wave transmittor, which was heavy and large, and limited the mobility of the patient. To counteract the latter disadvantage, the primary coil was connected to the transmittor by means of a long lead, about 6 m in length. Later LEVITSKY, GLENN, MAURO and EISENBERG (1962) reported their experiences with 8 patients using a portable unit of 310 grams and dimensions of 10.5 × 7.5 × 2.5 cm.

Prior to introduction of the receiver and electrodes, the heart rhythm is controlled by means of a stimulation catheter. The receiver is then introduced in a subcutaneous pocket, 5-7.5 cm beneath an incision near the midaxillary line. The receiver must not be placed lower than the eighth rib, because some space above the costal margin should remain for the aerial to be properly attached to the skin. In women with large mammae the receiver is usually implanted near the sternum. The electrodes are then attached to the heart, which is approached through a left hemithoracotomy. When the wound is sufficiently healed (after approximately 2 weeks) the aerial is attached to the thoracic wall, whereupon stimulation is continued by the radio frequency method, and the catheter electrode may be removed. In the first applications, transthoracic stimulation was applied instead of transvenous stimulation for the transition period.

In 1965 EISENBERG, MAURO, GLENN and HAGEMAN stimulated 26 patients in this manner, with a maximum stimulation period of 36 months. In 1961, CAMMILLI *et al.* applied their version the first time clinically, but initially had little success (CAMMILLI *et al.* 1964).

Advantages and disadvantages

The method is in fact a variation of the method using magnetic impulse transmission, affecting only the means of transmission itself. Compared with the simple induction method, impulse transmission using a modulated electromagnetic carrier wave shows four improvements and one disadvantage, which will now be discussed.

Advantages

A. The impulse itself is transmitted

With magnetic impulse transmission only the variations of the original impulse are transmitted. With the method discussed in this paragraph, the impulse as a whole is induced in the secondary coil in the form of the rectified shape of the envelop of the high frequency radio waves.

B. Higher efficiency

By employing impulse transmission using radio waves, a higher efficiency is obtained than by using magnetic impulse transmission.

C. Intracorporal leads not necessary

With this method of impulse transmission, due to the improved efficiency it is possible to attach the receiver directly on the heart. This renders intracorporal leads between the subcutaneous receiving coil and the heart superfluous. Defects in stimulation caused by fracture of the leads are then avoided.

D. Tuning reduces interference

The preceding inductive method was affected by any powerful external electromagnetic field. In impulse transmission by radiowaves, the implanted receiving circuit is tuned only to the carrier wave frequency band. Interference from external fields is only possible if they contain frequencies within the band of the receiving coil. This reduces considerably the chance of interference.

Disadvantages

A. Implanted unit more complicated

Compared with magnetic impulse transmission, transmission by radio waves has the disadvantage that the unit implanted in the body must include a diode and a condenser for rectification of the transmitted impulse in addition to the secondary receiving coil. These two components increase the risk of defects in the implanted unit to a certain extent.

Conclusion

It may be concluded that electro-magnetic impulse transmission had advantages, accompanied by one slight disadvantage, over magnetic impulse transmission. These advantages however do not eliminate the disadvantages of indirect impulse transmission as discussed in the preceding chapter. For this reason, this stimulation method, in common with simple induction has not yet found general clinical application.

VII. STIMULATION WITH AN IMPLANTED PACEMAKER

In this method the heart is directly stimulated by electrodes on or in the heart muscle, or by catheter electrodes which are connected by conduction leads to a subcutaneous implanted pacemaker (fig. IV-10).

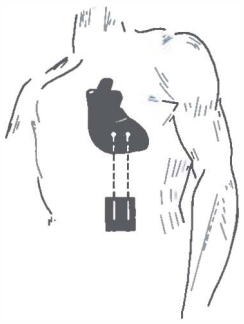


Fig. IV-10. Scheme of completely internal (implanted) asynchronous stimulation system (bipolar).

Introduction

In early versions of pacemakers vacuum-tubes were used; these tubes required a rather high voltage and moreover entailed the disadvantage of having a low efficiency due to their relatively large heater currents. For this reason they depended on the mains for their power supply with the danger of electrocution, whereas the resulting large dimensions of the pacemaker were likewise disadvantageous.

The development of transistors made these tubes obsolete. Transistors have far smaller dimensions than vacuum tubes and work at low voltages, available from batteries. They require no heater-current, making them highly efficient. Thus the dimensions and the weight of the complete electronic circuit including its power supply could be reduced to such an extent that it was possible to construct portable pacemakers. By replacing the germanium transistors by later types of silicium transistors which had far less current leakage and therefore greatly improved

efficiency, it became possible to prolong the life time of the pacemaker batteries considerably.

This development made it possible to design pacemakers with dimensions suitable for implantation in the body. The various aspects of these pacemakers will be discussed in detail in Chapter VIII.

Animal research

Although the development of an external pacemaker with an external power supply into a totally implanted pacemaker with a power supply of its own meant a considerable practical change in the method of stimulation, the results gained with the earlier methods on the excitability and stimulation threshold of the heart could serve as starting point.

The animal experiments carried out with implantable pacemakers were mainly intended for the development of new electrodes, stimulation units, and monitoring of implanted pacemakers. For this reason they will be discussed in the following chapters.

Clinical application

New possibilities in the field of electronics enabled ELMQVIST and SENNING to construct in 1959 'a compact pacemaker, which is intended to be implanted subcutaneously in the epigastrium.' Their pacemaker contained 2 series of nickel-cadium cells, each with a capacity of 60 mAh. The cells could be recharged inductively from outside the body by means of a secondary coil and a silicium diode in the pacemaker, but the frequency (80/min) and the impulses (2 V ; 1.5 msec) were fixed and could not be altered after implantation. They reported one clinical application of this pacemaker.

By replacing the nickel-cadmium cells with mercury cells a long term power supply was obtained without the necessity of frequent recharging. The first clinical implantation of such a pacemaker was performed in April 1960 by CHARDACK, followed amongst others by ZOLL in June 1960, ELMQVIST and SENNING in July 1960, KANTROWITZ in May 1961 and VAN DEN BERG, HOMAN VAN DER HEIDE and NIEVEEN in March 1962. The combination of an implanted pacemaker with a catheter electrode was first used in 1962 by LAGERGREN and JOHANSSON (1963).

Operation with transthoracic electrodes

Since it is known that the stimulation thresholds of the electrodes rise

after implantation, and because it is not possible to adjust the impulse to the requirement simply once the pacemaker is implanted, CHARDACK carried out the implantation of the stimulation unit in two stages in his first 9 patients. First the heart electrode – a bipolar pin electrode – was implanted and connected to an external pacemaker. The stimulation threshold of the electrodes was monitored. When the threshold no longer rose (generally 30-40 days after implantation) the external pacemaker was replaced by an implantable one. Because of the high risk of infection with this method of implantation (3 times in this first 9 patients) the pacemaker and the electrodes were implanted at one operation in the subsequent patients. Other investigators introduced the pacemaker with intramural or epicardial electrodes in one operation from the beginning.

The operation for implantation of a pacemaker system with transthoracic electrodes (epicardial or intramural) is performed under general anaesthesia. In emergencies external electrodes may be used for maintaining cardiac contractions, but the heart action is usually controlled preoperatively with a catheter electrode connected to an external pacemaker; this prevents cardiac arrest during the introductory narcosis. Apart from preventing Adams-Stokes attacks, this stimulation can be used to correct a poor circulation pre-operatively, thus improving the condition of the patient. The external pacemaker remains functioning during the preliminary anaesthesia and during the first phase of the operation, until the actual electrodes are fixed.

In order to fix the transthoracic electrodes, the heart is approached through the fourth or fifth left intercostal space, or according to the method of Sauerbruch by a pericardiotomia inferior longitudinalis (HIRSCH 1964, fig. IV-11) Other approaches are also possible. The heart electrodes are then attached in the same way as for stimulation with an external pacemaker.

Location of the pacemaker

The pacemaker is most frequently placed subcutaneously or under a muscle group in the left half of the abdomen, but the location varies and may be subcutaneous near the navel (KANTROWITZ), under the external oblique muscle against the inguinal ligament (LILLEHEI), or subcutaneous and medially just under the rib arch, in order to diminish the effect of body movements on the system (CHARDACK); implantation in the sheath of the rectus muscle in the abdomen is also performed

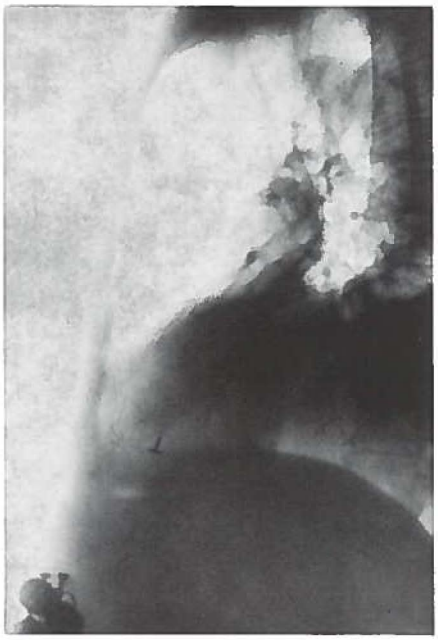


Fig. IV-11. X-ray picture of a stimulation unit with the pacemaker in the abdominal area and an intramural pin-electrode implanted in the 'contact area of Benninghoff'. (By courtesy of DR. H. H. HIRSCH).

(TRICOT, RICORDEAU). The pacemaker is implanted through a separate incision and the leads are drawn through the subcutaneous tissue towards the pacemaker by use of a clip or through a tube, which is then removed.

In order to limit to a minimum the effects of body movements on the pacemaker and electrodes, other surgeons (HOMAN VAN DER HEIDE, PARSONNET *et al.*, MARION and GONNET) attached the pacemaker near the upper ribs sometimes subcutaneously, but preferably beneath the pectoral muscles (fig. IV-12). The same incision is used for the implantation of the electrodes as for implantation of the pacemaker.

Operation with transvenous electrodes

In order to introduce a pacemaker system with a transvenous electrode, a smaller operation is necessary, local anaesthesia usually being sufficient. The catheter electrode is introduced through the right or left external jugular vein from above the clavicle. After introduction, the free end of the catheter electrode is taken across or beneath the clavicle or medially across the manubrium to be attached to the pacemaker which is generally implanted close to the place of entry of the catheter in the vein, or in the abdominal wall. Within a few days the catheter

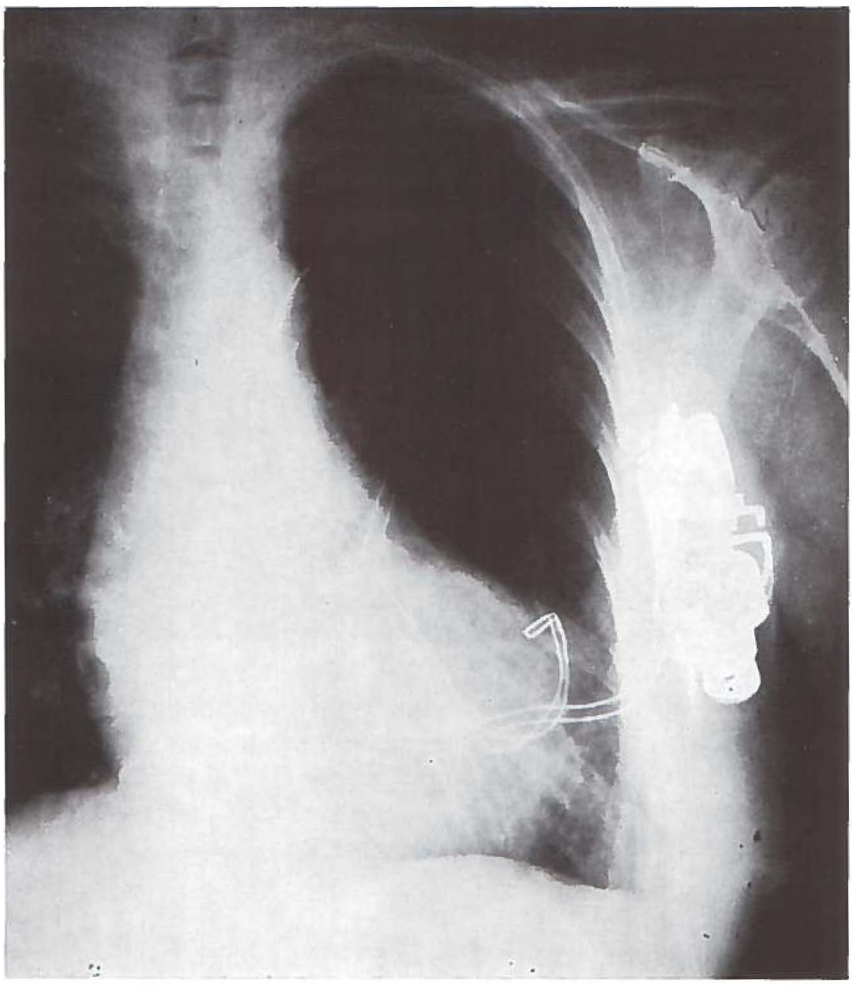


Fig. IV-12. X-ray picture of a stimulation unit with the pacemaker in the subpectoral area and an intramural loop-electrode implanted in the left ventricle.

becomes fixed in the heart, so that the operation is sometimes carried out in two stages in order to correct dislocations etc. of the catheter without resorting to a new extensive operation (SCHEPPOKAT, SOWTON). In this case, however, the risk of infection along the electrode is greater than when the implantation is performed as a single procedure.

The pacemakers used vary. Table IV-2 gives a synopsis of the characteristics of the first implanted pacemakers.

TABLE IV-2. *Synopsis of the characteristics of the first implanted pacemakers after* VAN DEN BERG *et al.* (1962).

	CHARDACK/GREATBATCH		ZOLL	ELMQVIST/ SENNING	KANTROWITZ	V.D. BERG
	until apr. '62	afterwards				
Voltage (V)	8–15	4–6	7,5	6	3,2	5–7,5
Current (mA)	10	3,5–6	15	–	–	5–10
Frequency (imp./min)	50	60	70	70	65	65/85
Impulse duration (msec)	1	1,5–2	2	2,5	2	2,25
Number of batteries	10	6	6	5	5	5
Weight (gr.)	225	170	170	170	140	150
Dimensions	–	Ø6	6,5 × 6	Ø7	6 × 4	9,2 × 4,4
Thickness (cm)	–	1,5	1,7	2,2	1,25	2,2

Advantages

A. No skin perforations by leads

Because the pacemaker is completely implanted, there is no perforation of the skin by leads. Lead fractures at the exit from the body are thus avoided, whilst infection through the skin perforation and passing along the leads is excluded.

B. The patient is ambulatory

Due to the implanted system the patient is completely independent of any external source of energy, so that he can be completely ambulatory and simple acts like taking a shower, a bath, and even swimming, are within his scope.

C. The patient suffers less mental stress

Special studies on the mental stress endured by the pacemaker patient have not yet appeared. Experience however shows that «à l'inverse de ce qui se produit avec des techniques utilisant un générateur externe, l'entraînement électrosystolique a l'aide d'un appareillage entièrement incorporé ne crée généralement pas de sentiment de dépendance chez le sujet qui en est porteur» (FAIVRE et *al.* 1964). Papers published in English regard the matter as 'out of sight, out of mind'. This feeling of comparative independence is augmented by the high degree of mobility.

Disadvantages

The disadvantages of this method of stimulation may be divided into 5 groups:

A. The pacemaker is implanted and therefore its action cannot be adjusted in a simple way.
B. The ECG of the patient is difficult to analyse.
C. The limited life of the batteries necessitates the eventual replacement of the pacemaker.
D. The chance of re-operation is greater because defects may occur in the pacemaker itself.
E. Infection or skin necrosis may occur with the implanted pacemaker.

Some of these groups, discussed below, will be dealt with in detail in Chapter VIII, within the framework of our own investigations.

A. The pacemaker is implanted and therefore cannot be adjusted

1. Impulse duration. The impulse duration of implantable pacemakers usually lies between 1-2,5 msec. A long impulse duration is favourable, because of the low stimulation threshold, but also means a large charge and thus a shorter life time of the pacemaker. A compromise was found in 1-2.5 msec. The impulse duration is not adjustable in any of the implantable pacemakers.

2. Impulse strength. Likewise, the strength of the impulse is fixed at a level above the stimulation threshold. This threshold rises during the first 4-6 weeks after implantation, after which it stabilizes (CHARDACK 1964). Since the impulse strength is determined at implantation, it is necessary to take this threshold rise into account. A safety margin of 3 to 4 times i.e. an operational value 3 to 4 times as large as the threshold value at the operation is generally thought sufficient. An impulse more powerful than necessary produces a wasteful loss of current which results in rapid exhaustion of the batteries. Another disadvantage of an unnecessarily great impulse is the increased risk of ventricular fibrillation, particularly if sinus rhythm returns.

In some pacemakers the impulse amplitude can be changed by way of a percutaneous intervention with a needle (CHARDACK) or by way of an external magnet (VAN DEN BERG), whereas a recently developed pacemaker enables extracorporal threshold analysis by inductively decreasing of the impulse (VAN DEN BERG and THALEN 1967; Chapter IX).

3. *Frequency of the impulses.* The frequency of the pacemaker impulse is also fixed. The general opinion is that the frequency should be fast enough to prevent attacks of syncope and to enable the patient to maintain a good physical condition. The optimal frequency for this varies according to the individual. The frequency of most implantable pacemakers is fixed at 60-70 imp./min.

A disadvantage of a fixed frequency is that on the return of the proper cardiac rhythm, interference arises between both rhythms as soon as the frequency of the spontaneous rhythm approaches and exceeds the pacemaker rhythm. The chance of ventricular fibrillation is then present, because the pacemaker impulse may fall in the vulnerable phase. Several types of pacemakers have therefore an adjustable frequency. The adjustment is possible in various ways e.g. by percutaneous intervention with a needle (CHARDACK 1964), by induction (GLASS *et al.* 1963; KANTROWITZ *et al.* 1963) or by an external magnet and a polarized relay incorporated in the pacemaker. (VAN DEN BERG *et al.* 1962, CARLETON 1964).

B. Difficulty of monitoring the ECG of the patient

Another disadvantage during pacemaker stimulation of the heart is that interpretation of the ECG is difficult and monitoring of the spontaneous rhythm is impossible. WEINMAN (1964) therefore constructed a pacemaker which may be switched off by means of a magnetic relay. In the latest version of our pacemaker, ECG monitoring is possible during inductive suppression of the impulse (see Chapter IX).

C. Limited battery lifetime

The most serious disadvantage of the completely implanted pacemaker is the fact that after certain time, which in most cases cannot be accurately predicted, the power supply is exhausted.

According to early publications, pacemakers with batteries having a capacity of 1000 mAh should function for a possible life time of 3-5 years, depending on the frequency and the load. In practice, however, the life time proves to be considerably shorter and at present pacemakers have to be replaced after about 2 or 3 years due to exhausted batteries (see Chapter VIII). An attempt was made to obtain some indications of the exhaustion by making the frequency dependent upon the battery voltage, but the changes in frequency were too slight or were not noticed

by the patients (CHARDACK 1965). With a new method of pacemaker analysis (VAN DEN BERG *et al.* 1967), to be dealt with in Chapter IX, we now have an improved insight into the time course of battery exhaustion.

To prevent reoperation due to battery exhaustion, rechargeable batteries were considered. These however have the disadvantage of a low capacity, necessitating periodic recharching and a short useful life time (ELMQVIST and SENNING 1960, SIDDONS *et al.* 1961).

Attempts have also been made to obtain electrical energy directly from the body; various aspects of power supplies are considered in detail in the chapter on stimulators (Chapter VIII).

D. Pacemaker defects

The fourth group of disadvantages of the implantable pacemaker is associated with defects in the electronic circuit, necessitating re-operation.

As the entire unit is implanted subcutaneously, each defect requires reoperation. Faults may occur at the connection of the electrodes to the pacemaker (to be discussed later) or in the pacemaker itself, either in the mass of the pacemaker or in the electronic circuit.

1. Defects in the mass of the pacemaker. The mass of the pacemaker must consist of material which insulates and protects the electronic circuit and is at the same time accepted by the body. At present most pacemaker circuits are embedded in epoxy resin, with another coating of silicon rubber in some models. Even using this insulation, moisture occasionally penetrates, entering through defects in the insulation (DEKKER 1966, LAGERGREN 1966, MEIJNE *et al.* 1967).

The consequences of penetration depend on the point where the moisture enters the circuit and are particularly important if Cl'ions are present. They vary from rapidly exhausted batteries (ANDERSEN 1962, APPLEBAUM 1962, ZOLL 1963) to an increase (DEKKER 1965) or decrease in the pacemaker frequency. These faults have now been partly overcome by the use of improved epoxy resins and electronic units with glass insulation.

2. *Defects in the electronic circuit.* Defects in the electronic circuit occur even without leakage, the frequency depending upon the reliability of the components used and the care exercised in checking the circuits constructed.

GLASS (1964) stated the total chance of failure of the average pace-

maker due to electronic defects is approximately 0.1%/1000 hours. This means that on average out of every 100 pacemakers implanted for a year, 1 will fail due to electronic defects. Failure rates of less than 1% each year will only be achieved when electronic components have reached a higher reliability.

E. Infections

A fifth group of disadvantages associated with a totally implanted pacemaker is formed by inflammation around the pacemaker.

To reduce the chance of infections to a minimum the pacemaker should be properly sterilized, but because of the electronic components and the batteries, sterilization at a temperature higher than 50°C is inadvisable. The methods of sterilization used are gas-sterilization (Ethylene oxide) or fluid sterilization (Acetone/Ether or Propiol Acetone which is afterwards removed by hydrolysis).

In spite of sterilization, infections still occur, especially when the implantation is carried out in two stages. The chance of infection around the pacemaker is inherent to the operation and its occurrence is related to the efficiency of sterilization and the technique of implantation.

The infection (e.g. staphylococcus) may appear after one week or be delayed for a year. It is usually manifest by a pyrexia and a fluctuent swelling full of inflammatory fluid around the pacemaker. The infection may result in extrusion of the pacemaker. This also occurs as a tissue reaction to a foreign body. This last reaction is becoming less frequent as more compatible materials are used to cover pacemakers.

Occasionally a prolapse of the pacemaker occurs without inflammation and in this case pressure necrosis may develop. To reduce the chance of pressure necrosis it is essential to use a pacemaker which is as small and light as possible, while the pacemaker should not have any sharp angles or edges. Pressure necrosis occurs less frequently in obese patients with a thick subcutaneous fat layer than in slim ones. The surgeon should take this possibility into account in selecting the location of implantation and the type of pacemaker.

Conclusion

The detailed consideration of the disadvantages might give the impression that they exceed the advantages of the implanted pacemaker. The advantages, however, were so evident that implanted pacemakers came

into general use, the disadvantages gradually being overcome during further development.

VIII. STIMULATION WITH A DRUG-PACEMAKER IN COMBINATION WITH AN ELECTRICAL PACEMAKER

In stimulation with a drug-pacemaker the ventricular rhythm is locally increased by a quantity of a suitable drug introduced into the ventricular wall. The diffusion of the drug in the heart muscle may or may not be influenced by means of electrodes, connected to an electrical pacemaker (fig. IV-13).

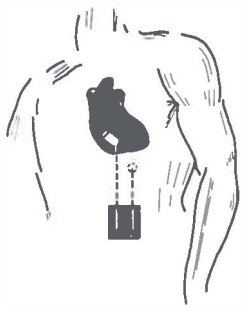


Fig. IV-13. Scheme of drug-pacemaker in combination with completely internal (implanted) apparatus for intermittent stimulation and/or drug release.

Introduction

Although this method occupies a place between pharmacological and electrotherapeutic treatment of heart block, it is discussed here because there is a close relation with electrotherapy, particularly in recent research. The method was applied first by FOLKMAN *et al.* (1959) and was developed further by FOLKMAN and EDMUNDS (1962).

To obtain a physiological and permanent pacemaker they placed autotransplants of endocrine glands in the ventricular wall of a dog with complete heart block. The original concept was that the small area of myocardium surrounding the endocrine transplant would be stimulated by relatively high local concentrations of the respective hormones. Thus the electrical activity of this area of myocardium might be increased to such a degree that it would become the dominant pacemaker for the ventricle and result in a faster heart rate.

Animal research

FOLKMAN *et al.* induced heart block in dogs and waited 2-6 months

before transplanting the endocrine tissue. One hour following transplantation of the adrenal medulla into a tunnel in the ventricular wall, an increase in rate from the average of 50 beats/min. to 100 or 200 beats/min. was observed. This tachycardia usually lasted about 4 days after which the previous slow rhythm returned. At autopsy, histological investigation revealed no intact medullar tissue. A few dogs died early in the experiments with very rapid ventricular rates.

Thyroid gland transplantations in the tunnel in the ventricular wall produced a less marked frequency rise of about 20-40 beats/min. becoming apparent 8-12 hours after the operation and lasting for some days. At autopsy performed several months after the transplantation, about half of the transplant was found to be intact.

When the arterial supply of the thyroid lobe was preserved intact and venous blood was allowed to flow around the transplanted lobe in the myocardial tunnel the frequency rose from an average of 52 beats to 120-130 beats per minute over 2-3 days, the thyroid tissue remaining intact. Tablets of tri-iodothyronine, inserted operatively into the ventricular wall produced a similar increase of frequency. Since liver, ovary, and muscle transplant had no effect, further research was pursued in relation to the thyroid hormones, and it was established that the rise of frequency was due to a local increase of tri-iodothyronine which produced a new focus of stimulation. Implantation of the hormone in the ventricular wall had no effect on other organs, while large oral doses produced no rise on frequency. FOLKMAN and EDMUNDS (1963) ascribed the effect to the combined action of tri-iodothyronine and catacholamines.

To create a long term endocrine pacemaker, FOLKMAN and LONG (1964) attempted to store a large quantity of tri-iodothyronine in the ventricular wall using silastic capsules, through which the drug was gradually released. To maintain stimulation for 30 hours, 10-25 mg. tri-iodothyronine were required. The capsules, with a maximum content of 30.000 mg. released 20-50 mg. per day, but even with these capsules it proved impossible to increase the heart rate for more than 4-5 days.

The short duration of stimulation was caused by the formation of a thin layer of connective tissue around the capsule which prevented the hormone from reaching the intact heart muscle in sufficient concentration. This was shown by the fact that transplantation of a capsule which no longer produced pacemaker activity to a fresh place in the ventricular wall led once more to an increase in frequency lasting 4-5

days, whereas implantation of a new capsule in an old wound did not affect the heart frequency.

To circumvent the disadvantage of the tissue layer by using myocardial iontophoresis, FOLKMAN and LONG (1964) introduced the negative (wire) electrode of a pacemaker into the shaft of a silastic tube impregnated with tri-iodothyronine. By boring small holes in the wall of the tube they showed it was possible to stimulate the heart electrically. A second pacemaker electrode was attached to the myocardial surface near the implanted capsule to ensure proper stimulation. When the heart no longer reacted to the thyroid hormone FOLKMAN and LONG hoped that electrical stimulation for 2-4 hours would carry sufficient quantities of tri-iodothyronine through the tissue layer by iontophoresis, thus enabling the heart to be stimulated by the hormone alone once more. In this way the life time of the pacemaker might be considerably extended.

No clinical data were given of this latest version, which is a combination between an electrical pacemaker and an endocrine pacemaker, but tissue formation will probably have been an obstacle, not only for the hormone but also for stimulation by electrical current. The intact myocardium was separated from the negative electrode, not only by the capsular wall in which small holes had been bored, but also by the tissue layer. The distance between the electrode and the intact myocardium thus increased, so that after some time excessive voltages probably became necessary. With bipolar stimulation it would be possible to reverse the direction of the stimulus, using the other electrode as negative electrode, but that would mean that the effect of the iontophoresis would be lost.

Advantages and disadvantages

The advantages of this method, the 'natural' endocrine stimulation of the heart, are extremely hypothetical, in view of the great disadvantage that long term stimulation with the drug pacemaker proved to be impossible. This method moreover, would require a fresh operation when the capsule became exhausted.

Conclusion

The disadvantages of this method proved to be so great and insuperable even during animal experiments, that the method has no practical value. It remains of great theoretical interest.

IX. STIMULATION WITH A P-WAVE TRIGGERED SYNCHRONOUS PACEMAKER

In stimulation of the heart with a P-wave triggered pacemaker the atrial depolarization is detected by an electrode attached to the atrium; this signal, after a delay corresponding to the duration of the atrio-ventricular conduction time, triggers an electrical impulse, which stimulates the heart via a ventricular electrode (fig. IV-14).

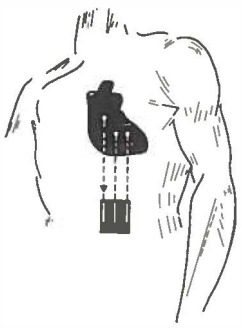


Fig. IV-14. Scheme of completely internal (implanted) synchronous stimulation system, P-wave triggered pacemaker (bipolar).

Introduction

In stimulation of the heart with a fixed frequency pacemaker, the ventricles are stimulated in a definite, fixed rhythm. During this stimulation, the heart frequency is not under control of the physiological regulating mechanism, and atrio-ventricular co-ordination is not maintained, resulting in the loss of the greater part of the contribution of the atrium to the cardiac output.

The importance of this atrio-ventricular co-ordination is clearly demonstrated when a patient with atrial fibrillation returns to sinus rhythm, so that the normal sequence of atrial and ventricular depolarization is restored. BRAUNWALD (1964) found in one such case an improvement of the cardiac output of 20-30%. A corresponding change is observed in a heart with an intermittent heart block, if a sudden interruption of A-V conduction necessitates changeover to electrical stimulation. If such a heart is asynchronously stimulated with a fixed frequency corresponding approximately to the frequency of the intact sinus rhythm, an immediate 25% drop of cardiac output (SOWTON 1964) is found. The heart recovers after a few minutes, so that the cardiac output increases again to 96% of its original value.

BRAUNWALD (1964) concluded that when the stress is submaximal,

reserve mechanisms resulting p.e. in an increased stroke volume, may be available to maintain the output at a normal level, despite the absence of an appropriately timed atrial systole. During stress however the heart adopts less well. The losses in cardiac output are then approximately 5-15% compared with the optimal values.

Since 'an ideal prosthetic device returns a function to a physiologic level of activity which is as close to normal as possible' (NATHAN 1963), an electronic A-V bridge to restore the co-ordination between atrium and ventricle during electrical stimulation was sought. This electronic prosthesis would also return the heart rate to physiological control. The final result of this research is the so-called P-wave triggered pacemaker.

In its simplest form the electronic unit consists of a P-wave detector, a pulse forming circuit and an output circuit. Regular atrial contraction and depolarization impulses of sufficient strength are required for correct functioning of the pacemaker. These depolarization impulses may be detected with epicardial or intracardiac electrodes.

In view of the low atrial voltages, the P-wave detector must be extremely sensitive. However, the sensitivity is limited by the risk of interference from other sources if the detector is too sensitive. In most versions the sensitivity is fixed at about 1.0 mV. The detected signal from the atrium is too weak to trigger the rest of the circuit, so that it first has to be amplified. The P-wave detector therefore consists of a detector proper and an amplifier circuit.

To obtain good co-ordination between the atrial and the ventricular contraction a delay corresponding to the P-Q time has to be included between the detection (and amplification) of the P-wave and the triggering of the ventricular impulse. This is achieved by means of a delay circuit between the P-wave detector and the pulse forming circuit. The P-wave finally triggers the pulse forming circuit through this delay circuit, resulting in a ventricular impulse by the output circuit.

To prevent the P-wave detector from detecting the pacemaker impulse and the ensuing heart reaction, in which case the pacemaker would react to its own circuit, it is necessary to have a final blocking circuit, starting at the beginning of the stimulation impulse, which renders the input refractory for a certain period (dead time).

If sinus bradycardia, sinus tachycardia or atrial fibrillation occur, there is a danger of the pacemaker continuing to stimulate the ventricles in the imposed rhythm. To counteract this complication, the circuit is constructed in such a way as to limit the minimum and maximum fre-

quencies. The minimum frequency is determined by the pulse forming circuit in such a manner that impulses at a preset fixed minimum rate are delivered whenever the heart rhythm drops below this frequency. The maximum frequency is determined by the delay time after a P-wave signal and the dead time of the detector after a stimulation impulse.

When the rhythm is too low or the detector electrode is defective, the heart is stimulated at the fixed minimum frequency and co-ordination between atria and ventricles is then lost. If the fixed maximum frequency is exceeded the pacemaker responds only to every second P-wave. If the ventricular frequency rises to 3 times the maximum pacemaker frequency, each third P-wave triggers a ventricular contraction.

Figure VIII-15 shows the P-wave triggered pacemaker with this additional development.

The ventricles may be stimulated with epicardial, intramural or intracardial electrodes.

Animal research

The principle of an electronic A-V bridge was applied first by BUTTERWORTH and POINDEXTER (1944) in an experiment aimed at reproducing the QRS-complexes of the Wolff-Parkinson-White-syndrome.

FOLKMANN and WATKINGS (1957) first applied the principle to dogs with total heart block, using two atrial electrodes to detect the P-waves. This signal was amplified to 450 mV and applied to the heart by 2 ventricular electrodes. In 5 of 24 dogs a rate of 90-130/min. could be maintained for three weeks in this way. In one animal, experimental auricular fibrillation caused a ventricular tachycardia and the maximum stimulation frequency was therefore limited to 130/min., which prevented supra-ventricular tachycardia causing ventricular tachycardia.

Further improvements in this electronic atrio-ventricular bridge were made by STEPHENSON *et al.* (1959). The advantage of their pacemaker was that the trigger signal obtained from the P-wave was led through a delay circuit – in the form of a monostable multivibrator – which reproduced the normal conduction time of the bundle of His (ca. 0.18 sec.) and was adjustable from 0-1.0 sec. A second adjustable multivibrator was included in the circuit, so that the impulse could be set at duration of a normal QRS-complex, the impulse duration of 0.1 sec. used by Stephenson corresponding with the time of a normal ventricular depolarization. However, since the stimulation impulse needs only to depolarize the ventricle at the electrode and not throughout the entire

cardiac muscle, a stimulus lasting no more than a few milliseconds is sufficient. A longer period only entails the danger of ventricular fibrillation. The second delay circuit therefore resulted in no improvement. The inclusion of a master oscillator in the circuit to function as an emergency system if detection of the P-wave failed or total atrial asystole occurred was, however, successful.

A disadvantage of Stephenson's circuit was the lack of a blocking mechanism in cases of supraventricular tachycardia or atrial fibrillation. Stephenson stated that with proper P-wave controlled stimulation the sinus rate rapidly reverted to normal; the incorporated P-R interval delay is an additional safeguard to prevent auricular fibrillation from producing ventricular fibrillation.

The concept of the P-wave pacemaker was also elaborated by KAHN *et al.* (1960) who established minimum and maximum frequencies. If the frequency of the atrial impulses passed outside the range of 45-120/min. the stimulator automatically functioned at a fixed rate of 75/min. The unit was tested in 4 animals, but was large and unsuitable for implantation.

NATHAN *et al.* (1963) ultimately succeeded in constructing an implantable P-wave triggered pacemaker and implanted it for prolonged periods in dogs. Ten days after heart block had been produced, electrodes were attached to the left atrium and ventricle through a left thoracotomy. The construction of this pacemaker is a further elaboration of the apparatus discussed above. The P-wave detected by epicardial electrodes measures 2-8 mV immediately after implantation. It is amplified 300 times before triggering the pulse forming circuit after a delay of 100 msec. To prevent pacemaker triggering by its own signal, a total refractory time of 0.4 sec. has been included in the circuit. The minimum frequency was 60 imp/min. and the maximum frequency 150 imp/min. Following preliminary external trials, pacemakers were implanted in 26 dogs for periods from one week to 7.5 months. A modification of this pacemaker is used clinically.

The above mentioned investigators detected the P-wave signals by means of epicardial atrial electrodes, in combination with either an indifferent electrode or a second electrode on the heart. BATTYE and WEALE (1960) considered the voltages obtained in this way to be too variable and attempted to detect the P-waves using a bipolar catheter. This had 2 silver electrodes 45 mm apart, one lying in the right ventricle for stimulation and the other in the right atrium as detector. A 20 cm^2 silver disc electrode was used as indifferent electrode. Battye and Weale

detected a negative P-wave signal that still varied in size, but with a minimum of several mV. Using this signal they were able to stimulate the right ventricle of canine hearts by way of the catheter tip, but no mention is made of the duration of the experiments. This method of detection was later elaborated in clinical applications by RODEWALD *et al.* (1964).

A third method of detecting the P-wave was developed by BONNABEAU *et al.* (1963). They investigated the possibility of detecting the atrial depolarization potentials from the ventricles, using 2 ventricular electrodes. In once case they placed both electrodes on the left ventricle, one just under the left atrium and the other one near the apex with an indifferent electrode elsewhere in the body. The atrial signals were approximately 2 mV, but dropped within a few days after implantation to 0-0.2 mV. By placing the electrodes far apart, one on the left and the other on the right ventricle parallel to the atria, they obtianed P-waves of 2 mV, which dropped to 0.6-0.8 mV within 24 hours after the implantation. Using these impulses, Bonnabeau *et al.* triggered the pulse forming circuit after a delay interval. The stimulation impulse reached the heart through the electrode on the left ventricle. However, the P-waves were of low amplitude and decreased further with time. Moreover, interference from external sources is more easily encountered when the sensitivity needs to be made high enough for such small P-waves. No clinical applications of this third method are known.

A variation in the power supply of an implantable P-wave triggered pacemaker has been developed by SUMA, TOGAWA and UCHIGAMA (1965). They constructed a P-wave triggered pacemaker as a combination of a battery pacemaker and an inductively coupled pacemaker. By using an extracorporal transmitter and an intracorporal receiving coil, energy to charge the nickel cadmium batteries can be transmitted by radiowaves. If necessary the stimulation impulses also may be directly administered to the heart by means of the electromagnetic system.

The animal research which led to the development of our P-wave triggered pacemaker is discussed in the chapter on stimulators (Chapter VIII).

Clinical application

The P-wave triggered pacemaker is applied clinically in three different versions viz.

A. epicardial P-wave detection and intramural stimulation
B. intracardial P-wave detection and intracardial stimulation
C. modified epicardial P-wave detection with intracardial stimulation.

A. In the first method the atrial depolarization is detected by an epicardial electrode and the heart is stimulated with intramural electrodes. This type was used for the first clinical application of an implanted P-wave pacemaker at 27th June 1962 (NATHAN *et al.* 1963). The operational technique is identical to that of the implantable pacemaker with transthoracic electrodes. After premedication and control of the rhythm with a catheter electrode connected to an external pacemaker, the heart is approached through the fourth left i.c.s.

The detector electrode consisted of a helical platinum wire, embedded in silicon rubber. The distal 6.5 mm of the spiral were lengthwise half embedded in the electrode frame, the other half making contact with the atrial wall where it is attached by a few sutures. One ventricular electrode was used for stimulation and a 5.5 cm diameter stainless steel disc on the pacemaker wall served as indifferent electrode. The pacemaker itself was a further development of the unit discussed under animal research.

During the first two years 21 patients were treated with this P-wave triggered pacemaker, but a number of defects occurred. An improved pacemaker brought about a decrease in the number of failures (CENTER *et al.* 1965) in subsequent clinical use.

B. In this version the atrial depolarization is detected with an intracardial electrode, the heart being stimulated with an intracardial electrode also.

This method was elaborated by RODEWALD *et al.* (1964). The low atrial voltage detected with this method is a disadvantage. From 313 measurements in 14 patients Rodewald *et al.* found that 47% yielded values below 0.9 mV. This is the limit of sensitivity of the pacemaker developed by NATHAN *et al.*, but Rodewald had nevertheless treated 7 patients with some success by 1964 with this unit.

C. In this third version the detector electrode consists of a catheter with a platinum tip 10 mm in length and 3 mm in diameter, attached between the posterior wall of the atrium and the anterior wall of the oesophagus. An identical catheter electrode in the right ventricle is used for stimulation.

This method was described by CARLENS (1965). Before the detector electrode is attached, the stimulation catheter and pacemaker are brought into position and the detector electrode is then attached by means of a mediastinoscope. After anaesthesia with intubation and the administration of a muscular relaxant, a small incision is made in the suprasternal fossa. Next, the tissue along the trachea is parted by the mediastinoscope, until a position is reached past the bifurcation of the trachea and the right branch of the pulmonary artery. When the thin layer of connective tissue between the posterior atrial wall and the oesophagus is reached, the detector electrode is inserted as near as possible to the atrial wall by means of a forceps, after which the electrode is left to fix itself. Immediately after introduction of the electrode, voltages of 1-7 mV are detected, which ultimately stabilise at 1.5-2.5 mV.

Twenty patients have been treated since February 1965 in this manner, with a P-wave triggered pacemaker developed by LAGERGREN *et al.* (1966).

Advantages and disadvantages

Advantages

A. Improved haemodynamic conditions

As was mentioned in the introduction to this chapter, co-ordination between the atrial and ventricular contractions gives a more effective circulation. CENTER *et al.* (1964) found that synchronous, compared with asynchronous stimulation, produced an improvement of the cardiac output of 10-30% at rest and 25-50% under stress. KARLOFF (1966) likewise found an increase of the cardiac output in 10 of Lagergren's thirteen patients. In one patient, the cardiac output rose from 3.8 l/min. during asynchronous stimulation to 5.5 l/min. during atrial triggered stimulation.

B. Neurogenous control

As the ventricles are stimulated at the rate of spontaneous atrial depolarization the heart is returned to physiological regulation.

C. No interference on return of sinus rhythm

Sinus rhythm returns in approximately 20-40% of patients with A-V conduction disorders treated with an implanted pacemaker (BOUVRAIN

1964; CENTER 1964; HARRIS 1965; SOWTON 1965; LAGERGREN 1966; THALEN 1967). If asynchronous stimulation is present in these cases, competition arises between the pacemaker impulses and the natural heart rhythm, which may in vulnerable hearts lead to ventricular tachycardia (BONNABEAU 1963) or fibrillation (ELMQVIST *et al.* 1963), if the pacemaker impulse arrives in the vulnerable period (i.e. in a period of 30 msec. preceding the T-wave (BROOKS 1955; LOWN 1962)). As the P-wave pacemaker is triggered by the atrial depolarization, even after return of the sinus rhythm, the stimulation impulse always arrives during the ventricular complex of the sinus rhythm. The chance of fibrillation due to the pacemaker impulse falling in the vulnerable period, is thus excluded. It should be noted that this is not the case when extra systoles arise.

Disadvantages

A. Extra (atrial) electrode on or in the heart

The P-wave triggered pacemaker requires an extra heart electrode, the atrial detector electrode. With respect to the 3 detection methods, discussed above, it can be stated that the first method, with electrode fixation by way of a thoracotomy entails the greatest operational risks, but thereafter provides the largest and therefore the most reliable signals; the second method, using intracardial detection and stimulation, entails the least operational risks, but at the same time detects the smallest and least stable signals, while the third method, with modificated epicardial detection, is a middle course between the two preceeding methods, both as regards operational risks and P-wave amplitude.

B. Division of the ventricular impulses at high atrial frequencies

At high atrial frequencies only each second P-wave is followed by a stimulation impulse. In Nathan's clinical version the maximum ventricular rate is 110 beats per minute. This means that during increase of the atrial rate the ventricle still receives 110 stimulation impulses per minute at an atrial frequency of 110/min., but when the atrial frequency rises above this limit for example to 112/min., the ventricle will suddenly drop to 56 stimulation impulses per minute. On the other hand, when the atrial frequency falls below 100 this division no longer takes place so that, when the atrial frequency reaches 99/min., the heart is suddenly subjected to an increase in impulse frequency from 52 per

minute, the minimum of the pacemaker, to 99/min. Although this division is necessary because of the dangers of atrial tachycardia, it is a disadvantage of the P-wave triggered pacemaker because of the sudden transitions in ventricular rate which it entails.

C. Interference by extraneous fields

The signals of atrial depolarizations are extremely weak and the detector circuit therefore needs a high input sensitivity. This, however, also increases the chance of interference by extraneous electric, magnetic or electro-magnetic fields.

In the first version of the pacemaker used by LAGERGREN *et al.*, the frequency band of the P-wave detector was 5-3000 Hz. During several applications of this pacemaker, extraneous fields triggered the detector with the result that several male patients abandoned their electric razors and several female patients were unable to use their electric domestic appliances. In later types the frequency band was limited to 5-100 Hz to decrease this influence.

The frequency band of the pacemaker developed by NATHAN *et al.* is 5-200 Hz. In this design an attempt to counteract the effects of external interference has been made by means of an indifferent electrode in the form of a stainless steel disc in the pacemaker wall, acting as a screen for the pacemaker circuit. The electrodes themselves, however, are not screened in this way and CENTER (1963) found that powerful low frequency sources of interference are still capable of affecting the pacemaker.

D. Complicated electronic pacemaker circuit

The number of electronic components is several times that of the asynchronous pacemaker. The chance of failure due to defects in the electronic circuit is therefore proportionally greater.

E. High current consumption, short life time

The P-wave triggered pacemaker consumes more current than the asynchronous pacemaker due to its additional circuits, especially those for pre-amplification and delay of the P-wave. The batteries are therefore exhausted earlier, and the life time is shorter.

F. Ventricular arrhythmia due to fluctuations of the atrial signal around the detection threshold

The P-wave signals may be extremely weak and even a slight further decrease may result in failure to trigger the pacemaker, which then starts to stimulate at its minimum frequency as an asynchronous pacemaker. When the P-wave signal increases again, the detection threshold is once more reached and the ventricle is suddenly stimulated again at the atrial rhythm. Variations in amplitude of the P-wave signals may thus manifest themselves as ventricular arrhythmia.

Fluctuations in the atrial signal may occur due to a poor contact between pick-up electrode and the atrial wall, but may also be caused by fatty degeneration, oedema or ischaemia of the atrial myocardium.

Conclusion

About 10-20% of the patients with conduction disorders are unsuitable for treatment with a P-wave triggered pacemaker, due to an irregular atrial activity (HANSSEN 1949; PENTON 1956; BURCHELL 1964, *et al.*).

Although the advantages for the remaining patients are obvious, the disadvantages were still found to be too frequent in practice, so that in comparison with asynchronous stimulation, this stimulation method is little used as yet.

X. STIMULATION WITH A R-WAVE CONTROLLED ON-DEMAND PACEMAKER

Principle

In stimulation with a R-wave controlled pacemaker, one or more ventricular electrodes are used to detect the R-waves of the ventricles and to stimulate the heart, the circuit of the pacemaker being such that the pacemaker is controlled by the R-waves and only evokes ventricular contractions if the heart frequency drops below the fixed frequency of the pacemaker (fig. IV-15).

Introduction

With the asynchronous pacemakers discussed in the preceeding chapters, the heart is stimulated continually at a fixed frequency. Only in the P-wave triggered pacemaker is this frequency coupled within certain limits to the atrial depolarization.

Sinus rhythm returns in approximately 20-40% of the cases in whom a pacemaker is implanted, as mentioned in the previous chapter. The explanation for the return of conduction is probably that the metabolism of the bundle of His and myocardium recovers, due to improved vascularisation. This recovery allows interference to occur between the spontaneous heart rhythm and the rhythm induced by the pacemaker. This phenomenon has provided the motive for the development of the 'on-demand' or R-wave controlled stimulation method (NICKS *et al.* 1962). There are 2 types of on-demand stimulation.

A. In one method, *R-wave blocked stimulation*, the pacemaker receives electrical signals from the ventricular ECG via an intravascular or

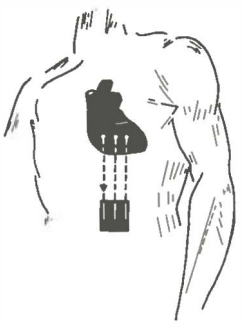


Fig. IV-15. Scheme of completely internal (implanted) on-demand stimulation system, R-wave controlled pacemaker (bipolar).

transthoracic electrode. The R-waves of this signal are amplified selectively in a detector circuit and are transmitted to a circuit which is capable of blocking the proper pacemaker. After a stimulation impulse a voltage is built up in the pulse-forming section of this pacemaker, and reaches a critical value after a predetermined time, whereupon a new impulse follows. At the arrival of a R-wave impulse during the build up phase of this voltage, the build up of the voltage is terminated the circuit returns to its initial condition whereupon the build up of voltage which ultimately leads to the critical value resulting in an impulse has to begin anew. This means that the pacemaker is blocked by the timely arrival of the R-wave and the cycle again starts from the beginning. When no R-wave impulse arrives in the pacemaker circuit within the build up phase of the above mentioned voltage, the pacemaker is not blocked and an impulse results. In order to prevent the pacemaker impulse and/or the electrical signal of the accompanying ventricular contraction from blocking the pacemaker prematurely via the detection electrode, the output signal is simultaneously added to a circuit which prevents the detector functioning for some time after the pacemaker impulse (dead

time). The R-wave blocked pacemaker therefore only then delivers impulses, stimulating the heart, when the heart frequency decreases below the fixed minimal pacemaker frequency determined by the build up phase.

B. The other method, *R-wave triggered stimulation*, is a modification of P-wave triggered stimulation. In this method the R-waves of the ventricles trigger the pulse forming circuit of the pacemaker after a short delay time, so that stimulation impulses are delivered to the ventricles but fall in the absolute refractory period of the ventricular cycle in case of a properly functioning heart. The pacemaker functions like an asynchronous pacemaker if the ventricular frequency dorps below the fixed pacemaker frequency. The R-wave triggered pacemaker therefore always delivers impulses even with a normally functioning heart, but stimulation becomes effective only when the heart frequency decreases below the fixed minimal pacemaker frequency.

In the latest versions using both methods, it has been possible to carry out detection and stimulation by means of the same electrode, so that only one heart electrode is required.

Animal research

A. R-wave blocked pacemaker

The first report of a clinically applied external unit after this principle being made in 1962 by NICKS, STENING and HULME, in 1963 SYKOSCH *et al.* described the development of a stimulation unit, which can be said to be the predecessor of the R-wave blocked unit discussed here. They constructed a pacemaker which could be blocked by means of a circuit in which a secondary coil was included and used it in dogs. The ECG was detected extracorporally with skin electrodes, the impulses reaching a transmitter with a primary extracorporal coil via an amplifier. The R-waves detected in this way were transmitted by a high frequency carrier wave to the secondary coil and thereupon blocked the pacemaker. Practical simultaneously completely implantable units were developed by MEYER *et al.* in the United States and by our group in Europe. MEYERS *et al.* did not report animal experiments. Our animal research is dealt with extensively in the chapter on the R-wave pacemaker (ChapterVIII).

B. R-wave triggered pacemaker

Animal experiments with a R-wave triggered pacemaker have not been

reported till now, although SOWTON (1967) mentions the development of such R-wave triggered units in three centers. Publications on this type of pacemaker are, however, limited to the design of the unit and the records of the first clinical applications.

Clinical application

A. R-wave blocked pacemaker

The principle of the R-wave blocked pacemaker is applied in many types of apparatus used in patient monitoring, but these are extracorporal units, which are especially intended for patients with short term arrhythmia or cardiac arrest. Generally they consist of an ECG monitor, plus a stimulation and alarm unit. A complicated unit, including an electrocardiograph and a defibrillator, is described by BOUVRAIN and ZACOUTO (1961). This unit is also completely extracorporal.

The development of implantable pacemakers and of temporary preoperative monitoring of patients with heart block led to a change of emphasis so that on-demand stimulation became the main consideration. LEMBERG, CASTELANOS and BERKOVITZ (1965) first described an on-demand pacemaker consisting of an asynchronous external pacemaker with external or intravascular electrodes.

As no clinical applications of the unit developed by SYKOSCH *et al.* (1963) were described the development from completely external to completely implantable R-wave blocked pacemakers took place without any intermediate forms. In 1966 the first R-wave blocked pacemakers were implanted. MEYER's pacemaker was implanted in 3 patients after a number of extracorporal applications (RODEWOLD 1966). The first implantable R-wave blocked Groningen pacemakers (VAN DEN BERG and THALEN) were also implanted in 1966. At the end of 1967 23 R-wave blocked pacemakers of the Groningen type were implanted.

B. R-wave triggered pacemaker

The principle of this pacemaker was reported by DONATO and DENOTH (1966) for the first time. One year later they reported good results with their pacemakers in combination with a catheter electrode in 30 patients (1967). Clinical use of R-wave triggered pacemakers has also been reported by ELMQVIST *et al.*, CHARDACK *et al.*, and RODEWALD *et al.*

Advantages and disadvantages

Both versions of the R-wave controlled pacemaker have some advantages and disadvantages in common.

Advantages

1. No interference with the spontaneous heart rhythm

R-wave control prevents interference between spontaneous cardiac activity and pacemaker activity. In view of the large number of patients who have an implanted pacemaker and sinus rhythm but do not develop ventricular tachycardia or fibrillation other factors apart from competition must be of importance. WIGGERS (1940) and MCLEAN and PHIBBS (1960) showed that the oxygenation of heart muscle plays an important part in determining fibrillation thresholds, and the impulse amplitude during the vulnerable period is also of great importance. Nevertheless it is a great advantage that the chance of fibrillation and ventricular tachycardia due to interference from sinus rhythm or extrasystoles is prevented in R-wave controlled stimulation.

2. Effective stimulation when necessary (on-demand)

As the pacemaker only stimulates effectively when the heart frequency has dropped below a minimal value, the heart activity is not interrupted during physiologic conduction. This results in an optimal circulation, as the ventricle remains under nervous control.

3. Large ventricular signal

Compared to the P-wave of the atrium the R-wave from the ventricle is so great that a large signal is obtained to control the pacemaker even during long term implantation. The signal detected with intramural electrodes is 3-4 times greater than with intracardial electrodes.

4. Longer life time of the R-wave blocked pacemaker

If the R-wave blocked pacemaker is blocked by the heart the energy consumption of the batteries is lower than that in the asynchronous pacemaker, since the current consumption of the detector and blockade circuit is lower than that of the output circuit of the pacemaker. If

the pacemaker is not blocked, the total current consumption is higher than that of the asynchronous pacemaker, because the non-effective blocking circuit consumes energy.

The life time of the R-wave blocked pacemaker is therefore dependent on the degree of spontaneous cardiac activity. On average the life time of our R-wave blocked pacemaker is approximately equal to that of the asynchronous pacemaker when the heart blocks the pacemakers 50% of the time, while the life time becomes longer when the blocking percentage increases.

Disadvantages

1. More complicated implanted unit

Compared to the asynchronous pacemaker, the R-wave controlled pacemaker is more complicated, increasing the chance of electronic defects and the attending complications. The electronic circuit of the R-wave pacemaker is simpler however than that of the P-wave triggered pacemaker.

2. Shorter life time of the R-wave triggered pacemaker

The R-wave triggered pacemaker will have a shorter life time compared to the asynchronous pacemaker, as the detecting and amplifying circuit consume energy and because the pacemaker also delivers impulses when the heart is beating spontaneously; in this case the rate is usually higher than that of an asynchronous pacemaker, with a consequent higher battery drain.

3. Interference by extraneous fields

The R-wave blocked pacemaker should only be blocked by the R-waves, but signals due to interference from extraneous fields may also block the pacemaker. This is of no consequence when the heart is itself blocking the pacemaker, but when pacing is required this interference may become fatal. The R-wave triggered pacemaker is not seriously affected by this interference, as extraneous signals are only capable of increasing the number of pacemaker imp./min. to a preset maximum. By suitable design of the R-wave blocked pacemaker (see Chapter VIII) the risks can be minimized, whereas in some R-wave pacemakers the circuit is developed such, that the pacemaker is not blocked if strong extraneous signals occur (BERKOVITZ; VAN DEN BERG and THALEN).

Conclusion

The R-wave controlled pacemaker has a number of important advantages over the asynchronous units, expecially for patients with an intermittent heart block or recovery of A-V conduction. These advantages by far outweight the disadvantages. Although the on-demand pacemaker has only been used in a small number of patients so far, it may nevertheless be assumed that this method of stimulation will play an important role in the future. Further experience will enable a choice to be made between the blocked and the triggered versions.

Postscript

Ten methods of stimulation have now been discussed. Ten times in the course of development of electrical stimulation of the heart an important change has taken place in the stimulation apparatus, the impulse transmission or the electrodes. The question arisis whether still more fundamental changes will take place, so that still more methods of stimulation will come into being. It seems unlikely that this will be the case and it is probable that the ten principles as laid down in this chapter will remain the basis for future treatment.

This by no means implies that the development of electrical stimulation of the heart will not continue. The development will however be restricted to technological modifications and other combinations of the principles dealt with above, such as a combination of the P-wave and R-wave pacemaker, sophistication of the components used, and especially a new approach to the problem of energy supply.

In the following chapters the development of the various stimulation units and stimulation parameters as mentioned in this chapter will be considered in more detail.

Methodology of the animal research

CHAPTER V

The prototype of the Groningen pacemaker was developed in 1960 by VAN DEN BERG. In co-operation with HOMAN VAN DER HEIDE and NIEVEEN, pacemaker and electrodes were tested in experiments on 11 dogs. In the light of these experiments a stimulation unit was developed, and the first clinical application took place on March 21st 1962.

The complications which occurred during the first applications led to an extensive investigation of electrical stimulation of the heart. An important part of this investigation was carried out on animals and the methodology of this research is dealt with in this chapter.

1. PURPOSE AND COURSE OF THE ANIMAL RESEARCH

The purpose of the animal research was to carry out tests in vivo and to apply the experience to the development of electrodes and stimulator into a reliable unit for heart stimulation. This stimulation unit then formed the starting point for the development of new stimulation methods in future animal experiments.

The research can be divided in two parts. It started with the development of a transthoracic pacemaker electrode. Electrodes of various metals and of various shapes were introduced in different combinations into dogs with heart block. The electrodes were tested in both acute and long term experiments by monitoring of the stimulation thresholds and operational values by means of our Cardiotest. The hearts were removed at the end of an experiment and examined macroscopically and microscopically for tissue reaction around the electrodes.

Simultaneously, research was carried out on the conditions for optimal stimulation of the heart, the difference between monopolar and bipolar stimulation being evaluated from the relative thresholds with different impulses. Optimal parameters for the stimulation impulse were identified

by studying in animals the effect of variations in the shape, amplitude and duration of the impulse.

Several pieces of auxiliary apparatus were developed for this combined first part of the animal research. These include the Cardiotest for measurement of the stimulation threshold and operational values and this instrument will be described in detail later. An automatic recording of the stimulation threshold was made possible by combining the Cardiotest with the Vasotest, an apparatus for monitoring of the peripheral circulation, in the so-called Autocardiotest. Likewise, a Monitor was constructed, which makes the pulses of the implanted pacemaker audible for a quick and simple check.

After the development of the electrode and stimulator this combination formed the starting point for the second part of the investigation, the development of new stimulation methods. The data needed for design of an R-wave controlled pacemaker were obtained by measuring the ventricular depolarizations recorded from this proven electrode in long term experiments in dogs. From the analysis of these impulses it was possible to develop the triggering of the 'on-demand' pacemaker. Subsequently, the R-wave pacemaker was tested in animals.

The P-wave triggered pacemaker was developed in a similar way, but the atrial depolarizations in a number of long term canine experiments were analysed.

The development of the phototest method, which allowed simple monitoring of the implanted pacemaker in patients, led to the development of a pacemaker with impulse suppression for the measurement of the stimulation threshold. This pacemaker was also subjected to a number of animal tests before its use in patients.

II. RESEARCH ANIMALS

For the development of the electrodes and stimulators it was necessary, after the technical and electronic tests, to test the units in vivo. Maximum information was obtained from each animal experiment by combining different measurements and tests.

About 60 mongrel dogs were used, varying in weight from 15-36.5 kg with an average weight of 25.5 kg; and varying in age from 1-6 years with an average age of 2.8 years. 70% of the dogs were male, 30% female. The dogs were kept under observation for some days in the kennel and, if they were in good condition, were given an intramuscular injection of 50 mg/kg Streptomycine and 400.000 units of Penicillin daily for 3 days before the operation.

In order to create physiological circumstances as similar as possible to those under which the pacemaker is used in patients, heart block was produced surgically in all animals.

An exception was made for the 'on-demand' pacemaker. Research with this pacemaker, which was constructed for patients with intermittent heart block, was carried out on dogs without permanent heart block, but during these experiments we created a temporary heart block pharmacologically.

A. Anaesthesia

After premediaction with Atropine (0.5 mg i.m.) anaesthesia was started with a short acting barbiturate, Sodium Pentothal (20-25 mg/kg i.v.). It was found that care should be taken in administering Sodium Pentothal during operations on dogs with pre-existing heart block, since the extra systoles, which may occur after administration of Sodium Pentothal, sometimes rapidly develop into ventricular fibrillation under these circumstances. One animal was lost due to this complication.

BONNABEAU *et al.* (1963) investigated the sensitivity of canine hearts with complete A-V block, and found that intravenous doses of 4-8 mg/kg Sodium Pentothal could cause fibrillation, although no arrhythmia occurred in dogs with sinus rhythm. This complication can be avoided by artificial stimulation of the heart and slow administration of the Sodium Pentothal. During the short Sodium Pentothal anaesthesia an endotracheal tube was inserted, after which anaesthesia was maintained with a mixture of Nitrous Oxide and Oxygen (N_2O-O_2) in the ratio of 2 : 1. Subcutaneous needle electrodes were used to monitor the heart action before and during the operation and connected to an electrocardiograph, while an infusion of saline was introduced into the saphenous vein for the administration of fluid (1 drop/sec.) and drugs.

For muscular relaxation, Succinylcholine (0.3 mg/kg) was administered intravenously, after which the respiration was maintained artificially with a Dräger pulmonat, or manually with a baloon. If necessary a supplementary dose of half the initial amount of Succinylcholine was administered.

The dog was laid on its left side and the right half of thorax was shaved and disinfected with 2% solution of Iodine tincture.

B. Operation

The thorax was entered through an incision in the fourth intercostal space on the right. The pericardium was opened with a door leaf incision, approximately 1 cm anterior to the phrenic nerve, after which the edges of the pericardial incision were sutured to the thoracotomy edges.

In all cases where a heart block had to be created, the ventricular electrodes were applied first. The advantages of this method are firstly that the electrodes can be attached to an intact heart, and secondly that it is possible to stimulate the heart via these electrodes with the Cardiotest immediately after the block has been created. In this way the heart can be stimulated immediately if there is undue depression of the circulation due to idio-ventricular rhythm or asystole.

C. Fixing of stimulation electrodes

One or more electrodes were fixed to the right ventricle and it was also possible to attach electrodes to the left ventricular wall through the right thoracotomy by lifting the heart slightly from the pericardium, thus making the left ventricle accessible. In doing this, care should be taken not to kink the vascular trunk too severely or for too long. The electrodes were fixed to the heart with atraumatic 2-0 silk sutures. One or more indifferent electrodes were placed in the subcutaneous tissue near the thoracic incision. In most cases a multistrand stainless steel suture electrode was chosen, but sometimes a disc electrode was used. For experiments with catheter electrodes, these were introduced into the right jugular vein under Sodium Pentothal anaesthesia and X-ray monitoring before the chest was opened. Here too, an intramural electrode was inserted for emergency stimulation of the heart after the production of heart block.

D. Heartblock

The first attempt to create a heart block in order to demonstrate the function of the A-V bundle was made by HIS JR. in 1895 by cutting the conduction bundle in rabbit's hearts. Since then a great number of techniques has been developed to create heart block, which indicates that no ideal method has yet been found, and that each method entails certain difficulties.

ERLANGER (1906) developed a special clamp, the 'Erlanger Clamp'; some attempted to cut the bundle with a special cardiotome, which

was introduced into the jugular vein (FRANKE 1951), while others created a heart block by freezing the conducting tissue (LISTER *et al.* 1964) or by injecting chemicals such as alcohol, phenol and formaline solution in the course of the bundle of His (BELLET *et al.* 1960 and KLOTZ *et al.* 1963). Some investigators introduce the chemicals with a closed method by a catheter inserted into the jugular vein, using a second catheter inserted in the ventricle via the femoral vein as a guide (WILLIAMS *et al.* 1964; FISHER 1966); HASHIBA (1965) created a heart block by ligation of the septal arteries. A method frequently used is that of STARZL (1955), who cut the A-V bundle through an incision in the auricular wall of the right atrium. The open methods are sometimes carried out under hypothermia (HUO-LUAN-CH'IANG *et al.* 1964), or with the help of a heartlung machine (THEVENET *et al.* 1958) to allow a longer time for manipulation.

We have used two methods under normothermic conditions; a closed method, in which the bundle is interrupted by coagulation, and an open method with temporary occlusion of the venae cavae, in which the bundle is approached through the right atrium and ligated.

In order to create a complete heart block, the atrioventricular conducting sytem, i.e. the bundle of His, has to be interrupted. This bundle should be crushed immediately after the bifurcation into left and right branch, or before that point, as there is otherwise the risk of creating only an incomplete block, such as right or left bundle branch block.

In creating a heart block by coagulation (WIEBERDINK *et al.* 1961), the method we used in our first experiments, a small 2 mm diameter copper rod completely insulated with nylon or silicon rubber except at the tip is used. The rod enters the right atrium through an incision with a purse-string suture in the atrial wall just before the sulcus terminalis (atraumatic 2-0 silk suture). The bundle of His is located by the non-insulated tip of the rod; the tricuspid valves serve for orientation as they can be felt beating against the rod if this is moved too far in the direction of the ventricle. Once the position has been approximately determined in this way, the rod is moved to that part of the atrio-ventricular junction which lies approximately half way between the recess of the inferior vena cava into the right atrium and the aortic root (recognisable by pressing the left index finger between the aorta and right auricle). The A-V bundle crosses the atrio-ventricular boundary approximately in this place. As pressure on the bundle causes conduction disturbances, which manifest themselves as ventricular arrhythmia, the bundle can be located more accurately by pressing the tip of the rod on the underlying tissues. As

soon as such a conduction disturbance is noticed, a diathermic current, powerfull enough to cause a necrotic area of approximately 5 square mm, is passed through the rod. This current can be tested in advance on the muscles of the thoracic wall.

In cases where the bundle cannot be located in this way, Wieberdink *et al.* advise palpating the atrial cavity with a finger inserted through an opening with a purse string suture made in the auricular wall. We have not used this extension of the technique. In order to counteract possible ventricular fibrillation, we administered 2-4 mg/kg Pronestyl intravenously 5 minutes before proceeding with this part of the operation. Using this method we were able to create permanent heart block in 9 out of 17 dogs. The other dogs succumbed during the operation, or had only temporary heart block, bringing the following disadvantages of this method to light:

1. Difficult localization of the bundle of His

Although the bundle can be traced by the ventricular arrhythmia which occurs when it is subjected to pressure, it is difficult to keep the tip of the rod at the correct place because of the heart action, thus making proper coagulation difficult.

2. Heart lesions

Because of the difficulty in location, the wrong areas were frequently coagulated. Perforations of the atrial septum, as well as lesions of the tricuspid valves occurred, which resulted in insufficiency and ventricular fibrillation.

3. Blood coagulation around the tip of the rod

If heart block was not obtained after the first coagulation, it frequently proved impossible to achieve effective coagulation afterwards. When the rod was removed from the atria it appeared that a clot had been formed around the tip, making coagulation of the tissue of the conduction bundle impossible.

4. Oedema formation

The main disadvantage of the coagulation method was the forming of oedema around the coagulated area. The oedema exerted pressure upon

surrounding tissue and so temporarily interrupted the A-V conduction completely, even though the bundle of His itself had not been coagulated. Conduction then returned within two days, when the oedema and the pressure were reduced, so that an orginally complete heart block returned to sinus rhythm.

In view of these disadvantages, we turned to a modification of the method of TAUFIC *et al.* (1955) developed by HOMAN VAN DER HEIDE. With this open method, ligating the bundle of His under direct vision, we were able to produce a complete heart block in 33 of 35 dogs. In two dogs an incomplete heart block was created, probably due to elimination of only part of the bundle of His. For this open method tourniquets were first placed around both venae cavae. After the pericardium had been opened and the electrodes had been fixed, as described above, the heart rate was reduced by intravenous administration of Inderal (0.5 mgr/kg). Then, both venae cavae were occluded and the right atrium was opened by an incision of approximately 1.5 cm in length (fig. V-1).

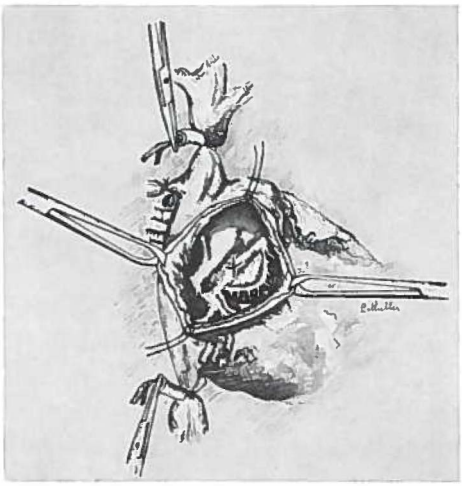


Fig. V-1. Production of heartblock by ligature. After ligation of the vena azygos and occlusion of the venae cavae, the atrium is opened and the bundle of His is ligated. (See text).

Using the coronary sinus as orientation point, we attempted to place a suture around the bundle of His, 1-2 cm anterior to the coronary sinus. To do this we inserted the needle with a 2-0 silk suture 2-3 mm under the annulus through the septal slip of the tricuspid valve. By taking hold of the septal slip with the end of a suction tube, and lifting the attached slip slightly, the location can be accurately performed and insufficiency of the tricuspid valve can be avoided.

The needle was inserted deeply, to incorporate the superior part of the ventricular septum with the bundle, or with both bundle branches. The needle was passed further through the inter-atrial septum and emerged approximately 3-4 mm superior to the atrioventricular junction. The suture was then tied, thus ligating the bundle (fig. V-2), whereupon the ventricle responded with standstill or an idioventricular rhythm. We did not observe extra systoles, as described by WEIRICH *et al.* (1958). After the occluding tapes around the superior and inferior vena cava had been loosened, the atrium filled again with blood which displaced the air. The edges of the atriotomy were then approximated by a non-crushing clamp, and the heart was immediately stimulated at a frequency of 70 beats per minute by switching of the Cardiotest. In this way circulatory arrest was kept to a minimum.

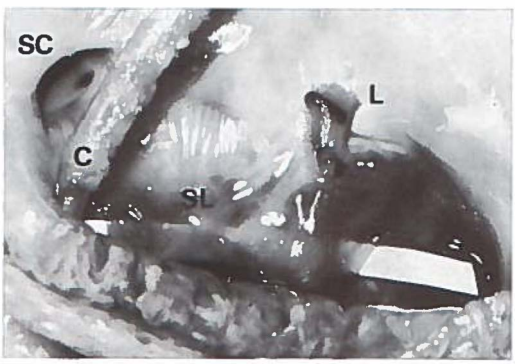


Fig. V-2. Ligature (L) around the bundle of His in a dog 12 days after the production of a heartblock. The heart has been stimulated by a catheter electrode (C) in the right ventricle. In the right atrium furthermore can be seen the sinus coronarius (SC) and the septal leaflet (SL) – made visible by white ribbon introduced below it – of the tricuspid valve.

After approximately one minute the stimulation by the Cardiotest was interrupted briefly, and the electrocardiogram was checked to confirm that the ligation has resulted in complete heart block. If the suture had caused an incomplete heart block or none at all, a second suture was placed after a period of at least 10 minutes. When complete heart block was diagnosed, the atrial incision was closed with an atraumatic 2-0 silk suture.

Unlike the closed coagulation method, which carries no time limit, the above open method requires that the operation does not last longer than 3 minutes, since the circulation must be restored within this period. On average the operation lasted 60-90 seconds, most of the time being necessary for orientation in the heart. In one case we exceeded the time limit by approximately 15 seconds and this resulted in cerebral

oedema with decerebration rigidity as a clinical feature. It was possible to clear the complication by post-operative administration of a highly concentrated glucose solution transfusion and oxygen.

In view of the good results with the above open method, this method was exclusively used during the best part of the experiments.

E. Fixing of atrial electrodes

In developing the P-wave triggered pacemaker, it was necessary to attach detecting electrodes to the atria. Since we approached the bundle of His by entering the right atrium, the detecting electrode could only be attached to this atrium after the heart block had been created. It appeared, however, that the lesion of the right atrium caused considerable changes in the impulses detected (fig. VIII-13). Although the impulses returned to normal as the wound healed, we decided to detect the atrial depolarizations from the left atrium. Therefore, 7-14 days after the right thoracotomy, a left thoracotomy was performed in which the left atrium was approached in a similar manner as in a right thoracotomy. The detecting electrodes were attached to the atrium with 2 atraumatic 2 - 0 silk sutures.

F. Electrode leads

To be able to perform measurements it was necessary for the electrode leads to perforate the skin. For this purpose the leads were extended with multistrand (49 strands) stainless steel wires, which were insulated with teflon. The wires were not led through the thoracic incision in the fourth intercostal space from the thoracic cavity to the subcutaneous tissue, but through the third or fifth intercostal space consecutively, to enable stimulation by the Cardiotest to be maintained. Subsequently, using a specially developed system of tubes (KORNELIS), the leads were led subcutaneously to the dog's neck, where they perforated the skin. This method, using thin conducting wires, offered least disadvantages in the form of infections. To prevent withdrawal of the wires, two small teflon bars were fixed around each wire, one subcutaneously and the other externally. The only complication occurring with this method was fracture of the extension wire at the perforation of the skin. Thanks to the subcutaneous teflon bar, however, it was a simple matter to trace the wire and repair the break.

G. Fixing of pacemaker

In the first experiments, the pacemaker was fixed subcutaneously in the neck between the scapulae. Frequently, however, the pacemaker would slide after some time, or cause necrosis by pressure, whereupon it prolapsed from under the skin. We soon abandoned this subcutaneous pacemaker pocket, and in the later experiments we hung the pacemaker in a bag round the dog's neck, like the famous St. Bernhards with their little barrels. The stimulating wires, like the wires of the detecting electrodes, were led through the skin to enable extracorporal measurements with any combination of electrodes. After the fixation of the leads in the neck, their wires were detached from the Cardiotest and connected to the pacemaker in the bag. For measurements during the course of a long term experiment the electrodes were detached from the pacemaker and connected to the measuring apparatus.

To prevent the dog scratching or biting at the wires or the pacemaker we took the precaution of binding up completely the pacemaker and the leads in strong broad sticking-plaster, which also covered the area where the electrodes perforated the skin. This method gave good results and dogs could be stimulated during a period up to 12 months in this way.

H. Post-operative treatment

Before the thorax was closed, a rubber tube was placed to drain the thorax by an ACM Stedman-pump. The thorax was drained again 4-8 hours and 12-18 hours after the operation, and the tube was then removed unless copious drainage persisted. Medicaments given postoperatively were 25 mg. Prednisolon, 50 mg/kg Streptomycin and 400.000 un. Pencillin, repeated daily for 5 days after the operation.

The heart frequency (via the femoral artery), the respiratory frequency, and the temperature (rectally) were checked thrice daily during the first week. After that, the function of the pacemaker was monitored daily by checking the heart frequency.

IV. AUXILIARY APPARATUS

A number of necessary auxiliary pieces of apparatus were developed during the research and further adapted in the course of the experiments. The results obtained with this apparatus are now used for clinical purposes as well. This apparatus will be discussed in this chapter.

A. Cardiotest

The Cardiotest (1962) is a stimulator which permits quantitative measurements of electrodes and their effect on the heart during stimulation (fig. V-3). It is an apparatus with essentially the same features as the Groningen pacemaker, so that the impulses administered to the heart have the same characteristics as those of the implanted pacemaker. This is essential if meaningful results are to be obtained.

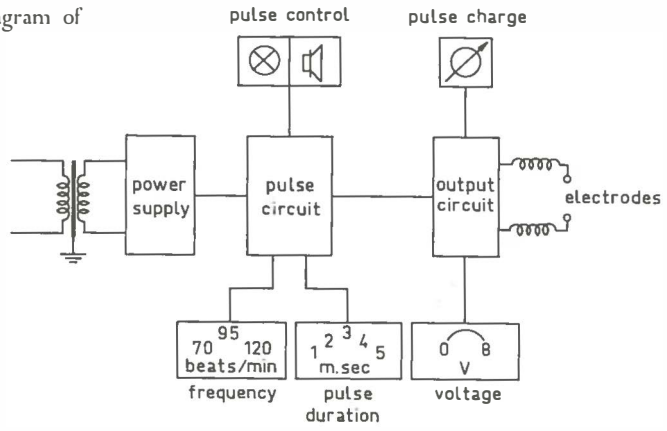


Fig. V-3. Block-diagram of the Cardiotest.

Construction. Like the Groningen pacemaker, this apparatus consists of a pulse forming circuit and an output circuit. The pulse circuit is identical to that of the pacemaker, but the frequency can be set at 3 values, viz. 70, 95 and 120 impulses per minute and the pulse duration at 5 values, viz. 1, 2, 3, 4 and 5 msec. The output circuit is also identical to that of the pacemaker with the addition that the output is continuously adjustable from 0-8 volt. The total charge per impulse, i.e. the charge which passes through the tissue via the electrodes, can be read in micro-Colombs on a meter having two ranges, one to 25 μC and a second to 50 μC. Since these charges are measured indirectly, no extra resistance is added to the stimulation circuit. The Cardiotest impulses are made visible by a lamp and audible by a loudspeaker with adjustable volume.

The Cardiotest receives its energy from the electric mains. To guard against the patient being electrocuted, the circuit is separated from the mains by means of an isolation transformer. Moreover, this circuit is completely free from earth – capacitively as well, thanks to high

frequency induction coils in the output – thus avoiding the inherent danger of ventricular fibrillation due to double earthing of the patient via an electrocardiograph or electric coagulator.

Procedure. When the Cardiotest is used for stimulation the electrodes are connected and then the optimal frequency and impulse duration are chosen. The voltage can be set at a value at which the heart follows the impulses well and stimulation can be monitored by comparing the heart action with the Cardiotest impulses which are indicated by a flashing light or by the loudspeaker. The contractions of the heart can be seen directly if the chest is open and can be identified either by the femoral pulse or by means of the Vasotest (to be discussed later) if the chest is closed. The heart responds to the Cardiotest when each electrical impulse is followed by a contraction, so that there is synchronization between the pacemaker impulses and the peripheral pulse. Allowance should be made for the time delay of the peripheral pulse which will be about 100-200 msec., according to the point of detection.

For quantitative analysis the Cardiotest is connected to the electrodes to be tested and frequency and impulse duration are then set at suitable values. If the electrodes are to be checked under pacemaker conditions, the frequency and impulse duration of the pacemaker to be implanted are chosen; the usual values are 70 impulses per minute and 2 msec. respectively. Two sets of values are then determined, the operational values and the threshold values; alterations are easily made as the voltage output of the Cardiotest is continuously adjustable.

The operational voltage is equal to the battery voltage of the pacemaker. With the voltage of the Cardiotest set at this value, the charge which passes through the electrode circuit at each impulse is read from the meter of the Cardiotest in microCoulombs. This charge is called the operational charge. The threshold value is defined as the corresponding charge at the threshold, i.e. when the impulses are just sufficient to stimulate the heart. These values are determined by slowly reducing the voltage of the Cardiotest and the threshold is reached when the impulses no longer result in cardiac contraction. The corresponding voltage is called the threshold voltage, the corresponding charge the threshold charge. From the operational values and the threshold values the safety margin of the electrode combination can be calculated and conclusions concerning the stimulation circuit can be drawn. This aspect will be considered in further detail in the chapter on the electrodes.

B. Vasophon

The Vasophon (1962) is an apparatus for checking the peripheral circulation, and so provides a check also on cardiac activity (fig. V-4).

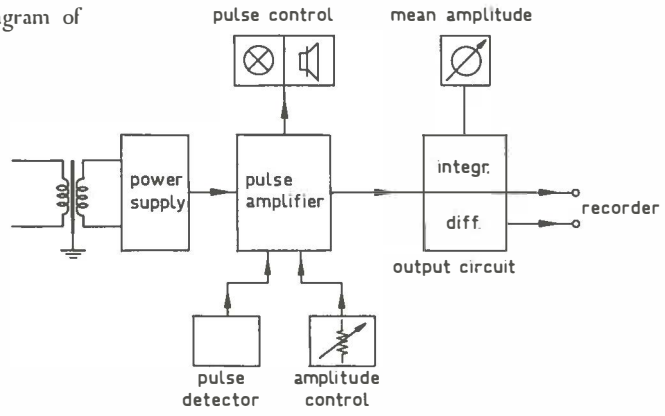


Fig. V-4. Block-diagram of the Vasophon.

Changes in the peripheral circulation are registered by photoplethysmography (DE PATER, VAN DEN BERG and BUENO 1961). Two methods can be used for this.

a. Transmitted light

This method makes use of the fact that the variation of the amount of transmitted light is related to the variation of the amount of blood in the transilluminated part. For this reason a method with transmitted light can only be applied to small extremities, such as fingers and toes, or to ears and skin-folds.

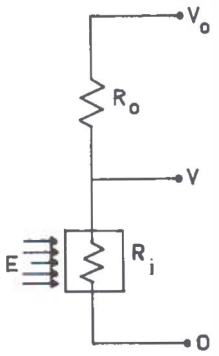
b. Scattered light

The peripheral circulation can also be detected by means of incident light, which penetrates the skin and after (multiple) scattering is registered by a detector. Variations in the intensity of the light returning to the detector depend on variations in the amount of blood present in the region concerned, i.e. in fact the skin between the point of entry of the light and the light detector. In principle, the method using scattered light can be used for each region of the skin, large enough to accommodate the detector.

Both methods can be used with the apparatus described here, in each

case the light being detected by means of a cadmium sulphide photoresistance (L.D.R. = Light Dependent Resistance). Cadmium sulphide is one of the semi-conductive materials whose crystals react reversibly to light and which has a spectral sensitivity suitable for the detection of blood. The electrical resistance (fig. V-5) of the cadmium sulphide unit (R_l) is inversally proportional to the intensity of the incident light. The photoresistance is connected in series with a constant resistance R_0 to a constant voltage V_0. Variations in the quantity of light E cause variations in the resistance R_l and corresponding variations in the voltage V. These

Fig. V-5. Scheme of the detector-unit of the Photoplethysmograph. (See text).



variations are fed into an adjustable amplifier, and the pulses corresponding to each heart beat are made visible by means of a lamp and audible by means of a loudspeaker. The integrated magnitude of the impulse can be read on a meter, while continuous registration of the signal and/or the differentiated signal is also possible.

The names 'Vasophon' for the simplest type and 'Vasotest' for a more complicated version were chosen because the apparatus is used to make the peripheral pulse audible. The Vasophon proved to be a useful piece of auxilliary apparatus for monitoring cardiac activity in pacemaker patients and the basic unit was used in three forms:

- merely as Vasophon;
- in combination with the Cardiotest in the Autocardiotest;
- in combination with an alarm circuit in the Vasoalarm.

The Vasophon is used for continuous monitoring of the peripheral pulse and is particularly effective during operations.

C. Autocardiotest

By using the Vasophon in combination with the Cardiotest an objective

and accurate determination of the threshold values in an electrode circuit is possible. Synchronization of the electrical impulses of the Cardiotest with those of the Vasophon is an indication that the Cardiotest is effectively stimulating the heart through the electrode circuit. The stimulation threshold is reached when the voltage of the Cardiotest is slowly reduced to the point where the synchronization of the Cardiotest impulses and the Vasophon pulses suddenly disappears, indicating that the impulses no longer produce heart contractions. The Vasophon then reacts to the idio-ventricular rhythm, which is not synchronous with the rhythm of the Cardiotest.

With the Autocardiotest (1965) the threshold values of the electrode circuit can be determined automatically. The Autocardiotest consists of a Cardiotest, a coincidence circuit and a pulse detection unit, from which electrical signals corresponding to the pulses are transmitted into the coincidence circuit (fig. V-6).

The Cardiotest in this apparatus gives block pulses with a set frequency (90/min.) and impulse duration (2 msec), and differs from the one described above in that the voltage of the output circuit is adjustable from 0-10 volt by means of a potentiometer operated by a motor. This motor has two stages, by which the output voltage can be increased or decreased at a rate of 0.15 volt/sec. In a third stage, the operational position, the motor is coupled to the coincidence circuit and the output voltage then changes at a rate of 0.08 volt/sec. The direction of rotation of the motor, and with it the increase or decrease of the voltage, is dependent on the polarity of the output signal of the coincidence circuit. Between each of the three stages there is a neutral position in which the motor is disengaged, thus fixing the voltage at the value concerned. The voltage across and the charge through the electrode circuit can be read on corresponding meters, and each impulse from the Cardiotest is indicated by a flashing light.

Stimulation can be carried out with the Autocardiotest by setting the voltage at a predetermined value with the motor in a neutral position, and feeding the impulses into the electrode circuit. If the heart is following these impulses, each flash of the Cardiotest lamp is followed by a deflection of the pointer on the pulse detection unit (Vasophon).

There is a certain time delay between the Cardiotest impulse and the reaction of the Vasophon, as the peripheral pulse travels at a limited speed, but this time delay is compensated so that the Vasophon signals and the Cardiotest impulses both enter the coincidence circuit simultaneously. The Cardiotest impulses to the coincidence circuit can be delayed

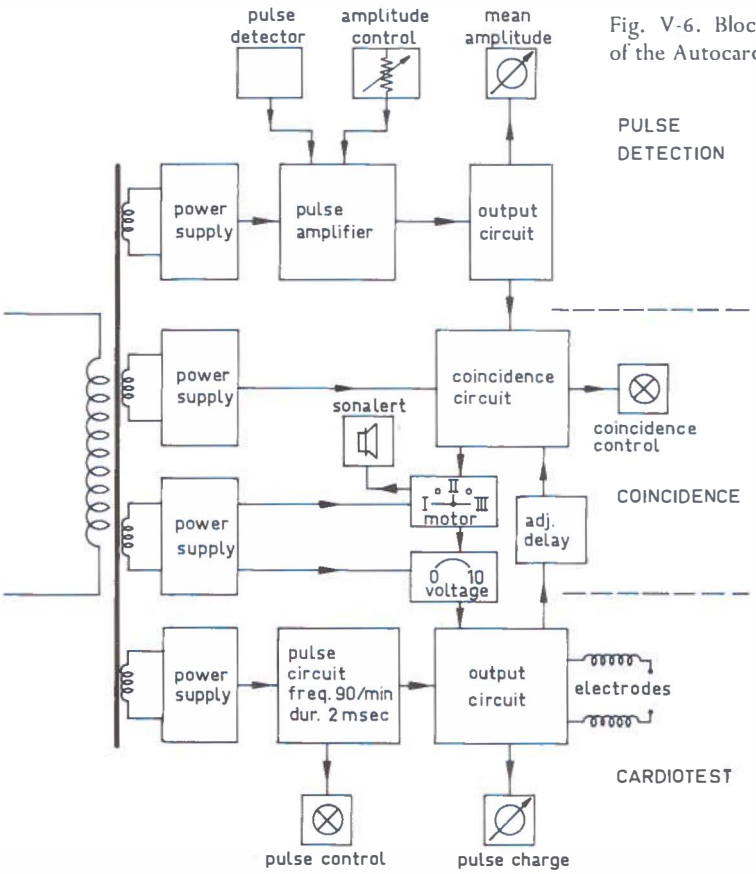


Fig. V-6. Block-diagram of the Autocardiotest.

(70-400 msec.) and coincidence is obtained by adjusting this delay so that Vasophon signal and Cardiotest impulse both reach the coincidence circuit at the same time. This coincidence can be checked by a lamp which increases in brightness as coincidence improves. Because slight variations may occur in the transit time of the peripheral pulse, the Cardiotest signal is transformed into an impulse with a duration of 100 msec. In this way coincidence is maintained even if the Vasophon signal is separated by 50 msec. from the Cardiotest impulse.

When coincidence has been optimally adjusted by means of the delay circuit, the threshold current can be determined automatically and for this the motor is switched to the working position (Position II). The motor is now controlled by the coincidence circuit, the voltage of the Cardiotest is automatically reduced as long as coincidence occurs, but

the motor immediately starts to counter-rotate when coincidence disappears because the stimulus has dropped below the threshold value. An acoustic alarm (Sonalert) is then automatically switched on to warn the operator that the threshold was reached and the Cardiotest voltage increases again. The voltage is then increased until the threshold voltage is exceeded in the other direction and coincidence re-occurs. As soon as this happens, the polarity of the signal of the coincidence circuit reverses once more, resulting in a reduction of the voltage of the Cardiotest, and the cycle repeats itself. Due to this circuit, the voltage of the Cardiotest automatically remains fluctuating around one value, which is the threshold value of the electrode circuit. The threshold voltage and threshold charge can be read from their meters on the panel of the Cardiotest. Once these thresholds values have been determined the voltage is increased to a suitable value by setting the motor in the correct position and blocking it when a reasonable safety margin has been reached.

The advantage of this method is that the threshold value is determined completely objectively. The frequency of the Cardiotest was set at 90 impulses per minute to enable the threshold measurements to be made even if sinus rhythm has returned, while the voltage is adjustable to a maximum of 10 volt to enable measurements despite an increased threshold.

D. Vasoalarm

The Vasoalarm (1963) is used for continuous monitoring of the peripheral pulse and gives an alarm signal in case of extreme bradycardia or cardiac arrest. The Vasoalarm consists of a Vasophon and an alarm circuit (fig. V-7). The Vasophon is identical to the unit described before, allows visual and acoustic pulse monitoring, and is equiped with an amplitude control.

A signal passes from the Vasophon circuit to the blocking circuit of the alarm. Simultaneously, this blocking circuit receives a signal from an adjustable circuit which determines the time delay of the alarm. This delay can be set from 1-12 seconds.

The alarm circuit is constructed in such a way that a signal from the Vasophon blocks the alarm for the preset time. When a Vasophon impulse has blocked the alarm circuit in this way an alarm will follow after the preset time, unless a new Vasophon pulse is received within this time, once more blocking the alarm. On the other hand, if no new

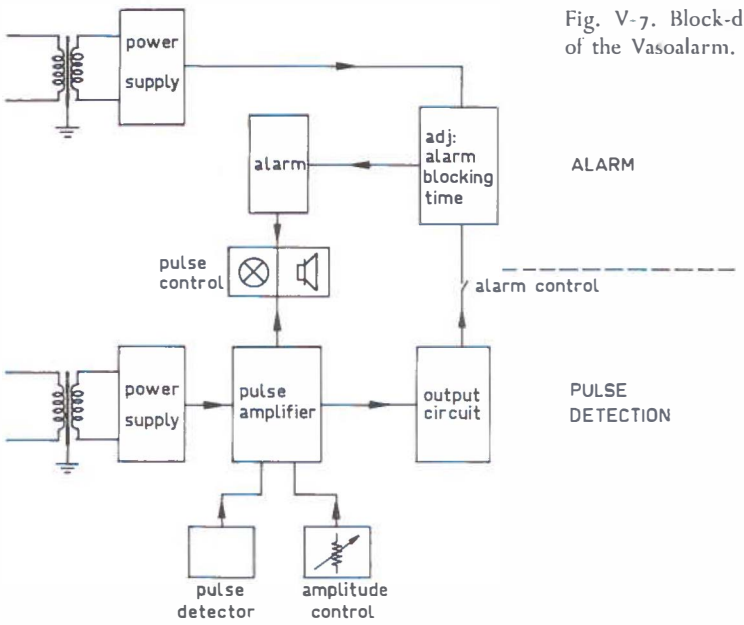


Fig. V-7. Block-diagram of the Vasoalarm.

Vasophon pulse is received within the preset alarm time, i.e. if there has been no new heart contraction within this time, the alarm circuit is no longer blocked. This results in a signal to the loudspeaker and lamp of the Vasophon, which thereupon gives a continuous alarm signal. The acoustic alarm signal can be switched off manually and the alarm stops automatically as soon as a heart contraction re-occurs. The Vaso-alarm is of especial importance for monitoring patients with cardiac arrhythmia, in particular patients with an unreliable implanted or external pacemaker, because the circuit is independent of the artefacts of the electrical stimulation.

To enable checking of the alarm time and the alarm circuit, the connection between the Vasophon and the alarm circuit can be interrupted by pressing a button. When this is done the alarm circuit receives no blocking impulses from the Vasophone and an alarm signal should result. Other alarm systems, besides those of the Vasophon can be connected to the alarm circuit by means of a special output.

E. Monitor

The pocket size Monitor (1962) has been used by us for simple inspection of certain pacemakers before we developed the photo-analysis method

described in Chapter IX. The inspection can be carried out both in the case of an external and of an implanted pacemaker without any contact between Monitor and pacemaker.

In order to make this inspection possible, a transmission coil was built into the output circuit of certain of our first pacemakers. The Monitor contains a tuned receiving coil, an amplifier and a sound circuit. The energy for these circuits is obtained from an ordinary battery, which is simple to replace.

By holding the Monitor with the receiving coil close to the transmitter coil of the pacemaker, the pacemaker impulses induce electrical impulses in the Monitor, which are made audible by means of the amplifier and sound circuit. The power of the induced impulse depends on

a. the distance between the two coils;
b. the current in the primary coil.

In order to activate the sound circuit of the Monitor, a certain induced voltage is necessary. The current in the primary coil being constant, i.e. determined by the pacemaker and electrode circuit, the Monitor will produce signals if the distance between the coils remains within certain limits. If the Monitor is moved further than this limit from the primary coil in the pacemaker, the induced voltage is too weak to cause sound signals. By increasing the current in the primary coil a greater voltage is induced at the same distance and the Monitor will resume giving signals. In our voltage pacemaker the output circuit is increased by a decrease of the load of the pacemaker. Thus there is a relation between the maximum distance between Monitor and pacemaker at which the Monitor will still give signals, and the load of the pacemaker.

Using the Monitor in combination with certain pacemakers it is thus possible:

1. to check the frequency of the pacemaker;
2. to examine simply and rapidly, by comparing the pacemaker impulses and the peripheral pulses, whether the pacemaker impulses are able to induce heart contractions;
3. to obtain a rough impression of the variations in the resistance in the electrode circuit.

Here it should be born in mind that after about 2-3 years of implantation the pacemaker impulses and therefore the voltage induced in the Monitor may decrease as the batteries become exhausted.

Consequently, the Monitor is suitable for rapid inspection and use in

clinical care of patients, but because photo-analysis proved a more reliable technique the Monitor was not used after 1966.

The results of the animal research, together with clinical experience, are discussed in the three following chapters, where the electrodes, impulse transmission and stimulation units will be dealt with.

Electrodes

CHAPTER VI

The transmission of the electrical impulse to the heart tissue plays an important role in electrical stimulation of the heart. This transmission requires contact between the lead from the stimulator or secondary coil and the tissues. The extremity of the conducting lead which makes the actual contact forms the electrode proper, and is contained in a specially insulated end of the conduction lead, the electrode-frame.

From investigations carried out with laboratory animals and later clinically, we attempted to develop a stimulation system with optimal electrodes. In this chapter this development will be discussed together with some important aspects of electrical stimulation of the heart.

I. ELECTRICAL STIMULATION OF THE HEART

A. Electrical excitability of the heart

As was described briefly in Chapter III by the end of the eighteenth century GALVANI had discovered already that it was possible to activate the heart muscle by electrical stimuli. Later investigation showed that the stimulus must exceed a certain threshold value, defined as the minimum stimulus required to cause the specific heart reaction to an electrical impulse, i.e. a contraction. If this threshold value is exceeded, the reaction of the heart muscle to all stimuli is equal as was noted by BOWDITCH in 1871. This phenomenon is described as the 'all or nothing' law. The threshold value is an important parameter in the development of heart electrodes.

Insight into the mechanism of the heart reaction to electrical stimulation became possible by the development of extremely small glass electrodes with a diameter of 1 micron, which enabled intracellular

measurements to be made. It was found that the transmembrane potential of the heart cells at rest is 85-95 mV, the interior of the cell membrane being negative in relation to the exterior. JENNERICH and GERARD (1953) and HOFFMAN and CRANEFIELD (1960) showed that the heart contracts as soon as the transmembrane potential has fallen to a critical value, the threshold potential. The threshold stimulus is the stimulus which is just capable of reducing the transmembrane potential to the threshold value.

Investigations by BROOKS *et al.* (1955), VAN DAM *et al.* (1956) and HOFFMAN and CRANEFIELD (1960) showed that the threshold values of the heart muscle cells are not constant, but vary during the heart cycle. In electrical stimulation with a negative electrode, four periods in the cycle of an individual cell are distinguished (fig. VI-1).

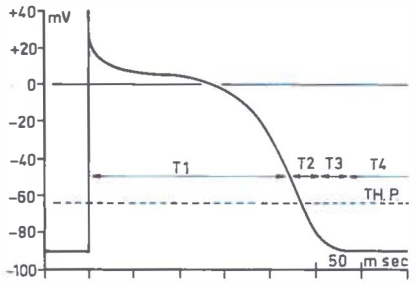


Fig. VI-1. Relationship between transmembrane-potential of a ventricular fibre after stimulation and cathodal excitability.
TH.P.: Threshold potential.
T_1: Absolute refractory period.
T_2: Relative refractory period.
T_3: Supernormal period.
T_4: Complete repolarization, normal excitability.

a. Absolute refractory period

During this period (T_1) the first part of the repolarization phase of the cell, it is impossible to initiate a specific heart action with electrical stimuli. DRURY and LOVE (1926) and LEWIS and DRURY (1926) showed, however, that a stimulus in this period may result in a prolonged refractory period, so that the stimulus nevertheless does have a certain effect. Therefore, it would be better to employ the term 'effective refractory period' (HOFFMAN and CRANEFIELD 1960). The period ends as soon as it becomes possible once more to excite specific reactions of the heart muscle cells with electrical stimuli, at which point the second period begins.

b. Relative refractory period

During this period (T_2) the specific heart muscle reactions can only be

excited by strong stimuli, although the latency period (i.e. the time between stimulus and reaction) is long. This period ends when the latency period becomes equal to the latency period of period-T_4, the period of complete repolarization.

c. Supernormal period

For a short time (T_3) at the end of the relative refractory period the stimulation threshold is lower than during period T_4. This period with low stimulation threshold is called the supernormal period. It should not be confused with the vulnerable phase, which is mentioned in the section on the R-wave pacemaker.

d. Period of complete repolarization

This period (T_4) commences at the end of the supernormal period, when both the threshold values and the values for the latency period have reached a constant and low level. The transmembrane potential is 85-95 mV during this period of diastole.

The stimulation threshold of a heart muscle cell is thus determined by the threshold potential and the transmembrane potential; the latter depending on the four above-mentioned periods.

It should be noted that among others these factors in particular are influenced by temperature, pH, electrolytes and drugs.

B. Methodology of the research into the excitability of the heart

In patients with an atrio-ventricular block, the ventricular cycle is no longer regulated by the S-A node, so that a slow heart rhythm results. This results a.o. in the fact that period T_4, the diastole, is of longer duration for ventricular cells than for nodal tissue. If pacemaker stimulation is applied to the heart of such a patient and the heart follows the stimuli, each subsequent stimulus falls in the diastole of the artificial heart cycle, the period with the low constant threshold value. The period between two pacemaker pulses is much longer than the total period required for repolarization ($T_1 + T_2 + T_3$). The natural ventricular cycle is completely suppressed by the pacemaker cycle, since the pacemaker frequency is much higher than that of the idio-ventricular frequency, so that the pacemaker stimuli continually interrupt the idio-ventricular pacemaker cycle.

To investigate the heart under identical condition in animal experiments, ensuring that all the pacemaker impulses fall in the same period of the heart cycle, the diastole, the present research on electrodes was carried out only in hearts in which heart-block had first been created as described in the previous chapter. The laboratory animals on which the measurements were made had a pre-operative heart frequency of 70-100 beats/min. at rest, but after ligation of the bundle of His, an idio-ventricular rhythm varying from 16 to 66 beats/min., with an average of 46 beats/min appeared. For threshold measurements the hearts were usually stimulated at a frequency of 70 impulses/min. with an impulse duration of 2 msec.

No threshold measurements were performed in hearts with an intact conduction system, although this has been reported by others (WEALE *et al.* 1960, DAVIES 1965, MANSFIELD 1965). In this situation interference can occur between the pacemaker impulses and the natural sinus pulses whenever the pacemaker frequency does not sufficiently exceed the spontaneous frequency. The heart is then stimulated by the pacemaker impulses during varying periods of the heart cycle, which reduces the accuracy of the threshold measurements.

For monitoring the threshold values of the stimuli an E.C.G. is essential, particularly if the natural frequency and the pacemaker frequency are practically identical. If the pacemaker stimuli control the heart activity completely because the natural rate is low, monitoring of the threshold values may also be performed by means of the peripheral pulse from the femoral or carotid arteries. As long as the heart is still following the stimuli, i.e. as long as the stimuli are still above the threshold value, each stimulus will be followed by a heart contraction. This contraction can be registered after the delay time taken by the pulse wave to reach the peripheral monitoring point. Since this delay time of the pulse wave is approximately 100-200 msec, and it takes approximately 860 msec. at a frequency of 70 beats/min. before a new impulse is transmitted, every stimulus can directly be monitored by means of the peripheral pulse.

If the stimuli drop below the threshold value, the heart will no longer follow the stimuli and the heart frequency will drop to the low idio-ventricular rhythm or possibly even stop altogether. This point can be accurately determined and indicates the threshold value of the stimulus.

Monitoring the peripheral pulse can be performed with the Vasotest, which is included in the Autocardiotest (see preceding chapter), or it can be performed by subjective monitoring. A high degree of objectivity

may be reached when two operators perform the monitoring, one operating the stimulator and the other monitoring the peripheral pulse.

C. *i-t* curve

The excitability of the heart is well displayed by determining the strength-duration (*i-t*) curve, which necessitates measuring the stimulation threshold for varying impulse durations. For these measurements we used a stimulator providing stimuli of constant current. The current strength was adjustable to the nearest 0.05 mA and the impulse duration was continuously adjustable for 0-10 msec, with an accuracy of 1%. The high degree of accuracy of this stimulator was achieved by using digital counters.

In a dog two intramural loop electrodes were attached to the left and right ventricle respectively, and two indifferent, long suture electrodes in the muscles near the thorax-incision (fourth right i.c.s.). Subsequently the stimulation threshold of each electrode combination was determined for rectangular impulses of 0.1-10 msec. In fig. VI-2 the *i-t* curve is

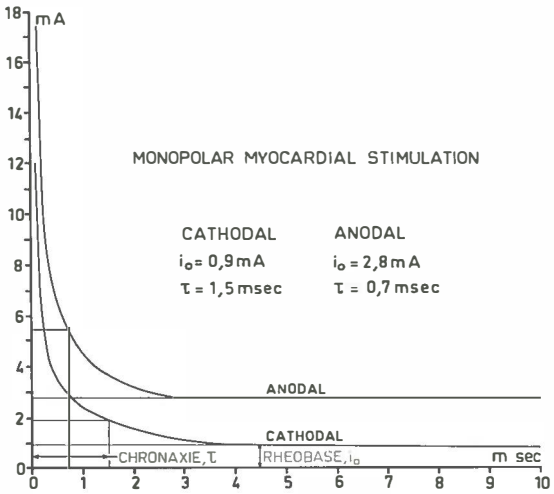


Fig. VI-2. Relation between threshold current and impulse duration at monopolar stimulation by an intramural loopelectrode in a dog. (Acute experiment).

shown for a loop electrode in the left ventricle and an indifferent suture electrode. The shape of this curve is identical to that of the loop electrode in the right ventricle, with the same indifferent electrode as is shown by table VI-1.

From the *i-t* curve it appears that with an increasing impulse duration the curve ultimately approaches a certain minimum current strength,

the rheobase, whereas for short impulse durations the current strength in excess of the rheobase is roughly inversely proportional to the duration of the impulses. The rheobase of the heart may be defined as the minimal current required to excite a specific reaction of the heart muscle at an infinitely long impulse duration. The rheobase is determined not only by the excitability of the heart, but also depends on the polarity, the size of the electrode and the time elapsed after implantation of the electrode in the heart. LAPIQUE and FREDERIQUE introduced the term 'chronaxie' to indicate the impulse duration required to excite a specific reaction at a current strength equal to twice the rheobase. The chronaxie was found to be practically independent of the size of the electrodes, but to depend on their polarity. If the polarity does not alter, the excitability is determined by the rheobase and the chronaxie. These values may be used to express the excitability of the heart in the following formula:

$$i_t = i_0 \left(1 + \frac{\tau}{t}\right),$$

i_0 = rheobase,

τ = chronaxie,

t = impulse duration and

i_t = threshold current at impulse duration t.

The i-t curve is also called the chronaxie-rheobase curve. This term however has found little acceptance for characterising the excitability of the heart. The rheobase and chronaxie are illustrated in fig. VI-2.

In determining the stimulation threshold it was found that the values differed according to whether a high output voltage was reduced to the threshold or a low output voltage was increased to the threshold voltage. The latter method produced somewhat higher values than the former. To eliminate this effect, we always determined the threshold by reducing the high voltage to the threshold voltage; the initial voltage was usually the operational voltage of a standard pacemaker. At the same time this method has the advantage that stimulation is only interrupted for a short period during measurement, when the threshold value is actually reached. As soon as the stimulation was interrupted we immediately increased the output voltage above the threshold voltage. Our interest was directed in the first place to determination of the most favourable stimulation combination; the polarity, the electrode combination and the location of the electrodes on the heart were investigated.

II. POLARITY AND LOCATION OF THE ELECTRODE, MONOPOLAR AND BIPOLAR STIMULATION

A. Polarity of the electrodes

If monopolar stimulation is applied to the heart (i.e. one electrode is placed on or in the heart and a second electrode elsewhere in the body) the question immediately rises what polarity this heart electrode should have as it may be included in the circuit either as anode, i.e. positive electrode (anodal stimulation), or as cathode, i.e. negative electrode (cathodal stimulation).

To gain an insight into the character of the difference between anodal or cathodal stimulation, the *i-t* curves for both types of stimulation were determined in an animal with two intramural loop electrodes and two indifferent suture electrodes. In fig. VI-2, the anodal and cathodal *i-t* curves are shown, and figures are given in table VI-1. The measurements show that in monopolar stimulation with intramural electrodes:

- the current threshold is (naturally) determined by the heart electrode for both anodal and cathodal stimulation.
- the cathodal current threshold is lower than the anodal current threshold.
- the *i-t* curve, both in anodal and cathodal stimulation, is independent of the indifferent electrode.

These conclusions were confirmed by the results of acute endocardial stimulation with a catheter electrode and a number of indifferent suture electrodes (fig. VI-3), and by the results of long term experiments, during which the threshold values were measured with the Cardiotest for block pulses with a duration of 2 msec. for a postoperative period of 8 weeks (fig. VI-4). Besides the threshold charge (mean current × impulse duration) the threshold voltage was measured. It appears that the cathodal threshold voltage is also lower than the anodal threshold voltage.

Incidental measurements in patients confirmed these observations, which corresponded to those of many other investigators in laboratory animals (WEIRICH *et al.* 1958; BROCKMAN *et al.* 1958) and in patients (CLARCK *et al.* 1959; DAVIES and SOWTON 1964).

A slightly different observation was made by FURMAN and SCHWEDEL (1959), who found in one patient a threshold current of 0.75 mA for cathodal endocardial stimulation and 1.5 mA for anodal stimulation which corresponds with our findings. The threshold voltage for both

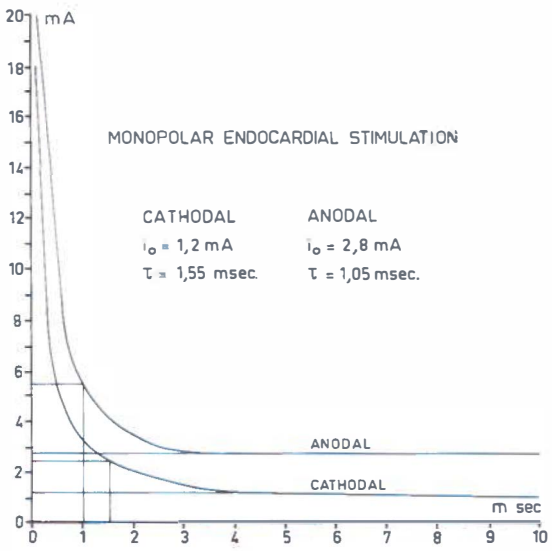


Fig. VI-3. Relation between threshold current and impulseduration at monopolar stimulation by a catheter electrode in a dog. (Acute experiment).

measurements, however, was 1.5 volts. Probably this was due to an altered position or a changed indifferent electrode. This matter will be discussed further in the course of this chapter.

An exception to our observations, not met elsewhere, are the measurements of DEKKER, BULLER and VAN ERVEN (1966). They tested 39 electrode combinations, with epicardial heart electrodes, in 11 patients; in 10 measurements the threshold values for the current proved to be identical for anodal and cathodal stimulation; in 6 combinations the anodal threshold proved to be lower than the cathodal threshold. Only 3 of the exceptions mentioned do not fall within the accuracy limit ($\pm$ 1 mA) given by the authors. As it is not clearly described whether the threshold values are determined by raising or lowering the output voltage, it is possible that an inaccuracy in the measurements may have occurred. In spite of these exceptions, these authors also conclude that cathodal stimulation has lower threshold values than anodal stimulation.

An explanation of the difference between anodal and cathodal stimulation may be given if we look at the polarity of a heart muscle cell. This cell has a transmembrane resting potential of approximately 85-95 mV in the diastole, period T_4, the voltage on the intracellular side of the membrane being negative with respect to the extracellular side. To cause this cell to contract the cell membrane has to depolarize until the

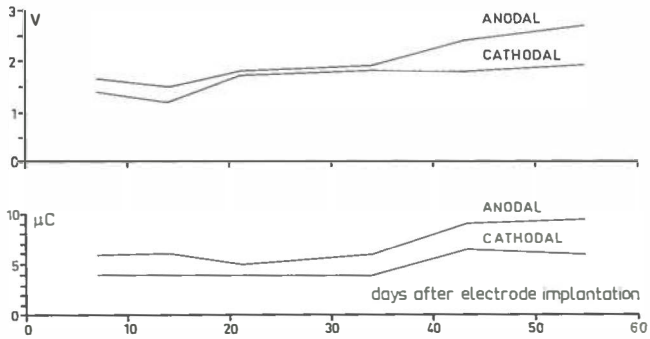


Fig. VI-4. Anodal and cathodal threshold voltage and threshold charge as a function of the days after electrode implantation. Monopolar myocardial stimulation with an intramural suture electrode and an indifferent suture electrode in the thoracic wall.

threshold voltage is reached. If the heart electrode is used as cathode, the transmembrane potential gradually decreases during the impulse. With a supraliminal stimulus the cell reacts as soon as the transmembrane voltage drops beyond the threshold value, resulting in a total depolarization of the cell.

If, however, we use the anode as heart electrode the stimulus will result in an increase of the transmembrane voltage, as the extracellular environment becomes more positive in relation to the intracellular environment. The cell membrane is thus hyperpolarized during the impulse. Stimulation nevertheless results in contraction of the heart due to a break excitation at the end of the impulse as the voltage drops again (CRANEFIELD, HOFFMAN and SIEBENS 1957). The hyperpolarized cell then depolarizes, producing an excitation. This comparatively secondary effect of break excitation is the explanation of the fact that anodal stimulation yields higher threshold values than cathodal stimulation. For clinical application this means that in monopolar stimulation the heart electrode should be negative for optimal stimulation.

B. Monopolar versus bipolar stimulation

Monopolar stimulation requires only one (negative) heart electrode. One might wonder whether bipolar stimulation, (i.e. stimulation with both electrodes on the heart) would yield lower threshold values.

To study this problem two ventricular electrodes and one or more indifferent electrodes elsewhere in the body were placed in dogs and the threshold values of these combinations were examined.

TABLE VI-1. *Monopolar versus bipolar myocardial stimulation. Acute experiments in a dog.* M_1: *intramural electrode in left ventricle;* M_2: *intramural electrode in right ventricle;* I_1: *indifferent electrode near sternum 4th i.c.s.;* I_2: *indifferent electrode near vertebra 4th i.c.s. First electrode of each combination is negative.*

Impulse-duration in msec.	Mean threshold current in mA					
	Monopolar		Bipolar		Monopolar	
	M_1-I_1	M_1-I_2	M_1-M_2	M_2-M_1	M_2-I_1	M_2-I_2
0,1	12,15	12,00	12,00	10,80	11,00	11,00
0,2	6,50	6,50	6,50	5,90	5,90	5,90
0,4	4,10	4,10	4,10	3,50	3,50	3,50
0,6	3,50	3,50	3,50	2,55	2,70	2,55
0,8	2,90	2,90	2,80	2,10	2,10	2,10
1,0	2,30	2,25	2,30	1,75	1,80	1,80
2	1,45	1,50	1,50	1,15	1,20	1,20
3	1,15	1,20	1,20	0,95	1,00	0,95
4	1,00	1,00	1,00	0,80	0,80	0,80
5	0,90	0,90	0,90	0,75	0,70	0,75
6	0,90	0,85	0,90	0,75	0,70	0,75
8	0,90	0,85	0,90	0,70	0,65	0,70
10	0,90	0,85	0,90	0,70	0,65	0,70

Analysis of the *i-t* curves for the two intramural loop electrodes, in combination with each other and in combination with each one of the two indifferent suture electrodes (table VI-1), showed within the accuracy limits that:

- the threshold value for the current, at a given polarity of the heart electrode under investigation, is independent of the type and the location of the other electrode.
  (the threshold value for the voltage however does depend on the sort and the location of the other electrode).

In other words, the threshold values for the current are the same in monopolar and bipolar stimulation, if the heart electrode used for monopolar stimulation does have the same polarity in bipolar stimulation.

Bipolar stimulation was first applied clinically on the 4th April 1959 by HUNTHER, ROTH, BERNADEZ and NOBLE.

The same conclusion holds for stimulation with a bipolar catheter electrode if in both cases the catheter tip was used as cathode. Monopolar stimulation with the catheter tip as anode gave higher threshold values (table VI-2).

TABLE VI-2. *Monopolar versus bipolar endocardial stimulation.*
Acute experiments in a dog, with a bipolar catheter electrode and an indifferent suture electrode.

Impulse-duration in msec.	Mean threshold current in mA.		
	Monopolar		Bipolar
	Anodal	Cathodal	
0,1	20,00	18,00	18,00
0,2	16,40	12,50	12,50
0,4	12,80	6,15	6,30
0,6	8,60	4,80	5,00
0,8	6,30	3,90	4,00
1,0	5,40	3,10	3,20
2	3,70	2,05	2,05
3	2,75	1,50	1,50
4	2,75	1,25	1,25
6	2,75	1,20	1,25
8	2,75	1,20	1,20
10	2,75	1,20	1,20

We also investigated the threshold values of monopolar and bipolar stimulation in a long term experiment, measuring the threshold charge and the threshold voltage in six electrode combinations, by means of the Cardiotest. These combinations were formed by two intramural loop electrodes in the left and right ventricle respectively (L_1 and L_2), one intramural suture electrode in the right ventricle (S) and an indifferent suture electrode (I), attached near the sternum close to the 4th right i.c.s. in the thoracic wall. A survey of the values measured during a period of four weeks is given in figure VI-5. These data also show that the threshold value for the charge, within the accuracy limits, is the same for a given heart electrode in monopolar stimulation as in bipolar stimulation, if the same heart electrode is used as cathode in both cases.

Although the threshold voltage also seems to be nearly independent of the choice of the second electrode, differences nevertheless can be observed. In the diagram, a clear difference is perceptible between the threshold voltages of the L_1 electrode combinations. In particular the combination where L_2 serves as second electrode shows a clear deviation in relation to the other two combinations with the L_1 electrode.

These differences in threshold voltage are also seen clearly in other combinations, and in table VI-3 a survey of a number of such combina-

tions is given. In 4 animals two heart electrodes and an indifferent suture electrode (I), were introduced, in each case the indifferent being in the 4th i.c.s. near the sternum, in the right thoracic wall. The heart electrodes were intramural, epicardial and endocardial. For a block pulse of 2 msec, the threshold values for the voltage and the charge were determined for each combination. For each heart electrode an electrode circuit was made using as second electrode the indifferent electrode or the other heart electrode. In addition to the threshold values the average of the operational value was also determined.

Table VI-3 shows also that the thresholds for the current (charge) with a certain negative electrode has identical values in bipolar and monopolar

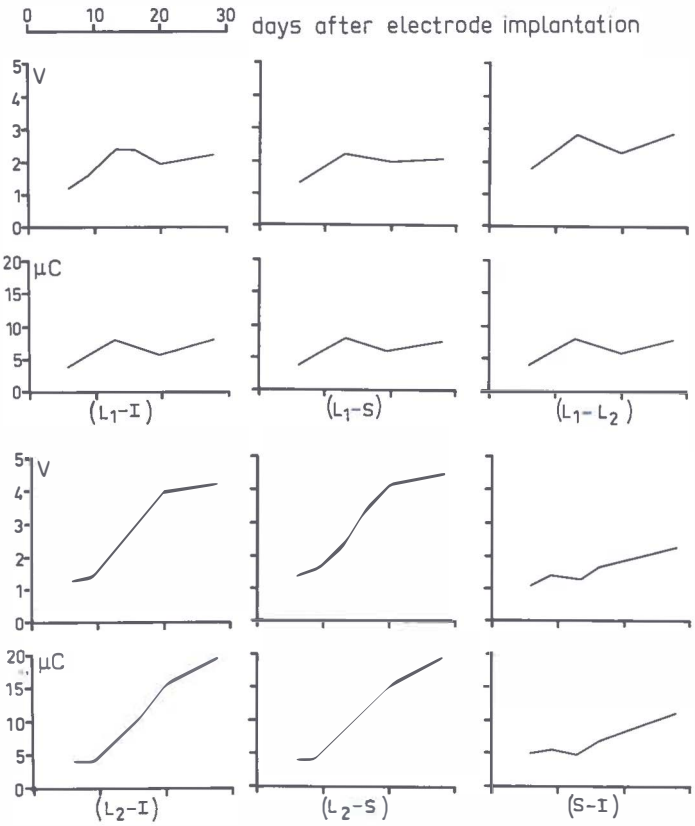


Fig. VI-5. Monopolar versus bipolar myocardial stimulation. Longterm experiments in a dog. Threshold voltage and threshold charge versus days after electrode implantation. L_1: loop, left ventricle; L_2: loop, right ventricle; S: suture, right ventricle; I: indifferent suture, thoracic wall. First electrode of each combination (..–..) is negative.

TABLE VI-3. *Monopolar versus bipolar stimulation. Semi acute experiments in 4 dogs. In each dog 2 heart electrodes and 1 indifferent electrode (I.) were implanted. Threshold voltage, threshold charge and operational charge (at 6,5 V) were measured for the various electrode combinations.*

Heart electrodes	Electrode-combination and polarity — - +	Threshold		Operational charge
		Voltage V	Charge μC	μC
I. Epicardial disk electrode,	E.D. -I.	0,8	2,5	28
E.D.	E.D. -M.C.	1	2	18,5
Myocardial coil electrode	M.C. -E.D.	0,55	1	21
M.C.	M.C. -I.	0,5	1	23
II. Epicardial helical loop	E.L. -I.	0,75	2,25	24,5
electrode, E.L.	E.L. -M.L.	1,1	2,5	19,5
Myocardial loop electrode	M.L. -E.L.	0,65	1,5	18,5
M.L.	M.L. -I.	0,7	1,5	19
III. Myocardial pin electrode,	M.P. -I.	0,75	2	12
M.P.	M.P. -E.C.	0,7	2	24
Endocardial catheter elec-	E.C. -M.P.	0,85	2,5	24,5
trode, E.C.	E.C. -I.	0,75	2	27
IV. Myocardial loop electrode,	$M.L._1$-I.	0,9	2	26,5
$M.L._1$	$M.L._1$-$M.L._2$	1	2	21,5
Myocardial loop electrode,	$M.L._2$-$M.L._1$	1,8	4	22
$M.L._2$	$M.L._2$-I.	1,4	4	31,5

stimulation. The threshold values for the voltage of any given negative heart electrode on the other hand were not found to be the same for monopolar and bipolar stimulation. The same holds for the operational charge.

It appears from the preceding data, that the threshold for bipolar stimulation determined as current or charge always corresponds with the threshold for monopolar stimulation with the same negative heart electrode and the threshold is determined by the cathodal threshold of the negative electrode. Under certain circumstances, however, the anodal threshold of the positive heart electrode may have a lower value than the cathodal threshold of the negative heart electrode. This phenomenon occurs if the positive electrode is relatively small in relation to the negative electrode, or when an extreme rise in threshold occurs at the negative electrode as a result of changes such as an inflammatory process (see fig. VI-6 electrode combination L_1-L_2). In such cases the current threshold for bipolar stimulation is determined by the anodal threshold of the positive heart electrode. In these cases there is no

TABLE VI-4. *Threshold voltage and charge and operational charge for 4 electrode combinations in a patient.*

$C_{1,2}$: identical intramural coil electrodes; I: indifferent disk electrode. High threshold of C_1 presumably caused by local inflammatory process. With bipolar C_1-C_2 stimulation threshold presumably determined by anodal threshold of C_2, see fig. VI-6. Circuit resistance not affected by tissue reaction around C_1, as shown by operational charge values.

Heart electrodes	Electrode-combination and polarity — - +	Threshold		Operational charge
		Voltage V	Charge μC	μC
Myocardial coil electrode, C_1	C_1-I.	4,5	9	15,5
	C_1-C_2	5,5	7	10
Myocardial coil electrode, C_2	C_2-C_1	2,8	3	10
	C_2-I.	1,7	2,5	15,5

correspondence between monopolar stimulation and bipolar stimulation, if the threshold current in bipolar stimulation is compared with the threshold current in cathodal stimulation with the same negative heart electrode. There is correspondence, however, if the bipolar threshold current of the combination is compared with the anodal threshold current of the same positive heart electrode.

Identical observations were also made clinically and are reported in table VI-4, which pertains to a 55 years old woman. The measurements were made when the pacemaker had to be replaced 11 months after implantation due to a defect. The measurements were performed with

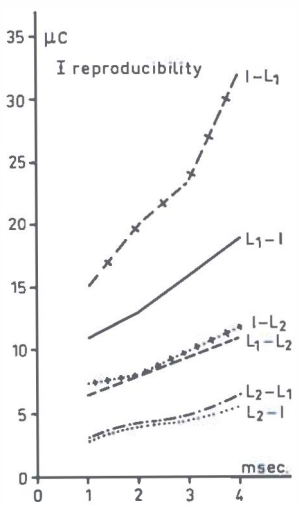


Fig. VI-6. Threshold charge versus impulse duration for 6 electrodecombinations in a dog, 1,5 month after electrode implantation.
$L_{1,2}$: identical intramural loop electrodes; I: indifferent suture electrode in the thoracic wall. First electrode of each combination is negative.
Large thresholds of L_1 were caused by inflammatory process around the electrode, with the result that the anodal threshold of L_2 was much lower than the cathodal threshold of L_1. L_2 determines threshold of bipolar stimulation, therefore, in combination L_1-L_2.

the Cardiotest, a stainless steel disc being used as indifferent electrode.

Within the accuracy limits of the Cardiotest it is clear, that with C_2 as negative electrode the threshold is determined in both cases by the cathode. With C_1 this is of course also the case in monopolar stimulation. The threshold of C_1 is however much larger than normal. In bipolar stimulation between C_1 and C_2 with C_1 as negative electrode the threshold is therefore presumably determined by the anodal threshold of the heart electrode C_2.

The threshold voltages depend on the choice of the second electrode. From the values of the operational charge it appears that the circuit resistance is not affected by the inflammatory proces around C_1.

If the published data on monopolar and bipolar stimulation are compared, it is found that there are considerable differences, resulting in different interpretations of these stimulation methods. These differences, however, may be explained by the failure of the authors to use the same electrodes and the same polarity for monopolar and bipolar stimulation or because threshold values for the voltage were the chosen parameter. Findings corresponding to ours were obtained, among others, by WEIRICH *et al.* (1958), LILLEHEI *et al.* (1960), TOOLE *et al.* (1960), ZOLL *et al.* (1961) and ANGELAKOS and TORRES (1964). DAVIES and SOWTON (1964 and 1966) reached a similar conclusion, although they measured the voltage threshold as well as the current threshold. ZUCKER *et al.* (1963), who also based their measurements on the voltage threshold, found lower values for bipolar stimulation than for monopolar stimulation. This voltage threshold however depends on the properties of the negative heart electrode and also on the nature and the location of the positive electrode as will be shown later. The difference in the dimensions of the positive electrodes used by Zucker may explain his conclusions. Since in the case investigated by Davies and Sowton there was little or no difference between the positive electrode in bipolar and monopolar stimulation, their measurements were not affected by the positive electrode. Although in both cases the conclusions on the voltage threshold for the electrode combinations used were correct, the experimental material does not allow a broader conclusion on monopolar and bipolar stimulation to be drawn.

Other and greater differences in the monopolar and bipolar current thresholds were observed by HUNTER and ROTH *et al.* (1959 and 1961), who compared monopolar stimulation with bipolar stimulation by their bipolar heart electrode, and measured average stimulation values of 17

mA and 6-7 mA respectively. It is not described in their publications, however, whether the stimulation electrodes in monopolar stimulation were identical to those used in bipolar stimulation. Different electrodes may show different thresholds. Neither do Hunter and Roth report the number of combinations used for their measurements. If they pursued a small number of combinations, a tissue reaction around one electrode may have affected the final conclusion.

A difference between both stimulation methods was also noticed by VAN ERVEN (1965). He determined the average values of 78 monopolar and 102 bipolar current thresholds for epicardial electrodes in 11 patients. The difference, 7.4 mA average for the monopolar and 5.8 mA for the bipolar, is explained by the polarity of the stimulation electrodes. In a later discussion of the same material (DEKKER, BULLER and VAN ERVEN 1966), the thresholds were arranged according to polarity and the conclusions then correspond with our own observations.

Finally the observations of CHARDACK (1960) should be discussed. His initial experience with the Hunter-Roth bipolar electrode was similar to that of the designers; in later publications (CHARDACK *et al.* 1964) he stated that bipolar stimulation yielded slightly lower threshold currents than monopolar, the differences being of the order of 10%. Although this percentage is normally within the limit of accuracy of the Cardiotest, we have not been able to observe it in measurements of the *i-t* curve carried out with the current stimulator, which has a higher degree of accuracy (see table VI-1 and 2). As Chardack did not report how his data were obtained and as no data are given, it is difficult to comment further on this information. Although doubtless some current concentration occurs between bipolar electrodes, we believe that this will not explain a difference of 10% between bipolar and monopolar stimulation. A possible explanation is that for example, the bipolar threshold may be due to the anodal threshold of the positive heart electrode in some of the measurements.

In summary it may be concluded from our experimental evidence that:

– the bipolar threshold for the current is equal to the lower of
  a. the cathodal threshold for the current of the negative electrode in monopolar stimulation and
  b. the anodal threshold for the current of the positive electrode in monopolar stimulation.
  In general, the cathodal threshold of the negative electrode is lower than the anodal threshold of the positive electrode, so that the threshold for the combination of both electrodes is determined by the negative electrode.

However, the threshold is determined by the positive electrode, when the negative electrode has a considerably larger surface area than the positive electrode, or when a considerably greater threshold rise has occurred at the negative electrode.

It may further be concluded that:

– the bipolar threshold for the voltage is not correlated with either of the monopolar thresholds for the voltage.

As to the application of the two stimulation methods, monopolar stimulation has the disadvantage that stimulation depends on only one heart electrode. Should a tissue reaction occur around this electrode, causing an excessive threshold rise, stimulation is interrupted. In a bipolar system stimulation may be maintained in such a situation by the positive electrode, provided that the anodal threshold of this electrode remains within the operational value of the pacemaker. Some investigators, however, interpret this aspect of bipolar stimulation as a disadvantage. They argue that under normal bipolar stimulation the heart is stimulated both at the negative and the positive electrode, since the applied stimulus is higher than the cathodal threshold of the negative and the anodal threshold of the positive electrode. According to CRANEFIELD, HOFFMAN and SIEBENS (1957) the ventricular fibrillation, which occasionally occurs after a stimulus in the vulnerable phase, may be caused by the stimuli at this positive electrode.

Other disadvantages of bipolar stimulation, in the form of electrolysis of the positive electrode and the risk of coagulation of blood around the positive pool of a bipolar catheter electrode will be dealt with later.

The need for both electrodes to be on the heart for bipolar stimulation inevitably increases the risk of lead fracture.

Finally it should be mentioned that during monopolar stimulation contractions of the muscles near the indifferent electrode may sometimes occur. This is due to the current impulses in the region of this electrode, which may be included in the pacemaker wall to avoid fracture. These contractions, are usually avoided by selecting a large indifferent electrode, but if they do occur they usually disappear some time postoperatively, as soon as the indifferent electrode has been encapsulated by fibrous tissue.

This is mostly not the case with contractions of the diaphragm which may be encountered in either stimulation methods, whether epicardial or intramural electrodes are being used. The cause is stimulation of the phrenic nerve and the chances of this complication are greater with

bipolar electrodes. As this phrenic stimulation can usually be observed during the actual implantation the location of the heart electrode may be altered a little or tissue may be interposed to prevent it.

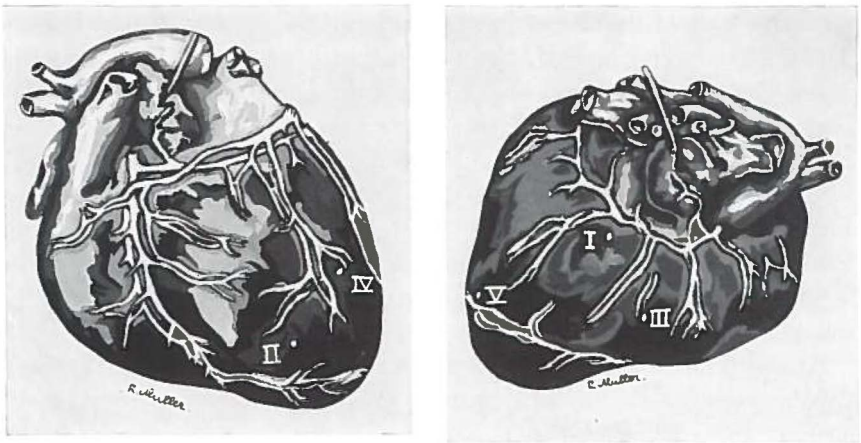
If a catheter electrode is used this type of contraction of the diaphragm does not occur at implantation, but in some cases diaphragm contractions occur shortly afterwards. These contractions are due to the catheter electrode penetrating into the ventricular wall or, in some cases, perforating the ventricular wall, allowing the catheter electrode to stimulate the diaphragm directly. In such cases re-operation is necessary.
It should also be mentioned here, that for monitoring of the implanted pacemaker with the photo analysis, monopolar stimulation entails larger detection signals and therefore easier and more accurate measurements than bipolar stimulation.

These advantages and disadvantages of monopolar (NATHAN, DAVIES *and others*) and bipolar (CHARDACK, ZOLL *and others*) stimulation are not outstanding and both methods are used clinically. For the Groningen pacemaker monopolar stimulation was chosen.

C. Location of the electrodes on the heart

It proved possible to stimulate the heart by electrodes on the atria or on the ventricles, but stimulation of the ventricles is much more efficient and offers more satisfactory attachment of the electrodes. The question whether the location of the electrodes on the ventricles affects the stimulation threshold therefore arises.

In order to investigate this aspect, we performed measurements on laboratory animals, using 3 intramural pin-electrodes of different lengths and diameters. These electrodes were inserted at five different locations on the heart, the electrode frame remaining fixed and the electrodes themselves being interchangeable. An indifferent suture electrode was inserted in the muscles near the thoracic incision. In all cases the measurements were acute, performed with the thorax open and the electrodes were inserted and their thresholds measured in the same sequence each time. The locations on the ventricle, where the measurements were carried out, are shown in table VI-5. The measurements were carried out with the current stimulator. The data show that the location of the electrodes on the ventricles has no effect on the threshold value for the current but the threshold proved to be dependent on the length and diameter i.e. surface of the heart electrodes.
WEIRICH (1958) reached a similar conclusion, finding no difference in the



Left ventricle	Right ventricle					
Electrode	Location					
	I	II	III	IV	V	Mean
PIN 1	0,3	0,3	0,3	0,4	0,3	0,32
PIN 2	0,4	0,5	0,4	0,5	0,4	0,44
PIN 3	0,5	0,5	0,6	0,5	0,6	0,55
Mean	0,40	0,43	0,43	0,47	0,43	0,43

TABLE VI-5. *Influence of electrode site and size on threshold current.*
Cathodal threshold values (mA) for (monopolar) stimulation with three pin electrodes ($P_1 < P_2 < P_3$) at five places in the left and right ventricular walls, in combination with an indifferent electrode in the thoracic wall.

effectiveness of the stimulation whether the electrodes were located in the left or right ventricular wall or in the ventricular septum. This was confirmed by LILLEHEI (1960). Neither FLETCHER *et al.* (1963), nor OLSSON (1963), who carried out an extensive investigation into the optimal location of the electrodes, were able to discover any differences related to the electrode site for either intramural bipolar or monopolar stimulation. In Olsson's study the cardiac output was the reference and although this factor was not included in the framework of our investigation, it is mentioned here because it was on this very indication that KLOTZ *et al.* (1963) indicated an optimal electrode location. According to the results of their animal experiments bipolar location of the electrodes on the anterior of the apex of the left ventricle and the

posterior base of the left ventricle results in the highest cardiac output. These data differ from those of Fletcher *et al.* and Olsson. It should be noted that the hearts on which the measurements of Klotz *et al.* were performed had undergone both an atrial incision for creation of heart block and a right ventriculotomy. Klotz found that the animals withstood these operations poorly, seldom surviving for more than three days and the authors considered a reduction in cardiac output to be one of the causes. As it was the cardiac output that was being measured as reference factor, this probably explains the variations in the results and limits the value of the conclusions.

At this point the research carried out by MEYLER *et al.* (1962) should also be mentioned. In intact canine hearts and also in a foetal heart maintained by Langendorf perfusion they noted that the activation began near the right pretrabecular area, and they concluded that for most effective stimulation the heart activation should take place from this area. The differences however did not prove to be so important as to offset the technical factors during surgery, such as the manner in which the heart is presented to the surgeon after a thoracotomy, and the local conditions of the myocardium. Fatty deposits and degeneration of the myocardium such as are caused by infarction, play an important role and may restrict the choice of electrode location. This was one of the reasons why HIRSCH (1964) advised attachment of the electrode(s) on the heart through a longitudinal inferior pericardiotomy since this technique offers a simple approach to the inferior edge of the heart, exposing 'the contact-area of Benninghoff', where the fatty deposition is slight (fig. IV-11). This also has the advantage that the area is part of the right ventricle, which is less affected by infarction. The disadvantage in this case is that the wall of the right ventricle is thinner than that of the left ventricle, and this factor must be considered if intramural electrodes are to be used. In conclusion it may be stated that:

– the threshold value for the current does not depend on the location of the heart electrode(s), provided these are fixed in the intact myocardium of the ventricles.

The independence of the threshold value for the current from electrode location applies both for monopolar and bipolar stimulation. The effect of the location of the electrode(s) on the mechanical activity of the heart and subsequent expulsion of blood from the ventricles, is only slight if any such effect exists at all.

The type of electrodes is also of importance apart from the location, and this aspect will be discussed in the following part of this chapter.

IV. MECHANICAL CHARACTERISTICS OF THE ELECTRODES AND ACCEPTANCE OF THE ELECTRODES BY THE TISSUE

The advantages and disadvantages of various electrode circuits have been discussed in Chapter III. Important factors in these electrode circuits are the electrodes themselves, their shape, and their behaviour in the heart muscle tissue. Apart from the electrical behaviour, which will be discussed in the next section, the mechanical stability and fixation of the electrode on or in the heart plays an important role.

A. Types of electrodes

The stimulation electrode can reach the heart by various paths and transmit the impulse to various heart structures. Three groups of electrodes for direct stimulation of the heart can be distinguished:

1. epicardial electrodes and

2. intramural electrodes,

according to the tissue where the electrodes stimulate the heart. These electrodes are usually implanted by means of a thoracotomy.

The third group of electrodes, the transvenous electrodes, reach the heart intravasally. This group comprises catheter electrodes, which are placed so, that the tip lies against the endocardium and these are known as

3. endocardial electrodes.

The groups of electrodes are dealt with separately.

1. Epicardial electrodes

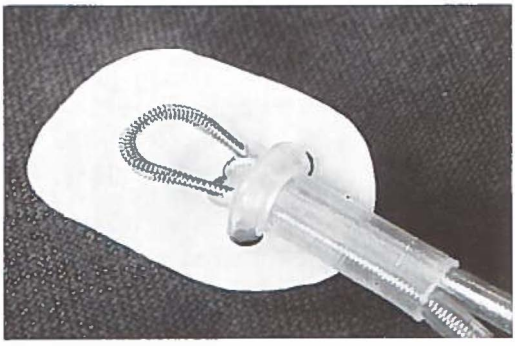
Epicardial electrodes are electrodes which contact the epicardium and whose frame is attached to the epicardium. They stimulate the heart via the epicardium.

Two forms of these electrodes are known:

a. Disc electrode. This electrode (fig. VI-7) was designed by ELMQVIST and SENNING (1960). It consists of a round platinum disc with a diameter of 9 mm, one side being insulated by epoxyresin. The total thickness of the electrode is approximately 5 mm. The electrode can be fixed on the heart with one or two sutures by means of two perforations in the disc and the insulation. Electrodes of similar design were also used by GLASS *et al.* (1963) and for the pacemaker with radio-frequency transmission described by ANAGNOSTOPOULOS *et al.* (1965).

Fig. VI-7. Epicardial electrodes.

Disc.



Helical loop.

b. Helical loop electrode. This electrode (fig. VI-7) was described among others by DAVIES (1962). The electrode is formed by a loose triple spiral of stainless steel wire with a diameter of 0.125 mm. On leaving the pacemaker, the electrode forms a loop connected by both ends to the pacemaker, the uninsulated part of the wires forming the electrode proper. The electrode proper is shielded at the side opposite the pericardium by a teflon disc and can be fixed to the pericaridium by sutures, making use of the disc and the leads.

The advantage of epicardial stimulation is that the electrodes are only subjected to small mechanical stress, sothat fracture is unlikely.

This advantage however is counteracted by a number of disadvantages:

- the electrodes are large and therefore have a high stimulation threshold (BLUESTONE *et al.* 1965; MEYNE *et al.* 1966), moreover
- the current density in the myocardium under the electrode is not optimal, since part of the current passes to the second electrode along the pericardium and not through the myocardium, whilst
- much connective tissue is formed under the electrode, due partly to friction between the electrode and the epicardium. This friction was

especially large in the early versions of the disc electrode, because the lead was connected to the electrode at an angle to the epicardium, rather than parallel with the surface of the heart. This allowed the lead to act upon the electrode as a lever, exercising mechanical forces on the myocardium.

These disadvantages are the cause of the relatively high threshold values which are often found after some time with these electrodes. In some cases the threshold rise due to tissueformation is so great that stimulation is interrupted.

Another disadvantage of epicardial electrodes is the fact that the fixation of the electrodes on the heart is poor, because it depends solely on the sutures.

A considerable number of these disadvantages are overcome by the intramural electrode.

2. *Intramural electrodes*

Intramural electrodes are inserted into the myocardium with the frame attached to the pericardium. They stimulate the heart via the myocardium.

As these electrodes transmit the current directly through the myocardium, the myocardial current density is maximal, resulting in a low stimulation threshold. The connective tissue formation around these electrodes is determined primarily by the flexibility of the electrodes.

A disadvantage of intramural electrodes is the fact that the proper electrode is inserted into the myocardium and therefore is subjected to forces arising from the local movements of the myocardium during the cardiac cycle, while the frame is attached to the epicardium and is subjected to forces from the surrounding tissue. In a heart being stimulated at a frequency of 70 beats per minute, the electrode undergoes $70 \times (60 \times 24) = 10^5$ movements per 24 hours i.e. approximately 36,5 million movements per annum. This mechanical stress can result in fracture of the electrode.

Research into the most favourable intramural electrode has led to a number of designs. This development was based on two prototypes, the suture electrode and the pin electrode.

a. Suture electrode. The intramural suture electrode is a flexible wire or a multistrand wire, which is sutured into the myocardium.

This electrode has been employed in many forms since the beginning of electrical stimulation of the heart. WEIRICH, LILLEHEI *et al.* (1958) used a suture electrode in the form of a silver plated copper wire with a diameter of approximately 0.25 mm, which was insulated with polyethylene along its course outside the myocardium. CLARK, ROSS *et al.* (1959) used a six strand fine wire of the type used in telephone equipment, each strand having a thin textile core, around which a fine tin plated copper ribbon, insulated with plastic, was wound. GLENN *et al.* (1964) used a four stranded coiled wire of elgiloy with a silastic cover.

Suture electrodes are usually made of stainless steel and have been used by BROCKMAN *et al.* (1958), KANTROWITZ (1962), ABRAMS (1964) and others. ZOLL (1964) after first using a platinum electrode, also switched to a suture electrode, consisting of 7 groups of 11 stainless steel wires, insulated by teflon and treated with a four fold layer of gold-platinum-gold-platinum respectively.

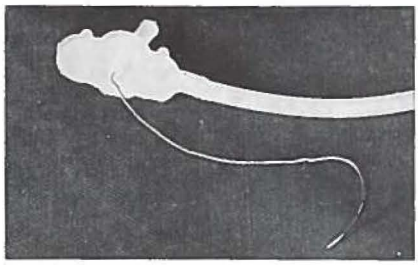
GLENN *et al.* inserted the electrodes with the help of a small tracheostomy tube, but the electrode is more usually attached at the tip to an atraumatic needle, which is cut off after insertion, whereupon the electrode is fixed with silk sutures. This method of fixation is not very reliable. In later versions therefore LILLEHEI *et al.* (1962) used stainless steel suture electrodes with a coiled tip to allow ingrowth of the tissue in order to achieve better fixation. Originally we also used suture electrodes, consisting of 7 × 7 groups stainless steel wires, protruding from an electrode frame, enabling good fixation of the electrode (fig. VI-8).

Compared with the epicardial electrode, the intramural suture electrode gives a far higher current density in the intact myocardium, while tissue formation is not particularly great, as the thin electrode is extremely supple (fig. VI-15). We did not observe any case of interrupted stimulation due to an excessive stimulation threshold. Moreover the electrode had the advantage of being easy to insert into the heart muscle.

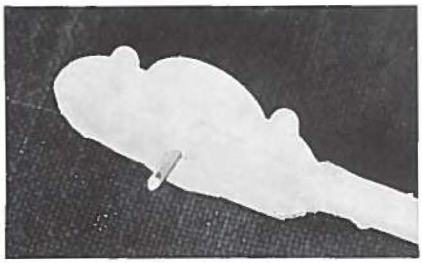
The great disadvantage associated with this electrode is the frequent occurrence of fracture. This explains the numerous versions, in which attempts were made to avoid fractures by the choice of the metal and the inclusion of several strands. In our experience it is not only the construction of this electrode that determines the occurence of fractures, but also the location of the electrode in the heart and the manner in which the electrode is fixed. Fracture can occur after as little as a few months if fixation is poor.

In Groningen 54 intramural suture electrodes were fixed in 26 patients

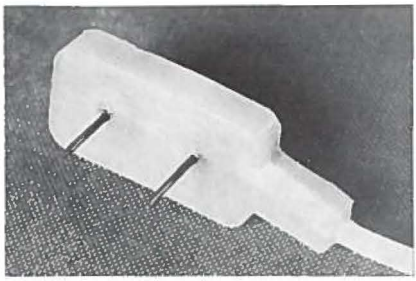
Fig. VI-8. Intramural electrodes.



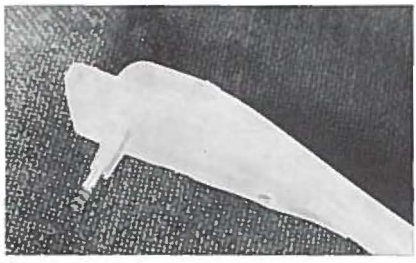
Suture



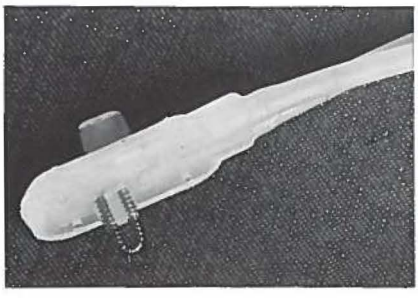
Pin



Bipolar pin



Coil



Loop

between December 1962 and August 1964, each patient receiving two suture electrodes or a suture electrode and a pin electrode. Of these suture electrodes 10 were still functioning in February 1966, the implantation period varying from 28 to 38 months, with an average of 32 months. Two years later 5 suture electrodes were still functioning after an average time of 59 months. In some cases the suture electrodes had to be removed because of infections, while in other cases further monitoring of the electrodes became impossible because the patients died of causes other than defects of the electrical stimulation. Out of the total of 25 fractures the percentages occurring in the heart muscle and in the lead cannot be accurately determined, but as the lead is of identical structure to the electrode itself, this figure gives an impression of the fragility of suture electrodes.

We had similar experiences with the intramural suture electrode, as developed by Zoll. In 10 electrodes with an average implantation period of 11 months (3-24 months), we found in February 1966 a fracture in 6 electrodes. Two years later only one electrode was still functioning after 40 months of implantation. Fractures of this electrode were not necessarily intramural either, but also occurred in the lead.

These observations show clearly that the suture electrode in its present form is not an optimal electrode for the electrical stimulation of the heart, neither in the heart, nor as indifferent electrode (see also Chapter VII: multistrand lead).

The other electrode which served as a basis for the intramural electrode is the

b. Pin electrode. The pin electrode consists of a rigid pin which is inserted into the myocardium and whose frame is attached to the epicardium.

There are several variants of the pin electrode. The bipolar electrode of HUNTER *et al.* (1959) consisted of a silicon rubber frame from which two stainless steel pin electrodes, 1.5 cm apart, penetrate the myocardium. The pins had a length of 7.5 mm in early versions (fig. VI-8), but were later altered to 15 mm long, the first 5 mm being insulated with teflon. CAMMILLI, POZZI *et al.* (1964) used a bipolar pin electrode located on the heart with their R.F. receiver, the platinum-iridium 10% electrode pins having a length of 7 mm and a diameter of 1 mm.

We have also used this type of electrode (VAN DEN BERG, HOMAN VAN DER HEIDE, NIEVEEN *et al.* 1962), in the shape of a 5 mm long platinum-iridium 10% pin with a diameter of 1 mm. In later versions the pin was extended to 7 mm (fig. VI-8), the first 2 mm being insulated.

The advantage of this electrode is the fact that it is mechanically so strong that no intramural fracture can occur. At the same time, however, this rigidity is a disadvantage, as the pin causes extensive tissue destruction and connective tissue formation in the surrounding myocardium. These tissue lesions occur especially at the tip of the electrode, and are probably caused by movements of the pin in relation to the myocardium (fig. VI-16). In the case of a bipolar pin electrode with one electrode frame, as in the other two applications of the pin electrode, these lesions may take on more serious forms. The tissue reactions result in a sharp rise of the stimulation threshold, even to the extent of interrupting stimulation altogether.

Of the 24 pin electrodes inserted in 21 patients between March 1962 and August 1963 in Groningen, 8 had to be replaced due to a rise of the stimulation threshold. The replacement took place after 10-53 months, with an average of 25 months. If the pin electrode is located in the myocardium in a place where the myocardial movements in relation to its surroundings are small, the rise in threshold is limited. Hirsch therefore inserted the pin electrode in the contact area of Benninghoff on the heart (fig. IV-11).

Like the epicardial electrode the pin electrode has the disadvantage that only its frame is fixed to the epicardium and the proper electrode does not anchor itself in the myocardium.

This poor fixation and especially the abundant tissue reactions prevent the pin electrode from being an optimal stimulation electrode. Based on the principle of the pin electrode, two intramural electrodes were designed which fix themselves in the myocardium, resulting in less tissue reaction and thus a lower and more stable threshold.

c. Coil electrode. The coil electrode consists of a semi-rigid spiral wire, which is inserted into a small stab wound in the myocardium and whose frame is attached to the epicardium.

The coil electrode was first reported by CHARDACK (1961). The proper electrode (fig. VI-8) is in fact an extension of the conduction wire, which, like the electrode itself, has been the source of many difficulties. Chardack used a spiral wire with Ø 0.25 mm and introduced its end, protruding from an electrode frame, vertically into the myocardium. This electrode, which is an intermediate form between the pin electrode and the suture electrode with the coiled tip as described by LILLEHEI *et al.* (1962), was first made of platinum-iridium. To introduce the electrode an incision is made in the myocardium to a depth corresponding to

about the length of the electrode. Then the electrode is introduced and the electrode frame is fixed to the myocardium by two sutures.

The advantages of this electrode are the fact that the myocardium can grow between the electrode coil, giving a reliable fixation, and the fact that the electrode has a certain flexibility, reducing the degree to which mechanical factors affect tissue formation. The weak point of this electrode is this very flexibility. Metal fatigue due to movement may cause the electrode to break at the transition from the frame to the myocardium. The risk of a fracture becomes greater if the electrode has been bent due to rough treatment before the implantation, or if it is not introduced perpendicularly into the myocardium at implantation. Under these circumstances a weak spot arises and may lead to fracture later.

The electrode frame is so constructed, that the electrode does not pass abruptly from the rigid into the flexible part, but in three stages: first the core ends, then the silicon rubber insulation and next the pitch of the spiral gradually increases towards the electrode tip.

The fractures which occurred in this version led CHARDACK *et al.* to use another material, elgiloy (see Chapter VII helical lead), instead of platinum-iridium 10%. Results with this material are better, as it has a higher resistance to mechanical stress. NATHAN *et al.* (1963) also adopted these electrodes, using the elgiloy version from the beginning.

Although CHARDACK *et al.* (1964) mentioned fractures of this latter electrode, in Groningen we observed no fractures in the intramural electrode, the longest implantation period in February 1968 being 49 months. The lead, however, (to be discussed in the following chapter) did pose difficulties. Moreover, in 11 of the first 35 patients the threshold value rose above the operational value of the pacemaker. The fact that the relatively small threshold increase manifested itself after an average of 10 months' stimulation (1-19 months) and increasing the operational value of the pacemaker in these 11 patients enabled the electrodes to function properly again for an average of 8 months (3-13 months), shows this to be attributable to the electrode and not to the pacemaker. These interruptions of stimulation were due to the operational value of the pacemaker being set too low initially.

The coil electrode has a low stimulation threshold due to its small dimensions and the slight tissue reactions (fig. VI-17) around the electrode. The only disadvantage of this electrode is its great vulnerability before and during the operation, while for bipolar stimulation elgiloy is not a suitable metal for the anode, in view of the risk of corrosion due to electrolysis.

We have tried to modify the pin electrode so that we could continue to use an alloy of platinum-iridium, which is optimally anti-corrosive and entails less polarization than elgiloy. The proper electrode however should be tougher than the coil electrode to make it less sensitive to careless treatment. Our investigations resulted in the

d. Loop electrode. Our loop electrode (fig. VI-8) consists of a loop shaped spiral, to be introduced into the myocardium. In the spiral is a loop shaped core, which is composed of platinum 90%-iridium 10% as is the spiral. The extremities of the loop are attached to two platinum-iridium spirals, insulated by silicone rubber, and connected to the negative pole of the pacemaker so that the heart electrode has a double connection with the pacemaker.

Fig. VI-9. Tissue growth through intramural loop electrode, 16 days after implantation in a dog.

The electrode is introduced into an incision made in the myocardium and the electrode frame is fixed to the epicardium by two sutures. The electrode becomes firmaly attached after some time, because the myocardium grows through the loop which is approximately 1.5 mm in diameter (fig. VI-9 and VI-19,20). The spiral around the core gives the tissue a good grip on the electrode. Because of this fixation no lesions are caused to the tissue around the loop electrode, and the thresholds of this electrode remain low unlike the pin electrode.

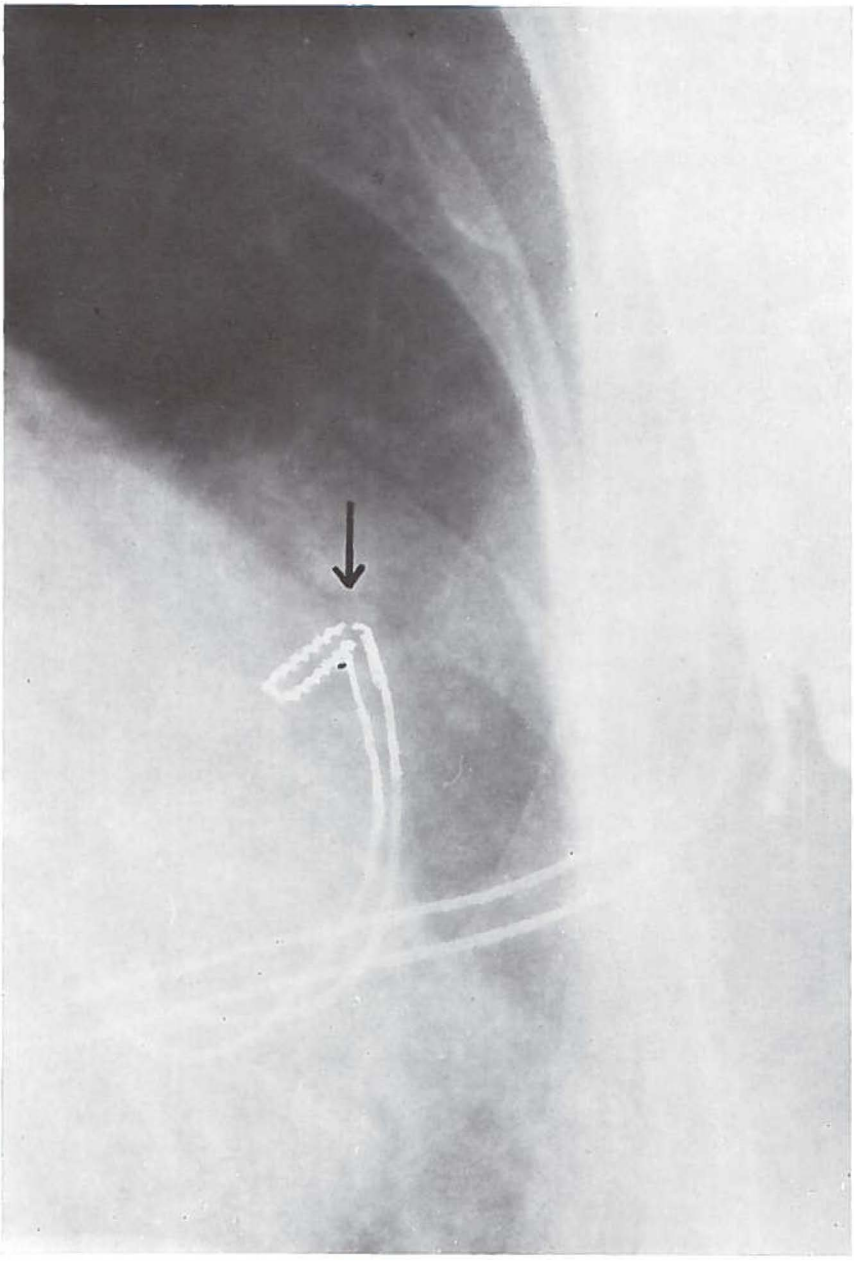


Fig. VI-10. Broken (arrow) intramural loop electrode, 12 months after implantation in a patient; dilated heart.

Since the loop gives the electrode a length of approximately 15 mm, we insulated the part below the frame for a distacce of 3 mm with silicon rubber, leaving ± 9 mm of this electrode uninsulated in the myocardium. The insulation of the loop in a region where connective tissue formation is relatively large and consequently the current is ineffective, decreases both the threshold and the operational values of the electrode, thus increasing the efficiency of the stimulation and prolonging the lifetime of the pacemaker.

In the early versions, the core of the electrode had a diameter of 0.4 mm. Although both the animal experiments and the first clinical applications were favourable, a weak point came to light in a certain series of electrodes. This was the angle made by the core in the frame and fracture occurred at this point due to metal fatigue in a number of patients (fig. VI-10). The movements of the heart proved to be of such a nature that the 0.4 mm thick core and the electrode spiral fractured in the frame. In this inferior group of 10 electrodes we discovered 5 cases of fracture after an average of 3.5 months within the first 6 months after implantation. The remaining 5 electrodes of this group were changed or fractured after 7-14.5 months (average 11 months). Of 6 other loop electrodes with an improved frame, two fractures occurred and 4 electrodes are still functioning in February 1968, after an average time of 24 months (20-28 months).

After experience with this inferior series of electrodes, a slight modification was made in the frame and in addition the core of the new version was given a diameter of 0.7 mm instead of 0.4 mm. In order not to increase the surface area of the electrode excessively and so affect the threshold unfavourably, the diameter of the wire around the core was reduced from 0.35 to 0.2 mm, while the insulated part was slightly increased in size so that the free section is now 7 mm in length (fig. VI-8). This proved to be a considerable improvement, as tests showed.

Test series of heart electrodes are only infrequently described in the literature. The reason for this is perhaps the fact that the forces to which an electrode in the heart is subjected are difficult to measure, so that the forces which have to be applied in testing are difficult to estimate.

In our testing apparatus the electrode was subjected to a force applied at the tip of the electrode (fig. VI-11). The deflection of the electrode tip was adjusted to 1.25 mm each way, the total deflection thus being 2.5 mm. This deflection was repeated at a frequency of 50 Hz i.e. at a rate approximately 50 times that of the heart. The results were as follows:

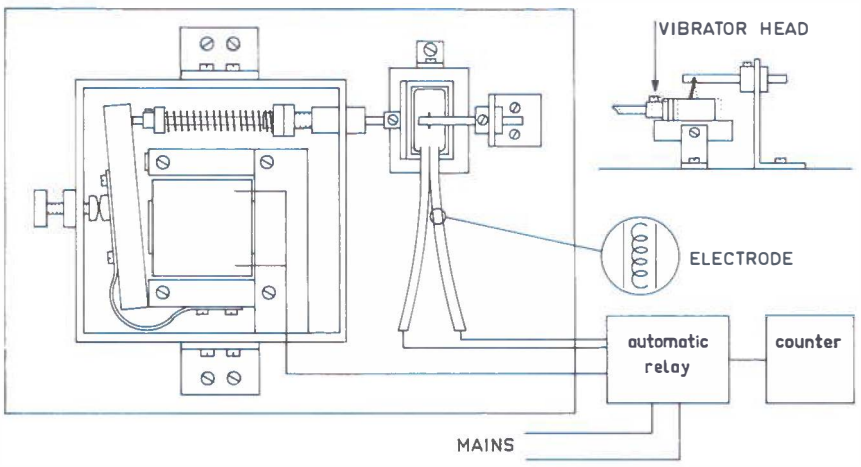


Fig. VI-11. Diagram of apparatus for accelerated fatigue testing of pacemaker electrodes.

A. 1 old electrode of inferior type with a core of 0.4 mm.
The electrode fractured after 4.2×10^4 vibrations.

B. 6 old electrodes with improved frame, but core of 0.4 mm.
The electrodes fractured after 1.3, 1.5, 2.3, 3.1, 4.6 and 8.5×10^5 vibrations respectively.

C. 5 new electrodes with improved frame and core of 0.7 mm.
One electrode fractured after 11.5×10^6 vibrations, the others remained intact to the end of the test at 11.5, 12, and 16×10^6 vibrations respectively.

It can be seen from these data that the new version of the electrodes (C) is much better than the old ones (B), which have now been functioning for an average period of 24 months.

It should be added that the forces which had to be exercised upon the electrodes in order to obtain a total deflection of 2.5 mm increased in the sequence (A)-(B)-(C), due to the improved frames, so that the stress on the electrodes also increased. In series C these forces were highest viz. 200 grams. The improvement is thus considerably better than the number of tolerable vibrations might indicate.

No fracture has yet occurred in these new electrodes, in about 200 implantations and the first of these electrodes has now functioned for 21 months. These electrodes are now produced uniformly, each fifth electrode being tested in the manner described above, thus reducing the risk of a series being faulty to practically nil.

The electrode has a low stimulation threshold, approximately 3.5 μC immediately after implantation, for an impulse duration of 2 msec. The tissue reactions are slight, as animal experiments showed, and there has been no failure of stimulation in patients due to an excessive threshold rise.

Although a definitive evaluation will only be possible after some years, we believe that this electrode is suitable for stable long term stimulation, especially since the conduction lead has also proved to be reliable as will be shown in the following chapter.

The poor results obtained with early versions of transthoracic electrodes led several investigators to the transvenous appraoch in which the heart is stimulated by

3. *Endocardial electrodes*

With endocardial catheter electrodes the conduction lead is situated in the catheter and the proper electrode stimulates the heart via its contact with the endocardium.

The monopolar versions of these electrodes, varying little from version to version, consist of:

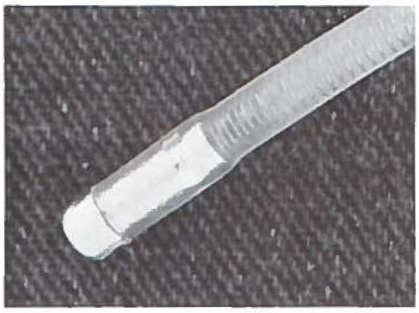
- an electrode at the catheter tip (fig. VI-12) or
- a ring electrode fixed around the catheter at some distance from the tip.

The latter version was employed by ABELSON, SAMET *et al.* (1961), DE VOS (1964) and others. In early versions the catheter electrode frequently penetrated and even perforated the myocardium because it was too rigid and to deal with this problem De Vos located the tip of the catheter in the outflow tract of the right ventricle and attached the ring shaped electrode some centimeters back. He claimed that this resulted in a more stable position of the electrode. A combination of both catheter electrodes is used in the bipolar endocardial catheter (fig. VI-12).

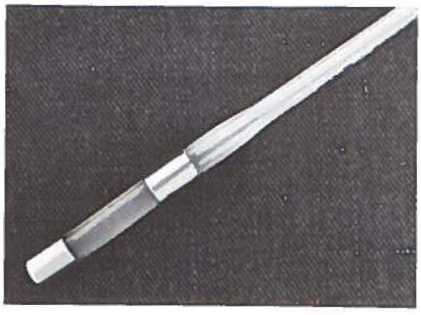
Although the electrodes occasionally consist of stainless steel (SCHWEDEL and ESCHER 1964), normally platinum is used (LAGERGREN and JOHANSSON 1963; GOETZ 1963). Since the electrode suffers almost no mechanical stress, fractures of the electrode itself are rare in most versions.

In order to limit tissue reactions around the electrode due to mechanical damage of the endocardium, the surface of the electrode should be smooth and the tip should have no sharp edges. Lesions of the endocardium may lead to local thrombosis around the electrode, increasing the

Monopolar 1



Monopolar 2



Bipolar

Fig. VI-12. Endocardial catheter electrodes.

threshold. Most catheter electrodes in use at present comply with these conditions.

For optimal stimulation the electrode should have reasonably small dimensions, as large electrodes have correspondingly high thresholds. In our own experience with the electrode of Lagergren and Johansson (fig. VI-12: monopolar 1) and those of others (KOOPS *et al.* 1966; VONK 1966) in 66 cases we found that some time after implantation 21 had a threshold higher than 10 μC for impulses of 2 msec. In 6 patients the threshold was higher than 20 μC and these high thresholds resulted in failure of stimulation in 12 patients which could only be restored by use of a pacemaker with a higher output.

Since stable low threshold values can be obtained with small electrodes

(fig. VI-23 and 24) we decided that our catheter electrode (1966; fig. VI-12: monopolar 2) should have smaller dimensions than that of Lagergren and Johansson, which in turn was already smaller than the bipolar catheter electrode developed by CHARDACK *et al.* (1963; fig. VI-12, 25).

As the main differences between the transvenous electrodes are in the type of conduction lead of the catheter, these electrodes will be discussed further in Chapter VII.

One remarkable variant of the electrodes discussed above should be noted here, viz. the bipolar endocardial-epicardial electrode (fig. VI-13) described by LILLEHEI *et al.* (1962). These authors were of the opinion that endocardial stimulation or stimulation near the endocardium gave better results than intramural myocardial stimulation, and they developed an electrode with two rings placed around an insulated core. The endocardial electrode and the core were introduced by way of a ventriculotomy, the core being led through the myocardium enabling the epicardial electrode to be fixed at this core.

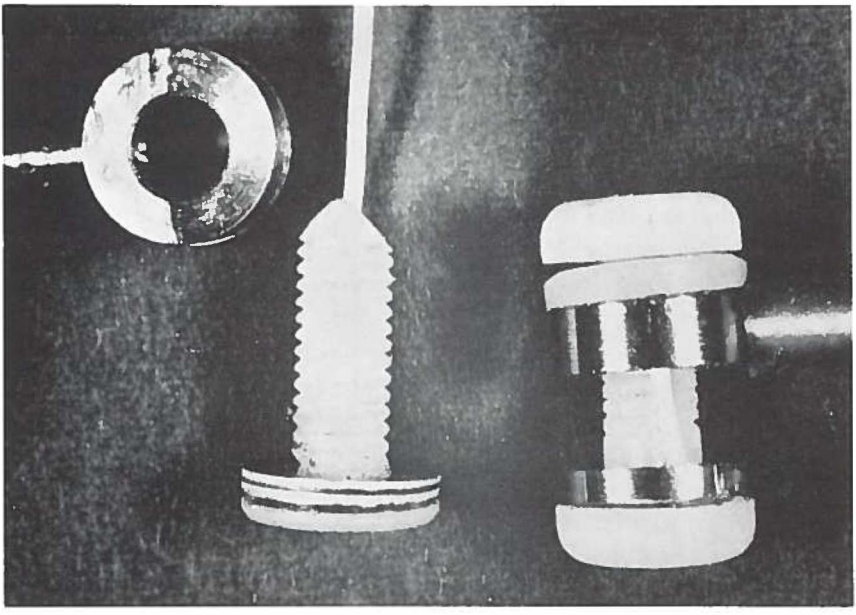


Fig. VI-13. Transthoracic endocardial electrode with epicardial plate.
Left: epicardial plate above, endocardial plate below. Right: assembled electrode. (After LILLEHEI *et al.*)

Although Lillehei *et al.* reported favourable results in animal experiments for periods of two months, further applications of the electrode are not mentioned. The operation required to fix the electrode probably limits its use clinically.

In all other cases bipolar stimulation with a combination of two comparable electrodes is chosen; transthoracic electrodes may be housed in one common or in two separate electrode frames, but for the transvenous electrodes only one catheter is used.

In monopolar stimulation, such as we use, an indifferent electrode is implanted in the body at some distance from the heart.

4. Indifferent electrodes

The indifferent electrode is used only to complete the electrode circuit and there is thus a far wider choice of location and versions.

The indifferent electrode used by LAGERGREN and JOHANSSON'S (1963) monopolar stimulation is practically identical to the epicardial disc electrode, although the dimensions are larger and stainless steel is used. DAVIES (1965) also used a version of his epicardial electrode.

For our indifferent electrode a platinum wire rolled into a flat sheet was used initially (1962) in order to obtain a large surface and thus optimal operational values. The rolled platinum wire was fixed in the muscles near the pacemaker and connected to it by means of an insulated stainless steel multiple strand lead. This electrode, however, was very prone to fracture due to electrolysis at the transition from stainless steel to platinum. In order to avoid electrolysis, we adopted a long multiple strand suture electrode, consisting of stainless steel, uninsulated for a distance of approximately 10 cm. However, metal fatigue and electrolysis caused many fractures of this lead also.

Metal fatigue was next combatted by fixing the electrode as a band around the pacemaker. To prevent any electrolysis, this electrode consisted completely of platinum. This electrode was applied clinically for the first time in 1962 in combination with a catheter electrode and gave good results. The electrode had one disadvantage in common with previous indifferent electrodes, however. The current density at the relatively small band electrode was so high that occasionally nervous and/or muscular tissue in the neighbourhood was stimulated. This resulted in troublesome muscular contractions which were easily avoided by fixing the electrode elsewhere in the body, but in the case of the platinum band this solution was not possible and the whole

pacemaker had to be moved. A solution was found by replacing the band by a large disc attached to or in the wall of the pacemaker (fig. I-1). The current density now became very low and skeletal muscle contractions were largely prevented. In the few cases where contractions became apparent post-operatively, the patient was treated with local anaesthetics for some time so that the unpleasant sensations were suppressed. After the formation of a layer of connective tissue around the pacemaker, the so-called pacemaker pocket, these contractions disappeared. In all our cases this occurred within 10 days. The very large area of the disc electrode had a second advantage in that the current density became so small that electrolysis was not a problem. As a result stainless steel could be used instead of platinum, particularly as the indifferent electrode is replaced each time the pacemaker is changed, since it is attached to the pacemaker wall. This solution proved to be so effective that since the first application in 1963 no more difficulties have been encountered in the form of fracture or electrolysis of the indifferent electrode. A similar type of indifferent electrode has also been used by ELMQVIST and SENNING (1962) and NATHAN *et al.* (1963).

B. Reactions at and near the electrodes

1. Electrolysis

Electrolysis accounts for the changes at the electrodes produced by the electrical current and it is therefore a phenomenon that should strictly be dealt with in the section on the electrical behaviour of electrodes. It is discussed here however, because electrolysis is an important factor in the choice of metals to be used for the electrodes.

Electrolysis occurs especially at the anode, as CLARCK *et al.* (1959) already reported after their experiments with tin plated copper electrodes. After a stimulation period of 21 days in one patient, during which the heart electrode had been connected to the positive pole and the indifferent electrode to the negative pole, Clarck found that the cathode was in good condition but that the anode 'had undergone a considerable amount of electrolysis where contact had been made with the heart.' Electrodes of other metals also suffered from electrolysis and ROWLEY (1963) found electrolysis of his positive stainless steel electrodes. LAGERGREN *et al.* (1966) noticed signs of electrolysis in several catheters which had probably functioned for some time as anodes. We ourselves frequently saw fractures of our previous positive indifferent electrodes partly due to electrolysis (fig. VI-14).

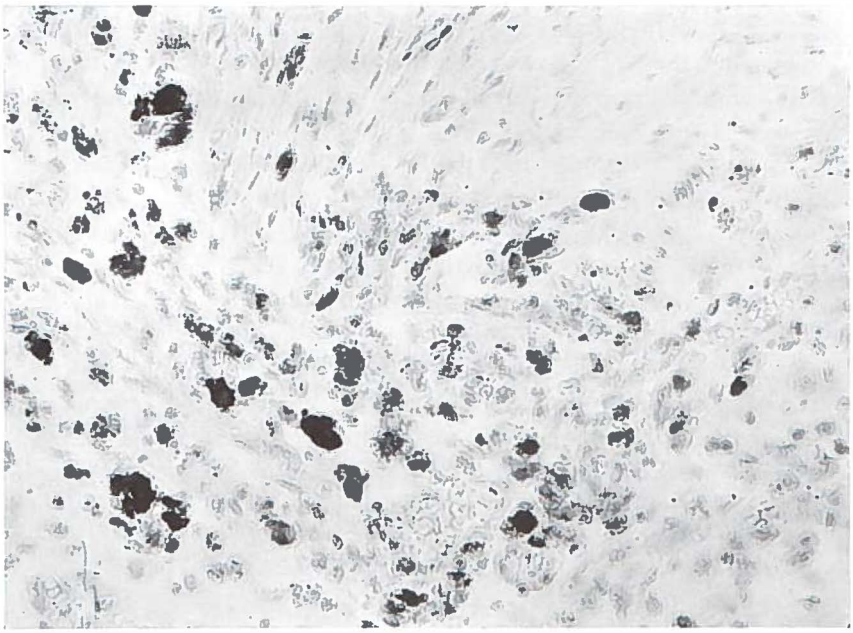


Fig. VI-14. Macrophages filled with iron particles near a positive stainless steel suture electrode (not shown) in the thoracic wall of a dog after 212 days stimulation. Magn. 335 ×. Stain: Perls' ferrocyanide reaction.

Electrolysis depends on

- the polarity of the electrode, which determines the nature of the ions concerned,
- the composition of the metal of the electrode,
- the current density at the electrode, the effect of electrolysis being roughly proportional to this current density.

Electrolysis has been investigated by WEINMAN (1964), who demonstrated experimentally that the over-potential (potential caused by the polarization current), is higher at the anode than at the cathode and thereby explains the electrolysis at the anode. We ourselves are inclined to believe that it is particularly the nature of the ions at the positive electrode, especially the negative chloride-ions, which are responsible for the specific phenomena.

The use of a bi-phasic pulse as suggested by ROWLEY (1963), ABRAMS (1964) and SCHNEIDER (1966) *inter al.* to prevent electrolysis therefore needs caution. When the critical current density is surpassed, it is disadvantageous, since then both electrodes are positive in turn. The

prevention of electrolysis of the positive electrode should be primarily sought in a low current density by choosing an electrode with a large surface-area, and, if this is still insufficient, in the choice of a non-destructable metal.

Metals which are proof against electrolysis are the precious metals and stainless steel is unfavourable for electrodes. ZOLL (1964) covered stainless steel electrodes with a coating of gold platinum. DITTMER, FRIESE *et al.* (1962) showed that even silver is not suitable for long term stimulation. We ourselves had unfavourable experiences with degular, an alloy consisting of 78 parts gold, 8 parts platinum and palladium and 14 parts copper and silver. Around these electrodes we found necrosis with areas of calcification which we ascribed to a reaction around particles which had been worn off the electrode. There was no question of bacterial infection from an external source. The bacterial inflammation which DITTMER *et al.* (1961) observed with stainless steel electrodes, was probably due to secondary infection and is not linked primarily with the electrolysis itself, as suggested by the authors.

A precious metal proof against electrolysis is platinum, but by itself it is too weak mechanically to be used for intramural electrodes. Therefore, platinum is combined with iridium, to form an alloy of platinum 90%-iridium 10%, being proof against electrolysis and having sufficient strength. This alloy is used for many electrodes.

As we described previously, the mechanical strength of this alloy is still insufficient for certain intramural electrodes. For this reason some investigators (TOOLE *et al.* 1960, GLENN 1964, NATHAN 1964, CHARDACK 1964, *a.o.*) changed to an alloy which possesses better mechanical characteristics. This alloy, elgiloy, which consists of 40 parts cobalt, 20 parts chrome, 16 parts iron, 15 parts nickel, 7 parts molybdenum and 2 parts manganese, was already in use in the watch industry, but it is less proof against electrolysis than Pt-Ir. GLENN (1964) described that at a current of 100 mA, flowing continuously for 3 hours through elgiloy electrodes, the cathode remained completely intact, but that the anode 'lost half its weight.' A similar experiment with platinum electrodes showed no variations in either electrode. Therefore Glenn advised that elgiloy should be used for the cathode and platinum for the anode, but in bipolar stimulation this is a poor compromise as it is sometimes desirable to change the polarity of the electrodes, e.g. where there is an alteration in stimulation threshold.

Although the current used for stimulation of the heart is much lower than that used during this experiment, the risk of changes occurring

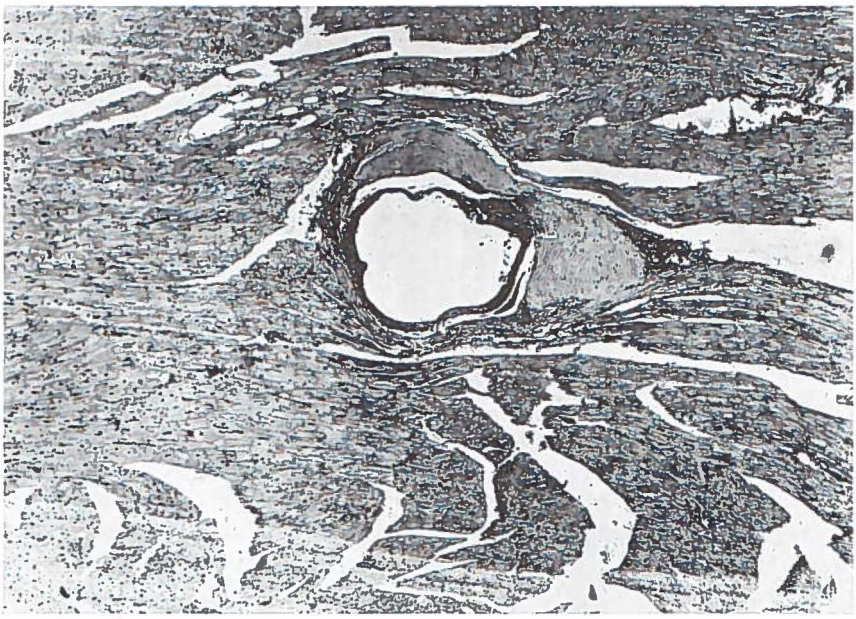


Fig. VI-15. Tissue reaction around an intramural suture electrode in a canine heart, 6 months after implantation. A thin layer of hyaline fibrous tissue can be seen around the channel of the electrode.
Magnif. 36 x, Stain: hematoxylin and eosin.

in elgiloy anodes in the course of time cannot be completely excluded and thus may also be of importance in bipolar stimulation using elgiloy electrodes.

We, ourselves, have been able to continue using a myocardial electrode of platinum 90%-iridium 10%, by modifying it, so that its mechanical strength is sufficient. With unipolar stimulation this electrode has been combined with a large stainless steel disc as indifferent electrode.

2. Tissue reactions around the electrodes

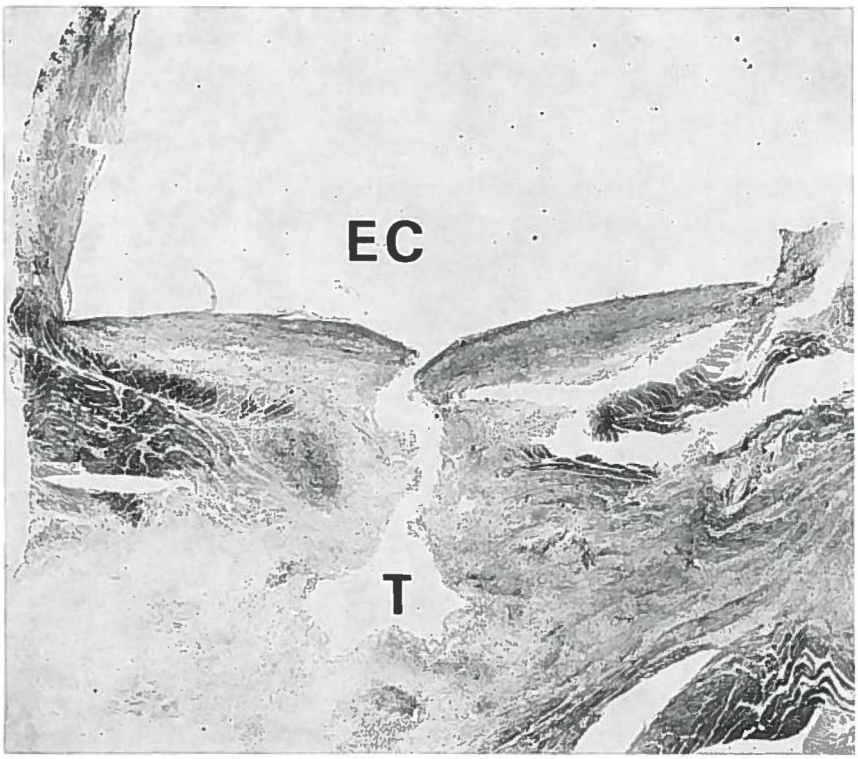
After implantation, tissue reactions occur around the myocardial electrodes which may lead to threshold rises.

In our animal experiments and in patients in whom both a stimulation and a reserve electrode was introduced, we observed a rise in threshold on both the electrodes. The mean increases of threshold on these electrodes were identical and we have therefore concluded in contrast to DIEZEL and FRIESE (1963) that the tissue changes occur as a result of a

foreign body reaction rather than prolonged electrical stimulation. This conclusion is supported by LAGERGREN (1966) who also found no correlation between tissue reaction and electrical stimulation. We only saw tissue reactions, probably caused by electrical stimulation, affecting the stimulation threshold on 4 electrodes, all of which were composed of material not proof against electrolysis (degular).

The tissue reactions around the electrodes, which we investigated in collaboration with DR. PH. J. HOEDEMAEKER (Pathological Anatomical Laboratory – University of Groningen) in 8 patients and 16 animals, were characterised by a circumscribed reaction of the myocardium to the foreign body with the electrode becoming encapsulated by connective tissue. This can be clearly seen in fig. VI-15, which shows the

Fig. VI-16. Tissue reaction and destruction around an intramural pin electrode in a canine heart, 33 days after implantation.
The figure shows that the tip (T) of the electrode has evoked much tissue destruction. At the epicardial site the fibrous wall around the electrode carrier (EC) is shown. Magnif. 10 ×. Stain: azocarmine.



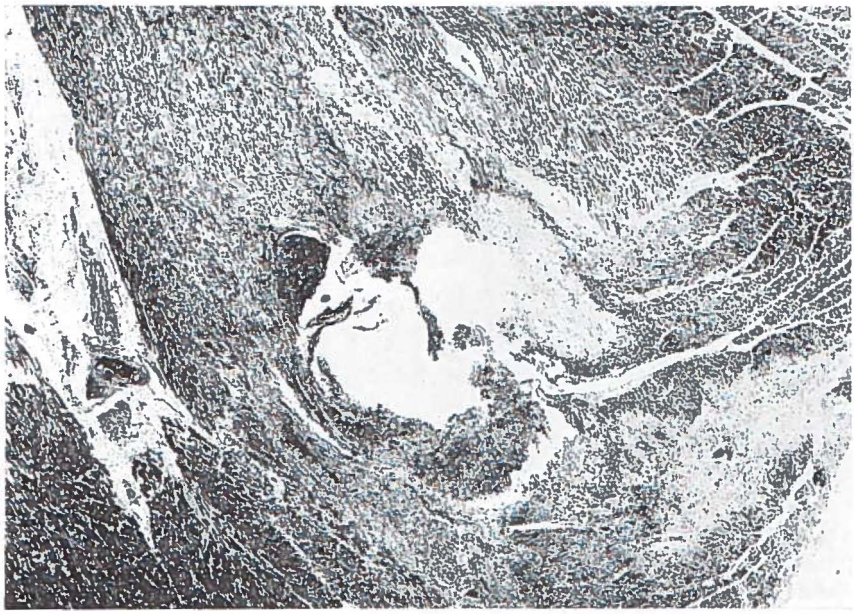


Fig. VI-17. Tissue reaction around the tip of an intramural coil electrode, 14 days after implantation in a patient (m., 63 y). See text.
Magnif. 15 ×. Stain: hematoxylin and eosin.

reaction around an intramural suture electrode, after 6 months implantation in a dog. The hyalinisation of the connective tissue is clearly visible here.

The reactions around a pin electrode, which had functioned for 33 days in an animal, are shown in fig. VI-16. It can be clearly seen that the rigid pin has caused much tissue degeneration, especially at its tip.

With a coil electrode because of its greater flexibility the tissue reaction was less pronounced and there was a relatively smaller rise in threshold on these electrodes compared with the intramural pin (fig. VI-17). The reaction around the silicon insulation of the electrode was less than that around the spiral tip as it is subjected to greater myocardial movement.

The tissue changes after 30 weeks around a platinum disc electrode fixed on the atrium to detect the atrial depolarisation for the P-wave triggered pacemaker, can be clearly seen in fig. VI-18.

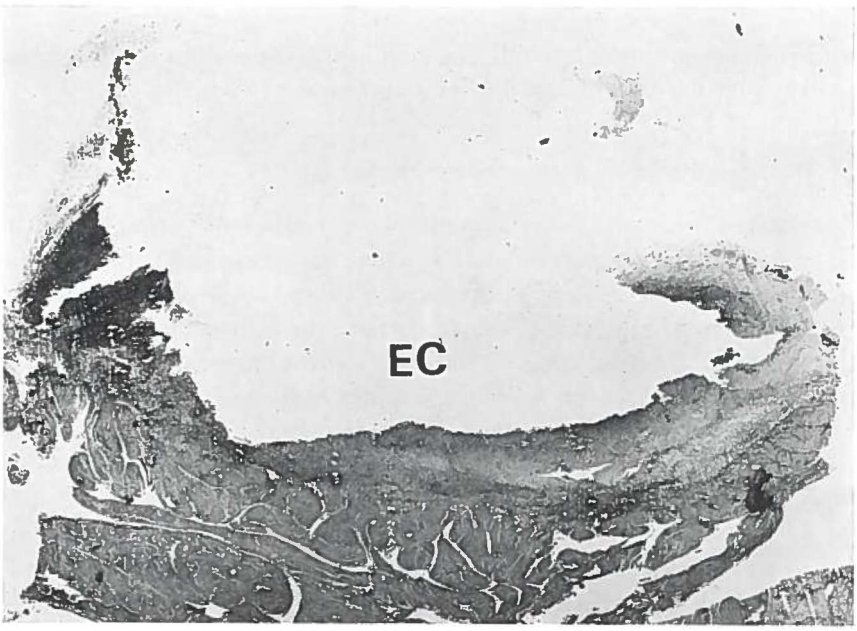
Examination of the reactions accompanying loop electrodes reveal that after 16 days (fig. VI-9) the tissue growth through the loop had

already assumed considerable proportions, and the myocardial tissue had fixed the electrode firmly in the myocardium.

In one experiment using a platinum-iridium electrode the animal was examined after 8 days, the loop cut and withdrawn from the myocardium in order to examine the tissue within the loop. The figs. VI-19 and 20 show that after 8 days there was already a well formed tissue structure through the loop.

Post-mortems showed that the electrode frame was frequently encapsulated by epicardial tissue, and there were pericardial adhesions overlying it. Few observations have been made with endocardial electrodes, but at post-mortem on a dog, we saw that at 12 days the catheter was encapsulated by an endothelial layer. This layer was not present on the part of the catheter between the tricuspid valve and the trabecular muscles (fig. VI-21). Post-mortems on patients with endocardial electrodes (fig. VI-22) were described by LAGERGREN (1966) *et al.* As with other types of electrodes, a thin layer of connective tissue

Fig. VI-18. Tissue reaction around an epicardial disc detection electrode on the atrium of a dog, 212 days after implantation.
The disc has evoked the formation of a layer of fibrous tissue, which separates the electrode from the heartmuscle. EC: chamber of the electrodecarrier.
Magnif. 8 ×. Stain: hematoxylin and eosin.



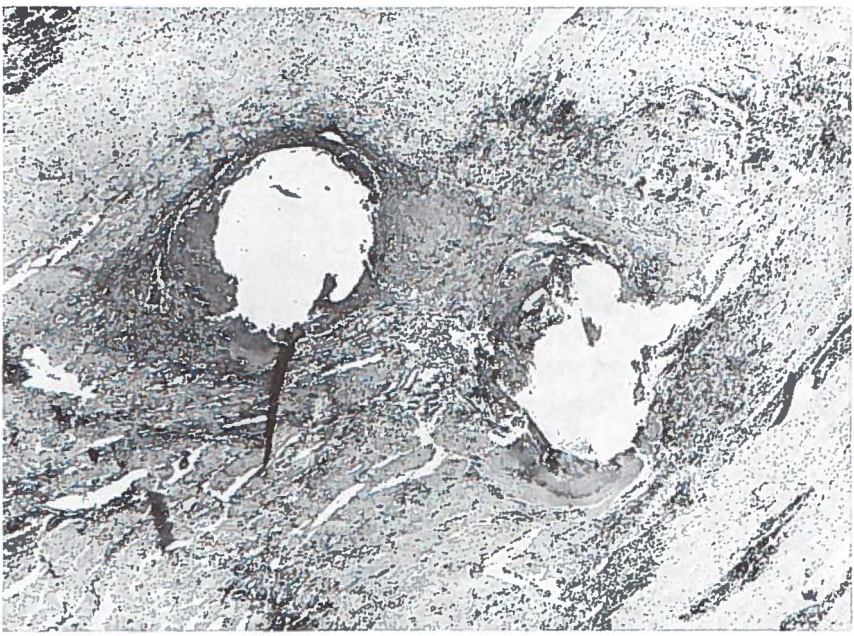


Fig. VI-19. Tissue reaction around an intramural loop electrode in a canine heart, 8 days after implantation. As shown by the figure, tissue has already grown between the legs of the loop.
Magnif. 24×. Stain: hematoxylin and eosin.

is formed around the electrode, varying in thickness from 0.5 to 4 mm, a slight infiltration with lymphocytes and monocytes being observed.

3. *Thrombus formation during endocardial stimulation*

Thrombus formation occurs sporadically in endocardial stimulation. It is influenced by polarity. Blood clotting has occasionally been found around the positive electrode, but not around the negative electrode.

To investigate this, we passed a current through definibrated blood at 37°C in a U shaped tube by means of two stainless steel electrodes. In 19 experiments, using a 2 msec impulse of 20 mA at a frequency of 70/min we found that thrombus formation occurred at the positive electrode after 10-30 minutes, and when a 6 mA current was used thrombus formation occurred in 2 hours. Thus the length of time before thrombus formation appeared was virtually inversely with the current. There was no thrombus at the negative electrode. With catheter electrodes used in practice under similar conditions thrombus only occurred

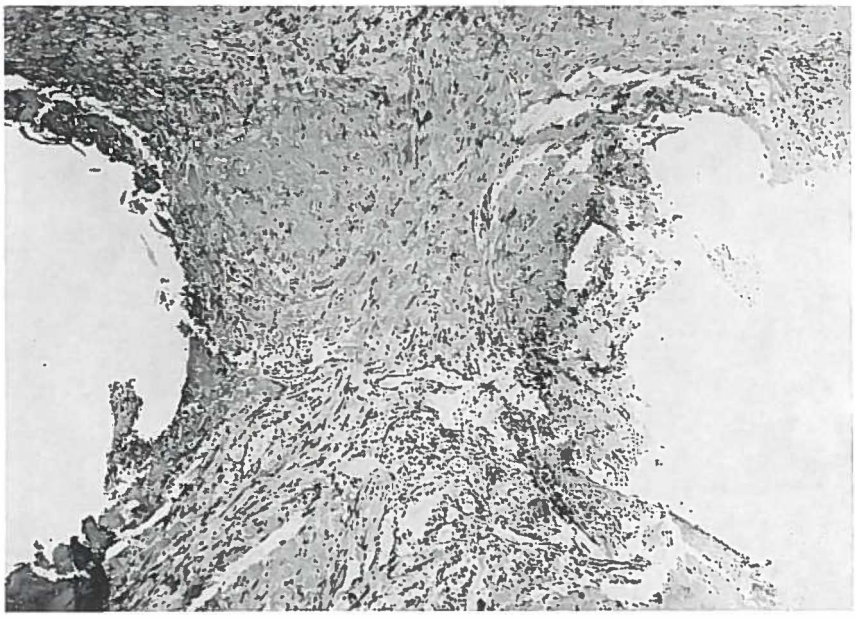


Fig. VI-20. Detail of fig. VI-19 showing the tissue between the legs of the loop, consisting of highly vascularized young fibrous tissue.
Magnif. 53 ×. Stain: hematoxylin and eosin.

at the positive electrode as both platinum (CHARDACK) and stainless steel (LAGERGREN – early type) were used.

We did not extend our investigation to clinical tests. The phenomenon, however, does occur clinically, as SAWYER (1961), ZUCKER *et al.* (1963), SCHWEDEL and ESCHER (1964) and ZOLL (1964) *inter al.* have shown.

The mechanism of this thrombus formation has not yet been explained. Some investigators suggest that thrombolysin is liberated locally at the negative pole (RICHARDSON and SCHWARTZ 1962), preventing coagulation there. This, however, does not explain why coagulation occurs only at the positive electrode. We favour the theory of SAWYER and PATE (1953), who ascribe the difference in reaction at the negative and positive electrodes to a microphoresis effect, where the negatively charged blood cells move towards the positive electrode. The high current density might explain coagulation occurring at electrode border and at places where the electrode is damaged.

Since coagulation only takes place at the positive electrode, this

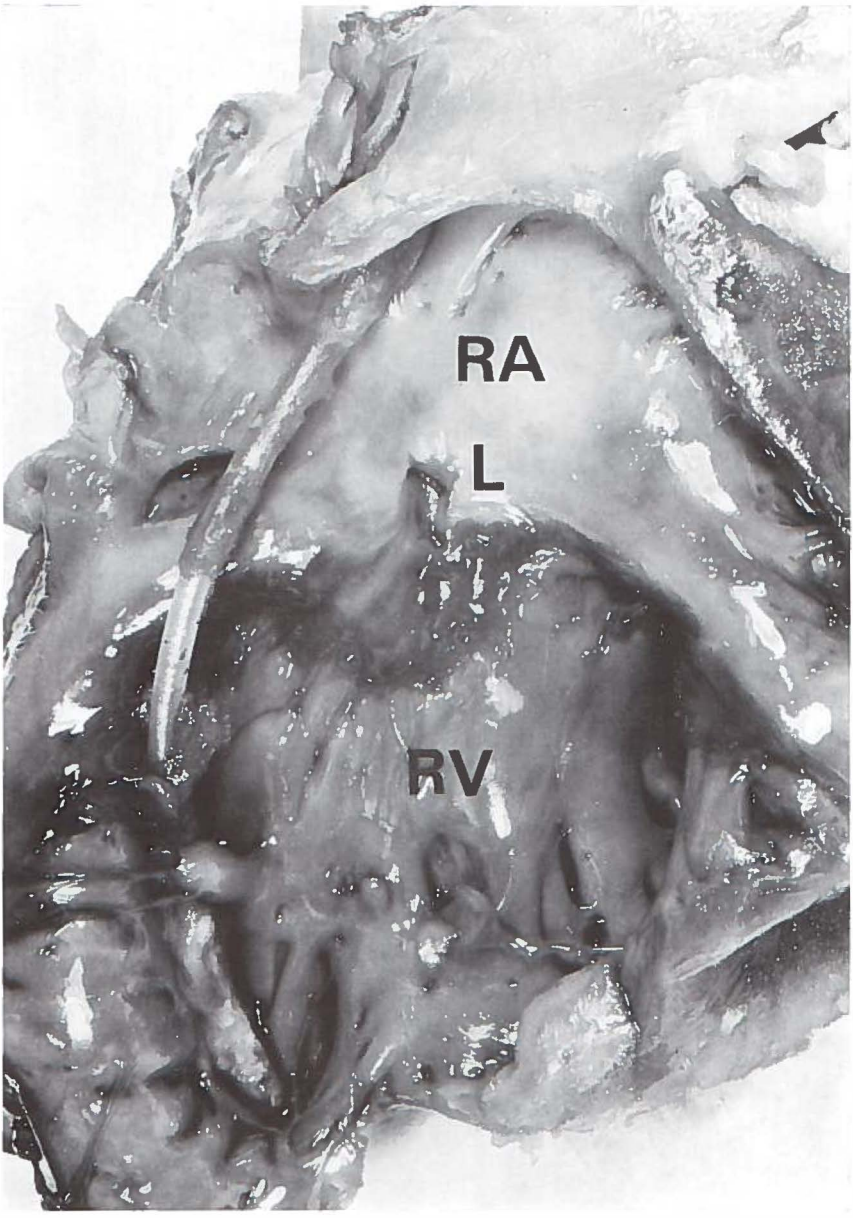


Fig. VI-21. Tissue reaction around a catheter electrode, 12 days after implantation in a dog. RA: right atrium; RV: right ventricle; L: ligature around bundle of His.
At the atrial side the catheter is surrounded by a fibrin layer. The part of the catheter between the tricuspid valve and underneath the trabecular muscles is clean. The distal end of the catheter is encapsulated by a layer of fibrous tissue.

Fig. VI-22. Tissue reaction near the tip of a catheter electrode in a human heart. The tip of the electrode is fixed between the trabecular muscles. (By Courtesy of DR. H. BORST).

phenomenon is not see during unipolar endocardial stimulation provided that the anode is placed outside the circulatory system.

The mechanical and histological factors discussed in this section are of importance in the design of electrodes. The factors which determine electrical behaviour will be discussed in the following section of this chapter, in relation to the various electrodes which we have used.

IV. ELECTRODE CIRCUIT AND ELECTRICAL BEHAVIOUR OF THE TISSUE

The electrical behaviour of the tissue around the electrodes and the effect of the electrodes upon it can be evaluated from the stimulation threshold and the operational value of an electrode circuit. These and

other concepts giving insight into the electrical properties of the electrode circuit will be discussed below.

We have defined the stimulation threshold as the minimal stimulus required to cause a specific heart reaction. In this chapter the terms stimulation threshold for current and stimulation threshold for voltage have also been introduced, and it was shown that these thresholds do not always bear their expected relationship. Which parameter represents the proper stimulation threshold and what determines this threshold?

Firstly, the stimulation threshold for energy may be defined by the formula:

$$W = V \times i \times t$$

the energy being determined by voltage, current and current duration. It may, therefore, be stated that the threshold for energy is the product of the threshold for voltage (V) and the threshold for charge ($i \times t$), the latter being the product of the threshold for current (i) and the impulse duration (t). From the experiments discussed with fig. VI-2,3 and table VI-1,2 it appeared that:

– in electrical stimulation of the heart with impulses of a given duration and polarity, the stimulation threshold of any myocardial electrode may be stated in terms of current (threshold current).

This threshold current is accompanied by a certain threshold voltage. The latter depends on the threshold current and the complex impedance of the electrical circuit, which consists of the resistance of the leads including the electrodes, R_l, and the impedance of the tissues between the electrodes, Z_t.

The following formula applies to the threshold voltage:

$$V_{thr} = i_{thr} (R_l + Z_t)$$

in which V_{thr} represents the threshold voltage and i_{thr} the threshold current. In this formula, i_{thr} is independent of the rest of the circuit for a given electrode. By using various other electrodes with identical lead resistances, the value of R_l is also found to be independent of the circuit. This, however, is not the case with Z_t, which depends on the properties of the myocardial electrode, on the nature of the electrode which completes the circuit, in particular the dimensions of this electrode, and on the nature of the tissue between the two electrodes. Z_t may be represented thus:

$$Z_t = Z_{e1} + R_t + Z_{e2}$$

where Z_{e1} and Z_{e2} represent the transitional impedances in the area of the electrodes, and R_t the resistance of the tissues between them. If the threshold voltage of a given myocardial electrode is determined in combination with other electrodes, the transitional impedance at the myocardial electrode, Z_{e1}, will be naturally identical in each measurement, and the transitional impedance, Z_{e2} at a second electrode, e.g. an indifferent electrode, depends on its geometry and the tissues around it. The tissue resistance R_t depends on the geometry and the location of both electrodes and the tissues between them.

This means however, that the threshold voltage is also dependent on the second electrode, and that different voltages will be found at constant current thresholds (or charge thresholds) for one given heart electrode when the type or site of the second electrode is varied (see fig. VI-5, 35 and table VI-3). The term threshold voltage of a particular myocardial electrode is therefore incorrectly used unless the other circuit details are also stated.

Also the definition of the stimulation threshold for energy must be given for an electrode combination and not for a myocardial electrode alone, as the threshold energy also depends on theother electrode.

A. Stimulation threshold for current

The stimulation threshold for current is approximately proportional to the size of the electrodes used.

In order to investigate this, we have plotted in fig. VI-23 the current threshold of intramural electrodes of varying dimensions. The intramural suture electrode was chosen as the large electrode, the loop electrode as the intermediate and the intramural pin and coil as the small electrodes. In 9 dogs one suture electrode and one or more of the other electrodes were attached to the heart, and combined with an indifferent suture electrode in the thoracic muscles. The charge thresholds were determined with the Cardiotest 7 days post-operatively at impulse durations of 1, 2, 3 and 4 msec, using 14 electrode combinations. The charge threshold in μC for the suture electrode combined with the indifferent electrode is plotted on the horizontal axis, and the charge threshold of the other electrodes in combination with the same indifferent electrode on the vertical axis.

This figure illustrates clearly that the suture electrode has a higher charge and therefore current threshold than the other electrodes. The difference is most obvious when it is compared with the pin and the

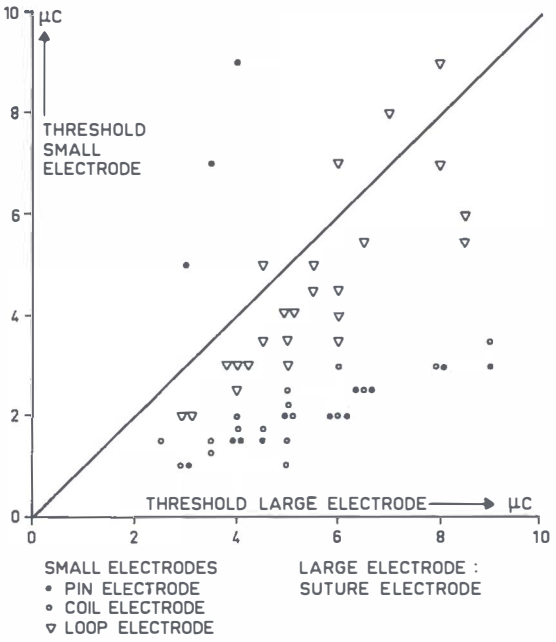


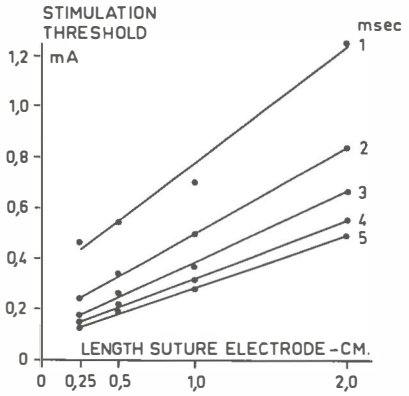
Fig. VI-23. Stimulation threshold (charge) of small electrode versus stimulation threshold (charge) of large electrode in the same dog. Semi-acute experiments in 9 dogs. Each dog had one large heart electrode and one (4) or two (5) small heartelectrodes. The monopolar cathodal stimulation threshold of each heart electrode was measured for impulsedurations of 1, 2, 3, and 4 msec. The symbols above the 45° line belong to infected small electrodes. See text.

coil electrode, whereas that between the relatively large loop electrode and the suture electrode is small. Very high thresholds due to infection were recorded on one pin and one loop electrode.

We also investigated the relation between electrode size and stimulation threshold using a suture electrode, partially insulated with teflon. The electrodes used were stripped of insulation for 0.25, 0.5, 1 and 2 cm respectively, the diameter in each case being 0.45 mm. The results of these measurements at impulse durations of 1, 2, 3 and 4 msec are shown in fig. VI-24. The relation between electrode size and stimulation threshold can be seen clearly.

This phenomenon was also investigated with endocardial electrodes. Three catheters with different electrode sizes were introduced successively in a dog. The *i-t* curves of these catheters were determined, using the current pulse stimulator (fig. VI-25). Here too it is clear that the

Fig. VI-24. Monopolar cathodal stimulation threshold (mean current) versus non-insulated length of intramural suture electrode, for 5 impulse durations. Acute experiment in a dog.



current threshold at a given impulse duration is approximately proportional to the surface area of the electrode. Hence the current threshold depends on the current density at the electrode, and its definition may be stated as:

– the current threshold is determined by the minimum current density at the electrode required for stimulation of the surrounding myocardium.

Investigations have shown that fluctuations occur in the current threshold. A rise during the first weeks after electrode implantation is

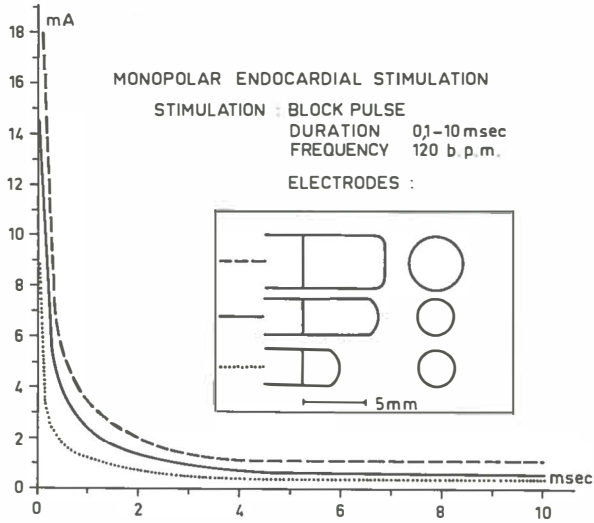


Fig. VI-25. Monopolar cathodal endocardial stimulation threshold (mean current) versus impulse duration for three catheter electrodes. Acute experiments in a dog.

followed by threshold stabilisation. In fig. VI-26 an example is given of the changes in the monopolar cathodal charge threshold of an intramural suture electrode (unipolar cathodal) during the first three post operative months.

Besides the charge threshold, this figure also shows the voltage threshold and the effective resistance, which is defined as the pura mean resistance which drains the same mean current from the pacemaker as the actual electrode circuit (VAN DEN BERG *et al.* 1962).

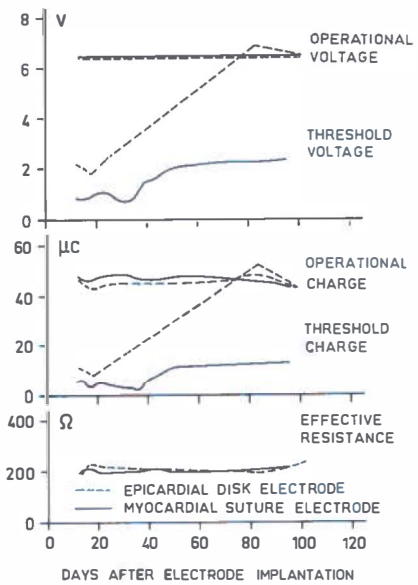


Fig. VI-26. Operational voltage, operational charge, threshold voltage, threshold charge and effective resistance versus days after electrode implantation, for two heart electrodes in a dog. Monopolar cathodal stimulation.

The effective resistance for both combinations of large electrodes recorded in fig. VI-26, is approximately equal, and this resistance remains almost unaltered even when the threshold value increases. It follows, that the increase in the charge (or current) threshold is not the result of an increase in the electrical resistance in the circuit. We have shown that connective tissue is formed around the electrode after implantation. The change in the effective resistance of the whole circuit due to this tissue formation is slight, (see: Impedance of the electrode circuit). The tissue encapsulation, however, does result in an increase in distance between the electrode and the intact (active) myocardium, thus reducing the current density in it.

For example, a spherical electrode with a radius of 1 mm has a surface area of $4\pi r^2$ mm^2 = 4πmm^2, which corresponds to the surface area

of the myocardium which is supposed to be still in contact with the electrode. At a threshold current of 1 mA the minimum current density in the boundary layer of the intact myocardium required for stimulation is

$$\frac{1}{4\pi}\ \frac{\text{mA}}{\text{mm}^2}.$$

If this electrode is encapsulated by a 1 mm thick layer of fibrous tissue, the surface area of the intact myocardium surrounding the electrode then becomes $16\pi\,\text{mm}^2$, so that at a current of 1 mA the current density at the boundary layer of the intact myocardium is

$$\frac{1}{16\pi}\ \frac{\text{mA}}{\text{mm}^2}.$$

The minimum current density in the boundary layer required for stimulation will remain the same, so that the threshold current then becomes approximately 4 mA. Since the effective resistance does not depend greatly on the current in the circuit, the threshold value for voltage will, as the electrode combination is identical, also increase approximately four fold.

This theory also explains why the threshold changes are relatively greater at a small electrode than at a large electrode. A sphere radius of 4 mm is an example of a large electrode, its surface area is $64\pi\,\text{mm}^2$. If a 1 mm thick layer of fibrous tissue – thickness of the layer of tissue is more or less independent of the size of the electrode – is formed around this electrode the surface area of the intact myocardium adjoining the electrode then becomes $100\pi\,\text{mm}^2$, and in order to obtain the same current density in the intact heart muscle tissue as there was before the connective tissue formation, the threshold current only needs to be 100/64 or about 1.6 times as great.

Thus, the rise in stimulation threshold depends on:

- the thickness of the connective tissue layer formed around the electrode and
- the relation between the dimensions of the connective tissue layer and the dimensions of the electrode.

The rise in threshold is greatest immediately after electrode implantation. This is due to the process of tissue formation itself, which occurs around all types of electrodes immediately after implantation. During this stage fluctuations may occur due to the fact that the electrode is

not yet properly fixed. When the myocardial tissue reaction is complete and the electrode fixed, the threshold stabilises.

When infection occurs around the electrode, tissue degeneration and accumulation of seropurulent fluid, displaces the intact myocardium further and further from the electrode. This necessitates a continually increasing current to achieve the threshold current density in the intact heart muscle surrounding the electrode, and the stimulation threshold rises higher and higher. This process frequently takes place faster than the usual mechanical reaction to the implantation of the electrode, and thus the threshold may rise far more rapidly. The tissue changes may be such that the minimum current density in the intact muscular tissue can no longer be supplied by the pacemaker, and therefore it cannot longer stimulate the heart. The disc electrode in fig. VI-26 illustrates this, the inflammatory process and tissue degeneration caused an excessive rise in stimulation threshold.

The electrode becomes poorly fixed in infected and degenerated tissue and movements such as respiration may cause threshold fluctuations. Fortunately, the threshold may decrease to an acceptable value after the inflamed tissues have been organised.

The importance of the current density in the intact heart muscle tissue adjoining the electrode enables us to understand more fully the differences between unipolar cathodal, unipolar anodal and bipolar stimulation (table VI-1, 2). We have seen that cathodal stimulation gives lower threshold values than anodal stimulation with identical electrodes because of the properties of cell membranes. In bipolar stimulation with equal-sized negative and positive electrodes in equivalent heart tissue, the stimulation threshold will be determined by the negative electrode. If the negative electrode is continually enlarged in relation to the positive electrode, the cathodal threshold of the negative electrode becomes continually higher, as the current density must remain constant, until a level is reached at which the cathodal threshold of the large negative electrode becomes higher than the anodal threshold of the small positive electrode. The stimulation threshold for bipolar stimulation with this combination of electrodes is therefore determined by the anodal threshold of the small positive electrode. A similar situation occurs with identical electrodes when the effective current density at the negative electrode decreases due to tissue reaction around it. Summarizing we may state now that:

– functionally, the dimensions of an electrode are equal to the dimension of the non-excitable tissue around the electrode.

In fig. VI-27 the observations from 6 combinations of two intramural loop-electrodes in the heart and one indifferent suture electrode in the thoracic muscles are shown for a period of 80 post-operative days. Of the two geometrically identical heart electrodes, L_1 displayed a rapidly rising threshold, whereas the other electrode L_2 showed little rise in threshold, as shown by their unipolar cathodal and anodal stimulation curves. With bipolar stimulation, the $L_2 - L_1$ curve was found to be almost identical to the unipolar cathodal L_2 curve. The stimulation thresholds were thus in both cases determined by the (negative) L_2 electrode. If we compare these curves with the $L_1 - L_2$ curve for bipolar

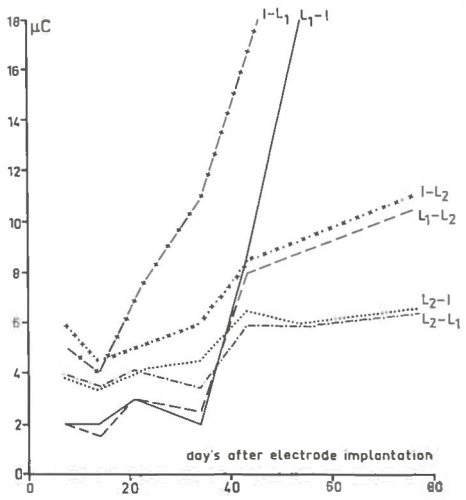


Fig. VI-27. Threshold charge versus days after electrode implantation for 6 electrode combinations in a dog. $L_{1,2}$: identical intramural loop electrodes, I: indifferent suture electrode. First electrode of each combination is negative.
Rapidly increasing inflammatory process around L_1, slowly increasing inflammatory process around L_2. After about 40 days the bipolar L_1-L_2 threshold is determined by the anodal threshold of L_2. See text.

stimulation, it appears that the $L_1 - L_2$ threshold is determined by the negative L_1 electrode during the first 40 days. Between the thirty-third and fiftieth day the cathodal threshold of this L_1 electrode rises, however, to such an extent that it exceeds the anodal threshold of the L_2 electrode at the forty-first day and the threshold of the $L_1 - L_2$ combination is therefore determined by the positive L_2 electrode.

Similar observations have been made in one other animal (fig. VI-32B) and in patients (table VI-4). Comparison of these findings with those of other investigators shows that some, SCHNEIDER (1964), ANGELAKOS and TORRES (1964), recognise current density as an essential factor in stimulation of the heart, although we do not concur with SCHNEIDER (1966) who claims that on this basis a stimulation apparatus should be of constant current (Chapter VIII). Other investigators draw similar con-

clusions to ours, although they do not use the concept of current density. MANSFIELD (1965) states that the threshold value is proportional to the electrode surface area and ELMQVIST *et al.* (1963) state that the threshold variation is due to differences in the distance from electrode to myocardium.

Increase in threshold during the initial period after implantation of electrodes has been noticed by practically all authors and most considered that tissue formation was responsible, but there were varying opinions as to the mechanism of the threshold rise.

For instance FURMAN and SCHWEDEL (1959), DITTMAR *et al.* (1962), FRIESE (1965) and GILMAN (1966) state that the threshold rise is the result of an increased resistance due to tissue formation around the electrode, but no resistance measurements were recorded by them. Presumably these theoretical conclusions have been drawn from histological observations. In contrast, ALBERT *et al.* (1962) found that the effective resistance in the circuit reaches its peak value fairly soon and then stabilises, in spite of threshold variations.

Another explanation for the rise in stimulation threshold was given by CHARDACK (1964). He argued that 'after insertion of an electrode there is always some increase in current requirement from scarring due to mechanical trauma. This increase is selflimited. Infection around the electrode tips and leadwires produces a considerable increase in current requirements because of the accumulation of seropurulent fluid around them. Since this fluid has a much higher conductivity than tissue, current is dissipated within it, leading to a rise of threshold in the presence of a normal or lower than normal electrical resistance.' This was also the view of RACE *et al.* (1963). It is not clear what CHARDACK means by 'dissipated'. The current must pass from one electrode to the other and does not get lost.

Fig. VI-26 shows that the effective resistance remains virtually the same in spite of variation of threshold values. Also fig. VI-28 illustrates that the threshold variations are not caused by changes in resistance in the electrode circuit. This figure shows the threshold values with effective resistances of some combinations of fig. VI-27. No difference is seen between the resistance of the electrode with the rising threshold and the electrode with the stable threshold.

We therefore conclude that neither an increase of resistance (see also Impedance of the electrode circuit) nor a dispersion of current are responsible for an increase of current threshold. Also it must be pointed out that an increase of resistance by connective tissue and a decrease of

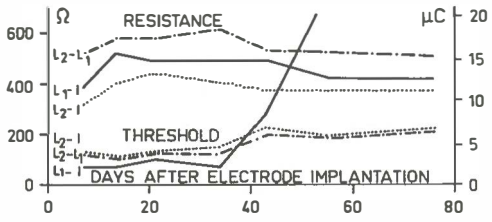


Fig. VI-28. Effective resistance and threshold charge versus days after electrode implantation for 3 electrode combinations of fig. VI-27. The figure shows that there is no relation between the rise of the charge threshold and the effective resistance of the electrode combination L_1-I.

resistance by purulent fluid are in competition with each other, as these resistances are connected in series, not parallel, in the electrode circuit.

Conclusions

– the current threshold is determined by the current density required to stimulate the intact heart muscle tissue adjoining the electrode.

This means that the current threshold for a given polarity and stimulation method depends on:

1. the shape and the dimensions of the electrode;
2. the tissue reaction around the electrode, determined by:
   a. the mechanical rigidity of the electrode,
   b. the time interval between implantation and measurement,
   c. infection around the electrode,
3. the excitability of the intact myocardial tissue adjoining the electrode.

In practice the electrode should therefore be small, causing little tissue reaction and incurring the least risk of infection.

The minimum dimensions of the electrode are determined by the large transitional impedance which accompanies small electrodes. This factor is discussed in the following paragraph.

B. Electrical impedance of the electrode circuit

The impedance in the electrode circuit Z_c, is complex and consists of:
– the resistance of the electrode leads and electrodes, R_l,
– the impedance of the tissue between the electrodes, Z_t, which may be divided into:
  – the complex resistance of the transition zones between electrodes and tissue where polarization occurs, Z_e,
  – the resistance of the remaining tissue between the electrodes, R_t.

The total impedance of the electrode circuit is equal to the substitu-

tional impedance, which may be calculated according to OHM's law:

$V = i \times Z_e$, where
V = potential difference in the circuit,
i = current in the circuit,
Z_e = substitutional impedance of the circuit.

The substitutional impedance of an electrode combination varies with the impulse duration and current, because the polarization in the electrode-tissue boundary area does not progress linearly. For this reason the term 'effective resistance of the electrode circuit' was introduced (see fig. VI-26). We shall now discuss the real constant ohmic resistance in the circuit, and then deal with polarization.

1. Resistance of the conduction leads and the electrodes, R_1.

The resistance of the wire of a conduction lead is:

$$R = \rho \times \frac{l}{O}$$

R = the total resistance of the lead
ρ = specific resistance of the metal
l = length of the wire in the lead
O = cross section of the wire

In practice the resistance of each lead is only a few tenths of ohm and only constitutes a small part of the total resistance of the circuit.

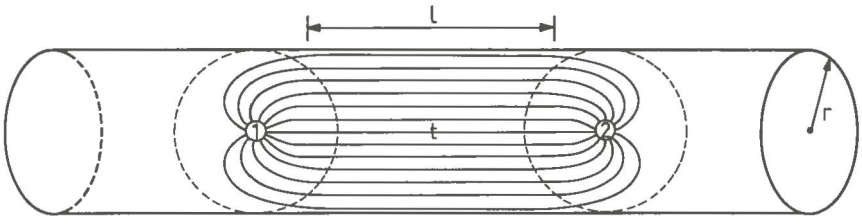
For example, a conduction lead with a platinum wire ($\rho = 1.05 \times 10^{-5}$ ohm cm.) 1 m in length and 0.10 mm in diameter has a resistance of

$$R = \rho \times \frac{l}{O} = \rho \frac{l}{\pi r^2} = 1.05 \times 10^{-5} \times \frac{100}{\pi \times 0.005^2} = 14 \text{ ohm}$$

2. Ohmic resistance of the tissue between the electrodes, Z_t

A simplified scheme has been conceived to investigate the contribution of the various factors with their complex geometrical relationships (fig. VI-29). Two spherical electrodes of radius r_0 were set at some distance apart in a cylinder of radius r which was filled with a liquid of specific resistance ρ.

In the vicinity of the first electrode, area 1, the current lines diverge, as also occurs in the area of the second electrode, area 2, and between



①	t	②
$R_1=\frac{\rho}{4\pi}(\frac{1}{r_o}-\frac{1}{r})$	$R_t=\rho\times\frac{l}{\pi r^2}$	$R_2=\frac{\rho}{4\pi}(\frac{1}{r_o}-\frac{1}{r})$
$r_o=0{,}175cm$	$r=10cm;\ l=30cm$	$r_o=0{,}175cm$
$R_1=\frac{\rho}{4\pi}(\frac{57}{10}-\frac{1}{10})$	$R_t=\rho\times\frac{30}{100\pi}$	$R_2=\frac{\rho}{4\pi}(\frac{57}{10}-\frac{1}{10})$
$R_1=\frac{56}{10}\times\frac{\rho}{4\pi}$	$R_t=\frac{30}{25}\times\frac{\rho}{4\pi}$	$R_2=\frac{56}{10}\times\frac{\rho}{4\pi}$
$R_1=45\%$	$R_t=10\%$	$R_2=45\%$

Fig. VI-29. Scheme to illustrate the approximate calculation of the electrical resistance between two electrodes.

them, area t, the current lines run practically parallel and equidistant from each other. Areas 1 and 2 are known as the transitional areas around the electrodes and area t as the transport area.

A. The resistance of area t may be calculated by the formula

$$R_t = \rho \times \frac{l}{O},$$

ρ is the specific resistance of the liquid, l the length and O the cross sectional area. In practice tissues have varying specific resistances in the transport area whereas also more or less blocking membranes will occur locally. From an electrical point of view the transport area must thereby be regarded as a collection of areas connected in parallel and in series, the above formula applying to each area. If desired, an effective specific resistance and an effective cross-section of the transport area may also be given. However in approximate terms the resistance is always directly proportional to the length and inversely proportional to the cross-section.

B. The resistance of a transitional area is more difficult to calculate. Because of the effect of the dimensions of the electrodes further simplification is necessary. This resistance is calculated on the basis of radial current lines and applying the formula:

$$R = \frac{\rho}{4\pi}\left(\frac{1}{r_0} - \frac{1}{r}\right)$$

where ρ is the specific resistance of the liquid, r_0 the radius of the electrode and r the radius of the transitional area. In practice the tissues here also have varying specific resistances. Because r is always far greater than r_0, however, the resistance of the transitional area is always approximately inversely proportional to the radius of the electrode. In the case of a small electrode of complicated shape, it is possible to consider as effective radius, the radius of a spherical electrode which has the same contact area with the tissue as the electrode in question.

It follows from the formula that with a smaller electrode and the distance between the electrodes remaining unchanged the resistance in the electrode circuit increases. Conversely, the resistance between the electrodes decreases when the radius of the electrode increases.

In considering the resistance of the tissue between the electrodes, the specific resistance of each type of body tissue is important, but insufficient knowledge is available at present concerning these specific resistances.

SCHWAN (1951) and SCHWAN and KAY (1956) performed measurements to determine the specific resistance of heart muscle, using two electrodes and alternating current to prevent polarization. In vivo, cardiac arrest was induced for the measurements to be performed. They found a value of 965 ohm cm for the specific resistance of heart muscle tissue. This is higher than the value found by us and other investigators (RUSH 1962, SCHNEIDER 1966). We used a four electrode method which was developed as early as 1898 by KOHLRAUSCH and HOLBORN.

A current was passed between two electrodes through the tissue to be measured, whilst the voltage across a part of the tissue was measured using two detector electrodes. This was performed in a perspex tray, which was completely inserted into a bottle with a constant temperature of 37°C to avoid changes of temperature. To prevent polarization the voltage was measured using an instrument with an extremely high input-impedance, so that the detection current was very small. The circuit was powered by an alternating current of 1000 Hz. Our measurements were performed on tissue taken from deceased patients, the maximum period between death and measurement being 12 hours. 25 measurements on 5 pieces of heart tissue ranged between 123 to 208 ohm cm, with an average specific resistance of 162 ohm cm. RUSH (1962) and SCHNEIDER (1966) found somewhat higher values for the specific resistance of the myo-

cardial tissue, viz. 252-563 ohm cm and 200-280 ohm cm respectively, using the four electrodes method, in situ in a dog. It should be added that our measurements were made within 12 hours after death, whilst measurements made in the following 12 hours gave about 40% higher values than the values found by us within 12 hours post mortem. The much higher values found by SCHWAN *et al.* may be explained by the differences in the method.

We also measured the resistance of connective tissue from the Achilles tendon. 25 measurements on the longitudinal axis of 5 tendons gave an average specific resistance of 172 ohm cm (range 135-273 ohm cm).

The slight difference between the specific resistance of connective tissue and heart muscle is probably partly explained by the longitudinal measurement of the tendon. The specific resistance is somewhat higher measured transversely, but we were unable to achieve great accuracy because of the small cross-section of the tendons. As the connective tissue around the electrodes has no longitudinal structure, it is probable that its specific resistance will have a slightly higher value.

The small differences in the specific resistances of the tissues are as important in the total resistance in the electrode circuit as the electrolyte balance at the moment of measurement, but the large differences, which are encountered in practice, are caused primarily by variations

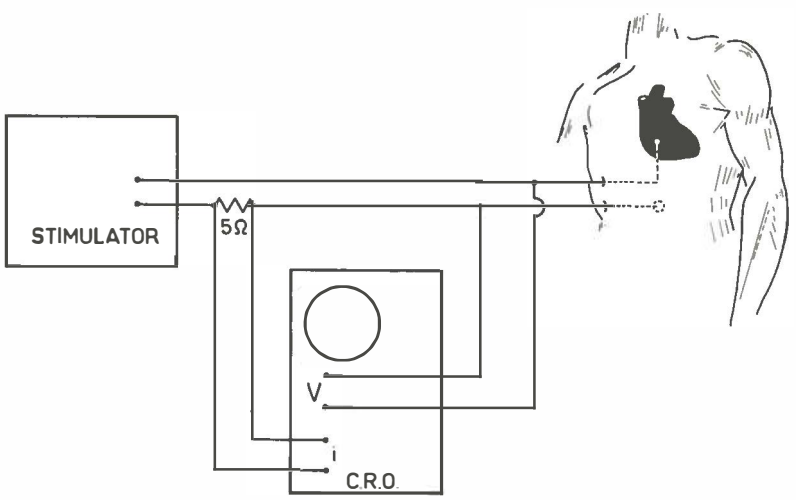


Fig. VI-30. Arrangement to detect the voltage across and the current through an electrode circuit.

in size of the electrodes and the distance between them. To investigate this it is necessary to determine the (real) ohmic resistance in an electrode circuit, and this can be performed by a simple technique.

Many investigators have already detected the potential difference of and the current in an electrode circuit by means of an oscilloscope, see fig. VI-30. The voltage is measured directly, the current by means of a small indicator resistance. The figures observed on the screen vary and depend on the stimulator, but the principle is universally applicable. The measurement is based on the fact that the polarization of the electrodes does not change during extremely rapid changes of current, because polarization is time related. These rapid changes occur at the beginning and the end of the impulse. Ohm's law may be applied to the changes in voltage during this rapid current change.

$$R = \frac{V}{i} = \frac{V_a}{i_a} = \frac{V_p}{i_p}, \text{ where}$$

V = the voltage at the beginning (V_a) or end (V_p) of the impulse and
i = the current at the beginning (i_a) or end (i_p) of the impulse and
R = the (real) constant ohmic resistance of the conduction leads and the tissue.

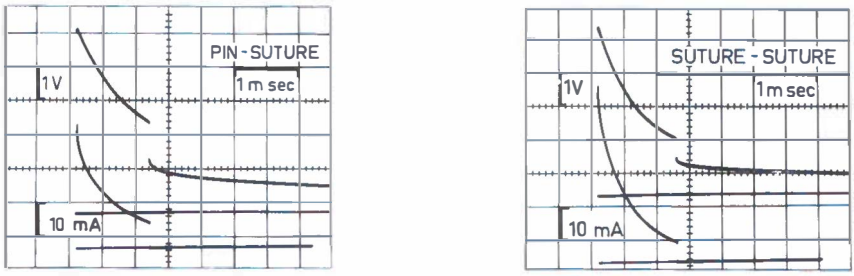


Fig. VI-31. Voltage across (upper curve) and current through (lower curve) an electrode circuit consisting of an intramural pin respectively an intramural suture electrode in combination with an indifferent suture electrode in a dog.
Upper horizontal line: zero voltage, lower horizontal line: zero current. The corresponding fast changes of V and i at the beginning and the end of the impulse are used to calculate the ohmic resistance. See text.

The accuracy of the measurements depends on the accuracy with which the impulses can be read off. By means of known resistances the accuracy has been estimated to vary from 2.5-5%. In figure VI-31 an example is given for the combination of a pin electrode and a suture electrode

with the same indifferent suture electrode for unipolar stimulation. It can be read off from the figure that for the pin-suture combination:

$$R = \frac{V_a}{i_a} = \frac{5.4\,V}{35\,mA} = 154 \text{ ohms at the beginning of the impulse, and}$$

$$R = \frac{V_p}{i_p} = \frac{1.05\,V}{6.9\,mA} = 152 \text{ ohms at the end of the impulse, the mean}$$

ohmic resistance of the pin-suture circuit therefore being 153 ohm and for the suture-suture combination:

$$R = \frac{V_a}{i_a} = \frac{4.95\,V}{53\,mA} = 93 \text{ ohms at the beginning of the impulse, and}$$

$$R = \frac{V_p}{i_p} = \frac{0.5\,V}{5.7\,mA} = 88 \text{ ohms at the end of the impulse, the mean}$$

ohmic resistance therefore being 90 ohm.

These values show that the suture electrode has a lower transitional resistance then the pin electrode.

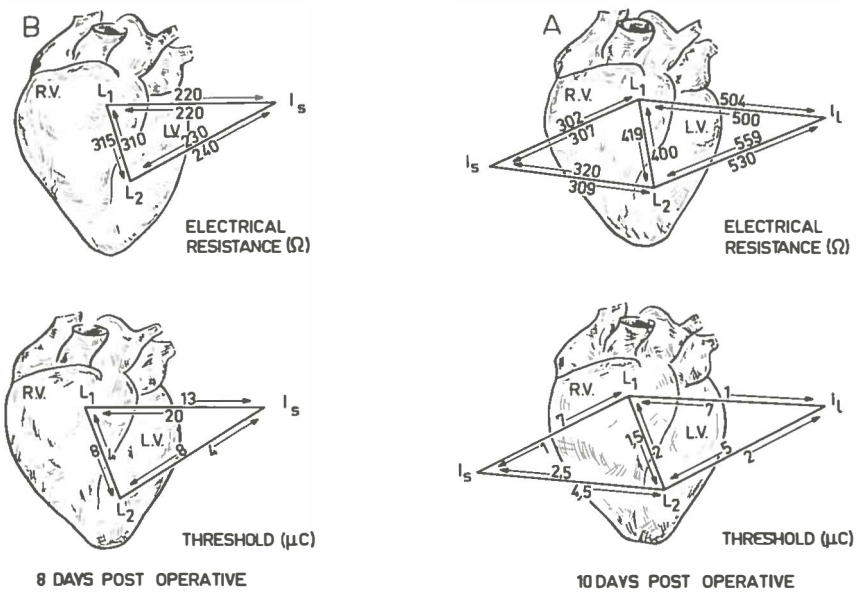


Fig. VI-32. Resistance of electrode circuits (see fig. VI-30,31) and threshold charge (arrow indicates positive pole) in two dogs.
$L_{1,2}$: identical intramural loop electrodes (larger in case B than in case A); I_s: indifferent suture electrode; I_l: indifferent loop electrode.

Qualitatively the same conclusions follow from the measurements on fig. VI-32, showing data from two animals. Two loop electrodes were attached to the heart and a loop electrode and a suture electrode to the thoracic muscles in one animal and in the other two loop electrodes to the heart and a suture electrode to the thoracic muscles. The ohmic resistance for the various electrode combinations was measured in each animal. At the same time the threshold value for each combination was measured with the Cardiotest. We have combined these results in order to demonstrate once more that the stimulation threshold is not dependent on the electrical resistance in the circuit. This is shown especially in figure VI-32B, where the L_1 electrode has a higher threshold than the L_2 electrode, but the resistance in the combinations of the electrodes is practically equal.

The transitional resistance values of the loop electrodes in fig. VI-32B are somewhat lower than those of the loop electrodes in fig. VI-32A. The former electrodes had a somewhat larger surface area due to a thicker core in the spiral loop as mentioned previously. The resistance of the helical conduction wires of the electrodes in the figure varied between 25 and 35 ohms.

Conclusions

- the ohmic resistance with small electrodes is determined primarily by the resistance of the transitional area around the electrode, this resistance being approximately inversely proportional to the radius of the effective surface area of the electrode,
- the ohmic resistance of the transport area between the transitional areas around the electrodes is proportional to the length and inversely proportional to the cross section of this area,
- the relative contribution of the transport area to the total ohmic resistance is higher the greater the size of the electrodes, the greater the length of the transport area and the smaller the effective cross section of this area,
- the above-mentioned resistances are proportional to the specific resistance of the tissues concerned.

The total impedance of the circuit is further determined by polarization.

C. Polarization

By polarization of an electrode we understand the changes which occur at its surface when an electric current passes through it. This current causes a change in the ion concentration around the electrodes, resulting in the formation of a so-called double layer at the electrodes.

The back e.m.f. which arises due to the polarization may be divided into:

- an activation potential caused by the processes at the electrodes, determined by the characteristics of the electrode material and the electrolyte and
- a concentration potential, which arises because ions are neutralised at the electrodes necessitating a supply of ions from the electrolyte to the electrodes, resulting in a concentration gradient of ions in the vicinity of the electrode.

The polarization voltage develops as soon as current passes through the electrodes, but since the build-up of the potentials is a kinetic electro-chemical process, requiring a certain time, no change in polarization voltage occurs during the extremely rapid initial and terminal phase of pacemaker stimulus.

The polarization voltage is therefore determined by:

- the current,
- the surface area of the electrodes and
- the period during which the current passes through the tissue,

and

reaches its maximum when the build-up of the double layer at the electrode is completed. The height of its peak is determined by the characteristics of the electrode material and the electrolyte.

If a polarized electrode is left to itself for sometime, the double layer gradually disappears. In pacemaker electrodes the double layer has practically disappeared after about 0.20 sec., and no polarization voltage is then detectable. As pacemaker impulses at 70 imp./min. follow each other at an interval of about 0.86 sec. and at 96 imp./min. at an interval of about 0.62 sec. any rest-polarization from a previous impulse has disappeared when a new impulse arrives.

The time course of the polarization voltage is clearly demonstrable during stimulation with constant current. Constant impulses at 90 imp./min. of 1, 2, 4, 8 and 16 mA with a duration of 0.25, 0.5 and 1, 2 and 4 msec were given to a dog with an intramural platinum-iridium loop electrode and a stainless steel suture indifferent electrode. The 1 mA

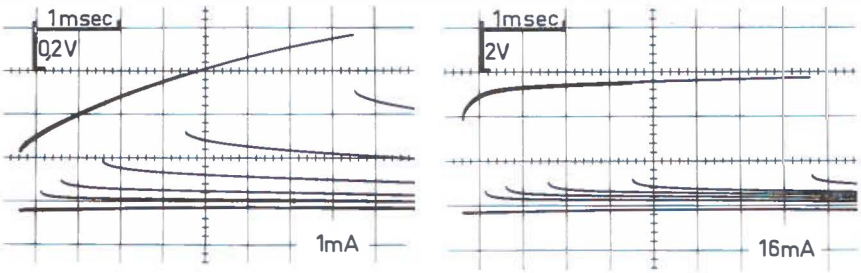


Fig. VI-33. Voltage across a negative platinum-iridium intramural loop electrode and a positive indifferent stainless steel suture electrode in a dog.
Square current pulses, 1 and 16 mA during 0,25-0,5-1-2 respectively 4 msec.

and 16 mA curves are shown in fig. VI-33, recording voltages with varying impulse durations. The rise in polarization voltage always follows the same pattern. The resistance in the circuit and the polarization voltage for the 25 combinations have been calculated from the curves and the latter is shown in fig. VI-34.

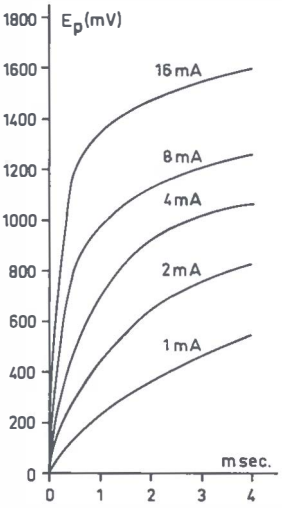


Fig. VI-34. Polarization voltage versus impulse duration for a number of currents through the circuit of fig. VI-33.

Within the accuracy limits of the method the resistance in the electrode circuit (mean 267 ohms – range 256 – 281 ohms) proved to be independent of the current and the time. It is interesting that closely similar findings were noted when the same electrode combination was placed in a bath of 20% physiological saline. The results of NIGHTINGALE and WEALE (1960) corroborate; they found higher resistance values for identical electrode circuits in patients than in normal physiological saline.

Polarization is an important factor in electrical stimulation of the heart. Fig. VI-34 shows that the polarization voltage, which opposes the pacemaker voltage ,reaches a value of about 1-1,5 V with pacemaker impulses. In general the importance of this factor in pacemaker stimulation is greatly underestimated.

In conclusion we may, on the basis of these and other experiments with various electrodes and fluids, state about polarization that:

- the polarization voltage and with it the complex impedance of the electrode circuit increases during the impulse,
- the polarization voltage rapidly increases to a maximum if a high current is maintained for some time,
- this maximum depends on the nature of the electrodes, but is almost independent of the composition of the tissue fluid,
- at a given current strength, the smaller the surface area of the electrode, i.e. the greater the current density at the surface of the electrode, the more rapidly the maximum is reached.

D. Stimulation threshold for voltage

The concept of threshold voltage has already been outlined in the first part of this chapter. Many investigators, amongst whom WEALE *et al.* (1960); NIGHTINGALE *et al.* (1960); BOUVRAIN and ZACOUTO (1961); DITTMAR *et al.* (1962); ZUCKER *et al.* (1963) and BLUESTONE *et al.* (1965), took the threshold voltage as the only parameter of myocardial excitation. We shall discuss here to what extent this is correct.

According to the formula

$$V_{thr} = i_{thr} \times Z_e$$

the threshold voltage is dependent not only on the threshold current i_{thr} but also on the impedance Z_e of the electrode circuit. The impedance has been analysed in section VI-B and C and can be divided into three components:

1. the ohmic resistance of the conduction leads R_l,
2. the ohmic resistance of the tissues between the electrodes R_t,
3. the complex impedance due a.o. to polarization of the electrodes Z_e.

The effect of these components on the threshold voltage is considered now.

1. The ohmic resistance of the conduction leads

The effect of the ohmic resistance of the conduction leads is self-

explanatory. Increased conduction lead raises the effective resistance and with it the threshold voltage.

2. The ohmic resistance of the tissues between the electrodes

Separation of the electrodes increases the resistance and the threshold voltage. With identical electrodes bipolar stimulation thus results in a lower resistance and a lower threshold voltage than unipolar stimulation with a distant indifferent electrode, see fig. VI-35. This figure shows

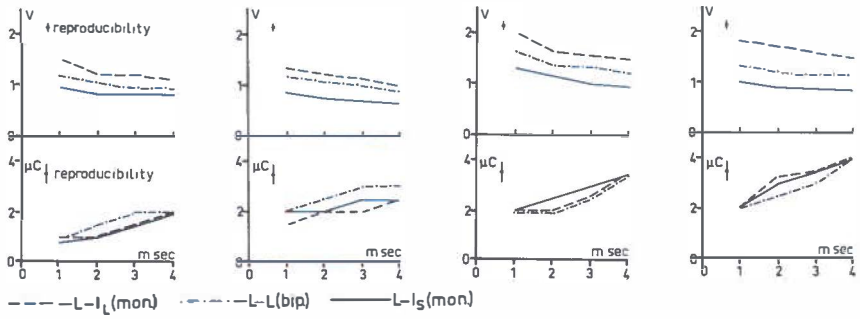


Fig. VI-35. Threshold voltage and threshold charge versus impulse duration in four dogs. L: intramural loop electrode; l_1: indifferent loop electrode (small); l_s: indifferent suture electrode (large). First electrode of each combination is negative.
Threshold charge within the reproducibility limits independent of the electrode combination. Threshold voltage virtually proportional to effective circuit resistance.

higher threshold voltages for unipolar stimulation with a loop electrode in the heart and an identical loop electrode in the thoracic muscles (right 4th i.c.s.) as an indifferent electrode, than for bipolar stimulation with two loop electrodes in the heart, because of the higher effective tissue resistance in the circuit in unipolar stimulation.

The transitional resistance of the area around the stimulation electrodes should be distinguished from that around the indifferent electrode, as it was demonstrated that the smaller the heart electrode is, the lower the current threshold becomes, but the higher is its transitional resistance.
Since the threshold voltage is the product of the threshold current and the resistance of the circuit it varies less with heart electrodes of differing dimensions than does the threshold current. This can be seen from fig. VI-36, where the threshold values of voltage and charge, in addition to the effective resistance in the electrode circuit, are shown

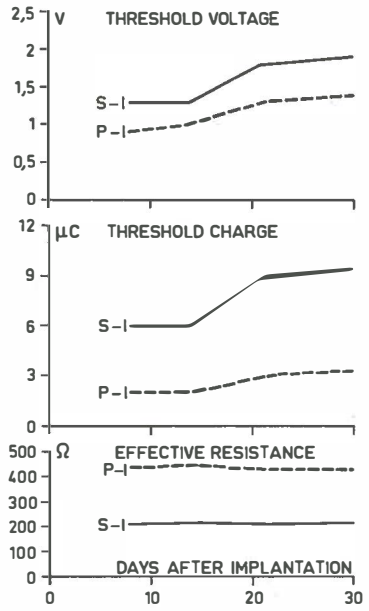


Fig. VI-36. Threshold voltage, threshold charge and effective resistance versus days after electrode implantation for two electrode combinations in a dog. Monopolar cathedal stimulation.
S: intramural suture electrode (large);
P: intramural pin electrode (small);
I: indifferent suture electrode.
Threshold charge (current) virtually proportional to dimensions of heartelectrode, threshold voltage dependent on threshold charge and effective circuit resistance, the latter almost inversily proportional to dimensions of circuit electrodes.

for a pin electrode and a suture electrode as intramural heart electrodes and a suture electrode as an indifferent electrode. The pin electrode has a higher transitional resistance than the suture electrode by virtue of its size, and its lower charge threshold is compensated by this difference in resistance, to the extent, that the differences in the threshold voltage are less than the differences in the threshold charge.

The indifferent electrode has no effect on the current threshold unless the anodal threshold of the second positive electrode in bipolar stimulation has become lower than the cathodal threshold of the negative electrode. If this is not so, the threshold voltage decreases with increasing dimensions of the indifferent electrode, because this reduces its transitional resistance and thus the effective resistance of the circuit (see fig. VI-35). With unipolar systems, the threshold charge of the loop electrodes are found to be identical within the accuracy limits of the method in all four cases, but the threshold voltages on the other hand are higher for electrode systems with a loop electrode than with a large suture electrode as indifferent electrode.

Inflammation around the positive electrode has no effect on the threshold current and little effect on the resistance in the circuit, and hence little effect also on the threshold voltage. An exception to this rule occurs in bipolar stimulation when the anode takes over stimulation.

Infection around the anode then results in a threshold increase for both current and voltage.

Regarding the effect of the electrodes with unipolar stimulation, we may therefore state:

- changes in the stimulating electrode cause greater variations in the threshold current than the threshold voltage,
- changes in the indifferent electrode have no effect on the threshold current, but do have effect on the threshold voltage,
- infections around the stimulating electrode result in rises of both the threshold current and voltage,
- infections around the indifferent electrode have no effect on the threshold current and little or no effect on the threshold voltage.

For bipolar stimulation the same rules apply. Normally the cathode is the stimulating electrode and the anode the indifferent electrode, but their roles are reversed when the cathodal threshold of the negative electrode has become greater than the anodal threshold of the positive electrode.

3. The complex impedance due to the polarization of the electrodes

Fig. VI-34 shows that the polarization voltage increases when the current increases at the same impulse duration, but the voltage is however not proportional to the current and ultimately reaches a maximum value. When there is an increase in threshold current e.g. due to inflammation around the stimulating electrode, the effective resistance of the circuit therefore decreases and the threshold voltage does not increase then linearly.

Polarization has a particularly great effect when the threshold current is low. Fig. VI-34 shows that the polarization voltage of the electrodes at an impulse duration of 2 msec increases from 0.37 to 0.9 V when the current threshold increases from 1 to 4 mA, but a further increase to 8 mA only increases the polarization voltage to 1.1 V.

For this reason we have always calculated the effective resistance of an electrode circuit at the operational current and voltage. The polarization voltage is then constant as long as the operational current is constant. RACE *et al.* (1963) determined the effective resistance of the circuit at the threshold voltage and the threshold current. The drop in resistance which they observed with a rise in threshold should not therefore be ascribed to a drop in the transitional resistance of the

electrode, but to the relatively smaller effect of the polarization voltage when the current increases.

To sum up threshold voltage is not only determined by the heart electrode, but also by the rest of the electrode circuit. It depends on the real resistance in the circuit, which is constant for a given combination of electrodes, and on the polarization voltage which depends in a complicated way on the current in the circuit. The threshold voltage therefore gives a distorted picture of the stimulation threshold of the heart and this is greatest at low threshold levels. Thus, when comparing various electrode combinations, the threshold voltage should not be used as an indication of the excitability of the heart.

E. Stimulation threshold for energy

Some investigators, NASH (1964) and PRESTON (1965) inter al. chose the threshold energy to determine the excitability of the heart.

The energy threshold, according to the formula

$$W = i \times V \times t$$
$$= i^2 \times Z_c \times t,$$

depends on the threshold current (i), the impedance of the circuit (Z_c) and the impulse duration, and therefore like the threshold voltage, it depends on the impedance of the circuit and is not suited to indicate the excitability of the heart. Confusion may result from its use for this, but it may be important in determining the optimal duration of pacemaker impulses, which will be considered in Chapter VIII with the stimulators.

F. Operational value

In discussing threshold values we took the minimal stimulus needed to stimulate the heart with various combinations of electrodes, but the artificial pacemaker delivers greater impulses than the threshold values. We have therefore introduced the term operational value for the actual current- and voltage used. These values depend on the type of output circuit of the pacemaker (see Chapter VIII).

The operational values are initially higher than the threshold values, to give a safety margin after implantation.

G. Relative threshold

The safety margin or the reserve for a possible rise in threshold depends

on the ratio between the operational current and the threshold current, which we have termed relative threshold and expressed as a percentage, thus:

$$\text{relative threshold} = \frac{\text{threshold current}}{\text{operational current}} \times 100\%.$$

The threshold current and the operational current may be replaced by the threshold charge and the operational charge respectively, giving the formula:

$$\text{relative threshold} = \frac{\text{threshold charge}}{\text{operational charge}} \times 100\%.$$

These currents and charges may be determined for any combination of electrodes by means of the Cardiotest. The duration of the Cardiotest impulse is then set at that of the particular pacemaker and the threshold values are determined. With a current pacemaker the relative threshold may be calculated, because its operational current is a given factor. With a voltage pacemaker the operational values are determined by setting the circuit voltage of the Cardiotest at the circuit voltage of the pacemaker and then reading off the operational current i.e. the operational charge and the relative threshold can then be calculated.

The relative current or charge threshold give a precise insight into the safety margin of the artificial stimulation, but this is not so with the relative voltage threshold as previously indicated.

As pacemaker life is inversely proportional to the operational current, an optimal electrode combination should give low threshold currents in the long term, facilitating a low operational current and therefore a low relative threshold.

Threshold current is lowest when the stimulation electrode is small, but this is negated by relative excessive tissue formation around the electrode after implantation. Our experience is similar to that of ZOLL (1963), CHARDACK (1964) and KANTROWITZ (1964) who expected a two-to-threefold rise in threshold current using medium sized electrodes.

For a given heart electrode the operational current of a current pacemaker can be fixed during construction, whereas the operational current of a voltage pacemaker can be made as high as possible by making the second electrode as large as possible and locating it as close as possible to the heart, or placing it on or in the heart. The relative threshold is then minimal but the high operational current will soon exhaust the

batteries. A compromise must therefore be sought, keeping the relative threshold low at minimal operational current. This may be achieved in various ways, both for unipolar and for bipolar stimulation with current, voltage or intermediate types of pacemakers. Experience and data collected with the threshold pacemaker (see Chapter IX) will show what initial safety margin is required for various heart electrodes. The relative threshold may then be adjusted to give maximal pacemaker life with a minimal operational current.

The relative threshold during prolonged clinical use will thus indicate the optimal electrode combination. This is not necessarily the electrode with the lowest threshold. If the relative thresholds are almost equal, the combination of electrodes with the lowest operational current is chosen. By determining the relative threshold each time a pacemaker is replaced, one can monitor the stimulation threshold and the safety margin of the combination of electrodes and gain an insight into the behaviour of these combinations after implantation.

Electrode analysis is followed in the next chapter by another important aspect of the electrode circuit – impulse transmission by the conduction leads.

Transmission of the impulses

CHAPTER VII

In the preceding chapter we discussed the electrodes or that part of the circuit where the electrical impulse reaches the heart muscle. Here we consider impulse transmission from the pacemaker to the electrode.

We have already distinguished between

1. direct impulse transmission and
2. indirect impulse transmission.

Both types have a number of variations.

1. DIRECT IMPULSE TRANSMISSION

By direct impulse transmission we mean the direct transmission of the stimulation impulse from the pacemaker to the electrode through one or more uninterrupted conduction leads. As indicated in Chapter IV, this principle is used with transthoracic and transvenous leads.

A. Direct transthoracic impulse transmission

The lead used for direct impulse transmission to conduct the impulse from the pacemaker to the electrode must fulfil these criteria:

a. it should be unbreakable;
b. it should be well insulated by material which will not be rejected by the body;
c. it should be of low electrical resistance, so that there is minimum loss of energy;
d. it should be of the same composition as the electrode, to avoid contact potentials between two different metals;
e. it should be flexible and slightly elastic, to avoid excessive force on the electrode frame and the pacemaker connection.

These requirements have led to the development of a large number of different types of lead. Wire fracture and insulation defects have in particular frequently interrupted stimulation, necessitating in most cases the replacement of the whole electrode.
Types of transthoracic leads:

1. Lead with single wire. This is the simplest type of the conduction lead. A semi-rigid stainless steel version was used by THEVENET *et al.* (1958) for a short time, in combination with an external pacemaker. This combination is still used by others, but the rigidity of the lead resulting in a high stimulation threshold and poor fixation of the electrode are great disadvantages.

2. Lead with braided wires. A stainless steel version was used by THEVENET (1958) *et al.*, and FURMAN *et al.* (1961) used it for their indifferent electrode. WEIRICH *et al.* (1957) employed a silver plated copper version.

This lead is more flexible than a single lead, but it is unsuitable for long term stimulation because it is very fragile. A variety of this lead is

3. Lead with multistrand wires. There are many versions of this lead. In its simplest form it consists of 6 interbraided wires. A copper version was used by CLARK (1959), while HUNTHER *et al.* (1959) used stainless steel for their bipolar electrode (fig. VII-1A), but it fractured frequently due to metal fatigue (CHARDACK 1964).

A more complicated version, consisting of 7 groups of 7 wires insulated by teflon, was used by ZOLL (1964 *et al.*) and by us (VAN DEN BERG *et al.* 1962, fig. VII-1B).

ZOLL (1964) used this lead first with an interposed platinum electrode but he noted fractures at the contact between the two metals, probably caused by corrosion due to contact potentials. Later versions, see Chapter VI, consisting of 7 groups of 11 wires and with an electrode of another material, also showed fractures.

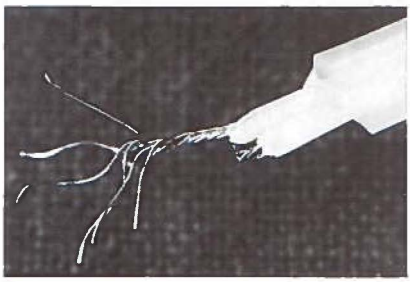
A 147 stainless steel wire type (EISENBERG *et al.* 1965) also showed fractures, and even a lead with 343 stainless steel filaments was developed (MORRIS 1966) but no further details are known about it.

Versions with other metals such as silver, gold and platinum (GLENN 1964) were also very fragile.

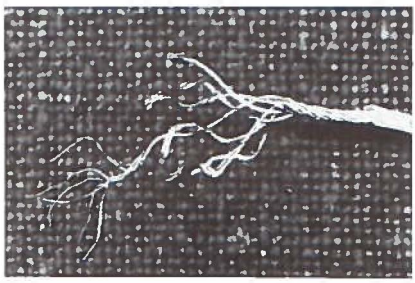
The frequent occurrence of fractures made this type of lead unsuitable for long term heart stimulation.

An improvement is found in:

4. Lead with bands and nylon core. This lead, described by ELMQVIST and SENNING (1960), consists of a braided nylon core surrounded by 4 flattened stainless steel bands insulated by a polyethylene coating (fig. VII-1C).

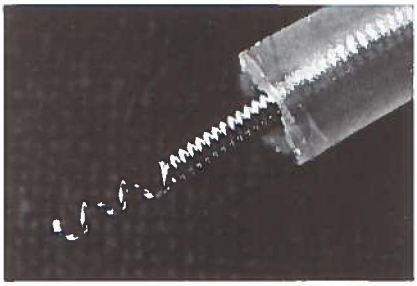


A. Lead with multistrand (1 × 6) stainless steel wires.

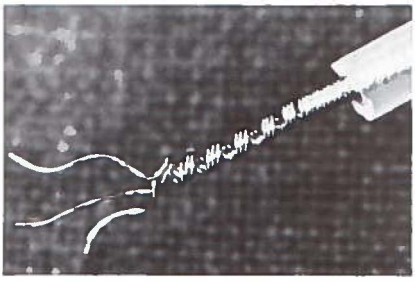


B. Lead with multistrand (7 × 7) stainless steel wires.

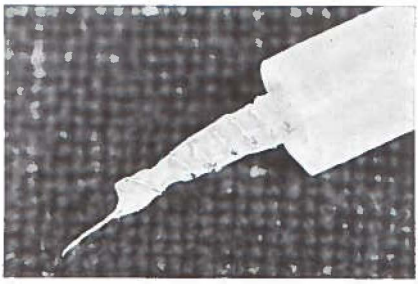
C. Lead with (4 flattened) stainless steel bands and nylon core.



D. Lead with single helical elgiloy wire.



E. Lead with three helical stainless steel wires.



F. Lead with single helical platinum-iridium (90-10) wire and silicon rubber core.

Fig. VII-1. Various types of electrode leads.

The insulation is one of the weak points of this lead, as the polyethylene is easily damaged, resulting in electrolysis and corrosion of the stainless steel. However mechanical characteristics of the bands are good, and reports of fracture are exceptional (FRIESE 1965; RODRIGO 1966) as the nylon core prevents sharp kinks in the lead. A disadvantage of the current version of this lead is that the bands consist of stainless steel, while the electrode is platinum, so that poor or damaged insulation results in electrolysis occurring at the contact between the two materials and separation of the electrode and its frame from the lead. This phenomenon has been observed especially when the lead is combined with the epicardial disc electrode (FRIESE 1965; OVERBECK *et al.* 1965) as the insulation in the electrode frame is not optimal, but its occurence is not known to us when the lead is combined with the endocardial electrode.

Compared with preceding types the disadvantages of this lead are small, but they exceed those of another type:

5. *Lead with helical wire.* This consists of a helical wire with a diameter of 0.25 mm, the diameter of the spiral itself being approximately 1.1 mm. (CHARDACK 1964) and others. The spiral is mobile in an insulating silicon rubber tube. The early versions of this wire consisted of a platinum-iridium alloy, which is still being used by BREDIKIS (1966) *inter al.*, but the low elasticity modulus of this alloy resulted in many fractures, and elgiloy is now widely used instead of platinum-iridium (NATHAN 1965; CHARDACK 1965; fig. VII-1D). Elgiloy has given better results because it possesses a higher elasticity modulus and is therefore more resistant to distortion. The lead also has the advantage that the electrode is an extension of the conduction wire, so that contact potentials are avoided. Furthermore, the lead is elastic and flexible, but the spiral contains no core and sharp kinks may occur. If the elasticity limit of the lead is exceeded the spiral is deformed at the point of flexion, a sharp kink remaining, where fracture may occur.

Another disadvantage of this conduction lead is insulation fracture. Within 2 years of implantation we observed 5 (14%) instances of torn silicon rubber insulation which was probably due to the silicon rubber becoming less elastic in course of time. In spite of this the lead represents a considerable improvement compared with the multistrand type.

Modifications of this lead are the stainless steel triple spiral wire, used by DAVIES *et al.* (1965, fig. VII-1E) and the spiral composed of 4 elgiloy wires used by GLENN *et al.* (1964). Increase in number of spirals in the lead gives an additional safety factor (GLASS *et al.* 1963).

6. Lead with helical wire and silicon rubber core. Our experience with multistrand stainless steel leads were equally disappointing, as was already mentioned in Chapter VI under the subheading suture electrodes. The fractures we observed were the result of metal fatigue or corrosion when two metals were used.

Fracture due to metal fatigue is dependent on the composition of the lead and the mechanical stress exerted upon it. By accurate choice of the location of the electrode and the transthoracic path of the lead, mechanical stress may be minimised, which explains the discrepancies in results obtained with this lead. Occasionally, fractures occurred after 3 months, where other suture electrodes inserted in Groningen functioned properly for 50 months.

In our experience the mechanical stresses on the lead are greatest
- at the exit of the lead from the pacemaker,
- at the place, where the lead passes under the ribs and
- at the place where the conduction lead perforates the skin when combined with an external pacemaker as reported by BLUESTONE *et al.* (1965) and others.

Since we have only used this lead with implanted pacemakers we have not observed this last type of fracture.

Fractures at the exit from the pacemaker occur especially when the electrode is connected perpendicularly to the pacemaker. The pacemaker then forms a lever during certain body movements, which may kink the lead and ultimately end in fracture of the wire. Such fractures in other types of lead were noted by CHARDACK *et al.* (1965) and KAHN *et al.* (1965) and others. To overcome this weakness, CHARDACK *et al.* built up this part of the lead with silicon rubber, while KANTROWITZ *et al.* (1962) adapted the pacemaker, but neither modification completely solved the problem. We have used a tangential function between lead and pacemaker, then winding the lead once round the pacemaker before it passes to the heart (VAN DEN BERG *et al.* 1962). This was a great improvement, fractures of stainless steel multistrand leads were not then observed at this site and we have used this type of junction in all later versions of pacemakers and conduction leads.

Although lead fractures close to the pacemaker interrupted stimulation, it was not necessary to replace the whole electrode, as the lead could be reconnected when the fractured section had been removed. Therefore a further thoracotomy was not necessary, as was frequently the case in fractures at the point where the lead passed under the ribs. This fracture was only observed in those cases in which the pacemaker

was placed in the abdominal area (MORRIS 1965) and may be explained by the forces to which the lead is subjected when the patient bends forwards or backwards. These fractures were obviated by placing the pacemaker on the thoracic wall (HOMAN VAN DER HEIDE 1962) e.g. under the pectoral muscles. KAHN *et al.* (1965) went so far as to attach the pacemaker to the interior of the thoracic cavity in one case. This, however, requires further thoracotomies when the pacemaker has to be renewed.

Although these improvements prevented fracture at the places described, we still observed fractures at non-specific points along the path of the suture electrodes. These fractures occur particularly when the lead has been bent sharply at a certain place, which predisposes to fracture. Using a flexible wire with several thin filaments, fracture occurs less often than with a solid thick lead. If, however, one of the wires of a multistrand lead breaks, its ends damage the insulation and the other wires, causing them to fracture more rapidly because of electrolysis and corrosion at the fracture area. For this reason we rejected this type of lead as being fundamentally unsuitable and we have therefore attempted to develop a better lead along new lines.

We started from the principle that the lead should have no place with a predeliction for fracture, i.e. the lead should be flexible and extensible but it should be impossible to kink it.

We experimented with a lead consisting of a double wire of steel wool and also with a rubber tube filled with mercury, which was also investigated by JACOBSON and TEEKEL (1961). We also tried filling the tube with stainless steel pellets and a chain of silver balls, but resorted to a helical wire of platinum-iridium embedded in silicon rubber. Platinum iridium was chosen because it is electrochemically optimal for the electrode and use of the same material in the lead prevents contact potentials. The wire was completely embedded in silicon rubber to attempt to absorb much of the mechanical stress in the insulating material and at the same time preventing sharp kinks in the lead.

To a spiral wire the formula applies:

$f = \frac{4\pi n R^2 \tau}{dG}$, in which

f = safe extension of the spiral along its axis,
τ = safe shear stress of the material,
n = number of turns of the wire in the spiral,
R = radius of the turns,
d = diameter of the wire,
G = shear modules of the material.

Thus it appears that the safe extension f can be made as large as desired by using a large number of turns of the wire, a large radius of turn and a small diameter of wire. This safe extension of the spiral can thus be made much larger than might occur under the most adverse conditions, as extension of the lead is determined by its body i.e. the silicon rubber embedding the spiral. This is also valid for forces perpendicular to the axis of the lead.

Leads constructed on these theoretical principles were tested for fracture by this technique. The lead was fixed at one point and 3 cm away it was oscillated through 120° at a frequency of 50 Hz. Thus it was subjected to 3000 vibrations per minute which were counted by a meter in the same electrical circuit as the lead. If a fracture occurred in the lead, the circuit of the vibrator and the meter would be interrupted. Tests of a 0.2 mm wire diameter (d) spiral lead ($n = 15$/cm, $R = 0.7$ mm) showed that fracture occurred after $5\text{-}10 \times 10^4$ vibrations whereas with an 0.1 mm wire diameter fracture did not occur until a mean of 2×10^7 vibrations and in this case it was due to the silicon rubber tube wearing out at the fixation point rather than primary wire fracture. The importance of the rubber core was shown in a number of experiments with 0.1 mm wires by leaving it out between five turns. The lead broke at these places after $5\text{-}10 \times 10^4$ vibrations or the same as the 0.2 mm type. Thus we chose for our lead a platinum-iridium wire with a diameter of 0.1 mm, an internal diameter of spiral of 0.7 mm and 15 turns/cm, the external diameter of the lead being 3 mm.

Similar experiments were carried out by GLENN *et al.* (1964), who showed that a spiral lead with a core gives better results than one without a core. They concluded that elgiloy gives better results than platinum-iridium, but they compared a platinum-iridium wire with a diameter of 0.25 mm with an elgiloy wire with a diameter of 0.15 mm. The importance of the wire diameter in this respect both in theory and in practice is shown before.

Although the experiments have shown that a thin wire gives mechanically better results than a thick wire, its disadvantage is its greater electrical resistance as, according to formula $R = \rho \times \frac{l}{O}$, the resistance is inversely proportional to the cross section of the wire. Since the wire is used as a spiral so that its length is several times that of the lead, it offers a considerable resistance. Thus, the wire diameter should not be too small because slight variations in thickness are then important. The resistance of our 70 cm single conduction lead is 140-160 ohm.

With the intramural loop electrode, however, it was possible to include a second conduction lead which halved the total resistance of the lead (i.e. 70-80 ohm) and caused no practical difficulties. Also with this lead fracture of one wire would not interrupt stimulation but merely increase the total resistance.

Although we had to modify the loop electrode after fractures occurred in the first version (see Chapter VI), no fracture has been observed by us or by others, in their conduction leads, either in the insulation or in the wires, and for this reason we believe that use of these leads gives reliable transthoracic stimulation.

B. Direct transvenous impulse transmission

The requirements for a satisfactory lead for direct transvenous impulse transmission are similar to the transthoracic leads with these additions:
- it should not cause any intravascular complications;
- it should be flexible to avoid perforation of the myocardium by its tip, but have enough rigidity to facilitate its introduction and positioning in the right ventricle.

Compared with the transthoracic lead, the transvenous catheter electrode is subjected to less mechanical stress which might result in fracture because of its location in the vascular system.

The insulation of the wires in the catheter and the acceptance of the catheter by the vascular system pose no difficulties. Both polyethylene (FURMAN and SCHWEDEL, 1959; LAGERGREN and JOHANSSON 1963) and silicon rubber (CHARDACK 1964) provide good insulation without disturbing the vascular system and after some time the catheter is largely coated by a layer of fibrin (see Chapter VI, tissue reactions).

The difficulty with catheter electrodes is the fact that their flexibilities should be different during and after introduction. This has led to the development of two types of catheter electrodes viz.:
1. the solid catheter electrode, and
2. the catheter electrode with stylet.

Variations of both these basic types have been tried.

1. Solid catheter electrode

a. Catheter electrode with single wire. This is the simplest form of catheter electrode. A stainless steel version with polyethylene insulation was used in the first clinical application of transvenous stimulation by FUR-

MAN and SCHWEDEL (1959). Its disadvantage was fracture occurring at the connection with the pacemaker and along the catheter (SCHWEDEL and ESCHER 1964) and it proved to be too rigid, causing perforation of the ventricular wall (SOWTON 1963). A modification of this catheter was used by BOUVRAIN and ZACOUTO (1961) in combination with an external pacemaker. Theirs had an open lumen, permitting perfusions through it.

b. Catheter electrode with braided wires. This catheter electrode was used by SCHWEDEL and ESCHER (1964). It consisted of a braided wire connected to a platinum electrode. The wire was less rigid than the single wire type, but also fractured, both at the pacemaker connection (SCHWEDEL and ESCHER 1964) and in course of the lead. These latter fractures were found especially in the bipolar version (PARSONNET 1964 and SOWTON *et al.* 1964).

c. Catheter electrode with bands and nylon core. This catheter electrode is identical to the lead used by ELMQVIST and SENNING (1960) for transthoracic stimulation. It was first used as transvenous lead in February 1962 by LAGERGREN and JOHANSSON (1963) in combination with a stainless steel indifferent electrode, which was later replaced by platinum.

This transvenous lead with an outer diameter of 1.2 mm, has of course the same weaknesses as the transthoracic one, namely, the vulnerability of the polyethylene insulation and the junction of stainless steel bands with the platinum electrode. However, no cases of electrolysis and corrosion at this point have been reported, probably because there is an extra silicon rubber insulation tube around the contact area. On the other hand in some cases fracture of one or more of the four stainless steel bands near the pacemaker were seen (RODRIGO 1965).

Compared with the two other catheter electrodes, results with this type are more favourable (LAGERGREN *et al.* 1966), but the lead has the disadvantage of being too flexible for easy introduction. LAGERGREN (1966) under X-ray screening uses as pecial rotating table to change the position of the patient for its insertion.

A simpler solution was reported by VAN DIJK *et al.* (1963) and BORST *et al.* (1965). They used a special hollow catheter whose internal diameter was greater than that of the lead (1.2 mm) but less than that of the electrode tip (2 mm). It was passed down over the whole length of the lead, thus affording the lead some rigidity during its introduction, and it was later withdrawn when a satisfactory position for the electrode in the

right ventricle had been obtained. To facilitate withdrawal the hollow catheter was split along its whole length, except the last few millimeters near the electrode tip. Electrode displacement occurs occasionally with this technique, but it is simple to reposition it at the initial procedure. However, repositioning may become difficult later, as the endothelial coating impedes the re-introduction of the hollow catheter.

In view of this, another type of catheter electrode was found to be preferable.

2. Catheter electrode with stylet

The catheter electrode was described by CHARDACK (1965) *inter al.* It consists basically of the helical wire used in transthoracic stimulation. The wire is wound around a thin teflon tube, through which a stainless steel stylet may be inserted giving a certain degree of rigidity during electrode introduction.

Chardack's catheter electrode is bipolar and in the early models, a stylet was used in one of the two spirals, but in later versions stylets were used in both spirals. This catheter electrode has the disadvantages that the electrodes are rather large, as mentioned in the preceding chapter and the catheter even without a stylet is rather rigid, and perforations of the ventricle have been observed by us (fig. VII-2) and by others (a.o. SYKOSCH 1966). This rigidity is apparently due to the thick twin helical wires (0.25 mm diameter) and the twin teflon tubes. This catheter electrode has been modified by NATHAN *et al.* to a unipolar electrode giving greater flexibility.

We also constructed a unipolar catheter electrode, consisting of a nylon tube with stylet surrounded by the helical wire used for the transthoracic leads (see Chapter VI) insulated by silicon rubber. The wire spiral is embedded in the silicon rubber, in contrast to Chardack's catheter, where there is no rubber between the teflon core and the silicon tube. With our catheter the conduction wire is single, not double as in the transthoracic lead. We therefore increased the diameter of the wire from 0.1 to 0.15 mm, giving a lower electrical resistance (90-100 ohms) and more rigidity enabling improved fixation of the electrode. Chardack and Nathan used elgiloy wires, whereas we have used platinum iridium. Our catheter electrodes have only been in use since 1967 but in this time no difficulties have occurred.

In conclusion, it may be said that after initial difficulties, a number of

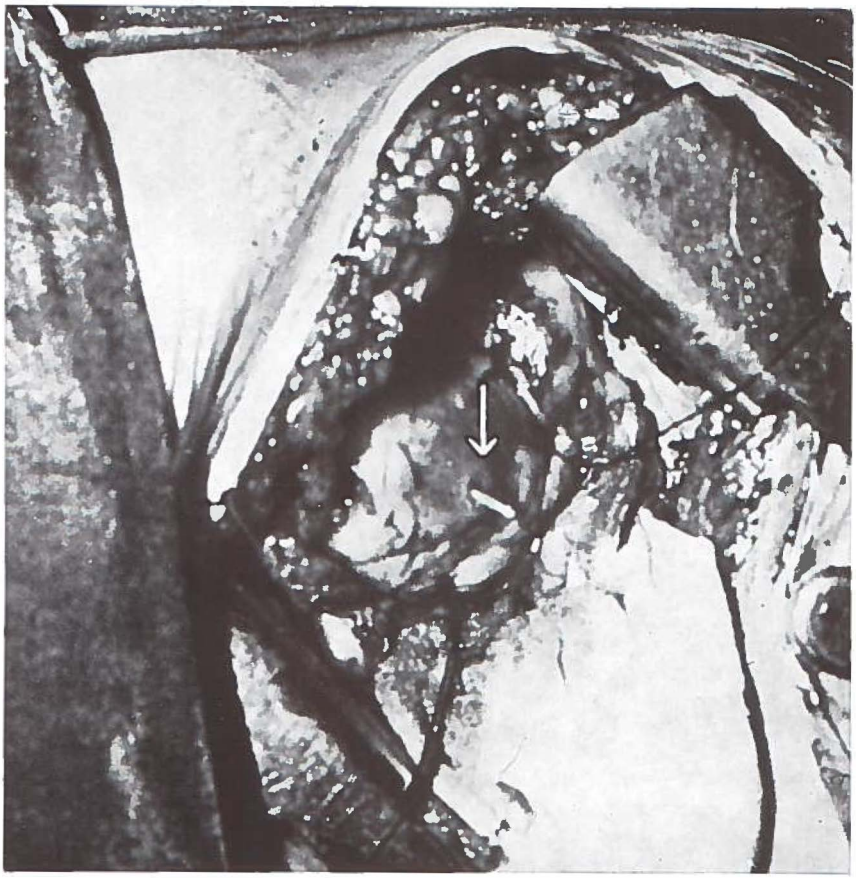


Fig. VII-2. Perforation of the wall of the right ventricle by a bipolar catheter-electrode (arrow) in a patient. The heart is exposed after a left hemithoracotomy and opening of the pericardium.

conduction leads has been developed which make both long term transthoracic and transvenous stimulation possible.

II. INDIRECT IMPULSE TRANSMISSION

Indirect impulse transmission means transmission of the stimulus without direct contact between an external pacemaker and internal electrodes, inductive impulse transmission, in some versions by means of a carrier-wave, being involved.

With indirect impulse transmission conduction leads are also neces-

sary in most cases, and the same principles apply as for the transthoracic and transvenous conduction leads. Here we will only consider briefly the principle of indirect transmission.
Induction methods of impulse transmission may be divided into
A. magnetic coupling
B. electro-magnetic coupling.

A. Magnetic coupling

Magnetic coupling is based on theprinciple of FARADAY (ca. 1830), who stated 'as long as that part of a magnetic field surrounded by a closed conductor changes in strength, an induction current exists in this conductor.'

In magnetically coupled impulse transmission the closed conductor consists of a subcutaneously implanted coil to which the stimulation electrodes are connected. The magnetic field is set up by a current in a primary coil, attached to the body (externally) and parallel to the secondary coil (fig. VII-3). The strength of the current induced in the secondary circuit depends on several factors.

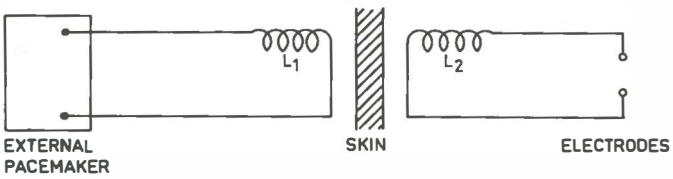


Fig. VII-3. Scheme of impulse transmission by magnetic coupling. $L_{1,2}$: coil.

1. the number of turns of the transmission coil.
2. the number of turns of the receiver coil.
3. the strength of the primary current.
4. the diameter of the primary coil.
5. the diameter of the secondary coil.
6. the distance between the coils.

Considerable energy is lost in this method of impulse transmission first applied clinically by ABRAMS (1960), and an improvement was introduced by SUMA, FUJIMURI *et al.* (1965) among others. They concentrated the magnetic field in the coils by introducing an iron core in the coils, but better results may be obtained by using a carrierwave in impulse transmission.

B. Electro-magnetic coupling

The e.m.f. generated in a coil is proportional to the rapidity with which the magnetic field within the turns alters. Such a rapid alteration is achieved by electro-magnetic coupling, using a high frequency current in the primary tuned coil. GLENN *et al.* (1964) and EISENBERG *et al.* (1965) use carrierwaves with a frequency of 2 MHz, CAMMILLI *et al.* (1964) 4-5 MHz.

The stimulation impulse is transmitted as the envelop of the high frequency (radiofrequency) signal and may have any desired shape. The radiowave itself has too high a frequency to stimulate the heart. To derive the stimulation impulse from the RF-signals via the secondary tuned coil, a diode is included in the secondary circuit as a rectifier, reducing the signals to half sinusoidal waves which have a cumulative effect in a condensor. In our example (fig. VII-4) they correspond

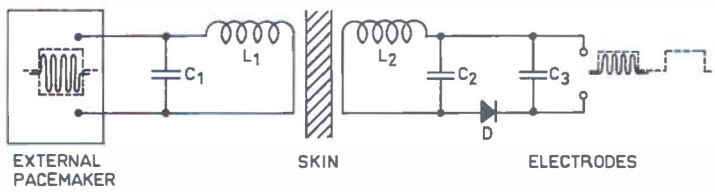


Fig. VII-4. Scheme of impulse transmission by electromagnetic coupling. $C_{1,2,3}$: condenser; $L_{1,2}$: coil; C: diode.

approximately to a rectangular impulse. SCHNEIDER (1966) calculated an efficiency of approximately 16% for conditions corresponding to clinical situations. SCHUDER (1965) increased the efficiency of the electro-magnetic coupling by introducing an iron core in the secondary coil.

This more efficient transmission by means of tuned primary and secondary circuits also enables the secondary coil to be placed directly on the heart (CAMMILLI 1962). Intracorporal conduction leads are then unnecessary.

Having considered electrodes and impulse transmission, in the next chapter the last section of the stimulation unit, the stimulator itself, will be discussed.

Stimulators

CHAPTER VIII

INTRODUCTION

The principal part of a stimulation unit is the stimulator itself, which determines the shape and frequency of impulses administered to the heart. In this chapter research into the optimal impulse and frequency and the applications to the design of the basic pacemaker circuit are discussed. The construction of the circuit will be considered in the second part of this chapter, and finally the various types of stimulators, which have been developed from the basic pacemaker, are discussed.

1. STIMULATION IMPULSE AND IMPULSE FREQUENCY

A. Stimulation impulse

1. Impulse shape

In contrast to the effect of frequency, the effect of varying impulse forms on stimulation has only been analyzed by a few investigators (ZOLL *et al.* 1954, ANGELAKOS and TORRES 1964). In our research the effect of 5 impulse forms was investigated (fig. VIII-1), in 540 measurements; they were:

- a rectangular impulse
- an impulse with a sawtooth upstroke
- an isosceles triangular impulse
- an impulse with a sawtooth downstroke
- a biased condensor discharge impulse.

The measurements were carried out with a specially developed constant current apparatus, the Multicardiotest. With this auxiliary apparatus it was possible to vary the duration of the rectangular impulse continuously from 0.5 to 22 msec., and that of the other impulses from 0.5-20.5 msec. in steps of 0.5 msec. The current for all the impulses

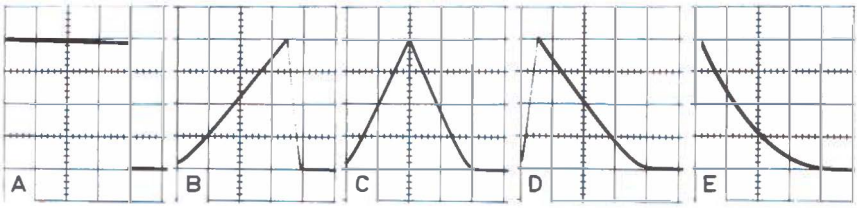


Fig. VIII-1. Impulses with various shapes used to study the influence of the shape of the impulses on the stimulation threshold. Current stimulator.
A: rectangular impulse; B: increasing sawtooth impulse; C: isosceles triangular impulse; D: decreasing sawtooth impulse; E: biased condenser discharge impulse.

was adjustable between 0.2 and 20 mA, with an accuracy of ca. 0.025 mA for the range 0.2-2 mA and ca. 0.25 mA for the range 2-20 mA.

The measurements were performed on 6 animals within 14 days of implantation of the electrodes. In one case the measurements were repeated after 3 months with essentially the same results, i.e. with the same ratio of the threshold values. All animals had a suture indifferent electrode in the thoracic muscles near the right fourth i.c.s. and two heart electrodes either epicardial disc or loop electrodes, intramural pin, suture, coil or loop electrodes or an endocardial catheter electrode. During the measurements it was possible to read off the current threshold on the Multicardiotest, and to determine the voltage threshold, visible on an oscillograph, for impulse durations of 1, 2, 3 and 4 msec, at a rate of 70/min. With a given impulse shape the threshold value appeared to depend on the electrode combination. The ratio of the threshold values for various impulse shapes with a given electrode combination, however, was virtually independent of the electrode combination.

In fig. VIII-2 the mean values of all measurements with various electrode combinations are shown in three groups, viz. the average values for unipolar cathodal and anodal stimulation, and for bipolar stimulation.

It is clear that the conclusions drawn in Chapter VI are confirmed for all impulse forms, i.e.

- anodal current thresholds are higher than cathodal current thresholds;
- bipolar stimulation and cathodal stimulation, within the accuracy of measurement, yield the same current thresholds if the negative electrode is the same in both cases.

Comparing the (peak) threshold current for various impulse shapes at the same impulse duration it appears that:

- the lowest threshold currents are found with a rectangular impulse,

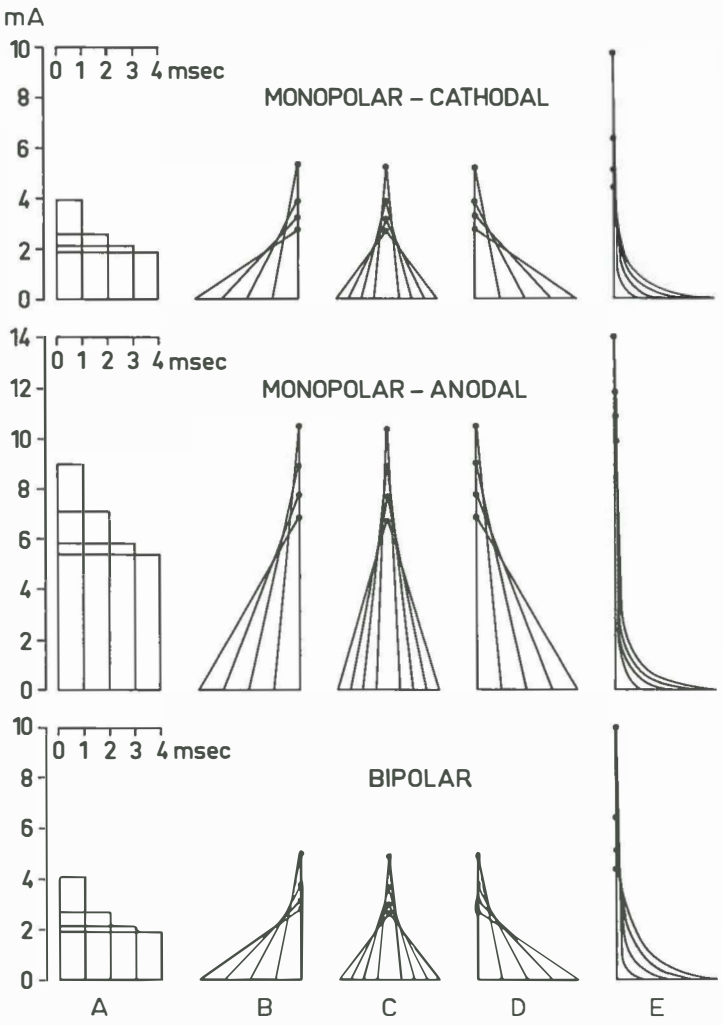


Fig. VIII-2. Threshold impulses for the 5 shapes of fig. VIII-1. Current stimulator. 4 impulse durations. Each block, triangle etc. represents the mean value for various electrode combinations in 6 dogs.

- the highest threshold currents are found with a biased condensor discharge impulse,
- the threshold currents with the triangular impulses lie within this range and the variations of the wave from of the triangular impulse do not alter the threshold current significantly.

The mean threshold currents at 2 msec. are shown in table VIII-1.

ANGELAKOS *et al.* (1964) also found higher threshold values for triangular impulses. They, however, only investigated rectangular impulses and triangular impulses with sawtooth upstrokes. ZOLL *et al.* (1954) reported few details of their investigations, but they concluded that 'rounded' electric impulses with an average duration of 2-3 msec. were optimal, whilst a variety of other monophasic and biphasic spikes, monophasic and biphasic rectilinear and sinusoidal impulses were found to be less effective.

The effectiveness of a given stimulus may be determined from the charge required for stimulation at the threshold value as this charge drains the batteries. This threshold charge is equal to the surface area of the impulses concerned. For a rectangular impulse:

$Q = i \times t$

and for a triangular pulse, (the impulse form according to a biased condenser discharge is not considered partly because of its extremely high peak value):

$Q = \frac{1}{2} \times i \times t$, where

Q = the charge of the threshold impulse

i = the maximum value of the threshold current at t, and

t = the impulse duration.

If the threshold charges at a given impulse duration are calculated from these formulae, the restangular impulse is found to be less effective than the triangular impulse. This is evident in table VIII-1, where the average threshold charges at 2 msec are calculated from the average threshold (peak) currents.

When applied to artificial cardiac stimulation these results indicate that at a given impulse duration, triangular pulses require less battery energy at threshold and therefore are more economical on battery life than rectangular pulses. However, triangular impulses can only be produced by a complicated circuit, which would make a pacemaker large and less reliable, and since the extra circuit components also require current, the gain would be illusory. The triangular impulse with a sawtooth downstroke may be produced simply however, as it corresponds to some extent to the impulse of a voltage pacemaker. Its advantage of more efficient stimulation, due to its lower charge threshold, easily outweights the disadvantage of the somewhat higher threshold peak value compared with the rectangular impulse. As the current threshold also depends on the impulse duration this parameter must also be considered.

TABLE VIII-1. *Effect of impulse shape, compare fig. VIII-1,2. Mean peak values of the current and mean charge for threshold impulses with 2 msec. duration, for 5 dogs with intramural heart electrodes.*

Impulse shape	Cathodal		Bipolar		Anodal	
	mA	μC	mA	μC	mA	μC
rectangular	2.60	5.20	2.70	5.40	7.10	4.20
increasing sawtooth	3.85	3.85	3.80	3.80	9.00	9.00
isosceles triangular	3.85	3.85	3.70	3.70	8.95	8.95
decreasing sawtooth	3.90	3.90	3.85	3.85	9.10	9.10

2. *Impulse duration*

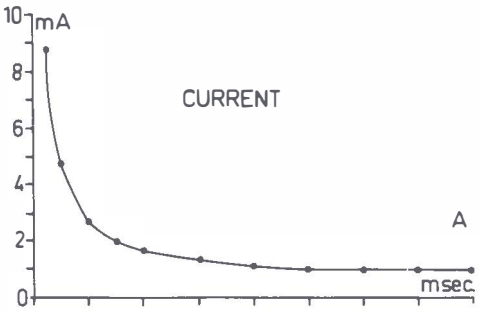
As previously shown, the choice of the optimal impulse duration of the stimuli is determined by two factors:
a. the life of the pacemaker,
b. the safety margin during stimulation.

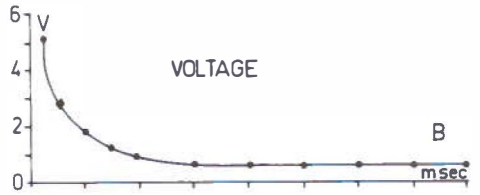
a. Relation between impulse duration and pacemaker life. The life of an implanted pacemaker is the time during which the pacemaker is capable of activating the heart. This time is proportional to the quantity of energy stored in the form of the electrical charge of the batteries. For a given quantity of energy and a constant frequency, the life is inversely proportional to the charge per impulse.

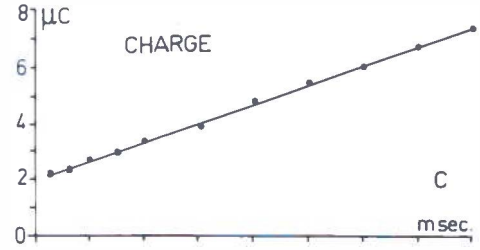
In artificial stimulation of the heart there is a relation between the charge threshold and the impulse duration. This relation, which is true for all the above-mentioned impulse forms, is shown in fig. VIII-3C. The measurements were made with two cathodal unipolar combinations of two intramural loop electrodes and one indifferent suture electrode in the thoracic muscles (4th i.c.s.r.), in a dog immediately after thoracic closure for production of heart block and introduction of electrodes; rectangular impulses from a constant current apparatus were used.

The results show that the charge threshold rises as the impulse duration increases. Hence it follows that:
– maximum life is achieved by using stimuli of minimal impulse duration.

b. Relation between impulse duration and safety margin. The relation between these two factors has already been discussed in Chapter VI, and is confirmed here by the results in fig. VIII-3A.







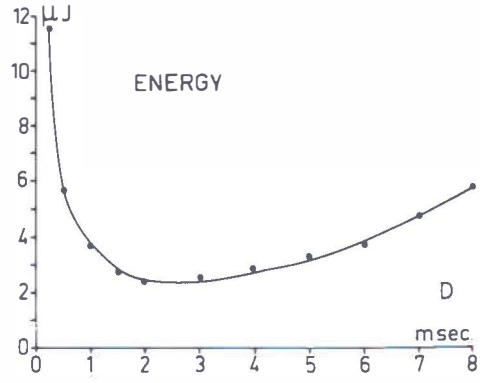
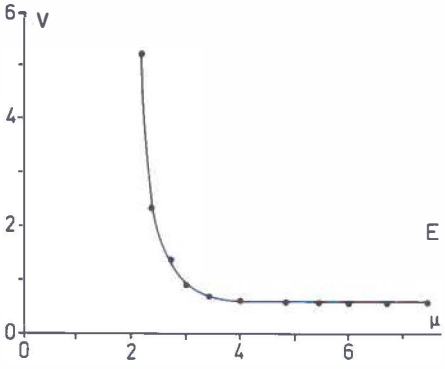


Fig. VIII-3A,B,C and D. Mean threshold current, voltage, charge and energy versus impulse duration, for two intramural loop electrodes and one indifferent suture electrode in a dog. Monopolar cathodal stimulation. Acute experiments.

Fig. VIII-3E. Threshold voltage (3B) versus threshold charge (3C).



– the current threshold decreases to a minimum value as the impulse duration increases.

This means that, at a given operational current, the margin between the operational and the threshold currents increases to a maximum value as the impulse duration increases. The safety margin, therefore, increases as the impulse duration increases at a given operational current, until the threshold reaches the rheobase.

If a large safety margin is desired together with a short impulse duration (for longevity) the operational current will have to be very high, and this may be achieved by:

a. a low electrical resistance in the electrode circuit, as is discussed in Chapter VI, and
b. a high operational pacemaker voltage, i.e. using a large number of batteries in series.

This number is limited however as the increase in size may make the pacemaker too large to implant. Generally 5 or 6 batteries of 1.3 V, each giving an operational voltage of 6.5 or 7.8 V, are used.

At a given operational current the minimum relative current threshold is reached when the current threshold is practically equal to the rheobase. In fig. VIII-3A the rheobase is reached at an impulse duration of 4-5 msec, so that with longer impulse durations the relative current threshold remains constant, but the life of the pacemaker is shortened by the larger impulse charges. Moreover, a further increase in impulse duration entails the risk of repetitive response and ventricular fibrillation. The above measurements were made with two combinations in a dog. Other experiments mentioned in Chapter VI and literature on this subject (SOWTON 1963 and ZOLL 1964) have shown that the current threshold remains constant at impulse durations greater than 5 msec.

Thus the optimal impulse duration should be between 0.5 and 5 msec., the minimum value being limited by the relative threshold and the maximum by the life of the pacemaker.

In selection of impulse duration the threshold energy is the third parameter which must be considered. The threshold energy or the amount of energy consumed at the threshold, is used partly for polarization of the electrodes being liberated later in the form of heat, and partly for overcoming the ohmic resistance, being released immediately as heat (see Chapter VI).

The threshold energy is minimal when the impulse duration is at the chronaxie point (fig. VIII-3D). This was also true for other dog experiments.

TABLE VIII-2. *Rheobase-chronaxie values for intramural stimulation in a dog. Mean values of 5 measurements with each electrode-combination. Current stimulator. L 1,2: identical intramural loop electrodes; Ind. 1,2: identical indifferent suture electrodes. First electrode of each combination is negative.*

Electrode-combination	Rheobase mA.	Chronaxie msec.	Rheobase mA.	Chronaxie msec.
L1 -Ind. 1	1,0	–	3,25	2,0
L1 -Ind. 2	1,0	2,0	3,30	2,25
L1 -L2	1,0	1,9	3,30	2,25
L2 -Ind. 1	–	–	2,80	2,0
L2 -Ind. 2	1,0	2,2	2,80	2,0
L2 -L1	1,0	2,0	3,00	2,0
Ind. 1-L1	–	–	13,75	0,8
Ind. 1-L2	–	–	12,00	0,8
Ind. 2-L1	6,1	1,0	13,75	0,8
Ind. 2-L2	6,0	0,8	11,50	0,9
Time of measurement	immediately after electrode implantation.		after 7 days stimulation.	

To determine the chronaxie, which varies in individual hearts, it is necessary to obtain an *i-t* curve for stimulation.

In one dog these curves were determined for two intramural loop electrodes, acutely and after one week. Also acute measurements using 3 catheter electrodes were performed in the same dog.

The results (see table VIII-2 and VIII-3) indicate that:

TABLE VIII-3. *Rheobase-chronaxie values for endocardial stimulation in a dog. Mean values of 5 measurements with each electrode combination of the catheter electrodes of fig. VI-25. First electrode of each combination is negative.*

Electrode combination	Rheobase mA.	Chronaxie msec.
Small catheter – Ind. suture	0,3	2,25
Medium catheter – Ind. suture	0,5	2,25
Large catheter – Ind. suture	1,1	2,0
Large catheter bipolar	1,1	2,0
Ind. suture – small catheter	0,9	1,0
Ind. suture – medium catheter	1,8	0,9
Ind. suture – large catheter	2,75	0,9

- given identical polarity, the chronaxie is identical for intramural and endocardial stimulation,
- the chronaxie is independent of any threshold rise after implantation of the electrode,
- the chronaxie for anodal stimulation (0.8-1 msec.) is less than for cathodal stimulation (1.9-2.25 msec).

Since anodal stimulation produces far higher threshold values, the threshold energy is far higher with this method than with cathodal stimulation. In intramural stimulation, the (minimal) threshold energy found from our acute measurements was on average ca. 60 μJ for anodal stimulation and ca. 4 μJ for cathodal stimulation. Higher values for the anodal threshold energy were also found clinically by SOWTON (1963), who noted that anodal stimulation required on average 16 times as much energy as cathodal stimulation. Remarkably, NASH (1964) on the other hand reported no significant differences between the threshold energy for anodal and cathodal endocardial stimulation. His curves are very irregular however, which may be due to poor contact of the catheter electrode.

In general, cathodal stimulation gives the lowest threshold energy values with impulse durations of 1-3 msec. This corresponds with the results of other investigators, although some reported very short durations. ORIAS *et al.* (1950), ALBERT *et al.* (1964) and ZOLL (1964) reported measurements in dogs, SOWTON (1963) reported clinical measurement and FURMAN *et al.* (1965) gave results of both clinical and animals investigations.

Thus, most investigators consider the optimal impulse duration, based on those parameters, to lie between 1.5-2.5 msec. Indeed, in practice most pacemakers have an impulse duration within these limits (ELMQVIST and SENNING, CHARDACK, NATHAN, ZOLL, KANTROWITZ).

FURMAN *et al.* (1966) advised an impulse duration of 0.5-0.75 msec., and SOWTON (1963) recommended 1 msec. In our opinion, however, the relative threshold is too high at these small impulse durations, resulting in too low a safety margin and we have, therefore, chosen a 2 msec impulse.

B. Impulse frequency

The total charge consumption is further determined by the impulse frequency.

The aim of artificial pacing for patients with complete heart block is

to prevent circulatory arrest and to promote the recovery of normal haemodynamics by stimulating the heart at an optimal frequency. Opinions differ regarding this optimal frequency, partly because different sets of parameters are used in assessing it.

The problem of frequency may be solved in five ways:

1. *Frequency variation by external control.* This method is used with external pacemakers with percutaneous transthoracic or transvenous electrodes, and with magnetic or electro-magnetic induction pacemakers. In all these methods, the pacemaker is outside the body and the frequency can be adjusted to an optimal level (Chapter IV). A modification of the induction pacemaker uses a receiver circuit in an implanted unit, so that temporary frequency regulation may be obtained by an external transmitter (KANTROWITZ 1962; GLAS 1963).

2. *Constant frequency in implanted pacemaker.* Most implanted (asynchronous) pacemakers have a constant frequency, which cannot be altered after implantation.

3. *Variable frequency in implanted pacemaker* (see also pulse forming circuit). In some implantable pacemakers the frequency may be adjusted by a minor procedure. This adjustment fixes the frequency at a new level in contrast to the temporary adjustments by induction mentioned above. Adjustments can be made in two ways:

a. Percutaneous technique.

This method is employed by CHARDACK *et al.* (1963) and others. The pacemaker has a special protrusion into which an angular needle is inserted percutaneously or through a small skin incision and using the needle as a screw driver the frequency can be adjusted within a range of 50-120 imp./min.

b. Magnetic relay.

Our pacemaker (VAN DEN BERG *et al.* 1962) has two frequencies (early versions 65-85, and currently 70-95 imp./min.). A magnet is used for extracorporal adjustment of the frequency and percutaneous techniques are unnecessary. Furthermore, if the patient is supplied with the magnet by the doctor, he can perform this adjustment himself.

4. *Frequency control by triggering the stimuli from the atrial contractions* (P-wave triggered or synchronous pacemaker). This is discussed later in this chapter in connection with the stimulator (see also Chapter IV).

5. *Intermittent asynchronous stimulation* (R-wave controlled or on-demand pacemaker). This R-wave controlled (asynchronous) stimulation was also discussed in Chapter IV, but the stimulator aspects will be discussed later in this chapter.

Determination of the optimal frequency is of special importance in method 2 and 3, and to a certain extent in 5.

The normal heart rate (frequency) in healthy people is about 70/min., but the amount of oxygenated blood which is pumped per minute by the heart to the tissues (cardiac output) also depends on the stroke volume: cardiac output = heart rate × stroke volume.

Cardiac output is therefore a useful parameter for determination of optimal frequency. Measurements of cardiac output fell beyond the scope of our investigation; we refer to research done by SOWTON (1963), who provided an excellent synopsis.

The slow rate accompanied by insufficient adaptation of stroke volume of patients with complete heart block results in low cardiac output. In 22 patients, investigated by Sowton, the average heart rate was 32/min. with an average cardiac output of 2.9 l/min. Pacing at an average rate of 72 per minute increased the cardiac output to an average of 4.4 l/min. at rest, which enabled the patients to lead a relatively normal life.

Sowton further investigated the relation between cardiac output and rate at rest. Measurements of cardiac output were made 8-10 minutes after rate change and within the range 55-100/min showed no alteration. This constant cardiac output is the result of alteration of stroke volume, which decreases as the rate in increases. Stimulation below 55/min. or above 100/min. caused a fall in cardiac output. At slow rates the stroke volume alteration is no longer able to compensate, but at high rates in heart block patients various factors, such as inefficient ventricular contractions, insufficiency of the atrio-ventricular valves and decreased atrial contribution, decrease the cardiac output.

Measurements four minutes after a rate change at rest, showed that the patients may be divided roughly into two groups based on their cardiac output in the frequency range 55-90/min. viz.

- patients whose cardiac output reached a steady state at four minutes, displayed a plateau with an insignificant maximum at 70/min. and
- patients whose cardiac output at four minutes reached a significant maximal level at an individual rate for each patient.

The patients of the second group all proved to have a so-called ischaemic heart condition in the form of an old infarction, E.C.G. abnormali-

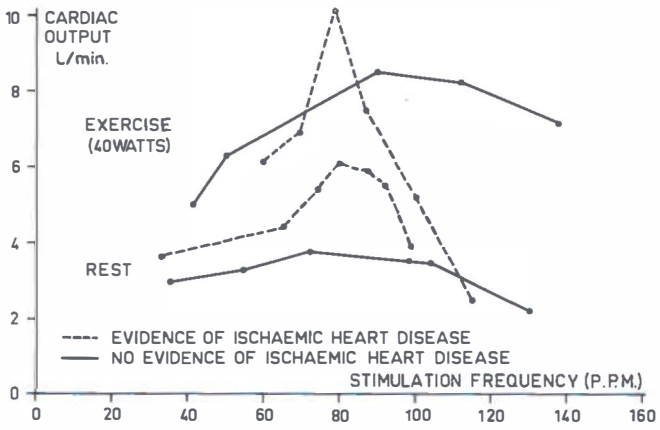


Fig. VIII-4. Cardiac output during rest and under stress versus stimulationfrequency for a patient with respectively without evidence of ischaemic heartdisease (by courtesy of DR. G. E. SOWTON).

ties, dyspnoea of effort or ischaemic heart conditions which were observed at operation or necropsy.

Determination of the cardiac output on exercise revealed further differences between the groups. In both groups the cardiac output increased. The first showed a rise in the plateau with a simultaneous shift of the optimal rate from 70 to 95-100/min., whereas the second group achieved the highest outputs at the same rate as at rest. Examples from each group are given in fig. VIII-4.

Sowton's findings were confirmed by other investigators. HAUPT *et al.* (1963) found an output plateau in the range 60-120/min., but most authors mention a range of 50-100/min. e.g. ESCHER *et al.* (1961), BEVEGARD (1962) and HUDSON (1962). None of these investigators however distinguished the two groups of patients defined by Sowton. Using cardiac output as a parameter, in assessment of optimal pacemaker frequency the rate should be between 50 and 100 per minute, with optimal outputs being obtained at 70/min. at rest and in some patients at 90-100/min. on exercise.

Rate change also affects blood pressure, increasing rate with compensatory diminution of stroke volume causes the diastolic blood pressure to rise and the systolic blood pressure to fall. As the greater part of coronary flow occurs during diastole, rate increase, which shortens diastole, results in reduction of myocardial blood flow. CHARDACK *et al.* (1963) on the basis of coronary blood flow in the rate range 50-100/min.

chose 60/min. for their pacemaker. They also considered that interruption of artificial stimulation at this rate resulted in idio-ventricular rhythm being more easily and rapidly re-established than with faster rates.

ABRAMS *et al.* (1964) were also of this opinion, but other authors (ZOLL *et al.* 1960; PORTAL *et al.* 1962; KANTROWITZ 1963 and ELMQVIST *et al.* 1963) apparently attached little importance to this factor as their pacemaker rates were between 65 and 80/min; a view shared by us.

Low stimulation frequency has the advantage of lower energy consumption per unit time than high frequency, and thus will result in longer pacemaker life. In our opinion, however, the primary aim should be the restoration of an optimal circulation, and therefore a basic frequency of 65/min., later increased to 70/min., was chosen for our pacemaker. This enabled patients to lead a relatively normal life.

In addition to the basic frequency, our pacemaker (VAN DEN BERG *et al.* 1962) has a second frequency of 85/min., raised later to 95/min. CARLETON *et al.* (1964) also described a pacemaker with two frequencies (75-100 min). The purpose of the high second frequency is to achieve an optimal increase in cardiac output in stress situations of any kind (work, infection) in certain patients, e.g. Sowton's first group.

Another important advantage of having a second higher frequency is, that, when interference occurs at the basic frequency due to a high idio-ventricular rate or return of sinus rhythm (see R-wave pacemaker), a more regular heart activity may be restored by switching over to the higher frequency. Thus the fast stimulation rate takes over the heart action and all or most of the naturally occurring stimuli fall within the refractory period and are suppressed.

A further advantage of a fast stimulation rate was reported by DRESSLER (1964), who stated that in heart block patients ventricular tachycardia may arise and may lead to ventricular fibrillation, even after implantation of a pacemaker, and suggested that tachycardia can be prevented by high frequency stimulation. The mechanism has not yet been explained and we have no data available in Groningen, but KANTROWITZ *et al.* (1964) reported experiences similar to Dressler's.

The pacemaker used by KANTROWITZ *et al.* has a basic frequency of 65/min., which can be increased to 120/min. by induction, using an extracorporal transmitter. The disadvantage of this method is that if a permanent increase in frequency is necessary, the patient is obliged to carry a permanent external transmitter. Kantrowitz also uses high frequency stimulation (80-85/min.) during the first post-operative days,

because 'the patients would normally also have reacted with a slightly higher frequency after a thoracotomy.'

GLASS *et al.* (1963) also control heart activity by induction during the first post-operative days. In contrast to Kantrowitz, they reduce their pacemaker rate, normally 60/min., to 30-40/min. in the post-operative period. Thereafter the frequency is gradually raised to a constant level, allowing a gradual adjustment by the patient to the new rate. However, in view of the rapid adjustments which the heart makes to a new frequency, demonstrated clearly by all the investigators mentioned previously, we doubt the benefit of this method.

In the Groningen clinic, the post-operative frequency chosen is that which gives the best results both subjectively and objectively, and in practice it may be either 70 or 95/min.

II. CONSIDERATIONS REGARDING THE CONSTRUCTION

The construction of an implantable stimulator entails special problems. Firstly, the circuit must have dimensions suitable for implantation. Secondly, in long term stimulation the power supply of the circuit is important: the energy must be stored in a form which can be introduced and used in the body. Thirdly, effective insulation of the circuit and power source is required and fourthly a simple and reliable connection between the electrodes and the pacemaker must be achieved.

A. Electronic circuit

The principal requirements which the electronic circuit of an implantable pacemaker must meet are:

- it should be of limited dimensions,
- reliable, and
- should use a minimum of power, to allow long term stimulation.

In the first external pacemakers, electronic vacuum tubes were used. These tubes operate with a heater current, requiring a relatively high amount of energy, resulting in low efficiency. These units were powered directly or indirectly from the mains.

A great improvement was brought about by the development of transistors, which are semi-conductors, consisting of an emitter, a basis and a collector, and behave like a triode. The germanium transistors used initially were replaced in later versions by silicium, which have a longer life and a considerably lower leakage current.

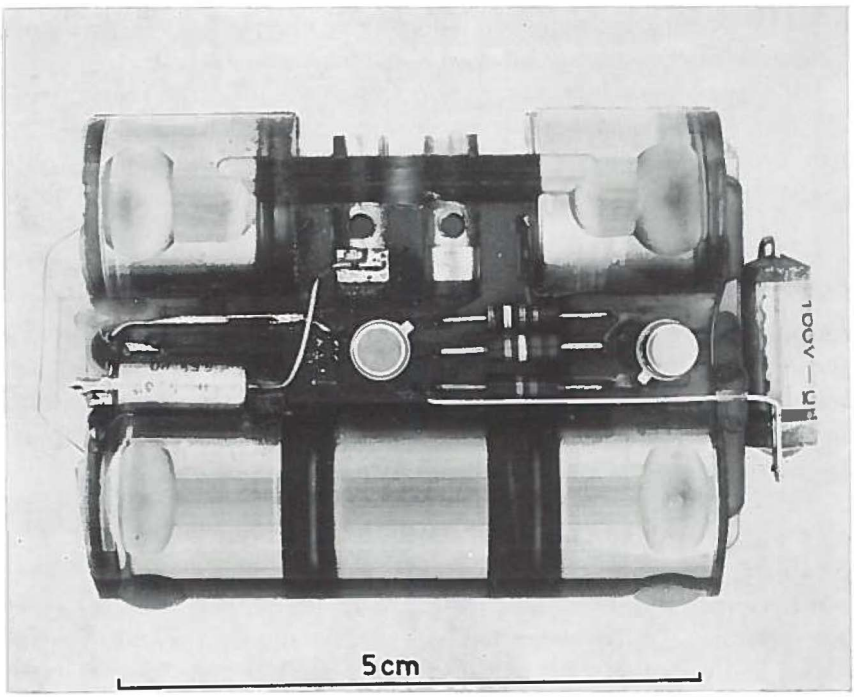


Fig. VIII-5. Stage of pacemaker mounting, showing a.o. five batteries, electrode connections and some of the electronic components.

Transistors have a three fold advantage. Their efficiency is high and they operate at a low potential, which enables a transistorised circuit to be powered by low voltage batteries. Moreover, transistors are small, so that with suitably small batteries and other electrical components an implantable circuit can be constructed which uses little energy, and makes long term stimulation possible (fig. VIII-5).

In reviewing circuit reliability, without taking into account the complications which may occur after implantation, these failure rates for components may be assumed (GLASS 1964):

transistor, condenser, and battery	0.01 %/1000 hours
resistance	0.001 %/1000 hours
welded joint	0.0001 %/1000 hours

For a basic pacemaker this means an overall failure rate of about 0.1 %/1000 hours or one in every hundred pacemakers will fail in 10.000 hours stimulation (1 year = 8.760 hours) according to the figures of 1964, but

in 1968 we already achieved a failure rate of 0,05%/1000 hours over 1500 of our pacemakers implanted for at least 1 year.

This percentage, however, will continue to fall as the refinement of electronic components leads to greater reliability. Space flight and extensive application of implantable circuits in the human body have greatly stimulated research in this direction.

B. Energy

Originally external stimulators were powered directly or indirectly from the mains. Later, design of smaller and more efficient external units made battery power possible. As the stimulator was then situated extracorporally, replacement of batteries presented little difficulty. External stimulators with inductive impulse transmission were also used.

The availability of a suitable power source delayed the development of the implantable pacemaker. Ideally a unit, once implanted, should be able to function continuously for a long period, and as batteries do not have an unlimited capacity pacemaker life is restricted. ELMQVIST and SENNING (1960) reported use of an internal stimulator with nickel and cadmium cells, capacity of 60 mAh, which were rechargeable by means of a receiver circuit. A similar system was later used by SIDDONS (1961). Apart from the low capacity of these batteries, necessitating frequent recharging (every 2-3 weeks) and the accompanying inconvenience to the patient, the chief disadvantage of this method is that the cells deteriorate relatively early because of the frequent discharging and recharging. As the power source must therefore be replaced regularly in any case, non-rechargeable batteries with a larger capacity have been favoured.

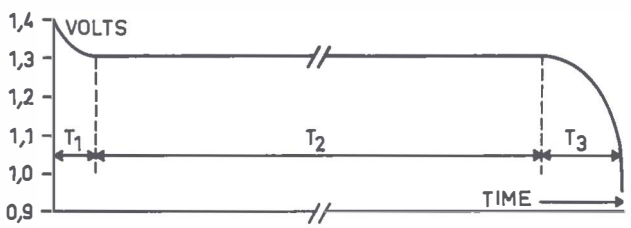


Fig. VIII-6. Voltage of mercury battery as function of time at constant load.
T1 : rapid decrease of voltage; T2 : constant voltage during the main lifetime; T3 : rapid decrease of voltage at exhaustion of batteries.

Special mercury batteries, with a volume of about 3 cm^3 and a weight of about 12-12.5 g, are used for this purpose. The electrolyte in this cell is sodium hydroxide, which is less active than the usual potassium hydroxide. The depolarizor contains approximately 10% magnesium dioxide. A new cell starts with an e.m.f. of 1.40 V which drops during the first 10% of its life to the 1.30 V of the normal mercury cell (fig. VIII-6). During this time, magnesium dioxide is reduced to magnesium-oxide, forming a residue in the matrix, which prolongs shelf-life. The mercury oxide protected in this way reacts with zinc and water according to the formula

$$Zn + HgO + H_2O \longrightarrow Zn(OH)_2 + Hg$$
$$\Updownarrow$$
$$ZnO + H_2O$$

two Faradays of electrical energy being liberated for each converted gram-molecule of the active component.

With a shelf-life of 10 years, the initial capacity of these batteries is 1000 mAh, which is reduced by 2.5% per year at a temperature of 25°C. This percentage is doubled for each increase of 8°C, resulting in a reduction in capacity of approximately 7% per year when implanted in the body.

Beside cell capacity the life of such a pacemaker depends on
- the current consumption of the pulse forming circuit and
- the current consumption of the output circuit.

The current consumption of the pulse forming circuit reflects its efficiency and, although there are differences between the various makes of pacemakers, it may be estimated to be approximately 80%, which means that the pulse forming circuit consumes 20% and the output circuit 80% of the total current. Consumption depends on the frequency of the stimuli and the operational value of the impulse charge, which, as shown in Chapter VI, is determined by the impulse duration, the output circuit itself (condenser, internal resistance), the resistance in the electrode circuit and the polarization at the electrodes.

The maximum period of stimulation can be calculated from the frequency and the operational value for a given unit. For example, the maximum stimulation period for a pacemaker with a frequency of 72/min., impulse duration of 2 msec. at a mean operational current of 8 mA

can be calculated thus: such a pacemaker delivers per second

$$2\ (\text{msec.}) \times\ 8\,(\text{mA}) \times \frac{72}{60}\ (\text{frequency}) = 19.2\ \mu\text{C},$$

which corresponds to a current consumption of 19.2 μA.

Given an efficiency of 80%, the total pacemaker consumes $\frac{100}{80} \times 19.2\ \mu\text{A} = 24\ \mu\text{A}$. With a battery capacity of 1000 mAh, this corresponds to a life of $\frac{10^3}{24 \times 10^{-3}}$ hours = 57 months. Taking into account the reduction in capacity, which is 7% per year of the initial capacity at 37°C, the life time in months can be calculated from the equation $1000\ (1 - \frac{7}{100} \times \frac{x}{12}) = 24 \times 10^{-3} \times 30 \times 24 \times x$.

Therefore $x = 43$, which is the maximum life of such a pacemaker in months. At a frequency of 96 imp/min., the life becomes y months, where

$$1000\ (1 - \frac{7}{100} \times \frac{y}{12}) = \frac{96}{72} \times 24 \times 10^{-3} \times 30 \times 24 \times y,$$

therefore $y = 34$, which is the maximum life in months in this case.

These calculations indicate shorter lives than the 3-5 years predicted initially when pacemakers were implanted. Possibly many authors (ZOLL 1964; LAGERGREN *et al.* 1966) may not have taken into account the reduction in capacity of the batteries themselves (7% per year). Since this reduction is approximately 30% after 4-5 years the predictions were 1-1.5 years too optimistic.

Naturally, these predictions only apply if no complications occur in stimulation, necessitating replacement of the pacemaker. It may be difficult to decide the exact moment to replace an implanted unit, but with further pacemaker development a method of monitoring has been established which enables this moment to be determined approximately in certain pacemakers. This will be considered in the following chapter.

Replacement at this calculated time is only necessary because the power source is exhausted. Some authors have suggested for economic reasons construction of a pacemaker which would require battery replacement only, but for reliability replacement of the whole circuit is preferable, because the electrical components also deteriorate. Although the calculated stimulation periods have not yet been achieved, greater reliability of the electronic components and insulation will cer-

tainly make this possible in the near future. The duration of stimulation will then only be determined by the power source in the pacemaker. Intensive research is now being directed toward this object.

Means of prolonging duration of stimulation using the energy sources presently available are being sought in:

- more efficient and economical continuous stimulation and
- intermittent on-demand (R-wave blocked) stimulation.

More economical stimulation is achieved by using a lower frequency and a lower operational charge. The latter is obtained by reducing the impulse duration, and if possible, the operational current. Thus CHARDACK *et al.* (1963) constructed their pacemaker in such a way, that it was easy to set the amplitude of the output-pulse before and after implantation. However, this involves the danger of too fine an adjustment of the operational value, so that even a very slight increase in threshold may result in an interruption of stimulation, with all its accompanying dangers. In Groningen this occurred 11 times in 35 patients (Chapter VI).

Our own voltage pacemakers (for definitions of voltage and current pacemakers see: Types of stimulators) are equipped with a second magnetic relay besides the frequency regulating relay. Under normal conditions the operational voltage of this pacemaker is about 5.2 V. However, it can be raised to the maximum of 6.5 V by holding a special magnet continuously against the skin near the pacemaker, using the polarity of the magnetic field for the frequency relay. The special purpose of this was to enable stimulation to be maintained easily in a situation of imminent battery exhaustion or a temporary rise in threshold (fig. VIII-7). Although the stimulation thresholds remained within the operational value of 5.2 V in practically all cases and although the new method of monitoring provided timely warning of exhaustion of the batteries, we have retained this relay in our pacemakers with continuous current limitation as well (see fig. VIII-10).

In combination with our electrodes the operational value is in fact limited to 16-18 μC by the electrode circuit. The maximum operational charge was chosen somewhat higher, 20 μC, to allow use of other electrodes with the pacemaker. As shown in Chapter VI, the threshold current rises as the dimensions of the electrodes increase. The combination of a large electrode and a pacemaker with a low operational value would have a high relative threshold (stimulation threshold/operational value × 100%), which means a small safety margin. However, to ensure a large safety margin with these combinations also, a current limit of 10 mA was chosen. Since a small electrode has a low threshold value,

it is clear that use of such an electrode in combination with our pacemaker gives a low relative threshold.

The principle of the current limited pacemaker offers another advantage; a large electrode and a high threshold associated with a low resistance in the electrode circuit, automatically results in a high operational value, limited to a maximum value of 10 mA. A small electrode on the other hand has a high resistance in the electrode circuit, which results in a lower operational value. This is the case with our own electrodes, the operational charge does not reach the maximum of 20 μC but remains restricted to 16-18 μC. Thus the pacemaker automatically stimulates more economically with the small electrode, but with either large or small electrode, a sufficiently wide safety margin is maintained.

In a current pacemaker which has its constant operational value determined by the pacemaker circuit, this automatic regulation is absent. When such a pacemaker is set at a low operational value, caution is advised when larger electrodes are used. The relative threshold may be obtained simply by the Cardiotest at implantation of the electrodes or at later operations.

A second possibility of prolonging the duration of stimulation using present power sources is offered by the on-demand (R-wave blocked) pacemaker, which will be discussed in the last section of this chapter.

Although these methods achieve some increase in the duration of stimulation, further increase depends on research into the power supply itself, e.g. by developing batteries of the same or a smaller volume with a greater capacity (FURMAN *et al.* 1966).

At present atomic energy is being investigated as a power source (MORROW 1966), in which the radio active isotope Plutonium 238 is used. A disadvantage of this source of energy is the heavy screening required when implanted, not so much for the α-radiation, but especially for the neutrons.

Intensive investigations are also being carried out in the field of bioenergy, attempting to make use of body energy. In some cases the power obtained in this way is combined with rechargeable batteries in order to ensure stimulation being maintained if the natural power supply fails. This work is still in the experimental stage, however, although some animal experiments have already been performed. This energy source will be easily used for pacemaking because heart stimulation is already effective at low voltages and currents. Various methods investigated with negative results are:

- electrical energy liberated by heart muscle contraction: insufficient energy, voltage being only about 10 mV.
- insertion of a turbine generator in a blood vessel: causes haemolysis.
- thermo-electricity: temperature differences too small.

More possibilities were offered by conversion of mechanical energy into electrical energy (ZUCKER and PARSONNET 1964) by means of piezo-electrical ceramic crystals, which, when deformed, produce an electrical potential and thus must be sited in the body at a point where there is constant movement. The investigators chose two such sites. A double cuff, containing 9-10 crystals, on the aorta was subjected to pressure variations of 20-30 mm Hg, which produced voltages of 12-25 V. In dogs, using a modulator, impulses of 1.6 msec. with a potential of 0.75-1 V were produced and gave short periods of cardiac stimulation. Attachment of the cuff presented difficulties, and it was replaced by two rigid discs. However, this system does not seem to be acceptable as a routine measure in patients and long term clinical use of either version has not been reported. One complication may be stenosis of the aorta at the crystals site with accompanying post-stenotic dilatation.

Attempts have also been made to use other body movements, such as the excursion of the diaphragm and rib movements, but again no clinical use has been reported. PARSONNET and ZUCKER (1964) have designed a mechanical system with springs and crystals, to convert this mechanical energy into electrical energy, but in practice the disadvantage of this system is the reduced amplitude of movement which occurs in sleep or pathological conditions (pleuritis, pulmonary emphysema).

DREIFUS, SATINSKY *et al.* (1965) attempted to harness body energy by using an electrochemical power supply in the form of a positive platinum electrode and a negative steel electrode, each with a diameter of 2.5 cm, inserted at first in the abdominal cavity, and later on the left ventricle and the pericardium. These discs gave a D.C. potential of 0.5-0.6 V, which was transformed by an electronic circuit into impulses by which the heart could be stimulated by a bipolar catheter. Stimulators operating on this principle have already been successfully used for short perdiods (max. 40 hours) both in dogs and during clinical operations. Long term tests are now being carried out, but apart from the disadvantage of the complicated circuit, it seems inevitable that deterioration of the discs will take place during long term trials, necessitating their replacement. Even a small increase in threshold may result in pacing failure because the maximum voltage available is limited, and an increase in impulse current results in a drop in voltage due to the internal resistance

of the source. This latter disadvantage would be less significant with larger discs, but their size is limited by the practical difficulties of implantation. A modification of this principle was reported by TALAAT *et al.* (1967) and SCHALDACH (1968).

JUHASZ (1965) investigated the possibility of using photo-cells under the skin of the neck to increase life of nickel-cadmium cells, as used by ELMQVIST and SENNING in their first implantable pacemaker, from 2-3 weeks to 6-8 weeks in normal sunlight. However, Juhasz did not report clinical use of this sytem but suggested that a 100 watt light bulb every 14 days may be used as an alternative to sunlight. It seems that this method, investigated also by others (YERUSHALMI *et al.* 1966), has little future and it is merely included for completeness.

This survey has shown the many ways in which energy production is being approached, but at the present time construction of almost all implantable pacemakers, still depends on mercury cells with a voltage of 1.30 V and a capacity of 1000 mAh. In the near future, improvement and perfection of these batteries will probably make longer stimulation possible, whilst bio-energy and possibly nuclear energy offer even longer periods, but in the more distant future.

C. Insulation of stimulation units intended for implantation

Implantation of an electronic circuit and batteries requires effective insulation. The insulating material should satisfy these requirements:
- effective insulation of the pacemaker components,
- acceptance by the body,
- no release of toxic matter after implantation,
- effective up to a maximum temperature of 50°C,
- not only impermeable to moisture, but no absorption of moisture by the material also,
- unshrinkable and
- capable of strong attachment to the electronic components.

The insulation material used at present in practically all pacemakers is epoxy resin. Some investigators use epoxy resin alone (LAGERGREN and NATHAN), others embed the components in epoxy resin and cover the whole with an extra layer of silicon rubber being more acceptable to the body (CHARDACK, ZOLL, VAN DEN BERG *et al.*). Epoxy resin offers good electrical insulation and is not rejected or toxic.

An important factor, in regard to sterilisation, the maximum temperature to which the insulation material should be effective, is determined by the temperature tolerance of the batteries, i.e. 50°C. As a result of this limit, the choice of epoxy resins is restricted. Recently problems with permeability to moisture, shrinkage after embedding and attachment to the electronic components have presented and have been approached in various ways. Prior to processing, a diluant is added to the epoxy resin to liquify it sufficiently, but shortly before embedding of the components the diluted epoxy resin is mixed with a hardener, which takes effect after a certain time and partly determines the final consistency. Variations occurring during processing may be due primarily to the raw materials, but also to the relationship between the components. These properties may cause not only a difference in the ultimate insulation material, but also in the speed at which the hardening process takes place. A definitive solution to these problems has not yet been found, although improvements have been made. Thus the permeability to moisture, which is a feature of every epoxy resin, may be reduced considerably by addition of a third element e.g. special quartz.

Difficulties encountered with insulating materials are:
- air bubbles in the epoxy resin due to incorrect embedding of components,
- shrinkage of the epoxy resin, as a result of the so-called hardening process, which may even occur after several weeks, and manifest as detachment of
- the epoxy resin from the electronic components, allowing hygroscopic fissures to develop and
- rupture of the epoxy resin insulation.

Difficulties may also arise if there is an excessive difference between the thermal expansion coefficient of the epoxy resin and electronic components. This may be so if, for instance, processing takes place at 18-20°C and the pacemaker is then implanted. The material is then subjected to an increase in temperature of about 17°C. This increase is even greater if the pacemaker is sterilised at 50°C, but only for a brief period. Besides these complications the electrical circuit may also exhibit defects as a result of pressure on the components, which may be avoided by choosing an epoxy resin with a high degree of elasticity. The disadvantage of this, however, is that an increase in elasticity is generally accompanied by an increase in permeability for water, and also high

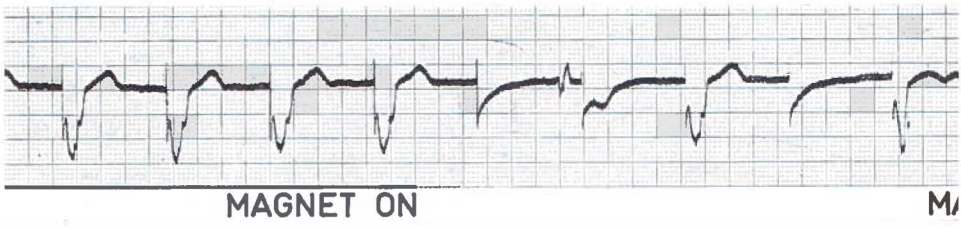


Fig. VIII-7. Effect of changing the operational pacemaker value in the case of a patient with an increased threshold. The patient was stimulated by means of our pacemaker, containing a second magnetic switch to change the operational value. With the (external) magnet 'on' the impulse charge is increased beyond the (increased) threshold.

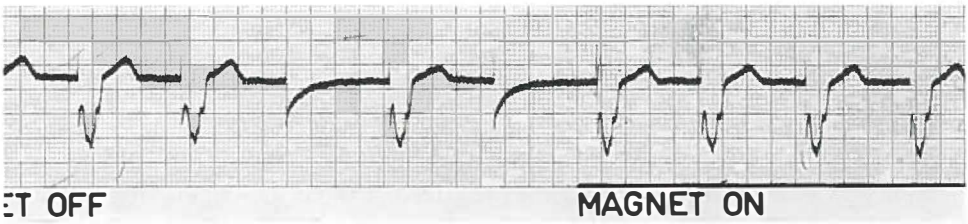
external pressures can cause difficulties. These may occur in gas sterilization, where occasionally pressures of 5-6 at. are used. Thus an elastic epoxy resin may be more deformed by an external pressure, with resultant effects on the components, than if a hard epoxy resin were used.

To combine the advantages of various epoxy resins, the insulation is sometimes applied in several layers, for instance an elastic coating around the circuit combined with a hard external coating. However, the disadvantage of this is that epoxy resin layers adhere poorly to each other, allowing hygroscopic fissures to develop.

Thus inadequate insulation may be the result of a number of insulation defects and entry of moisture (especially the Cl'ions), their effects being accelerated by body temperature. These faults may cause total failure of the pacemaker due to rapid exhaustion of the batteries (ANDERSEN 1962; APPLEBAUM 1962; ZOLL 1963), pacemaker tachycardia which may induce ventricular fibrillation (COSTEAS *et al.* 1965; ALDRIDGE and KAHN 1965; NASH 1965; DEKKER 1966), pacemaker bradycardia or changes in impulse duration as was noted by us.

Some authors (DEKKER *et al.* 1966) ascribe the fissures around the batteries to their expansion as a result of the chemical processes inside them. Since the type of pacemaker used by Dekker has the same batteries as other types, where the phenomenon occurs far less frequently, it would seem that the fault was associated with an insulation defect, presumably primarily in the epoxy resin.

In conclusion it may be stated that the greatest number of failures in



artificial stimulation of the heart, where the defects are in the stimulator itself, are due to faults in insulation. Experience has led to improvement in this field, but further investigation into epoxy resins, as well as into other materials like glass and polyethylene, may offer improvement.

D. Electrode connection

Two vulnerable points in the insulation are where it is perforated for the connections of the positive and the negative electrodes.

In some early types of pacemakers (ZOLL) the electrodes are permanently attached to the pacemaker unit. This may achieve more effective insulation, but, when the pacemaker has to be replaced in the course of time, either the leads must be cut and new connections made or the whole system must be replaced.

To facilitate simple and rapid replacement of the pacemaker, most have a plug and socket connection with the electrode. The plug being on the lead and the socket in the pacemaker. A screw in the wall of the socket, vertical to its axis, fixes the plug, and establishes contact (CHARDACK and VAN DEN BERG *et al.*).

In most cases insulation of the connections is accomplished by pressing the lead insulation (mostly silicon rubber) and the pacemaker insulation close together and applying silicon grease or silicon adhesive at the junction. Experience has shown that adhesive generally gives better results than grease. The adhesive, however, may cause difficulties at

pacemaker replacement because of its excessive strength. The connecting screws are generally also insulated by silicon grease or adhesive, and screened by e.g. a teflon cap or screw. A disadvantage is that for connecting screws with their screening caps or teflon screws proper, holes have to be made in the insulating material, and if the screws are tightened too forcibly, fissures in the epoxy resin around the connection may develop. This, in certain pacemakers, leads to oxidation and rust formation around the electrode connection, as moisture penetrates through the fissures. This results in a current between different poles, causing electrolysis and corrosion of the contact plugs and sockets.

It is possible to connect the indifferent electrode without a screw contact: a disc in the wall of the pacemaker is used as the indifferent and is connected to the circuit by a loop. This method was used by ELMQVIST *et al.*, NATHAN *et al.*, and also by us for some time. Due to the large contact surface and the poor fixation of the disc to the epoxy resin, there is a rather high risk of fissures developing under the disc where fluid readily accumulates. NATHAN *et al.* still use this method which we have modified to obviate the complications of fluid penetration. This disc, with a silicon rubber coating underneath, is both connected and fixed by two screws in our latest pacemaker units (fig. I-1.) This modification retains the advantage of the disc-shaped indifferent electrode (Chapter VI) with almost optimal pacemaker insulation and also provides an extra safeguard to the heart electrode. Because the screws are held in stainless steel sockets, the forces exerted on the resin are much smaller than if the screw were fixed in the resin itself. This method of fixation is partly made possible by the fact that the heart electrode leaves parallel to the pacemaker wall, preventing fractures of the conduction lead which occur when it leaves vertically (Chapter VII). Such breakages are a drawback to the plug method of Nathan *et al.* Their method of connection of the heart electrode has the advantage of simplicity. The screws are not used and instead a small pawl fixes the plug. There are large areas of contact between the pacemaker- and electrode-insulating material which, with silicon grease or adhesive, makes insulation effective.

Basically all pacemaker electrode connections conform to these descriptions, but individual variations may cause difficulty in connection of one type of pacemaker with another type of electrode. Some investigators have made special attachments for various electrodes to various pacemakers. A certain degree of uniformity in this matter is desirable for the future.

Having considered the problems of constructing an implantable pacemaker, in the following section the electronic circuit of various types of stimulators will be discussed briefly, with particular reference to the clinical possibilities opened up by modern electronics.

III. TYPES OF STIMULATORS

The basic unit is described first, then the various types of pacemakers developed from it.

A. Asynchronous continual stimulator

The asynchronous continual stimulator is a unit which stimulates the heart continually at a pre-set constant frequency. The early types of implantable pacemakers were constructed on this principele. There are two distinct circuits in such a pacemaker:

- the pulse forming circuit and
- the output circuit.

The pulse forming circuit determines the frequency and impulse duration of the stimuli, while the output circuit determines the amplitude and (generally) the shape of the impulse. These sections of the pacemaker circuit are discussed separately.

1. *Pulse forming circuit*

Two different methods are used in the construction of the pulse forming circuit.

a. Blocking oscillator circuit. Early versions used the blocking oscillator circuit principle, which is still used in a number of pacemakers (CHARDACK and GREATBATCH, ZOLL, ELMQVIST and DAVIES).

An example of a blocking oscillator circuit is shown in fig. VIII-8. It has several variants. The circuit is best described by beginning at the moment an impulse has just been emitted. At that moment condensor C_1 has a maximum charge and the transistor Ts_1 is blocked, because the base is positive in this phase. The condensor C_1 discharges through the resistance R_1, causing the voltage at the base of the p-n-p transistor Ts_1 after a certain period (the interval between impulses) to drop so far that the transistor is bottomed. This generates a current from the emitter to the collector and through the primary coil L_1 of the transformer,

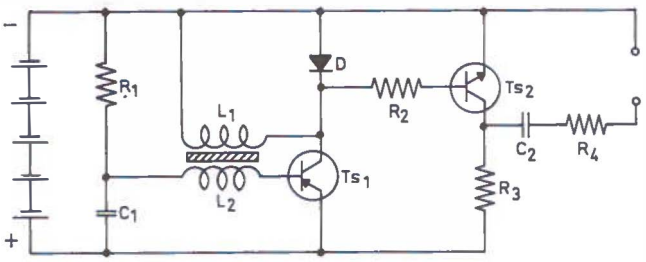


Fig. VIII-8. Scheme of asynchronous pacemaker with blocking oscillator impulse generator and current output circuit.

inducing a voltage in the secondary coil L_2, which is so directed that the potential at the base of the transistor Ts_1 is decreased and the current in the primary coil increases further, the effect being cumulative. As long as the current in the primary coil continues to increase a voltage is induced in the secondary coil. After a certain period (the impulse duration) the transistor Ts_1 is maximally saturated, then no further current increase in the coil L_1 takes place, so that the induced voltage in the secondary coil L_2 suddenly falls off. Since the condensor C_1 has been charged during this period, the decrease in induced voltage results in a positive voltage on the base of the p-n-p transistor Ts_1, causing it to be cut off, while at the same time the current in the primary coil also falls away completely. To prevent this causing a reversed potential over the primary coil due to self-induction, a diode D is included in the circuit as a rectifier. The process is repetitive with the condensor C_1 discharging once more through the resistance R_1, until, after the interval between the stimuli, the basic voltage of the transistor Ts_1 has dropped so far that the transistor bottoms again.

This cycle is transmitted via the resistance R_2 to the base of the n-p-n transistor Ts_2, which becomes positive and bottoms when a current flows through the transistor Ts_1 and the coil L_1, as occurs during the impulse. This part of the circuit will be discussed in the section on the output circuit.

In this circuit, the frequency is determined by the condensor C_1 and resistance R_1. If this resistance is reduced, the condenser discharge is accelerated, resulting in faster bottoming of the transistor Ts_1 and the frequency will be increased. Conversely, an increase in resistance will reduce the frequency. The same holds for a decrease or increase of

the capacity of the condenser C_1, the frequency being determined by the time constant R_1C_1.

The impulse duration is determined by a number of components, viz. the condenser C_1, the transistor Ts_1, and the transformer with the two coils L_1 and L_2. Besides complications which may occur in the transformer, this circuit has the disadvantage that the spread in electrical characteristics of transistors is great, and correction to a standard impulse duration by choosing other condensers and transformers is difficult, with the result that the impulse duration of the blocking oscillator circuit is difficult to standardize. Impulse duration should be as constant as possible for the photo analysis method discussed later, therefore a totally transistorized circuit, the free running complementary multivibrator circuit is used in our pacemaker, and is also used by KANTROWITZ and RAILLARD and GLASS and NATHAN inter al.

b. Free running multivibrator circuit. A free running multivibrator circuit is shown schematically in fig. VIII-9. Similarly, this circuit is best described by beginning immediately after an impulse. At that moment the transistors Ts_1 and Ts_2 are blocked and the condenser C_1 is positively

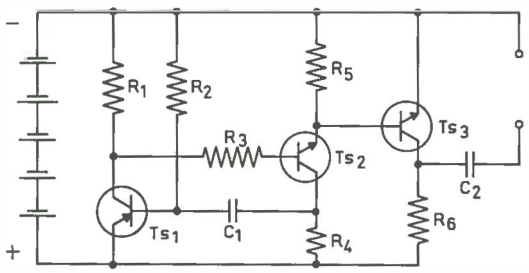


Fig. VIII-9. Scheme of asynchronous pacemaker with (free running complementary) multivibrator circuit impulse generator and voltage output circuit.

charged. The condenser then discharges through the resistance R_2. At a given critical negative voltage at the base of the p-n-p transistor Ts_1 current begins to flow through it, whereupon the collector voltage of the transistor rises, and is transmitted via the resistance R_3 to the base of the n-p-n transistor Ts_2. This transistor then bottoms and a current flows through the resistances R_4 and R_5. The collector voltage of Ts_2 then drops being transmitted via the condenser C_1 to the base of Ts_1 and the current at this transistors is further augmented. This effect is cumula-

tive and continues until both transistors have reached maximum conductivity. This process lasts a few microseconds and corresponds to the initial period of the impulse. The condenser C_1 is now charged further from the emitter base of Ts_1, the conducting Ts_2 and the resistance R_5. After a certain time – the impulse duration – the condenser is charged and further increase in charge increases the voltage at the base of the p-n-p transistor Ts_1 beyond the critical negative value, so that the transistor cutts off. The base of the n-p-n transistor Ts_2 becomes negative following the closure of Ts_1, so that this transistor also cutts off. The whole process is repetitive. Condenser C_1 discharges again through the resistance R_2 until after a certain time – the interval between the impulses – the voltage has dropped to such an extent that the transistor Ts_1 bottoms once more.

This cycle is transmitted to the transistor Ts_3. While Ts_2 is blocked, during the interval between the impulses, the base of this n-p-n transistor has the same potential as the emitter, blocking the transistor. However, if Ts_2 conducts current via R_2 and R_5, the base of Ts_3 becomes positive, thus the transistor bottoms. Ts_3 therefore only conducts during the impulse. The output circuit is discussed later.

In the free running complementary multivibrator circuit, the frequency depends on the condenser C_1 and the resistance R_2. An increase in resistance causes a fall in frequency, as in the previous circuit, and a decrease in resistance causes a frequency increase. Similarly, an increase in capacity of the condenser C_1 results in a fall in frequency and a decreased capacity in a frequency increase. This frequency is determined by the time constant R_2C_1. The impulse duration can be set accurately with this circuit, by selection of the resistance R_3 and the transistor Ts_2. An increase of the resistance R_3 results in a lower current through Ts_2, so that it takes longer for the condensor C_1 to become charged, causing the impulse duration to increase. If the resistance R_3 is reduced the impulse duration is shortened. The spread of transistor characteristics may thus be corrected by careful choice of R_3. Within certain limits variations in R_2 therefore only affect the frequency and variations in R_3 only affect the impulse duration, while, variations in the other resistances in the circuit have no effect on either. The circuit is affected by reduction in battery voltage, however, resulting in a decrease of the current amplification of Ts_2, so that the condenser C_1 is charged less rapidly and the impulse duration is increased. But frequency is less affected by battery voltage; the condenser C_1 discharges more slowly because of the smaller difference in

voltage, but there is a smaller fall in potential before the transistor Ts_1 is opened.

Our pacemaker conforms to this circuit description. Other investigators have modified the circuit in such a way that a decrease in battery voltage results in a considerable drop in stimulation frequency, both in the blocking oscillator circuit (CHARDACK and GREATBATCH) and in the completely transistorized circuit (ZOLL *et al.*). Our view was, however, that a great frequency drop was not desirable. Since the impulse duration of our pacemakers is uniform if the batteries are fully charged, an increase in impulse duration gives a good indication of their exhaustion as will be described in the section on photo analysis in the next chapter. Moreover, as increase in impulse duration is accompanied by decrease in relative threshold giving a greater margin of safety, we have selected this pulse forming circuit for our pacemakers.

2. Output circuit

The output circuit is the second section of the pacemaker circuit. It determines the shape and amplitude of the impulse. Two types of circuit, voltage or current, may be used, either of which may be combined with either of the pulse forming circuits.

The output circuit (see diagrams of the various circuits) is connected to the pulse forming circuit via a transistor, which protects it against resistance variations in the electrode circuit. Initially we and other investigators (KANTROWITZ *et al.* 1964) constructed the output circuit in such a way that resistance variations resulted either in an increase in frequency or an increase in impulse duration. The first method of connection of the two types of output circuit is used by us and most other investigators at present.

a. Voltage circuit. A voltage output circuit (see diagram fig. VIII-9) is best described by beginning immediately before an impulse. At this time the transistor Ts_3 is still blocked and the condenser C_2 is fully charged. The pulse forming circuit now delivers a positive voltage to the base of the n-p-n transistor Ts_3 for a certain period, the duration of the impulse. This opens the transistor, and results in the condenser C_2 beginning to discharge through the tissues for the duration of the impulse. At the end of the impulse, the positive voltage of the base of the n-p-n transistor Ts_3 falls off, so that this transistor closes, terminating the current impulse through the tissues. Whilst a new impulse is being developed in the

pulse forming circuit the condenser C_2 is being charged via the resistance R_6, the electrode circuit and the batteries. When the base of Ts_3 becomes positive again, the condenser discharges once more, and the cycle is repeated. Thus, during the impulse, a current flows through the tissue between the electrodes, its value being called the operational value. During the interval between the impulses, current flows in the reversed direction, the two currents neutralising each other, because of the condenser coupling. The biphasic impulse eliminates polarization phenomena at the frequency and impulse duration used, as described in Chapter VI.

The maximum amplitude, i.e. the maximum current of the impulse, is determined by the resistance R_5 and the properties of the transistor Ts_3. The resistance R_5 limits the maximum base current of Ts_3, which in turn determines the maximum current which Ts_3 can transmit from emitter to collector. Generally, however, this maximum current does not flow through the electrode circuit because of its relatively large resistance.

The principle of the pacemaker with a voltage output circuit is condenser discharge during the impulse depending on the (rest) potential of the condenser and the resistance in the electrode circuit. A decrease in resistance results in a higher maximal current, according to the formula

$$V_{max} = i_{max} \times R$$

The maximum current is thus inversely proportional to the resistance. It also follows that, the resistance in the circuit being constant, the maximum current is proportional to the voltage V of the condenser. Since this voltage depends on the battery voltage and the resistance R_6, these factors also affect the amplitude.

The shape of the impulse is determined by the condenser C_2. To a condenser the formula applies:

$Q = C \times V$, where

Q = charge of the condenser,

C = capacity of the condenser, and

V = potential difference over the condenser.

During a stimulation impulse, the condensor charge falls with the operational charge, and since the capacity is constant the voltage V falls. In a low capacity condenser the operational charge will cause a relatively greater drop in voltage than one of large capacity. The minimum voltage across the electrode circuit, which is equal to the voltage at the end of the impulse, will therefore be higher with a large capacity condenser. The impulse slope, which depicts the drop in voltage during the impulse, will therefore be steeper for a small condenser than for

a large one. This may be elucidated by an example.

For a condenser with a capacity of 60 μF and a battery voltage of 6.5 V, the charge of the condenser at the beginning of the impulse is

$$Q = C \times V = 60 \times 10^{-6} \times 6.5\ C = 390\ \mu C$$

provided that R_6 is small. At an operational charge of 20 μC, the charge at the end of the impulse is 370 μC. As a result of the operational charge, the voltage over the condenser has then dropped by

$$V = \frac{Q}{C} = \frac{20}{60} V \approx 0.35\ V.$$

At a polarization potential of 1.5 V, the voltage available at the end of the impulse i.e. the voltage available to send a current through the resistance R is then

$$V = 6.5 - (1.5 + 0.35)V = 4.65\ V$$

The minimum current is then 4.65 V : R ohm.

For a smaller condenser with a capacity of 10 μF, the charge at the beginning of an impulse is

$$Q = C \times V = 10 \times 10^{-6} \times 6.5C \approx 65\ \mu C.$$

At an operational charge of 20 μC, the potential over the condensor drops by

$$V = \frac{Q}{C} = \frac{20}{10} V = 2V.$$ At a polarization potential of 1.5V, the voltage available at the end of the impulse is

$$V = 6.5 - (1.5 + 2) = 3V$$

The minimum current is then 3V : R ohm.

Thus, it follows that the minimum current is larger for the large than for the small condenser, the latter giving a steeper impulse slope at a given operational charge.

The slope itself is not perfectly exponential, because the load is complex during the pacemaker impulse. When current flows through the electrodes the back e.m.f. of polarization is not linearly related to the current, as it increases at a constant current strength to a final value, taken to be 1.5V in our examples (measurements in fig. VI-34). As the back e.m.f. develops rapidly, however, current decrease is almost exponential after a short time, so that the following formula may be

applied to current at a fixed time interval, 0.5 msec after the onset of the impulse.

$$\frac{i_0}{i_{0.5}} \approx \frac{i_{0.5}}{i_1} = \frac{i_1}{i_{1.5}} = \frac{i_{1.5}}{i_2}$$

This provides another method of monitoring the stimulation unit, (see Chapter IX).

From the equation $V = \frac{Q}{C}$ it also follows that a larger operational charge Q, which may be due to a decrease in the resistance of the electrode circuit, results in a steeper impulse gradient (fig. IX-8, 11). At an operational charge of 30 μC, the condenser of 60 μF will then provide an available potential of:

$V = 6.5 - (1.5 + 0.5)V = 4.5V$ and the condenser of 10 μF an available potential of:

$V = 6.5 - (1.5 + 3)V = 2V$ at the end of the impulse.

In conclusion it may be stated about the output circuit in a voltage pacemaker that:

- a condenser with a large capacity provides a higher available voltage at the end of the impulse, i.e. the impulse has a smaller slope, than with a small capacity condenser,
- the available voltage at the end of the impulse of a given condenser decreases with increasing operational charge, i.e. the impulse has a steeper slope for a high operational charge than for a low one.

The advantages of the voltage circuit are that the operational charge is adaptable to various electrodes (Chapter VIII-energy), and that analysis of the effect of variations in resistance in the electrode circuit indicates the condition of this circuit (Chapter IX-photo analysis).

b. Current circuit. A diagram of the output circuit of a current pacemaker is shown in fig. VIII-8. In comparison with the circuit in fig. VIII-9 the important difference is the extra resistance R_4, which is much larger than the resistance in the rest of the electrode circuit, and thus ensures a virtually constant current during the impulse. This current is proportional to the battery voltage, and variations in resistance in the rest of the electrode circuit, provided that they remain much smaller than R_4, do not affect the shape and amplitude of the impulse. A transistor circuit may also be used (SCHNEIDER 1966) as an alternative to this high output resistance, but the large volume of such a circuit prevents its use in implantable pacemakers.

The current output circuit, used by ZOLL and CHARDACK and GREATBATCH *inter al.*, has the advantage that the output impulse remains constant in spite of variations in the electrode circuit, but analysis of the condition of the circuit by the photo analysis method is then impossible. Moreover, the operational charge is not adaptable to other electrodes (Chapter VIII-energy). Another drawback of this circuit is that the amplitude of the impulse is limited to relatively low levels at a given battery voltage. ZOLL, who uses large suture electrodes with a high threshold, thus needs 6 batteries to obtain an operational current of 15 mA and a sufficient safety margin, but the coil electrodes used by CHARDACK *et al.* have a lower threshold and 5 batteries are sufficient for their pacemaker. According to their pulse forming and output circuit asynchronous fixed-rate pacemakers may be classified into four groups.

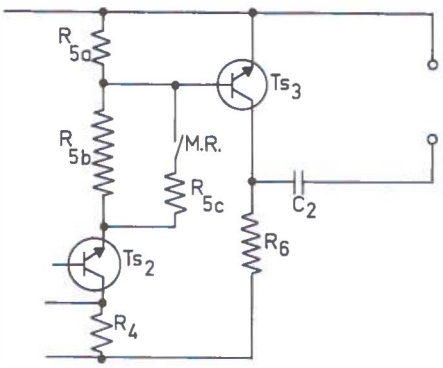
pulse forming circuit	output circuit	example
– blocking oscillator	current	CHARDACK *et al.*
– blocking oscillator	voltage	ELMQVIST *et al.*
– free running complementary multivibrator	current	ZOLL *et al.*
– free running complementary multivibrator	voltage	VAN DEN BERG *et al.*

c. Current limited voltage circuit. This pacemaker was developed to increase the life of implanted voltage pacemakers by governing the maximum current flow in the electrode circuit. From threshold measurements (Chapter VI) it was found that with a maximum operational current of 10 mA for both the intramural and intracardiac electrodes used by us, a sufficient relative threshold was obtained. This means that a sufficient safety margin exists throughout the 2 msec impulse. The maximum charge transmitted through the tissues per impulse is 20 μC, thus battery discharge per impulse is restricted and high operational values, which otherwise occur with a low resistance in the electrode circuit, are limited to this value and the charge difference is saved.

The current limitation may be accomplished simply by selection of R_{5a}, R_{5b} and the transistor Ts_3 in the output circuit (fig. VIII-10) to give the maximum desired current from the emitter to the collector through the transistor and thus through the electrode circuit. This is 10 mA in our pacemaker.

Because of this current limitation, the impulse shape is not identical with that of the unlimited voltage pacemaker, except with large re-

Fig. VIII-10. Diagram of output circuit (see fig. VIII-9) with two operational values, chosen by means of a magnetic switch.



sistances. The impulse exhibits the same pattern as long as the initial operational current does not reach the maximum value of 10 mA. This means that with a battery voltage of 6.5V a polarization voltage of 1.5 V and a resistance in the circuit of

$$R = \frac{V}{i} = \frac{5.0\,\text{V}}{10\,\text{mA}} = 500\ \text{ohm}$$

the current limitation is not in use. Therefore, with resistances of 500 ohm or more, the impulse shape will be that of a voltage pacemaker, the operational current being determined by the effective resistance in the electrode circuit.

However, with small resistances in the circuit the impulse is totally determined by the current limitation, which is calculated simply; during the 2 msec impulse, the charge of the condenser has decreased by 20 μC, and with a 6.8 μF condenser as used in our pacemaker, the potential over it has dropped by

$$V = \frac{Q}{C} = \frac{20 \times 10^{-6}\,\text{C}}{6.8 \times 10^{-6}\,\text{F}} = 3\,\text{V}$$

as a result of the reduced charge. Moreover, at the end of the impulse the available potential is decreased by 1.5 V due to polarization. At the end of a totally limited impulse the available potential is therefore

$$V = 6.5 - (1.5 + 3)\,\text{V} = 2\,\text{V}$$

Since the limited current is 10 mA a resistance of

$$R = \frac{V}{i} = \frac{2}{10 \times 10^{-3}}\ \text{ohm} = 200\ \text{ohm}$$

is just compatible with the requirement. With a resistance equal to or lower than 200 ohm the impulse is limited by the circuit, as in a current pacemaker. With a resistance larger than 200 ohm but smaller than 500 ohm the shape of a voltage pacemaker impulse appears later in the impulse, making the whole impulse shape different from previous patterns. There is a plateau (fig. VIII-11) at the beginning of the impulse,

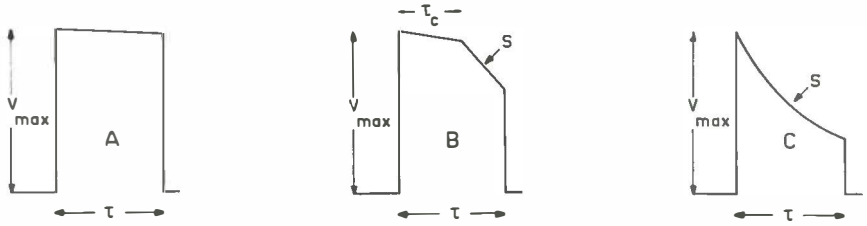


Fig. VIII-11. Scheme of the impulses of the three types of pacemakers.
A. Current pacemaker; B. Current limited pacemaker; C. Voltage pacemaker.
Vmax: maximal voltage; τ_c: plateau with virtually constant voltage; S: slope; τ: impulse duration.

caused by the current limitation, followed by a slope similar to that of a voltage pacemaker. For example, with a current limited voltage pacemaker loaded with a resistance of 350 ohm, for maintenance of the maximum current of 10 mA through this resistance, an available potential is required of

$$V = i \times R = 10 \times 10^{-3} \times 350 = 3.5 \text{ V}$$

At the beginning of the impulse there is a potential of 6.5 V over the condenser. The available potential is, however, very rapidly reduced to 5.0 V by the back e.m.f. of polarization. The potential over the condenser may thus drop $6.5 - 1.5 - 3.5 = 1.5$ V to meet the requirement that the maximum current is still 10 mA. With our condenser of 6.8 μF, a drop in potential of 1.5 V means a charge loss of

$$Q = V \times C = 1.5 \times 6.8 \times 10^{-6} = 10.2 \ \mu\text{C}$$

The current is 10 mA during this discharge, so the discharge of 10.2 μC takes place in

$$t = \frac{Q}{i} = \frac{10.2 \times 10^{-6}}{10 \times 10^{-3}} = 1.02 \text{ msec}$$

After this time, the voltage over the condenser has fallen to such an

extent, that the condenser is no longer able to supply 10 mA through the circuit, and the current then decreases with increasing discharge, resulting in a bend followed by a slope comparable to that of a voltage pacemaker, since the current is now determined by the available voltage over the electrode circuit.

It follows that the duration of the plateau decreases as the resistance in the circuit increases from 200 towards 500 ohm.

In practice, with the resistance being a.o. heart muscle, the impulse shape is unchanged, but the calculation of the point at which the kink occurs is more complicated, because during the impulse the polarization potential builds up to a maximum of 1.5V causing the effective voltage through the condenser to decrease due to the current drain, the calculation is outside the scope of this report.

A number of variations of the most common types of asynchronous fixed rate pacemakers have now been discussed. Many other modifications are possible, but any alteration of the circuit entails greater complexity and thus greater risk of defects, and the complications of such a change must be carefully weighed against its advantages. Considerable changes were necessary for new methods of stimulation, viz. the P-wave triggered and the R-wave controlled pacemaker. These types of stimulators are in some respects extensions by means of additional circuits of the fixed rate pacemaker.

B. P-wave triggered synchronous pacemaker

The principle of this stimulator is the replacement of the defective atrio-ventricular conduction by an electronic circuit, as already mentioned in Chapter IV.

Such a circuit requires:

a. detection of the atrial depolarization,
b. additional circuits to modify the atrial signal to be suitable after a delay (the artificial P-R interval) to initiate the impulse,
c. stimulation of the ventricles,

and these aspects were examined for the development of such a pacemaker.

a. Detection of atrial depolarization

Detection of the atrial signal is only practicable at the myocardial surface, either endocardially or epicardially, because of the thinness of the atrial

wall. We used epicardial disc electrodes with Elmqvist's and Senning's technique (fig. VI-7) or semi embedded coil detector electrodes, a modification of Nathan's method (fig. VIII-12).

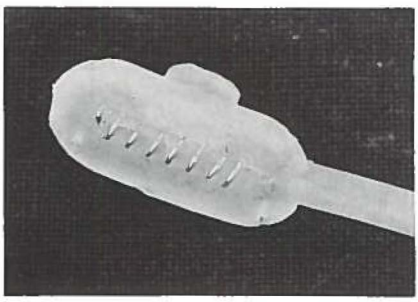


Fig. VIII-12. Epicardial electrode for the detection of atrial depolarisation, the frame is fixed by two sutures. The top structure is used for holding the frame during the fixation and is removed afterwards.

The detections were performed in 5 dogs, potentials were determined for combinations of seven indifferent electrodes (suture-, disc-) and eight ventricular electrodes (pin-, suture- and loop-). In three of the dogs heart block was created via the right atrium, and following this, the depolarization potential was found to be totally different from the pre-

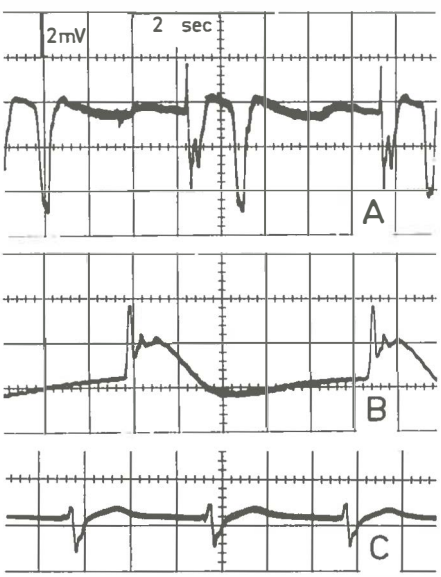


Fig. VIII-13. Voltages detected from the right atrium before and after the production of a heartblock (open method) in a dog.
The detection electrode was located between the atrial incission and the annulus fibrosis. Indifferent electrode in the thoracic wall.
A. before production of heartblock, atrial depolarizations, followed by ventricular signals,
B. atrial depolarizations immediately and
C. 7 days after production of heartblock.

operative pattern. In one dog the signal recovered after some time (fig. VIII-13), and in the other two dogs after a second thoracotomy in approximately 2 weeks left atrial potentials were detected. In the two dogs who did not have heart block, the signal was detected from the left atrium.

The signal achieved in all these dogs showed a variable initial positive deflection followed by a powerful rapid negative phase, and return to the zero point. We, therefore, chose the negative phase to trigger the pacemaker.

The amplitude of this signal using a unipolar detector was practically identical to that with a bipolar detector electrode. The mean amplitude detected from the seven unipolar systems was 7.3 mV (6.1-8.3) immediately after introduction of the electrodes and 7.4 mV (7.1-8.3) from the eight bipolar systems. During the first 4 to 6 weeks after implantation this amplitude decreased to 25-30% of the initial value, thereafter the detected voltage stabilized; one dog (fig. VIII-14) was

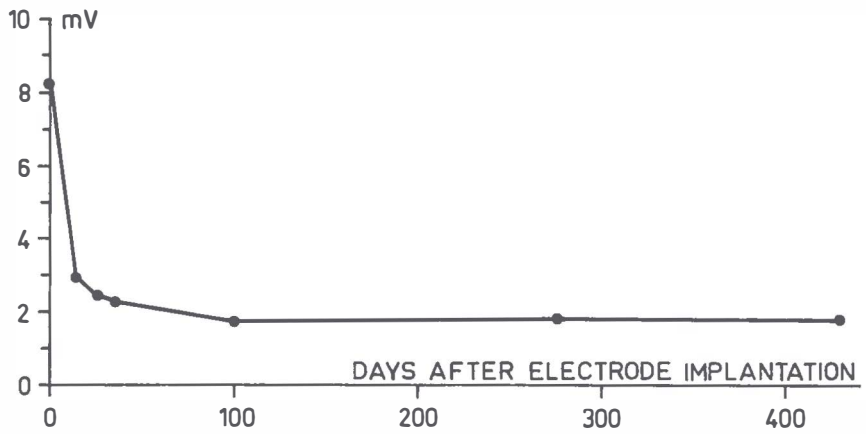


Fig. VIII-14. Maximal amplitude of negative peak of electro-atriogram versus days after electrode implantation in a dog.
Epicardial disc detection electrode on the left atrium. Voltages virtually independent of the place and the type of the indifferent electrode, suture or plate in the thoracic wall, loop electrodes in the left and right ventricle.

followed up for longer than one year. The decrease in amplitude was a result of tissue formation around the electrode, increasing the distance between the active tissue and the electrode, as was also seen in R-wave detection described later.

Our final mean value of 1.6 mV (1.4-2.0 mV) is somewhat lower than those given by CENTER *et al.* (1963). In their animal experiments they found 2-8 mV on implantation, and after 4-6 weeks 3 mV on average, and values of 2.0-4.5 mV after 3-21 months in patients. CARLENS (1965) using epicardial detection on his patients found initial values of 1-7 mV, which stabilised at 1.5-2.5 mV.

RODEWALD *et al.* (1965) reported clinical experience with intracardiac detection finding that 47% of the initial measurements proved to give values lower than 0.9 mV immediately after introduction of the catheter electrode.

On this basis our P-wave triggered pacemaker of which a block diagram is given in fig. VIII-15, was set at an input sensitivity of 0.9 mV with the frequency band of the input circuit set at 25-150 Hz. Other authors mention a frequency response of 20-200 Hz (NATHAN, CENTER *et al.* 1964) and 5-100 Hz (CARLENS *et al.* 1965).

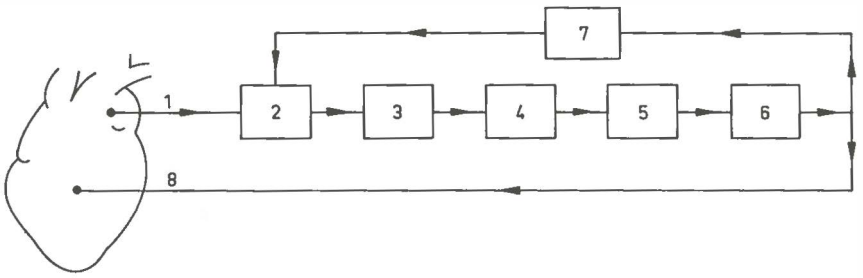


Fig. VIII-15. Block scheme of the P-wave triggered synchronous pacemaker.
1. atrial detection electrode (P-wave).
2. detector.
3. amplifier.
4. delay circuit (atrio-ventricular delay time).
5. pulse forming circuit.
6. output circuit.
7. blockade of detector.
8. ventricular stimulation electrode.

b. Delay circuit

The detected signals are amplified and modified, and then fed through a delay circuit into the pulse forming circuit. The purpose of the delay being both to allow physiological activation of the ventricles if sinus rhythm returns, the pacemaker stimulus then falling in the ventricular refractory period, and when complete A-V block exists, to stimulate

the heart only after complete ventricular filling. In order to meet both these requirements, the delay should be equal to or a little longer than the P-R period of a normally functioning heart. We set this to be 190 msec; NATHAN *et al.* (1964) chose a time of 160 msec, whereas the 70 msec delay used by Carlens was so chosen that the heart is continually stimulated by the pacemaker, and normally conducted system beats do occur in the refractory period of the artificial contractions. Return of sinus rhythm cannot then be utilized.

After this delay the signal reaches the pulse forming circuit.

c. Ventricular stimulation

The pulse forming circuit and the output circuit are identical to the asynchronous circuits dealt with above. Our P-wave pacemaker consists of a free running multivibrator circuit as the pulse forming circuit, and a voltage output circuit. The impulse frequency of the former is set at 65/min. Therefore, if P-wave signals are absent or too weak to be detected, the P-wave pacemaker stimulates the heart at a constant frequency of 65/min. This also occurs if the atrial rate falls below this constant value. When the P-wave rate is higher, the signals reach the pulse forming circuit in the phase in which the voltage of the condenser C_1 has not yet decreased enough by its discharge through the resistance R_2 to open the transistor Ts_1 (fig. VIII-9). The circuit of the P-wave triggered pacemaker is now such that the delayed P-wave impulse affects the base of the transistors Ts_1 and Ts_2 which are opened. An impulse is formed in the manner previously described and stimulates the heart via the ventricular electrode(s) of the output circuit.

To prevent the electrical stimulus from being detected by the atrial electrode and triggering the circuit, causing the pacemaker to react to its own signals, the impulse is also administered to a blocking circuit, which blocks the detector circuit for 200 msec. A P-wave signal detected after (190 + 200) msec. can once more trigger the circuit. The maximum frequency attainable through this circuit is determined by the total delay in the circuit, i.e. the delay time and the blocking time. In our P-wave pacemaker in dogs the maximum frequency is $\frac{60.000 \text{ msec.}}{390 \text{ msec.}} = 154$ impulses per minute. If the atrial frequency rises above 154 per minute, each second detected signal falls in the delay period, so that for atrial rates between 155-309/min the ventricular rate is half that of the atrial rate. For their P-wave triggered pacemaker

Nathan, Center et al., in clinical use probably increased the total delay period by increasing the blocking time, giving a maximum frequency of 110/min; Carlens et al. used maximum frequencies of 150-170/min.

d. Application

We used the circuit for synchronous stimulation in animal experiments (fig. VIII-16). Although the advances made in the field of electronics now make it possible to construct a reliable circuit, in spite of its complexity, the restricted life of this pacemaker deterred us from developing an implantable unit. The additional circuits of a P-wave triggered pacemaker require a relatively high current, for the amplification of the signal, the delay circuit and the blocking circuit, leading to rapid exhaustion of the batteries. In our case the current consumption of the extra circuits at a frequency of 72/min. is 20 μA. As discussed before (see Energy) the pulse forming and the output circuit have a current consumption of 24 μA. Without the extra circuits the unit would have a life of 43 months, but using the same number of batteries of 1000 mA and connecting the additional circuits at an atrial rate of 72/min. the life of the unit is reduced by 17 months. NATHAN (1964) mentioned a life of 3 years for his pacemaker, and LAGERGREN and CARLENS two years, at a mean frequency of 70/min., but it should be born in mind that the life of an atrial triggered pacemaker is approximately inversely proportional to the atrial rate thus rates above 70 further reduce pacemaker life.

It is relatively easy to achieve a similar life for the P-wave pacemaker as for the asynchronous pacemaker however. The extra circuits only require a low voltage, which can be supplied by two additional batteries in series with the 5 other batteries serving only to power the pulse forming and output circuits. A total of 7 batteries must then be included in the pacemaker, making it too large and heavy.

For this reason and others mentioned in Chapter IV we have not constructed an implantable unit of this type for clinical use. The R-wave controlled pacemaker offered several of the advantages of the P-wave pacemaker but was less complicated and had a longer life. Its development is discussed now.

C. R-wave controlled on-demand pacemaker

The principle of the R-wave controlled pacemaker (see Chapter IV) is

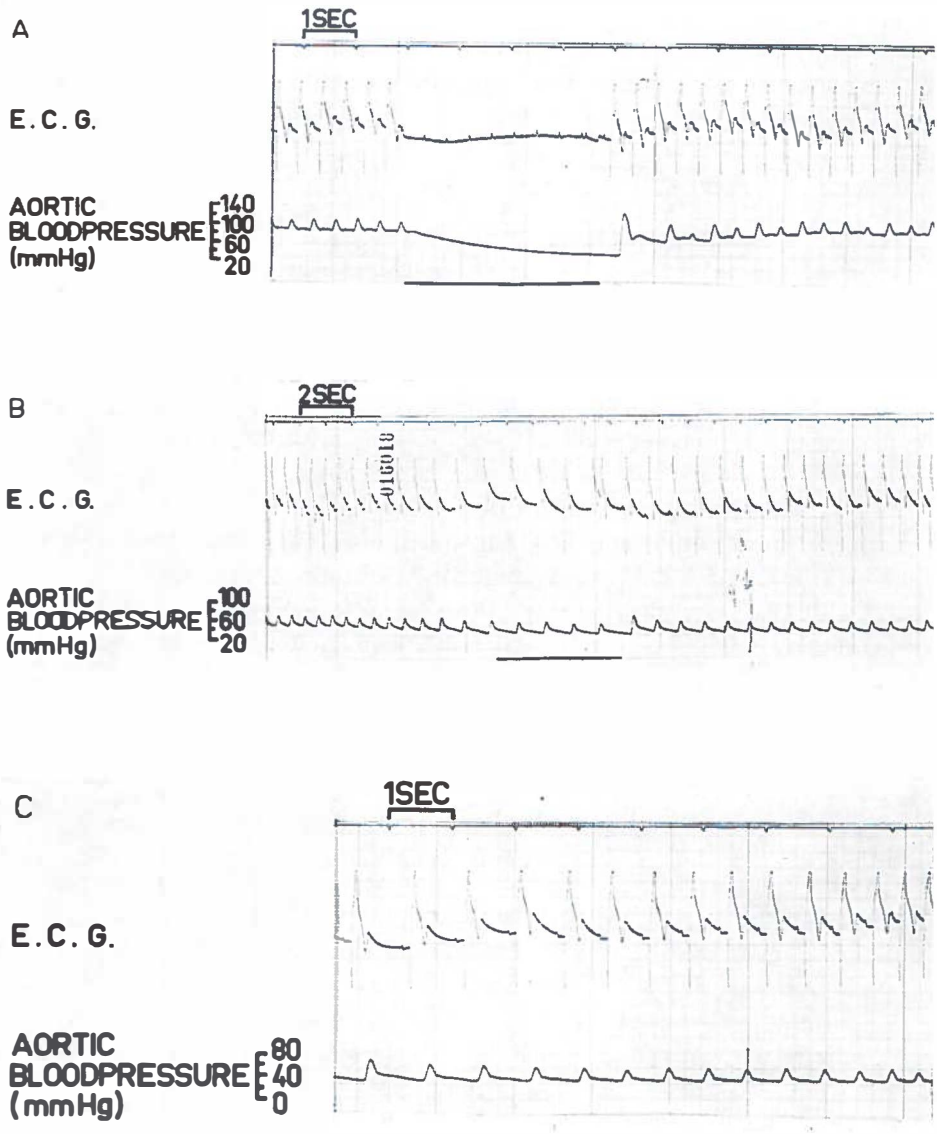


Fig. VIII-16. P-wave triggered pacemaker in a dog.
A: Disconnection (—) of the atrial detection and ventricular stimulation electrode.
B and C: Recordings after injection of Acetylcholine.
B: The proper heart frequency drops temporarily to such an extent that the heart is stimulated at the fixed minimal frequency of the pacemaker (—).
C: Recovery of the heart, synchronous stimulation at increasing heart frequency.

that it should only effectively stimulate the heart if the ventricular rate falls below its predetermined rate or if a complete cardiac arrest occurs. The R-wave controlled pacemaker may be subdivided into R-wave blocked and R-wave triggered types, according to the effect of the detected R-wave on the pulse forming circuit. The R-wave triggered pacemaker is similar to the P-wave triggered pacemaker, i.e. a triggered pacemaker with a very short or negligible delay.

Here we shall describe our R-wave blocked pacemaker where the detected signal, in contrast to that with triggered pacemakers, blocks the pulse forming circuit instead of activating it. This pacemaker requires:

a. detection of ventricular activity,
b. additional circuits, primarily a blocking circuit, which modifies the ventricular signal, so as to block stimulation of the ventricles,
c. stimulation of the ventricles.

It was first investigated experimentally and after the development of a prototype, research continued clinically.

a. Detection of ventricular depolarization

It has been previously shown (Chapter IV) that with an extracorporal unit, e.g. monitoring apparatus, skin electrodes can be used to detect heart activity. This type of intermittent stimulation is only used for a limited period. The implantable unit for long term stimulation, discussed here, requires direct pick-up of the ventricular ECG and for this purpose heart electrodes: epicardial, intramural or endocardial (see Chapter VI) may be used.

The shape, size and frequency of the detected signal are of particular importance. Research carried out by ROOS (1964) showed that the shape of the signal depends on the location of the electrode on the ventricles. However, all signals displayed a negative phase, suitable to trigger the pacemaker. Roos' experiments were investigating the propagation of the depolarization wave over the ventricles, and were therefore of a short term nature only. So we investigated the ventricular signal with long term experiments in 5 dogs. 2 pin electrodes and 8 loop electrodes were placed at random in the ventricular myocardium of each dog. The ventricular potentials were measured in combination with indifferent electrodes (disc, suture) and in combination with other cardiac electrodes, both ventricular and atrial. In all, 10 ventricular electrodes were used in 21 combinations to detect ventricular activity. The size of

the rapid negative phase of the potentials immediately after implantation of the electrode was a mean of 20.8 mV (15.5-33 mV). As with atrial signals, this amplitude decreased during the first 4-6 weeks due to tissue formation, after which time a stable level was reached at a mean of 8 mV (6.6-11 mV). The signals from pin electrodes were observed for over a year in one animal. The average values of the negative phase of pin electrodes in combination with suture and disc indifferent electrodes are shown in fig. VIII-17. Analysis of the slope of the negative phase of the signal gave values corresponding to the maximum slope of a wave of 35-45 Hz. Based on this result, the sensitivity of the detector circuit of the pacemaker was chosen so that signals in the frequency-range 20-150 Hz and with a minimum amplitude of 4 mV were sufficient to

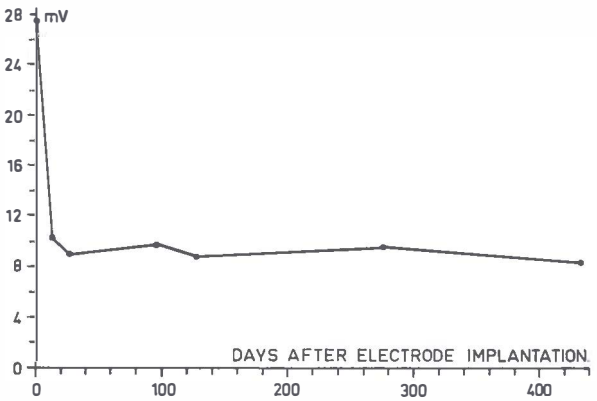


Fig. VIII-17. Maximal amplitude of negative peak of electro-ventriculogram versus days after electrode implantation in a dog. Intramural pin electrode on the left ventricle. Voltage virtually independent of the place and the type of the indifferent electrode, suture in the right and disc in the left thoracic wall.

block the pulse forming circuit, see block diagram fig. VIII-18. It was also possible to reduce the sensitivity to extraneous electrical signals (A.C. mains of 50 and 60 Hz) to such an extent that the pacemaker is not blocked when the patient comes in contact with badly insulated household apparatus etc.

b. Blocking circuit

The signals detected in this way are amplified and modified in the input circuit of the pacemaker. In contrast to the P-wave pacemaker, the signal is not delayed, since in this case A-V conduction is not being

replaced, but it is transmitted directly through the blocking circuit to the pulse forming and output circuits through which ventricular stimulation occurs.

c. Ventricular stimulation

The pulse forming and output circuit of our R-wave pacemaker are identical to those of our asynchronous fixed rate pacemaker. There is a voltage output circuit and the pulse forming circuit is set at a constant frequency of 65 imp/min. If no signal is detected, if the signal frequency falls below 65/min, or if the signal is too small to be detected,

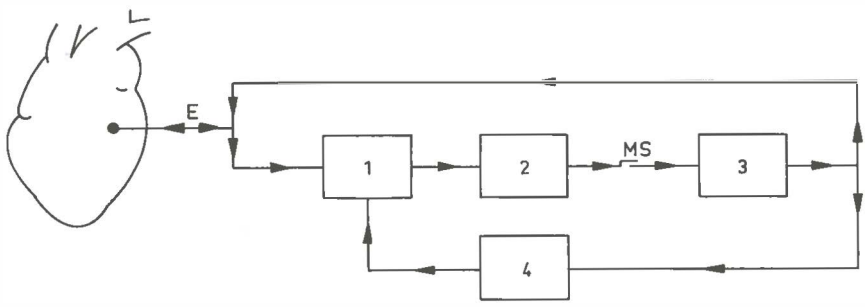
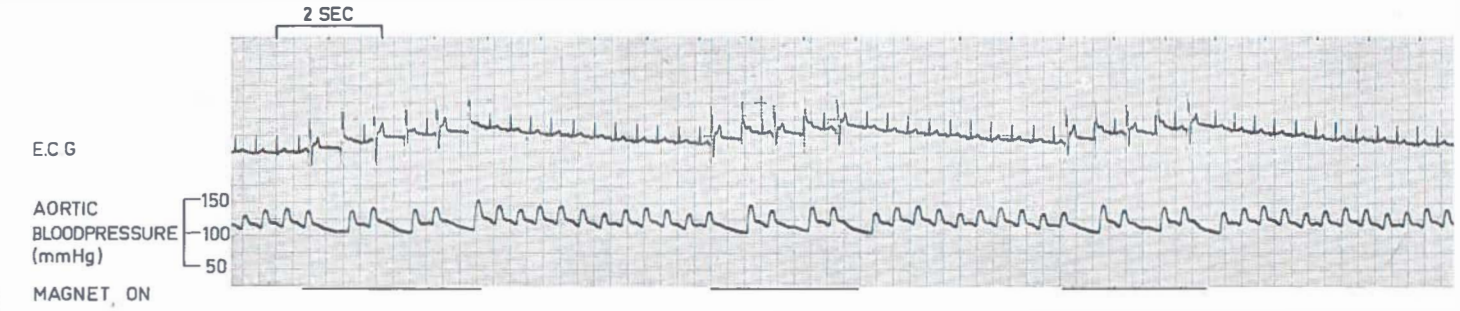


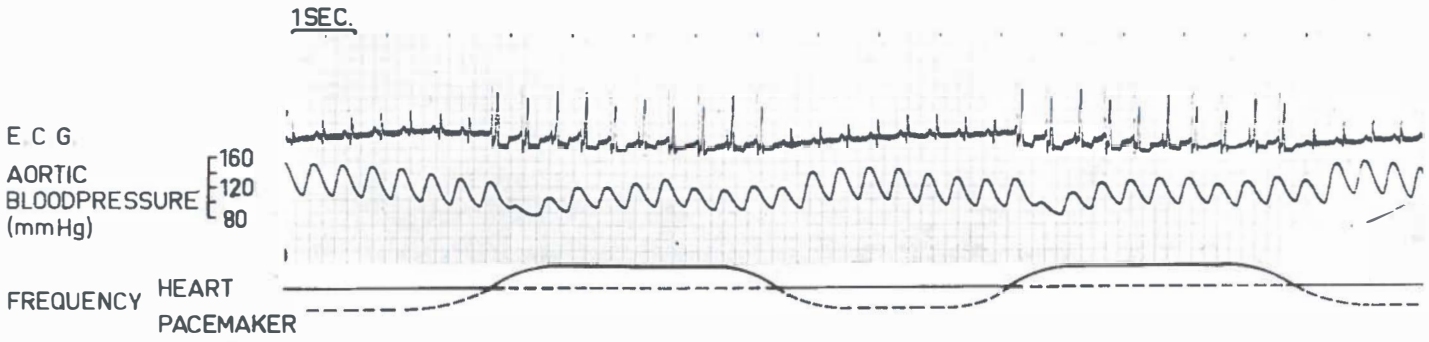
Fig. VIII-18. Block scheme of the R-wave blocked – on demand – pacemaker.
1. detector
2. blockade of pacemaker
3. pacemaker
4. blockade of detector.
E: ventricular detection and stimulation electrode.
MS: magnetic switch.

the heart is stimulated at a constant frequency of 65 imp/min. by this circuit.

If sinus rhythm returns or there is a rapid idioventricular rhythm and the natural ventricular activity exceeds 65 /min., the ventricular signals detected continually block the pacemaker, preventing it from stimulating the heart. The blocking circuit then acts at two points in the pacemaker circuit. If the ventricular frequency is higher than the pacemaker frequency, the ventricular signals reach the pulse forming circuit when the condenser C_1 in fig. VIII-9 has not yet discharged enough to open the transistor Ts_1. The blocking circuit now operates in such a manner that the transistor blocks the output circuit and the discharge from the condenser C_1 is reset to its initial phase immediately after an impulse. The condenser discharges again and the cycle is repeated. If this discharge is not interrupted prematurely however by a detected


2 SEC
E.C G
AORTIC
BLOODPRESSURE
(mmHg)
150
100
50
MAGNET, ON

A


1SEC.
E C G
AORTIC
BLOODPRESSURE
(mmHg)
160
120
80
FREQUENCY
HEART
PACEMAKER

B

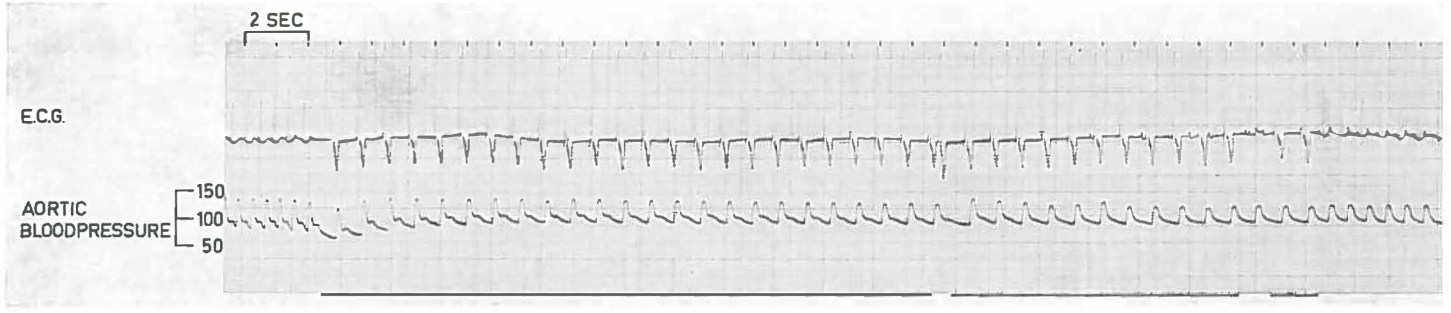


Fig. VIII-19. R-wave blocked pacemaker in a dog.

A: Blocking disconnected (—) by means of magnetic switch. Interference.

B: Effect of a variation of the minimal pacemaker frequency. When this frequency is increased beyond the heart frequency, the ventricle is asynchronously stimulated by the pacemaker.

C: Effect of a variation of the heart frequency, after an injection of Acetylcholine. When the heart frequency drops beyond the minimal pacemaker frequency (—), the ventricle is stimulated by the pacemaker. The pacemaker stimulation is two times interrupeed by a proper ventricular contraction.

signal, the voltage over C_1 drops so far that the transistor Ts_1 is opened and an impulse passes as in asynchronous fixed-rate pacing to stimulate the heart.

To prevent this stimulus from being detected, which would result in a prolonged interval between stimuli and a lower, irregular frequency, a portion of it is fed into the blocking circuit, as in the P-wave pacemaker, to block the detector circuit for approximately 350 msec. After this period the detector circuit is again able to sense ventricular activity.

d. Application

This R-wave pacemaker was used in the 5 dogs, and the results are shown in fig. VIII-19. In the experiment shown in fig. VIII-19A blocking of the pacemaker by heart activity was checked. The ECG shows correct pacemaker function. Variations in the blood pressure occurred due to interference when the pacemaker was not blocked by the detector circuit, by interruption with the magnetic switch.

Further tests were performed to ascertain whether the pacemaker would be blocked at a high cardiac frequency and whether stimulation would begin immediately after the cardiac frequency had fallen below that of the pacemaker and vice versa. In these experiments too the aortic blood pressure was recorded. Thus, the pacemaker frequency (fig. VIII-19B) was gradually increased to a level above the heart rate and subsequently reduced to the initial level.

In the final experiment (fig. VIII-19C) the pacemaker was set at a constant frequency of 65/min. and Acetylcholine (2.5 mg/kg) was given intravenously; approximately 30 seconds after the injection the heart rate fell below the pacemaker frequency for a period of 33 seconds, during which time the pacemaker was stimulating the heart.

In view of these results, the R-wave blocked pacemaker was used extracorporeally in a number of patients. Their ventricular signals were analysed firstly, during sinus rhythm; these measurements, using our pacemaker, were carried out in university clinics in Frankfurt, Groningen, Leiden and London. Using intramural ventricular electrodes the same pattern as in the dog experiments was observed. The mean of 6 ventricular signal measurements made soon after electrode insertion was 15 mV (10-27 mV). In 5 patients all of whom had returned to sinus rhythm with electrodes (suture, pin or loop) implanted for a longer period (4-23 months), the mean amplitude was found to be 7.5 mV (4-12 mV).

Measurements were also made using catheter electrodes. The endocardial signal proved to be considerably weaker. In 5 measurements soon after electrode insertion the mean amplitude was found to be 6.7 mV (6-7.5 mV). In 4 measurements on catheters in sites for longer periods (8-12 months), the amplitude was found to have fallen to a mean 3.5 mV (3-4.5 mV). One exception was noted in these measurements, a signal of 17 mV was detected from a catheter electrode which had been in use for 9 months. Probably the reason for this strong signal was the fact that the catheter tip had penetrated the myocardium shortly before the measurement was carried out.

Since the frequency range of the signals was practically identical to that found in dogs, it was decided to retain the circuit described above, but to increase the sensitivity from 4 to 2 mV to allow combination of the pacemaker with catheter electrodes. This pacemaker gave satisfactory clinical results. The first R-wave blocked pacemaker was implanted in a patient in 1966 (fig. VIII-20).

One complication of the R-wave blocked pacemaker is that following implantation, no analysis of the stimulator circuit is possible, so that it is impossible to check whether the pacemaker would be capable of stimulating the heart if there is a sudden fall in ventricular rate. MYERS *et al.* (1966) slowed the heart by carotid sinus pressure in order to analyse pacemaker function. In our case, analysis can be performed by means of a magnetic relay, which is included between the blocking circuit and the pulse forming and output circuits, so that inhibition of the pacemaker is interrupted if the magnet is held near the pacemaker, thus allowing fixed rate heart stimulation and photo analysis of the unit.

Since it is possible to use the detector electrode also as stimulation electrode only one heart electrode is required for the R-wave controlled pacemaker. In the block diagram in fig. VIII-18 the definitive version of our pacemaker is shown.

In Chapter IV, the longer life compared with the asynchronous fixed rate and particularly the P-wave triggered pacemaker was mentioned amongst other things as one of the advantages of the R-wave pacemaker. This life is simple to calculate. It was seen above that the current drain of the fixed rate pacemaker at a frequency of 72 imp/min is about 5 μA for the pulse forming circuit and 19 μA for the output circuit. In the R-wave controlled pacemaker, there are additional circuits consuming approximately 7 μA. It was calculated that the fixed rate pacemaker has a life of 43 months, with a total current consumption of 24 μA. The same calculation shows that the R-wave pacemaker with a current con-

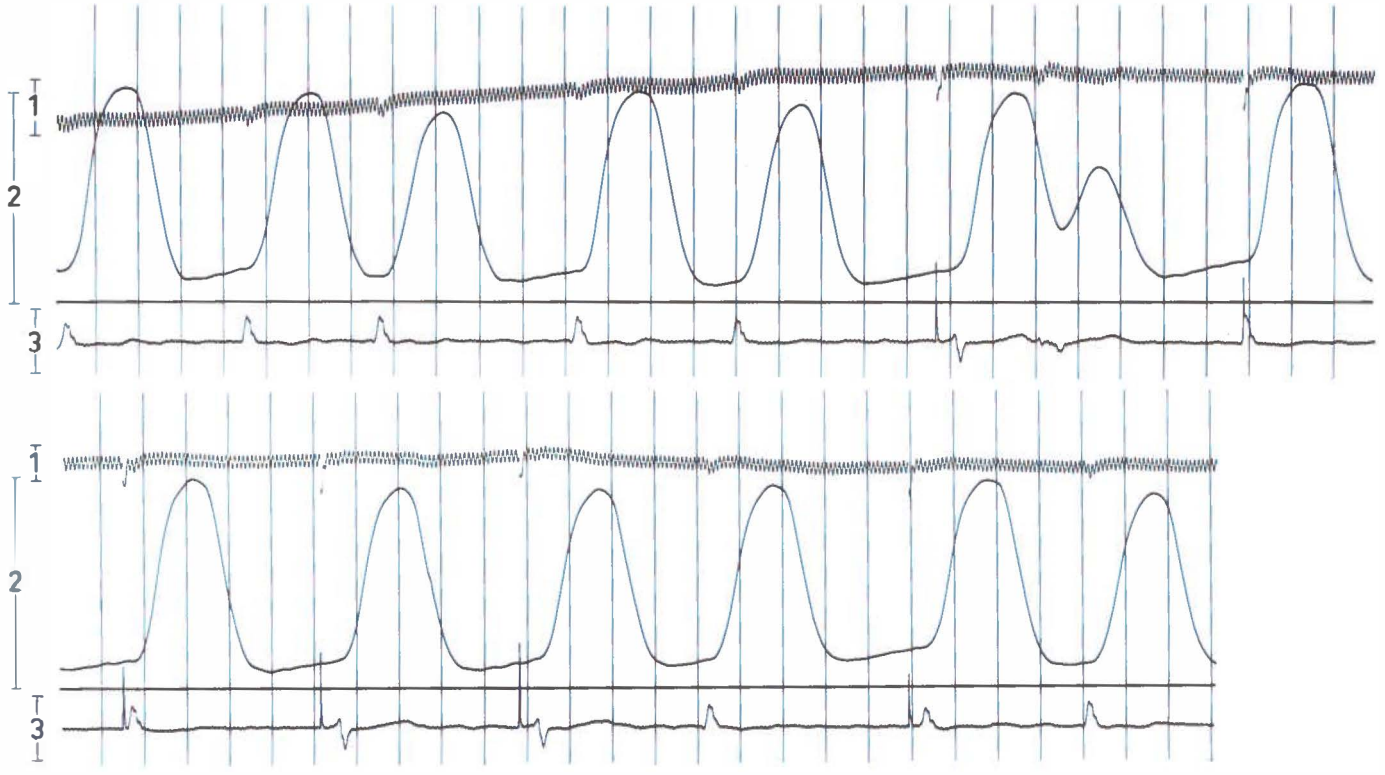


Fig. VIII-20. R-wave blocked pacemaker in a patient. (By courtesy of DR. H. H. HIRSCH and DR. E. STAUCH).
1. ventricular E.C.G.; 2. ventricular pressure; 3. E.C.G. lead II. The ventricle is stimulated by the pacemaker (large peaks) when the proper heart stimulus does not arrive in time.

sumption of 31 μA has a life of 35 months if there is no inherent cardiac activity to inhibit it, but if it is inhibited throughout its implanted life, with a current consumption of 12 μA (additional circuits 7 μA, pulse forming circuit 5 μA) a life of 69 months is expected. It follows that the R-wave pacemaker has a life equal to or longer than that of the fixed rate pacemaker if heart activity inhibits the pacemaker for 40% or more of the implantation period.

After the electrodes and the conduction leads, the active component of a stimulation unit, the stimulator itself, has been discussed in this chapter, a comparative survey of the various methods of stimulation in clinical use already being given in Chapter IV. In the following chapter the general clinical application of stimulation units will be discussed with special attention to methods of examination of the implanted pacemaker.

Clinical application of the electrical cardiac pacemaker

CHAPTER IX

In the preceding chapters a survey of the different stimulation methods is given and the components of the stimulation circuit are discussed. In this chapter the clinical applications of the artificial cardiac pacemaker and in particular the problems of follow-up of implanted pacemakers and pacemaker patients are dealt with.

1. INDICATION FOR THE IMPLANTATION OF A PACEMAKER

The difficulties which were met in the initial period of long term pacemaker application prevented wide indications and so drug therapy was maintained if possible. As the improvements discussed in the preceding chapters came about pacemaker treatment increased in relation to drug therapy (dealt with in Chapter II).

In Groningen (NIEVEEN 1965) pacemaker implantation is absolutely indicated in patients with A-V block, whose Adams-Stokes attacks persist despite medical treatment. Relative indications apply to those patients who react poorly to drug therapy and have a potential chance of Adams-Stokes attacks. These indications are similar to those in most clinics.

Opinions as to the stimulation method to be applied vary in different centres, and in this regard reference can be made to Chapter IV where the advantages and disadvantages of the various methods are discussed. In the choice of the stimulation method, a selection should not only be made from the various pacemakers but also from the various methods of impulse transmission. In the latter case there is now a tendency for the transvenous catheter to be used instead of the transthoracic electrode, probably because the transthoracic electrode was the source of many difficulties during early application; transvenous stimulation also avoids

the anaesthesia and thoracotomy necessary for the insertion of the transthoracic electrodes.

As complications arising from the thoracotomy have seldom been experienced in Groningen (HOMAN VAN DER HEIDE 1967), the transthoracic method is chosen here wherever possible, guaranteeing a more stable stimulation than the transvenous method, especially during the initial post-operative period. Moreover further evolution in the field of heart stimulation has resulted in improved transthoracic electrodes, which now only rarely cause complications. In Groningen the catheter electrode is only used in cases where a thoracotomy is contra-indicated, such as in very old patients, in cases where implantation on the left ventricle is impossible for example because of ventricular aneurysm or fresh myocardial infarction, or in cases of pulmonary diseases.

II. IMPLANTATION OF THE PACEMAKER

Once it has been decided to implant a pacemaker, the patient is hospitalized in the Cardiological Department, where a bipolar catheter is inserted in those patients who are known with Adams-Stokes attacks. During the observation period the patient is connected to a monitor which detects the cardiac activity by means of skin electrodes. In the case of cardiac standstill or bradycardia the heart is immediately stimulated by an external pacemaker connected to the skin electrodes or the bipolar catheter incorporated in the monitoring unit, on the principle of the R-wave controlled pacemaker.

During the period the catheter is inserted in the patient, anticoagulants are administered, short acting drugs, such as Heparin, being given in view of the impending implantation operation.

When the patient's condition has improved, implantation of the permanent stimulation unit is performed. For this surgical intervention an initial dose of Sodium Pentothal is given, after which anaesthesia is maintained by a mixture of Nitrous Oxide and Oxygen (DORLAS 1963; HOWAT 1963). The transthoracic electrodes are inserted via a left hemi-thoracotomy. During the initial induction and the implantation of the electrodes, the heart activity is registered by the Vasophon (Chapter V) and the bipolar monitoring catheter remains connected to the external pacemaker. If the heart is able to maintain a sufficient circulation by itself during the operation the external pacemaker is switched off, but remains continuously in the standby position during the entire procedure.

For the insertion of a transvenous catheter electrode for long term

stimulation in the right external jugular vein, X-ray monitoring is used. During the procedure the heart action is also monitored as described above, by an external pacemaker connected to electrodes on the skin of the thoracic wall.

Once the permanent stimulation electrodes are fixed they are connected to the Cardiotest (Chapter V) for measurement of the threshold and operational values of the implanted electrode combinations. When the optimal electrode combination for permanent stimulation has been determined in this way, the permanent pacemaker is connected and inserted into the preformed pacemaker pocket; this is located subpectorally on the thoracic wall for minimum risk of lead-fracture (Chapter IV and VII).

The monitoring electrodes are removed when the operation is finished and an X-ray picture is taken to record the position of the pacemaker and the electrodes. If the pacemaker continues to function well, and if the wound heals without complications, the patient is discharged 8-10 days after implantation. Accurate post-operative monitoring is especially important when catheter electrodes are used.

III. FOLLOW-UP OF THE PACEMAKER PATIENT

Once the patient has been discharged the question arises as to what extent a follow-up will be possible. Such a follow-up will only be appropriate if both the condition of the patient and the condition of the stimulation unit can be analyzed. In view of the great importance of this analysis, the circuit of our pacemaker has been modified, so that the condition of the implanted stimulation unit can be simply analyzed. In this section follow-up methods are discussed and the so-called photo analysis method is dealt with in detail.

A. Analysis of the condition of the patient

The analysis of the condition of the patient should consist of:
1. taking a careful history,
2. physical examination.

Special attention should be paid to those facts which are related to the artificial stimulation of the heart (tractus circulatorius, wound inspection, pacemaker perforation etc.) and the etiology of the heart block.

B. Analysis of the stimulation unit

Because pulse monitoring and the ECG provide information about the functioning of the pacemaker unit, they are incorporated under this heading, although they are in fact components of the above-mentioned examination. However, they give only an indication of the condition of the stimulation circuit at the moment of the examination and do not permit an extensive analysis. The X-ray examination to a certain extent and especially the photo analysis method have greater possibilities in this respect. The four methods will be dealt with separately.

1. Pulse monitoring

This examination gives a rough impression of the cardiac activity, and enables the cardiac frequency to be determined, whereby

- a regular pulse with a normal frequency generally indicates a correctly functioning pacemaker or regular sinus rhythm after failure of the pacemaker.
  Differentiation in this respect is possible because the spontaneous sinus rate is not quite constant.
- an irregular pulse with a normal or increased frequency generally indicates interference between the pacemaker stimulation and the physiological control of the ventricles.
- a regular pulse with a low frequency indicates a decrease of the pacemaker frequency or an idioventricular rhythm in case of pacemaker failure.
- a regular pulse with a high frequency may be an indication of an increase in pacemaker frequency or a high sinus rhythm in combination with a defective pacemaker. Differentiation is possible in the manner mentioned above.

These rules only apply for asynchronous stimulation, although as the P-wave triggered and R-wave controlled stimulation change into asynchronous stimulation in the case of an insufficiently functioning detection circuit, these rules also hold for synchronous and on-demand stimulation in such cases.

Analysis of the P-wave triggered and R-wave controlled stimulation, when the detection circuit is functioning correctly, is only possible by means of the ECG.

2. ECG analysis

By analysis of the electrocardiogram it is possible in continual asynchronous stimulation to determine whether the stimulator is emitting impulses, and to record the frequency of the impulses. Moreover, the ECG provides information about the ability of the impulses to activate the heart and whether sinus rhythm has returned.

It is difficult to differentiate by ECG between the various defects when the pacemaker is no longer stimulating the heart, although it can be stated that

- if the ECG records pacemaker impulses, which are not followed by heart contractions, this usually points to a decrease of the pacemaker output beyond the stimulation threshold, to an intact stimulator in combination with either a defect of an electrode lead or an electrode (insulation defect or breakage), or a rise in stimulation threshold. Further differentiation is impossible, because of the fact that the standard ECG record only indicates the pacemaker impulses.

The R-wave blocked pacemaker, provided it is not blocked, may be analysed in the same way. If the pacemaker is blocked by the QRS-complexes, it may be unblocked by decreasing the heart frequency (e.g. pressure on the carotid sinus) or by cancelling the blocking circuit, for which purpose a magnetic relay is included in our design of this pacemaker. If the unblocked pacemaker emits impulses to the heart this proves at once that the detection electrode is functioning correctly.

Proper functioning of the detection and triggering circuit of the P-wave and R-wave triggered pacemaker is shown by the synchronous appearance of P-waves respectively R-waves and pacemaker impulses at a constant delay period.

3. X-ray analysis

Radioscopy enables analysis of:

a. Location of the electrodes. This is especially important with catheter electrodes. X-ray photographs then make it possible to differentiate between:

- a detached catheter, one potential cause of intermittent stimulation of the heart;
- a catheter pushed up in the outflow tract of the right ventricle or a catheter slipped back to the right atrium, both interrupting stimulation or
- a perforation of the ventricular wall by the catheter, causing inter-

mittent or interrupted stimulation, frequently accompanied by contractions of the diaphragm.

b. Breakage of the electrode or electrode leads. It should be noted at this point that an interruption of stimulation in combination with a clearly visible breakage allows a clear cut diagnosis, but that an interruption in combination with an intact lead on the X-ray photograph does not exclude breakage in the electrode circuit. It is frequently difficult to observe breakages by means of X-ray photographs, the more so when the wires are kept together by the insulation.

Within this framework it should be mentioned that radioscopy also makes a rough analysis of the available battery energy possible; the chemical processes in the batteries delivering energy cause changes in the X-ray picture of the batteries. A number of batteries photographed in various phases of discharge is shown in fig. IX-1, where the changes which occur stand out clearly, especially in the central contrast circle. For such a picture the battery cells must be photographed exactly along their long axis. This is a great drawback in clinical application and makes practical application of this X-ray analysis almost impossible. The method is used by most manufacturers for checking the batteries before they are incorporated in the pacemaker circuit. In practice, when about 1% of batteries appear to show aberrations in this way, according to our experiences, this means that 5% of pacemakers would have been faulty had the test not been used, because each pacemaker contains 5 batteries.

4. Photo analysis method

This method, also reported in principle by KNUCKY *et al.* (1965) has been elaborated by us in co-operation with the Department of Cardiology (PROF. DR. H. A. SNELLEN) of the Academic Hospital in Leiden. The circuit of our pacemaker is adapted in view of the analysis which we think to be the most important method. This method, reported by VAN DEN BERG, RODRIGO, THALEN and KOOPS in 1967 will now be discussed in detail.

a. Principle

The new method makes use of the fact that the operation of all types of pacemakers can be detected externally in the same manner as an ECG.

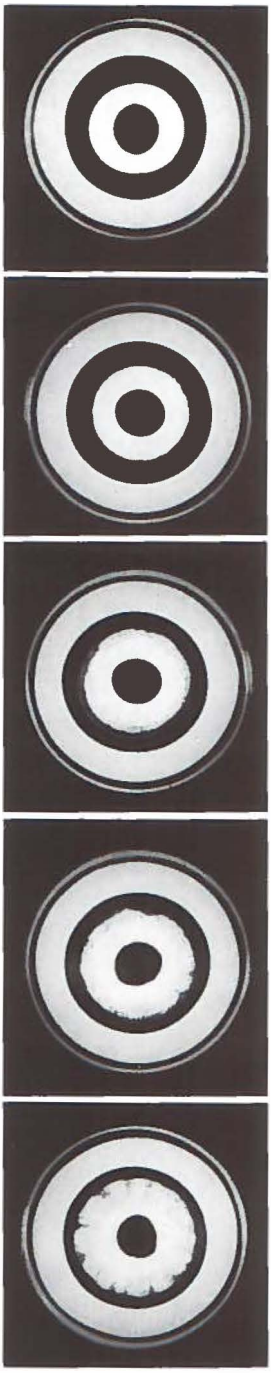


Fig. IX-1. X-ray pictures of Mallory mercury pacemaker batteries at various phases of discharge.

The pacemaker signals have a duration of some milliseconds, and this makes them too fast to be examined properly with an electrocardiograph. The pacemaker signals are fed by means of the Einthoven leads I, II and III into an oscilloscope with a fast time base which therefore allows accurate study and recording of the impulses.

The signal detected with the oscilloscope originates from the two poles introduced into the body at the implantation of the pacemaker. A voltage is applied between these two poles for a short period (ca. 2 msec) and consequently current flows between the electrodes (fig. IX-2). The

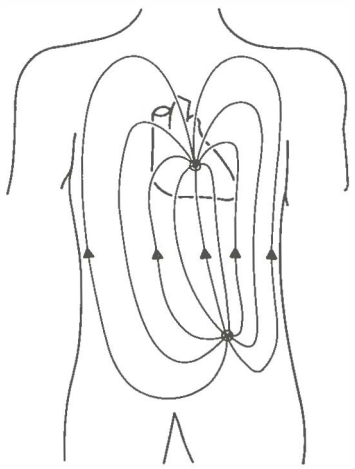


Fig. IX-2. Monopolar stimulation with implanted pacemaker. Indifferent electrode on or near the pacemaker. Streamlines of electrical current during the impulse from pacemaker toward heartelectrode. Circles around the electrodes denote arising double layer.

current density is largest centrally i.e. between the poles, and decreases toward the periphery. The current density can be depicted by stream lines.

Following a stream line from the positive pole to the negative pole, there is a gradual change of voltage. In the region of the poles this change is not proportional to the current, because the current density there is so great that the tissues are considerably polarized, particularly at the poles and the back e.m.f. is not proportional to the current. These areas of non-negligible polarization are schematically depicted in the figure by circular discs around the poles. The voltage at the margin is uniform throughout, and at some distance from the poles the current density has become so low that the polarization is very low and approximately proportional to the current. Following the stream line, the further change in voltage is then proportional to the current.

The voltage between the detection electrode on the right shoulder, and the margin of the disc around the negative pole is therefore pro-

portional to the current. The same applies to the voltage between the detection electrode on the left arm and the margin of the disc around the negative pole. In this respect it is tacitly assumed that the detection electrodes are not polarized by the impulse of the pacemaker but this condition is satisfied when the input impedance of the oscilloscope is sufficiently large (1 Mohm or more).

Consequently the voltage between the detection electrodes on the right and left arm, corresponding to ECG lead I, is virtually proportional to the current, so that

$$V_{\text{detection electrodes}} = g.i._{\text{ pacemaker}}$$

The constant g depends on

- the Einthoven lead selected, i.e. on the geometry of the detection electrodes, factor g_d, and on
- the localization of the stimulating electrodes in the body, i.e. on the geometry of the poles and the heterogenity of the tissue between the poles, factor g_e.

The constant

$g = g_d \cdot g_e$ is known as the geometry factor.

Thus, with the method described, a voltage impulse is measured which is approximately proportional to the current impulse sent through the heart by the pacemaker, as demonstrated by fig. IX-3, recorded from

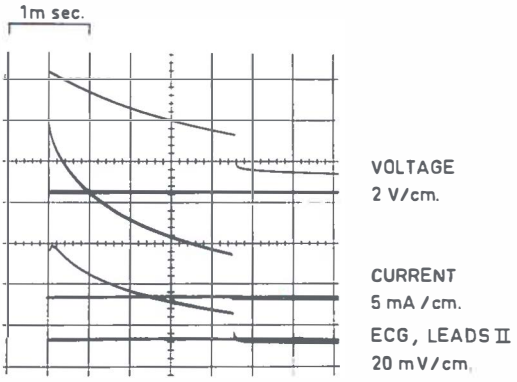


Fig. IX-3. Implanted pacemaker, monopolar stimulation in a dog.
Upper curve: voltage across the electrodes; Middle curve: current through the electrodes; Lower curve: voltage across Einthoven lead II. Straight lines: zero voltage, zero current, zero voltage.

a dog. The upper curve represents the voltage across the implanted electrodes. The impulse induces polarization, which then disappears slowly so that the voltage reaches zero level only some time after the impulse. The middle curve represents the current through the electrodes, as detected by means of a small 5 ohm series resistance. The

lower curve was obtained by means of Einthoven lead II. This detected voltage is proportional to the current of the pacemaker. The upstroke and downstroke are somewhat rounded off due to the inevitable capacity of the skin electrodes.

As visual analysis of the pacemaker impulses on the oscilloscope screen can be very difficult, a photograph of all three Einthoven leads is taken with a Polaroid camera, and for this reason the method is known as photo analysis.

The impulse registered by the photo analysis method depends on the type of pacemaker used. In principle, four quantities of the signal are distinguished for the analysis (fig. VIII-11):

I. maximum impulse amplitude, V_{max},
II. impulse duration, τ,
III. impulse slope, S,
IV. plateau duration, τ_c.

The follow-up of the pacemaker frequency and the comparison of the above values at the moment of measurement with those found at previous measurements, can provide important information about the condition of the pacemaker and the electrode circuit. Before discussing the impulses associated with various stimulation defects, it is necessary to know how the quantities depend upon the proper parameters.

I. *Maximum impulse amplitude*, V_{max}.

The maximum impulse amplitude satisfies the equation

$$V_{\text{max. detection electrodes}} = g.i._{\text{max. pacemaker.}}$$

The current i delivered by the pacemaker to the electrode circuit depends on

1. the voltage generated by the pacemaker, V_p, and
2. the total electrical impedance in the electrode circuit, Z_e.

The geometry factor g depends on

3. the direction and the length of the dipole, formed by the stimulating electrodes, factor g_e, and
4. the Einthoven lead selected, factor g_d.

I-1. *Voltage generated by the pacemaker*, V_p. This voltage has in general a rectangular shape, with a duration τ, and an amplitude virtually equal to the voltage of the batteries, $V_p \approx V_b$. The maximum current and thus V_{max} is therefore proportional to the battery voltage ($V_{max} \approx V_b$), if there are no defects in the pacemaker circuit. As illustrated in fig.

VIII-6, the battery voltage of a pacemaker with the customary 5 batteries is almost stable at 6.5 V; after a somewhat higher initial value (phase T 1) during the implantation, this voltage is maintained (phase T 2) until the batteries are nearly exhausted, and the voltage then falls rapidly to zero in the course of a few months (phase T 3). The pacemaker ceases to function when the voltage has dropped to a few volts, and this drop in voltage manifests itself in a corresponding fall in V_{max}.

I-2. *Total electrical impedance in the electrode circuit.* The total electrical resistance (see Chapter VI) is complex and consists of
a. the internal impedance of the output circuit of the pacemaker, Z_i,
b. the resistance of the electrode leads, R_l and
c. the complex impedance of the tissues, Z_t.
a. The internal resistance of the output circuit of the pacemaker is formed by both the transistor circuit and the coupling condenser in the pacemaker. This condenser has a complex impedence, which is constant apart from the effect of ageing. The Z_i of given pacemaker is therefore constant.
b. The resistance of the electrode leads R_l of any electrode combination is also constant (Chapter VI, VII) apart from breakage of one of the leads, in which case this resistance increases, the increase depending on the type of leads and the size of the breakage.
c. The complex impedance of the tissues between the electrodes, Z_t, is determined by
– the resistance of the tissue around the electrodes, which correlates amongst other things with the surface area of the electrodes, and the resistance produced by the polarization around the electrodes, Z_e, and
– the resistance of the tissue between the electrodes, R_t.
Thus V_{max} satisfies the equation

$$i_{max} = g\frac{V_p}{Z_i + R_l + Z_t}$$

In this respect it is necessary to distinguish between:
voltage pacemakers, where

$$Z_i \ll R_l + Z_t \text{ and}$$

current pacemakers, where

$$Z_i \gg R_l + Z_t$$

With current pacemakers, i is practically constant during the impulse.

The current strength is determined by the high internal impedance of the pacemaker, so changes of R_l and Z_t have no effect (see Chapter VI and VIII). At implantation of a current pacemaker it is therefore impossible to draw conclusions about the tissue reactions and the electrodes by means of the photo analysis method. The detected voltage is only proportional to the battery voltage V_b.

In voltage pacemakers, i decreases during the impulse. The current strength depends greatly on the relatively high tissue resistance, Z_t, and the possible changes in the resistance of the conduction leads R_l. Therefore, in the case of an implanted voltage pacemaker it is possible to get an impression of the reaction of the tissue and the electrode circuit by analysing V_{max}.

In Chapter VIII it was shown that, in certain types, the difference between current pacemakers and voltage pacemakers is only relative. Thus increasing the output current of a pacemaker by decreasing the resistance in the output circuit in the manner described by Chardack et al. causes a current pacemaker gradually to change into a voltage pacemaker.

Our current limited voltage pacemaker, as previously described, is also an intermediate form. In the limited state V_{max} corresponds with I_{max} of a current pacemaker. On the other hand, if the impulse shows no plateau I_{max} corresponds with V_{max} of a voltage pacemaker, and the operational value is then primarily determined by the electrode circuit. If the operational value is partly limited by the pacemaker circuit, changes in the Z_t and R_l correspond with changes in the duration of the plateau, enabling analysis of changes in the electrode circuit and the tissue resistance.

Since V_b is constant during the greater part of the pacemaker lifetime, V_{max} will also be constant in those cases, where it depends on Z_t and R_l provided that these are both constant. In practice however, V_{max} shows small variations, because Z_t also varies a little in normal circumstances. These variations arise because Z_t depends on:

- the geometry of the stimulating electrodes, which is influenced by the posture and respiration of the patient. To keep the geometry factor constant, all measurements have to be made in the same position and the same respiratory phase. We therefore photograph the impulses in recumbent patients with maximum inspiration.
- the tissue reactions around the electrodes after implantation. However, variations caused by this reaction are small and a stable condition is generally reached within a week.

– the condition of the tissues at the moment of measurement, as variations in electrolyte balance may cause certain changes. (These variations themselves can provide information concerning the effect of certain pharmacological drugs on the tissues between the electrodes.)

I.-3. *Direction and length of the dipole, geometry factor* g_e. The dipole is formed by the stimulating electrodes and the direction of the dipole depends on the localization of the electrodes and their polarity. The strength of the dipole is proportional to the current at a given distribution of the current through the body. At a given current the greater the distance between the stimulation electrodes the greater the dipole, and thus the greater the geometry factor g_e.

In bipolar stimulation, both electrodes are close together on or in the heart, providing a small dipole, i.e. a small g_e. The detectable voltages are then small, resulting in difficult and inaccurate measurements. Monopolar stimulation with an indifferent electrode at some distance from the heart provides a large dipole, and a large g_e, resulting in high accuracy of measurement.

Naturally, the dipole depends on the posture of the patient and varies with respiration. The latter situation is particularly obvious in monopolar stimulation with the indifferent electrode located on the ribs, so that all measurements must be performed under the same conditions. The location of implanted electrodes, notably that of indifferent electrodes, may vary a little after implantation with a corresponding effect of g_e. For the measurements to be reproducible, g_e has to be as constant as possible and so our photographs are always taken with the patient in the above mentioned standard position.

I.-4. *Selected detection leads, geometry factor* g_d. The dipole is a vector, so that the voltage measured between the detection electrodes depends on the orientation of these with respect to the vector. It is possible to make g_d reproducible in a simple way, by using Einthoven leads I, II and III. This cannot be done with electrodes on the thorax.

A simple test of the reproducibility of the measurements can be made since the algebraic sum of the voltages in the three leads must equal zero at any moment (KIRCHHOFF's law),

$$V_I(t) - V_{II}(t) + V_{III}(t) = 0$$

This test is easiest for V_{max} $(t = 0)$, but applies also at any time during the impulse. The negative sign before $V_{II}(t)$ is due to the cardiological convention in this respect.

The amplitude of the signal in various Einthoven leads depends on the direction and the strength of the dipole. Monopolar stimulation with an indifferent electrode in the left axillary region produces high voltages in leads I and III and low ones in lead II, whereas monopolar stimulation with an indifferent electrode in the lower quadrant of the abdomen gives large voltages in leads II and III, and small ones in lead I (fig.IX-4).

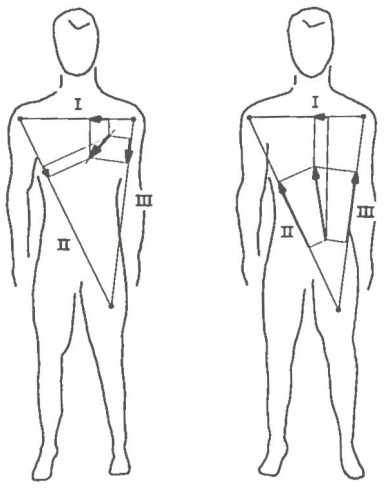


Fig. IX-4. Scheme of two methods of monopolar stimulation.
Projection of the dipole arising from the current between the heart electrode and the indifferent electrode.

II. *Impulse duration*, τ.
The impulse duration depends on the type of pacemaker and to a variable extent on:

1. the voltage of the batteries, V_b,
2. the temperature of the pacemaker, T,
3. the load of the pacemaker, $Z_t + R_1$;

Besides timely diagnosis of defects, the principal purpose of the method of analysis is timely diagnosis of the beginning of phase T_3 of the batteries (fig. VIII-6). The relation between the impulse duration and the voltage of the batteries is most important in this respect, because, as we have already shown, it is sometimes difficult to reconstruct the course of the battery voltage from the detected voltages, on account of the variable geometry factor. The geometry factor does not affect the impulse duration, however, so that the course of τ, in combination with V_{max} and S, may supply information about the condition of the batteries. Therefore it is desirable that τ does not depend on the other

parameters: the temperature, the load, and the ageing of the pacemaker, and further implies that changes in these parameters can not be deduced from the time course of τ. In the early types of some pacemakers, τ was made dependent on these parameters intentionally to analyse the load.

II-1 *Voltage of the batteries*, V_b. The dependence of the impulse duration on the voltage of the batteries varies with the type of pacemaker. Our pacemaker has been modified so that at a constant temperature the impulse duration, also dependent in earlier types on other factors, is now determined by the voltage of the batteries only. Figure IX-5 shows the relation between the voltage of the batteries and the impulse duration, in addition to the influence of the voltage on the frequency.

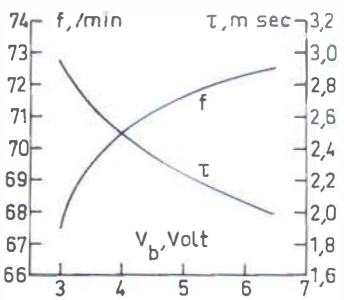


Fig. IX-5. Dependence of frequency (f) and impulseduration (τ) on voltage (V_b) of our implantable pacemaker.

II-2. *Temperature of the pacemaker*, *T*. The implanted pacemaker assumes the temperature of the body and is therefore only subject to temperature variations of a few degree centigrade, which cause only minor variations in the impulse. However, great differences in temperature such as from room temperature to body temperature, can appreciably affect the impulse duration. To determine the exact impulse duration of a pacemaker before implantation, the measurements should therefore be performed at body temperature.

The dependence of the impulse duration on temperature varies with the type of pacemaker. Figure IX-6 shows the relation between τ and *T* and also the relation between f and *T* for our pacemaker. In general, τ depends much more on *T* than does f, as is shown in this figure, because the impulse duration is determined by more components than is the frequency.

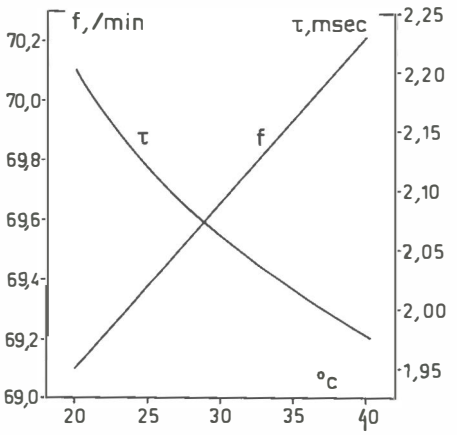


Fig. IX-6. Dependence of frequence (f) and impulse duration (τ) on temperature (T) of our implantable pacemaker.

II-3. *Load of the pacemaker*, $R_1 + Z_t$. Coupling the impulse of the output circuit to the pulse forming circuit causes the impulse duration and the frequency to vary with the current through the electrodes and thus with the impedance Z_t of the tissues. This was the case in our early types, and also those of others (KANTROWITZ). In more recent versions of our pacemaker the impulse duration is independent of the load, because such dependency influences analysis of battery voltage by the photomethod.

III. *Impulse slope*, S. At every moment during the impulse the voltage between the detection electrodes satisfies the equation

$$V_{\text{detection electrodes}} = g.i_{\text{pacemaker}}$$

The course of the voltage is therefore determined by

1. the course of the geometry factor g during the impulse and
2. the course of the current i of the pacemaker during the impulse.

III-1. *The course of the geometry factor g during the impulse.* The impulse is so short, about 2 msec., that small movements of the patient in the standard position cannot affect the geometry factor. The same applies to other mechanical factors, such as cardiac movements.

III-2. *The course of the pacemaker currenti during the impulse.* With a current pacemaker, the current is by definition constant during the impulse. The detected voltage will therefore also be constant.

In a voltage pacemaker however, the current is not constant during the impulse, but shows a decrease caused by the discharge of the condenser

in the output circuit and the polarization of the electrodes, resulting in a slope. This slope, S, may be defined by the formula:

$$S = \frac{V_{max} - V_{min}}{V_{max}} \times 100\%,$$

which allows the slope to be expressed as a percentage.

The slope (see Chapter VIII) depends on

- the capacity of the condenser in the output circuit, a condenser with a greater capacity showing a less rapid decrease in slope during the impulse, and
- the magnitude of the operational current causing the discharge, determined by the total impedance in the circuit.

To summarize, it may be said that the impulse slope depends on the time-constant

$(Z_i + Z_e)C$ of the circuit, where

C = capacity of the output condenser

Z_i = internal resistance of the output circuit of the pacemaker, and

Z_e = resistance of the leads and the tissue between the electrodes,

as soon as the back e.m.f. of polarization is virtually constant.

In practice the course of the detected voltage in a normal circuit rapidly becomes approximately exponential. Any obvious deviation from an exponential course points to a pathological tissue reaction or a defect of the pacemaker and/or the electrode leads. The exponential course of the impulse may be analyzed by measuring the voltages at constant time intervals, e.g. at 0; 0.5; 1; 1.5 and 2 msec. If the curve has an exponential course, it should satisfy the equation

$$\frac{V_0}{V_{0.5}} \approx \frac{V_{0.5}}{V_1} = \frac{V_1}{V_{1.5}} = \frac{V_{1.5}}{V_2}$$

With experience the deviations may also be diagnosed visually from the screen. As τ may vary for different types of pacemakers and even individually in the same type of pacemaker, even under otherwise constant conditions, there may be variations in the values for S, which hampers analysis. S is therefore standardized by us to a constant impulse duration of 2 msec. If $\tau \gg 2$ msec. no problems arise, but if $\tau < 2$ msec. the curve must be extrapolated to an impulse duration of 2 msec. Shorter basic periods may be chosen as standard for S if the impulses are so short, that extrapolation would cause too great an error.

It is possible to determine the resistance of the leads and the tissues after implantation by preoperative measurement, at body temperature, of

the slope at different loads, and comparing these values with the slope values after pacemaker implantation. Variations in the load correspond to variations in the resistance of the leads, which normally remains constant, and the tissue impedance.

Since variations in the load also cause a variation in V_{max}, as previously shown, a correlation exists for each implanted pacemaker circuit between V_{max} and the slope S. If variations correspond to this relationship, the cause of the variations should be sought only in changes of load. If the variations of S and V_{max}, within the accuracy of the method, do not correspond to this relationship, a defect in the pacemaker may be indicated.

IV. *Plateau duration*, τ_c.

The current limited pacemaker, as previously discussed, becomes, in principle, a voltage pacemaker after a certain time. This means that without this limitation the slope of this pacemaker may be analyzed in an identical way, just as the impulse slope after the plateau. In this situation the duration of the plateau τ_c also gives an indication of the resistance in the electrode circuit (Chapter VIII). If the current limited voltage pacemaker is limited during the whole impulse duration, as is the case in the current pacemaker, only battery analysis is possible by the photo analysis method. The limitation used by us has been chosen in such a way that for almost all types of electrodes the limitation does not cover the total impulse duration, resulting in all cases in a V_{max} plateau shorter than the impulse duration.

It is mentioned here that under normal operational conditions, ageing of the components produces only a small alteration in their characteristics, but as a result of embedding the components in epoxy resin and penetration of body fluid after implantation, ageing may produce larger variations.

As these variations need not indicate danger, a range of variation in the characteristics of the pacemaker (frequency, output-voltage and impulse duration) must be accepted, provided that variations remain within the range and stability is achieved rapidly.

Ageing of the components affects impulse duration most, followed by frequency and then output voltage, as the number of components involved decrease in the same order.

In conclusion, this principle gives a good analysis of the pacemaker and the electrode circuit for a voltage pacemaker or a current limited

voltage pacemaker, but is restricted for a current pacemaker. This has been one of the reasons for us not to use pacemakers with a current output circuit.

b. *Application of photo analysis*

In principle, photo analysis is performed in the same way as electrocardiography. The detection leads, however, attached to the patient in the Einthoven positions, are connected to an oscilloscope, rather than an electrocardiograph. A number of practical points should be considered in the use of this method, and the apparatus should also meet certain requirements.

I. *Patient*

The patient should be in a standard position to achieve reproducibility of measurements, the recumbent position being the most favourable. The arms and legs must be separated from each other and from the body to avoid capacitive disturbances. To avoid the effect of respiration, the impulse is always photographed during the inspiratory phase.

II. *Apparatus*

II-1. *Detection electrodes.* Any type of normal ECG electrodes can be used as detection electrodes. They should be firmly attached and make stable contact with the skin using electrode paste. One electrode is necessary as an earth (fig. IX-7).

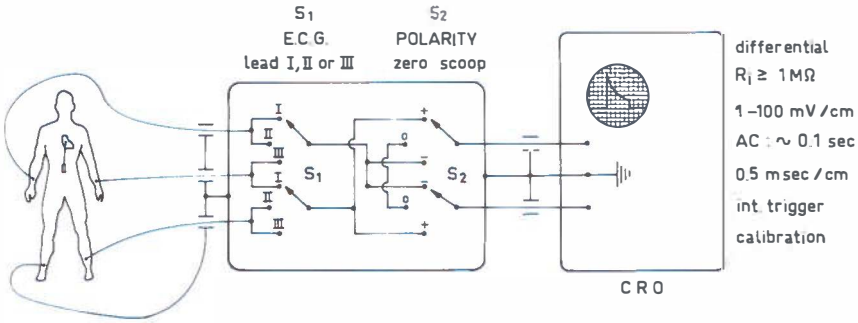


Fig. IX-7. Scheme of arangement for photo analysis of the implanted pacemaker. Finthoven leads; switching apparatus for selection of leads, polarity and zero scoop; cathode ray oscilloscope with requirements.

A small switch-box, shown in the figure, may be used to avoid errors and to promote speedy measurements with the three Einthoven leads. Thus, the three electrodes are fixed to the left arm, the right arm, and

the left leg and the patient is earthed by the fourth electrode on the right leg, and the desired Einthoven lead may now be selected by the switch on the box. For speedy signal analysis it is desirable that all photos are made with the same impulse direction on the screen, so a 'polarity' switch is added. We select the polarity of the signals so that they are always positive (upward) on the screen. The positive or negative position of the polarity switch is denoted by a plus or a minus sign in the measurement results. The switch also has an intermediate position, for adjusting the zero line of the oscilloscope.

II-2. *Oscilloscope.* When photos are to be made of patients with unipolar systems (large signals) as well as bipolar systems (small signals) the oscilloscope should satisfy the following requirements:

- differential input with high input resistance of 1 Mohm or more;
- input sensitivity adjustable at least between 1 and 100 mV/cm;
- time constant of the A.C. input about 0.1 sec;
- time base to at least 0.5 msec/cm;
- provision for internal triggering, a single sweep for photos being desirable;
- provisions for easy calibration of the amplification factors and the time base by means of internal calibrated signals.

Many oscilloscopes meet these requirements.

If only unipolar systems are to be monitored, an oscilloscope without a differential input is sufficient, although it should meet the rest of the above requirements. For monitoring in this way one of the electrodes is earthed via the oscilloscope, and a separate earthing electrode on the right leg is then superfluous. As the pacemaker impulse is very short, about 2 msec., the electrodes can be connected to the A.C. input with a time constant of about 0.1 sec., low frequency disturbances thus being reduced. This is of special importance for monitoring bipolar current pacemakers with a very small signal, because they are of approximately the same amplitude as the ECG.

Once the electrodes are connected, the image should be fixed on the screen by means of the internal triggering and by choosing an appropriate input sensitivity (beginning with about 10 mV/cm) and time base (0.5 msec. preferably). If the oscilloscope is incorrectly triggered the first part of the impulse is not detected, and V_{max} is measured incorrectly.

Incorrect triggering will result in differing impulse durations in the three detection leads, so that, if variations are found, re-checking is necessary, especially the triggering of the lead with the shortest impulse duration.

Because the amplification and the time base of an oscilloscope may become inaccurate in the course of time, a regular check by means of the available calibrated signals is imperative.

Once a stable, reproducible figure has been obtained, it should be recorded.

II.-3. *Camera*. We use a Polaroid camera for instant recording and evaluation of the pattern. Also the following data are recorded:
- the detection lead selected;
- the polarity of the signal;
- the input sensitivity of the oscilloscope;
- the time base (0.5 msec/cm).

From these data the impulse values are calculated. A conversion factor being necessary because the photograph does not depict the true dimensions seen on the screen. We designed a reading frame, which is standardized to the camera picture of the oscilloscope screen, and permits rapid analysis of the pattern eliminating the need for a conversion factor. Such a frame can be made for any combination of camera and screen.

The accuracy of measurements is determined by application of Kirchhoff's law. If the algebraic sum of the voltages, $V_I(t) - V_{II}(t) + V_{III}(t)$, is not zero within 10 per cent of the measured values, an error has been made. This needs not be true for a bipolar catheter with a fixed tip, as the indifferent electrode may move with respect to the heart. However error is especially marked when the tip is not fixed and in this case stimulation may eventually be interrupted. In contrast poor fixation of a unipolar catheter is not observed in this way, but may also interrupt stimulation; therefore X-ray monitoring is necessary.

III. *Results and their interpretation*

Photo analysis aims at timely diagnosis of changes in the stimulator and the stimulation circuit, enabling the cause to be removed before the change endangers effective stimulation.

However, normal values and their variations must be known before diagnosis of a change is possible. Because individual differences may occur in normally functioning pacemakers of the same type, the photoanalysis recordings made 4-10 days after pacemaker implantation may serve as a standard. It is also possible to check the individual pacemaker before implantation by placing the electrodes in physiological saline, diluted 5 times (20%) at body temperature. When no previous data are available,

which will be the case with the majority of the patients during the initial period of application of this method, it is possible to draw conclusions by comparing the recordings of several pacemakers and electrodes of the same type, as deviations of a certain type of pacemaker normally present specific patterns. As the circuits and systems of most types of pacemakers differ, we will only consider the variations in a current pacemaker, specially designed for this purpose, our voltage pacemaker and our current limited voltage pacemaker. Some of the patterns of possible deviations are shown.

A number of deviations have been recorded for various types of pacemakers and electrodes in about 1050 measurements, performed between March 1966 and March 1968 in 104 of our patients. As it is impossible however to record both the normal and the deviation pattern for one patient in one picture, a number of standard pictures were made for each defect with the stimulation and detection electrodes in a glass tank containing a dilute (20%) solution of physiological saline. Some of the pictures were obtained by recording the current impulse with a small 5 ohm series resistance in the electrode circuit, as in figure IX-6. In some cases the results of clinical measurements are also given.

To avoid overcomplicated standard figures only the results for unipolar stimulation, by our loop electrode and an indifferent disc electrode are depicted. The curves labelled as normal are normal for this electrode combination. With other electrode combinations the normal curves are shifted to the left or right depending on the resistance.

The same principle holds for bipolar stimulation, which usually has a higher electrode circuit resistance due to the small positive electrode, and at the same time a small detection signal due to the small dipole. Where bipolar stimulation defects show basically different patterns, these are also recorded.

The figures of frequent defects will be discussed below.

III-1. *Normal situation, with small variations in the resistance of the electrode circuit.* Figure IX-8 gives a survey of the standard patterns. Three hundred ohm is taken as mean value for the ohmic resistance of the tissues and leads in unipolar stimulation. With clinical experience, variation between —23 and + 30 percent of the ohmic resistance of the electrode circuit is at present accepted as normal. These variations are caused by variations of the tissue resistance. The patterns at the limits are also depicted in figure IX-8 in addition to those found at resistance variations of —50 and + 100 percent. The latter figures may be recorded

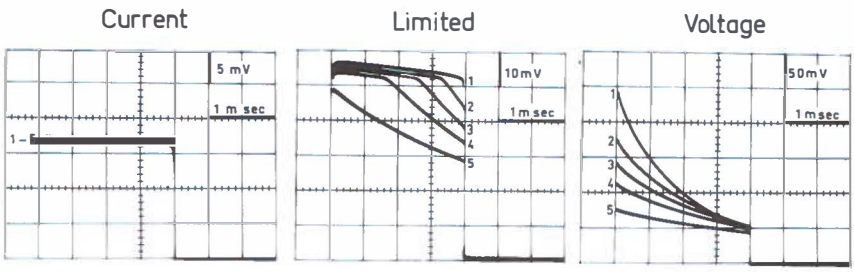


Fig. IX-8. Normal behaviour of pacemakers. Influence of tissue resistance.
1. –50%, 2. –23%, 3. normal (R = 300Ω.), 4. + 30%, 5. + 100%. f and τ normal.

when other types of electrodes are used, larger electrodes giving a smaller resistance and smaller electrodes giving a larger resistance (Chapter VI). The figure shows that:

- in a voltage pacemaker the maximum voltage (V_{max}) and slope (S) increase with decreasing resistance and decrease with increasing resistance of the electrode circuit. In the case of our voltage pacemaker, the impulse duration is independent of the load, in other pacemakers this need not be so;
- in a current pacemaker the above variations in the resistance of the electrode circuit are not reflected in the impulse shape;
- in a current limited pacemaker the plateau (τ_c) and slope (S) increase with decreasing and decrease with increasing resistance of the electrode circuit.

Variations in each measurement which remain smaller than –23% and + 30% need not cause concern, but if there is a trend in a certain direction, the slope and the maximum voltage decreasing in the same direction, this may be an indication of an incipient fracture of the electrode leads. This phenomenon may occur for example in conduction leads of the multi-strand type, more and more wires of the lead fracturing in the course of the measurements.

We diagnosed such a fracture in a patient stimulated by our voltage pacemaker. This 78-year old man had already been stimulated for 30 months by the same suture electrode. Three photo analyses over 6 months, the last being reproduced under A in table IX-1, had shown no variation outside standard limits. But 2 months later deviant values were recorded as noted under B, and as the maximum voltage and the slope decreased in all three leads, the diagnosis was an increase in the resistance of the electrode circuit. A recording after 7 days (C) showed a continuation of the downward trend and the patient was hospitalized. A further

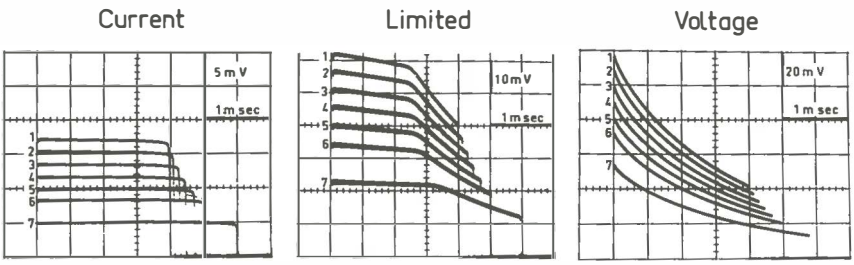


Fig. IX-9. Normal behaviour of pacemakers. Emptying batteries, phase T_3 of batteries (see fig. VIII-6).
1- 6.5 V; 2- 6 V; 3- 5.5 V; 4- 5V; 5- 4.5 V; 6- 4V and 7- 3 V.

decrease in the maximum voltage and the slope is seen in the last recording (D) just before the surgical intervention. Although the heart was still being stimulated at a frequency of 72 impulses/min., a partial fracture of the multistrand lead was found inside the insulation after surgical removal.

III-2. *Battery exhaustion.* In the previous chapter (fig. VIII-6) we saw that after a short initial period (T_1) the voltage of the batteries remains almost constant (T_2) until the batteries are exhausted to such an extent that the voltage suddenly drops (T_3). This drop in voltage has been correlated in our pacemaker with the impulse duration. Figure IX-9 gives a survey of the impulse variations in normal functioning pacemakers and electrode circuits, when the batteries reach phase T_3.
The figure shows that:

- with a current and a voltage pacemaker the maximum voltage decreases and impulse duration increases when the battery voltage falls, while the slope of a voltage pacemaker remains constant
- with a current limited pacemaker the maximum voltage decreases and the impulse duration increases when the battery voltage falls, while the ratio between the plateau τ_c and the impulseduration τ remains constant, as does the slope of the unlimited part of the impulse.

Battery exhaustion is also accompanied by gradual frequency decrease, but this is slight in our circuits (fig. IV-5)

In other types of pacemakers, this relation between voltage and impulse durations does not always exist, while in some types it is complicated by the impulse duration being influenced by the load. The dependence of the frequency on the voltage varies from type to type.

In many patients it has been possible to diagnose exhaustion of the

TABLE IX-1. *Measurements of a patient with a breaking suture electrode. See text.*

	Days after last analysis with normal values	Impulse-duration msec.	V_{max} mV	V_{min} mV	S %	
A.	0	2.10	76	24	68	LEAD I.
B.	60	2.00	42	21	50	
C.	67	2.00	36	20	44	
D.	74	2.00	26	16	38	
A.	0	2.05	24	6,5	69	LEAD II.
B.	60	2.00	6,4	3,2	50	
C.	67	2.10	10	5,6	44	
D.	74	2.00	5,2	3,2	38	
A.	0	2.00	108	32	70	LEAD III.
B.	60	2.00	48	24	50	
C.	67	2.00	44	25	43	
D.	74	2.00	30	19	37	

batteries in time. Table IX-2 shows measurements recorded on a 76 year old woman, the heart being stimulated by a suture electrode and a voltage pacemaker. At the recording shown first (A), the pacemaker

TABLE IX-2. *Measurement on a patient with exhausting pacemaker batteries. See text.*

	Days after last analysis with normal values	Impulse-duration msec.	V_{max} mV	V_{min} mV	S %	
A.	0	2.45	240	54	77	LEAD I.
B.	30	3.00	200	42	79	
C.	51	3.20	98	21	79	
A.	0	2.45	33	7	79	LEAD II.
B.	30	3.00	25	5	80	
C.	51	3.20	11,5	2,5	78	
A.	0	2.40	200	45	78	LEAD III.
B.	30	3.00	175	35	80	
C.	51	3.20	86	18	79	

had been functioning for 19 months. The impulse duration was already too long at that time, therefore the patient received a montly check-up. After 30 days (B) the impulse duration had increased and the maximum voltage decreased. The patient was checked again after 3 weeks (C), and the measurements revealed that the trend in B had continued whereupon it was decided to replace the pacemaker. Even at the last measurement the pacemaker was still functioning correctly, and the frequency had only fallen from 72 to 68 imp./min.

The optimal time of replacement is difficult to determine. We take as a rule that an increase in impulse duration should have been diagnosed at a number of consecutive measurements, replacement of the pacemaker becoming necessary if the increase exceeds 25% of the standard value. It should be noted that the voltage decrease with impending battery exhaustion is very progressive, as can be seen in figure VIII-6 period T_3.

III.-3. *Defects in the pulse forming circuit.* These defects manifest themselves by variations in frequency and impulse duration.

Variations in frequency, pacemaker tachycardia in particular, which can be ascertained by means of the peripheral pulse and the ECG, pose a perilous complication. They may result from a short-circuit of the resistance or defective transistor in the frequency determining circuit as was shown in Chapter VIII. Immediate intervention is essential for this complication, which is frequently of sudden onset.

Defects in the pulse forming circuit may result in a decrease or increase in impulse duration. The latter can be differentiated from an increase in impulse duration caused by impending battery exhaustion, which is always accompanied by a drop in the maximum voltage. If a variation in the impulse duration is recorded and is not caused by a decrease in the battery voltage i.e. is not associated with a correlative change of the V_{max}, pacemaker replacement is advisable, especially if there is accompanying frequency variation, as the chance of the frequency determining circuit producing an acute serious defect is rather great.

It should however be noted that variations in impulse duration and frequency do not always occur in combination. These variations occur in all types of pacemakers, but early diagnosis of these defects in those types in which the impulse duration also depends on the load of the electrode circuit is very difficult.

Pacemaker tachycardia was diagnosed twice by us. In both cases the impulse duration remained constant while the frequency rose to 145 imp./min. and 200 imp./min. respectively.

III-4. *Defects in the output stage of the pacemaker.* With defects of the pacemaker output stage, impulse duration and frequency will generally be normal. On total failure of one of the components the amplitude of the impulse becomes zero. When failure is not total, it may be due to insufficient amplification of the end transistor, a leak in this transistor or a leak in the coupling condenser to the electrode circuit.

The resulting variations of the pacemaker impulses depend on the various types of pacemaker. In fig. IX-10 the normal values and the values related to some defects are shown for our pacemaker. No clinical data are available as these defects were not diagnosed in patients.

III-5. *Large resistance in the electrode circuit, without a fluid layer at the location of the defect.* A large resistance in the electrode circuit may be due to:
- a bad contact at the connection of an electrode lead to the pacemaker, or
- a fractured electrode lead, with contact only just being made.

Those cases in which there is no fluid layer between the metal surfaces and intact insulation are considered here.

In fig. IX-11 the impulses are shown for normal values and for resistances of 500, 1000 and 2000 ohm in the electrode circuit. This figure shows that:
- with a voltage pacemaker the maximum voltage and slope drop considerably with a rise in the resistance of the electrode circuit;
- with a current limited pacemaker, the current limitation by the pacemaker circuit becomes ineffective, due to limitation of the operational value by the high resistances, the pacemaker behaving like a voltage pacemaker;
- with a current pacemaker only a very large resistance will cause a slight fall in the maximum voltage.

It should be noted that variations in resistance caused by these defects are often accompanied by large fluctuations in amplitude and slope. These fluctuations depend on the position and the movements of the patient. Intermittent or complete interruption of stimulation is a frequent feature of these defects.

This kind of defect has not been encountered in our experience of photo-analysis monitoring.

III-6. *Large resistance in the electrode circuit, with a fluid layer at the location of the defect.* This kind of defect is a variation of the previous defect, and may likewise be due to:

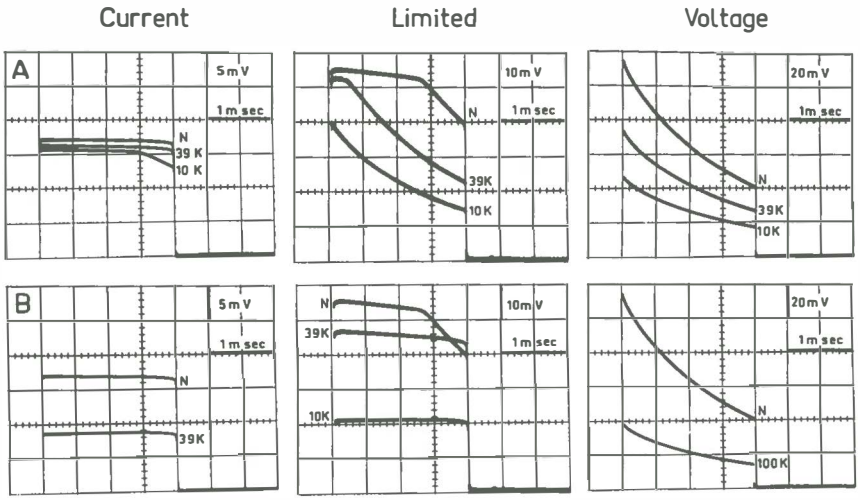


Fig. IX-10. Defects of the output stage of the pacemaker.
N: normal curve. A: leaky coupling condensor, virtually the same profile with base-collector leak. B: base-emitter leak. f and τ normal

- a bad contact at the connection of an electrode lead to the pacemaker, or
- a fractured electrode lead.

In both cases the remaining contact is provided by a fluid layer between the metallic surfaces, but the insulation may still be considered as intact. The maximum voltage decreases and the slope shows a peculiar deviation from the normal as can be seen in fig. IX-12. In this figure a peak is observed at the beginning of the impulse, and the curve is not exponential, especially at the beginning of the impulse. The deviant shape is

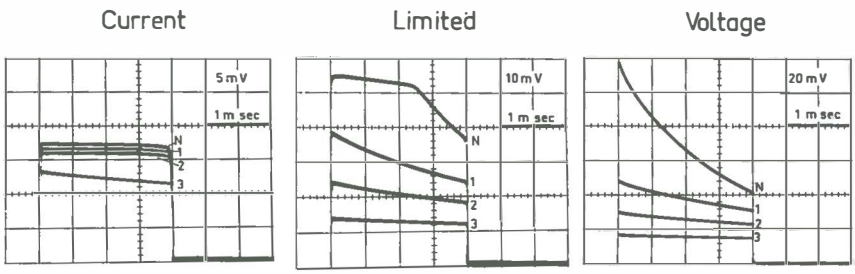


Fig. IX-11. Broken electrode or bad contact between electrode and pacemaker, no fluid layer between metal surfaces, intact insulation.
N: normal curve. 1. + 500Ω, 2 + 1000Ω, 3. + 2000Ω. f and τ normal

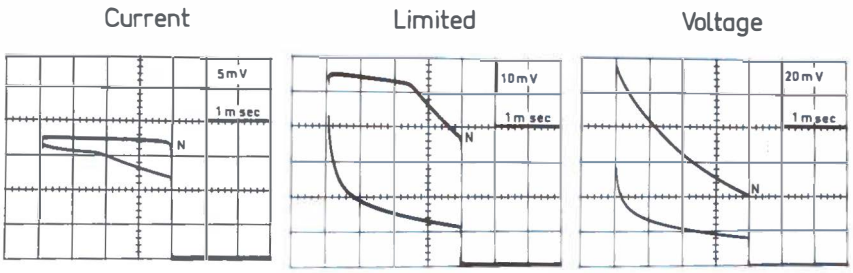


Fig. IX-12. Broken electrode or bad contact between electrode and pacemaker, fluid layer between metal surfaces, intact insulation.
N: normal curve. f and τ normal

determined by polarization, due to the current through the fluid layer between the metallic surfaces of the defect. The current density is very high, as the areas are small, so that both surfaces are almost completely polarized after a very short time. Thus, at both surfaces a back e.m.f. develops rapidly.

This pehenomenon may be recorded with voltage, current limited voltage and current pacemakers, and in our experience is more common than mere increase in resistance. Mostly it occurs without the fracture being visible on an X-ray picture.

III.-7. *Defective insulation of the electrode lead.* The curve recorded with defective insulation of the electrode leads differs for the various types of pacemakers and electrode combinations, and also depends on the location of the defect. In fig. IX-13 the normal values are shown, and the curves recorded for defects in the insulation, the leak being relatively small and located halfway along the heart electrode.

The variations are caused by a parasitic tissue circuit arising through the leak, in parallel with the normal circuit, and the leak has the same polarity as the lead in which it arises. The consequences of this parasitic circuit are two fold:

1. the dipole of the stimulation unit in the body is altered, the change being dependent on the location of the defect. The changes occurring in the geometry factor also depend on the relation between the new dipole and the detection electrodes. As a result of the insulation leak the largest geometry factor i.e. the largest V_{max} in unipolar stimulation will decrease, whereas it will increase in bipolar stimulation.
2. the resistance of the electrode circuit decreases because of the parallel circuit. This results in an increase in the slope and the maximum voltage

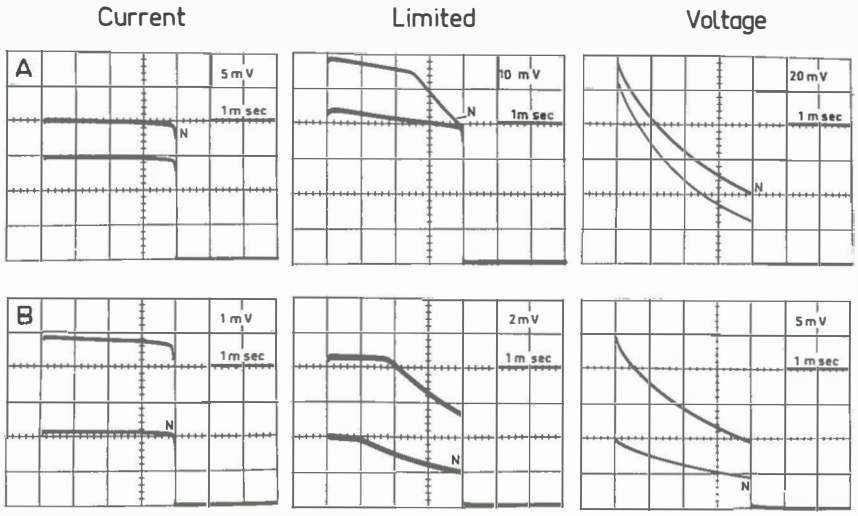


Fig. IX-13. Broken insulation of electrode with monopolar and bipolar stimulation. N: normal curve. A: Unipolar stimulation. B: Bipolar stimulation. f and τ normal

in a voltage pacemaker, in a stable V_{max} but an increasing plateau τ_c in a current limited voltage pacemaker, and in a stable V_{max} in a current pacemaker.

In conclusion with an insulation defect in unipolar stimulation:

- with a voltage pacemaker the slope increases but the variation in V_{max} depends on the resultant of an increase in V_{max} caused by the fall in resistance and a decrease of the largest V_{max} caused by a decrease in the geometry factor. This results in incongruity between the variations in S and V_{max}.
- with a current limited voltage pacemaker the plateau and the slope of the unlimited part increase as a result of the fall in resistance, but the largest V_{max} decreases consequent upon decrease in the geometry factor.
- with a current pacemaker the largest V_{max} decreases as a result of the decrease of the geometry factor. Differentiation from the pattern due to impending battery exhaustion is difficult, however the time elapsed since pacemaker implantation may be helpful.

In contrast with unipolar stimulation, in bipolar stimulation V_{max} increases with all those types of pacemaker due to the enlarged dipole.

The defect may sometime be attended by muscular contractions near the insulation leak. Certain body movements may cause a part of the uninsulated electrode lead to make tissue contact.

TABLE IX-3. *Measurements on a patient before (A) and after (B) defect of the insulation of electrode lead. Bipolar stimulation. Current pacemaker. See text.*

	Impulse-duration	Lead I		Lead II		Lead III	
	msec.	Vmax mV	Vmin mV	Vmax mV	V min mV	Vmax mV	Vmin mV
A.	2.30	5	5	0,7	0,5	5	5
B.	2.20	10	9,5	3,5	3	14	13

This phenomenon was not recorded clinically with our electrodes in combination with a voltage or current limited voltage pacemaker, but it was encountered with a current pacemaker and Chardack type intramural coil electrodes (Chapter VII). The defect occurred amongst others in a 56 year old man 19 months after implantation of the electrodes (table IX-3). The measurements B, made about 1.5 months after the last normal measurements, were accompanied by intermittent stimulation and because a current pacemaker was in use the current during the impulse was virtually constant, so that the slope was negligible. Note also the small amplitudes of bipolar stimulation (see also fig. IX-13).

It is possible that there may be two or more defects present at the same time. These multiple defects are hard to combine in a two dimensional table, but their distinctive features allow them to be successfully analysed from the figs. IX-6-13.

One complication is as yet not diagnosable by photo analysis with pacemakers available at present, viz. rise in stimulation threshold. In our experience this occurred with a patient, aged 83, who had already been paced for 48 months using a pin-electrode. The impulses recorded before and after the threshold rose beyond the operational value showed no difference, which is, of course, expected because the stimulation threshold is determined by other parameters (Chapter VI). A threshold rise is not necessarily attended by an increase in the resistance of the electrode circuit, and the impulses are normal as the circuit remains normal.

With a pacemaker, which has two operational values, such a diagnosis is theoretically possible when the threshold lies between the two values. The heart is then not stimulated at the lower operational value but is stimulated at the higher operational value (fig. VIII-7,10). These values can be switched by a simple extracorporal adjustment.

In this situation, the threshold rise can only be diagnosed when the pacemaker is no longer stimulating the heart at the lower operational value. Any rise in stimulation threshold below this operational value is not diagnosible, making early intervention impossible. In view of the importance of a timely diagnosis of this complication our aim has been to develop a method of diagnosis (VAN DEN BERG and THALEN 1967). The principle is described here, the method and the accompanying apparatus being clinically applied for too short a time to give results already.

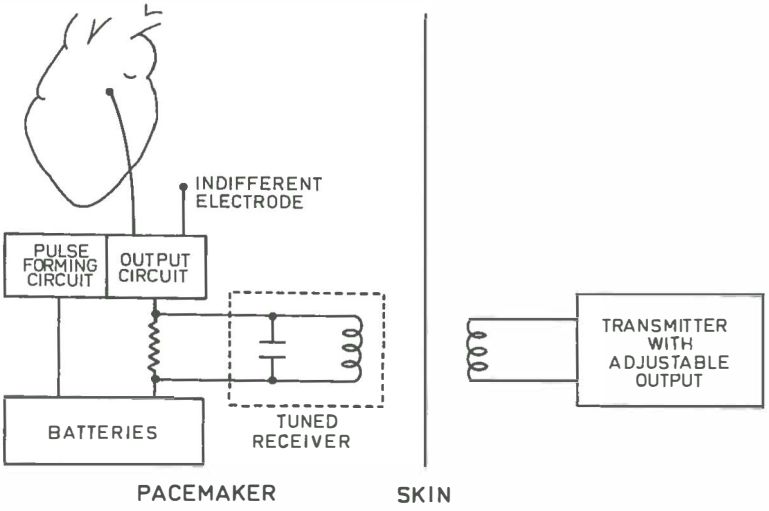
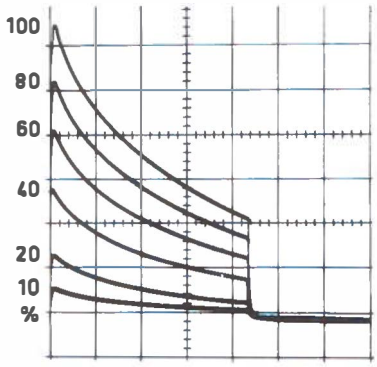


Fig. IX-14. Scheme of the implanted pacemaker with external reducible impulse, to measure the stimulation threshold of the heart.

The method is based on recording the impulse by photoanalysis. The pacemaker is slightly more complicated (fig. IX-14) as a receiving circuit is included in the output circuit, in which a voltage, opposed to the battery voltage, can be induced extracorporeally. The operational voltage and current of the pacemaker can be decreased by increasing the output of the extracorporeal transmitter. It is then possible to decrease the operational value of the pacemaker to such an extent that the threshold value is reached, and may be diagnosed by means of the ECG or the peripheral pulse, as the heart no longer reacts to the pacemaker impulses when the operational value decreases beyond threshold. By photoanalysis of the impulse at the operational pacemaker value and at the threshold value, the relative threshold, i.e. the safety margin, can be determined (fig. IX-15).

Fig. IX-15. Voltages across Einthoven leads of pacemaker with threshold control. Normal impulse, 100%, and impulses reduced to 80, 60, 40, 20 respectively 10% of the operational value during an animal experiment.



As this method of analysis has been used clinically since 1968, after it had been functioning satisfactory already for one year in animal experiments, complete monitoring of the stimulation unit, using voltage and current limited voltage pacemakers, is now possible by the photo-analysis. However, this will remain impossible for current pacemakers.

c. *Frequency of photo analysis*

Photo analysis aims at timely diagnosis and localization of defects, allowing intervention before the heart is no longer being adequately stimulated by the pacemaker. This makes frequent measurements of the patient necessary.

Photo analysis is performed on each of our pacemaker patients for the first time before leaving hospital, generally about 10 days after implantation but not within 2 days after implantation, as the circuit resistance varies somewhat during the first 2 post-operative days. After 6 weeks the patient is seen again, and special attention is paid to physical examination, particularly of the surgical wound and the effect of artificial stimulation on the circulatory system. The second photo analysis is also performed at this time. If the results are satisfactory the patient then returns for a general check-up every three months. During the three month periods between check-ups the patient can be seen by his family doctor or a specialist, and can be sent to the pacemaker clinic for analysis immediately if any complications arise. If an incipient defect

is thought to be present at a routine check, the patient is re-checked 2-4 weeks later, depending on the nature of the defect, to verify whether the deviation is progressive and whether there are indications of a dangerous defect already present.

In spite of this intensive monitoring, defects may still occur that have not been diagnosed in time. This may be the case especially with current pacemakers, but also with other types of pacemakers when e.g. a sudden complete lead fracture occurs in a single-strand lead. But even in these cases photo analysis is helpful at re-operation, as the cause and location of the defect can be diagnosed. The photo analysis enabled us after one year application a timely diagnosis of 65% and after two years of 90% of the defects.

IV. RE-OPERATION

A defect, resulting in inadequate stimulation of the heart, in an implanted stimulation unit necessitates re-operation. The pre-operative care of such patients sometimes entails difficulties, especially in those patients where the pacemaker is still functioning, but where the stimuli are no longer able to induce heart contractions, e.g. because of a fractured lead or a rise in stimulation threshold. These patients cannot be monitored by an apparatus on the principle of the R-wave pacemaker, for this will be triggered by the pacemaker impulses, resulting in a continuous blocking of the stimulator. These patients need fixed-rate stimulation or monitoring by the Vasophon (Chapter V), which detects the peripheral pulse. By connecting the Vasophon to an alarm signal, an extreme bradycardia or asystole can be recorded in time and the stimulator switched on. Because disturbances affect pulse detection it is not yet advisable to switch the stimulator on by means of an automatic circuit. More stable pulse detection will make this feasible in future, however.

The period within which re-operation has to be performed depends on the nature of the defect, and the condition of the patient. The limit varies from emergency intervention for pacemaker tachycardia to a period of 2-4 weeks for impending battery exhaustion.

An important role in the definitive determination of the cause of the stimulation defect is played by the Cardiotest (Chapter V). Comparison of the measurements of the threshold value, operational value and relative threshold with those of the previous implantation provides important data on the electrodes. Moreover the effective resistance of the electrode

circuit can be determined by using the Cardiotest. These results make it also possible to verify those of photo analysis.

The defect is repaired during the operation, depending on the nature of the complication:

- a defective or exhausted pacemaker is replaced by a new one inserted at the same site,
- when a conduction lead is fractured the defective part is removed if the defect is located close to the pacemaker or, this being impossible, a new or reserve electrode is connected to the pacemaker,
- with a rise in stimulation threshold a reserve electrode with a low threshold is connected, the electrode is also replaced, or, if the threshold rise permits this, a pacemaker with a higher operational value is implanted.

Post-operative treatment is required for infection. It is advisable to remove the old stimulation unit as far as possible by a simple intervention and to stimulate the heart via a temporary catheter electrode and an external stimulator until the infection has been overcome, after which a new unit may be implanted. Follow-up for some months may be necessary in these cases.

V. CONNECTION OF THE MONITOR EQUIPMENT

The danger of ventricular fibrillation should be mentioned with respect to monitoring and surgical intervention. WHALEN *et al.* (1964) found that very small (180 μA) alternating currents of 60 Hz reaching the heart via a catheter, were capable of producing ventricular fibrillation in patients. This is especially dangerous in artificial stimulation of the heart, as the stimulation catheter or transthoracic electrode presents direct low resistance access to the myocardium. With extra corporal skin electrodes the danger is much smaller because they have a high transitional resistance and the current is dispersed throughout the body.

The risk of ventricular fibrillation is also closely linked with the dimensions of the stimulation electrodes, as it depends on the current density, which is inversely proportional to the electrode dimensions.

Ventricular fibrillation may arise when a pacemaker patient, whose heart is stimulated by an extracorporal stimulator connected to the mains, is attached to other apparatus such as a monitor or an electrocardiograph, which is also connected to the mains. Leakage currents from these apparatus may reach the heart directly via the electrode and cause ventricular fibrillation. This was encountered twice in our animal

experiments. Others (NOORDIJK *et al.* 1961, BURCHELL 1961 and FURMAN *et al.* 1961) recorded this complication in clinical practice.

In those cases where the heart of the patient is stimulated by a mains powered pacemaker, leakage currents can be excluded by properly earthing all the other apparatus. These and the pacemaker should all be connected to the same earth, as connecting the equipment to different earths can give rise to complications as a result of small potentials between them. As the chance of a human error in connecting up apparatus cannot be completely excluded, complications may also arise at this stage. All risks are eliminated however if the stimulator is completely separated from the mains by :

– a separating transformer, as used in the Cardiotest, or
– using a battery powered stimulator.

Most stimulators receive their energy from one of these sources, reducing the risk of dangerous complications to zero. However, care should be taken in the treatment of patients with these apparatus, as current circuits may arise in various ways. Even contact via the body of a doctor, who wishes to check an electrode connection, may be dangerous. It is therefore advisable to disconnect the other apparatus from the patient or the mains when working on the stimulation unit, thus eliminating these complications.

This survey of present-day electrical stimulation of the heart has discussed the three components of the stimulation unit and has been concluded by the important subject of monitoring methods. For it is complete monitoring, which enables proper escort of the pacemaker patient in particular, some of the mental stress can be alleviated and this form of therapy can be made more easily acceptable to the patient.

Prospects

In the preceeding chapters an attempt has been made to show the various facets of artificial cardiac stimulation. Basic principles were discussed and a review of the already satisfactory present situation (fig. X-1) was given with indications of future development.

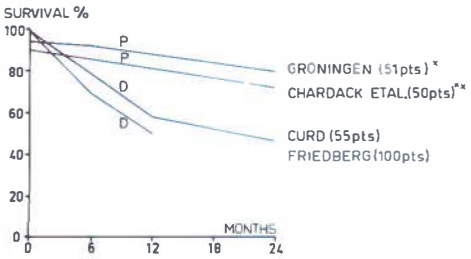


Fig. X-1. Follow-up of two groups of patients with total A-V block treated with medicaments (D) and pacemakers (P) for a period of 2 years after the treatment started.
* period March 1962-March 1967
** period April 1960-May 1965

Many operations and re-operations have been necessary to achieve the present results. The reliability of stimulation units has improved in recent years and further advance is to be expected. For instance, improvements in insulating material and electronic circuits, e.g. integrated circuits, are anticipated.

Further improvement in the source of power is needed. Perfection of batteries with smaller cells, which store more energy, will make long-term stimulation with smaller units possible. The use of atomic energy or bio-energy offers a longer period of stimulation without the inconvenience and possible complications of frequent pacemaker replacement. Furthermore, there would be a resulting decrease in the work-load of medical clinics. In this respect it should be reminded, that if the mean stimulation period per unit is 2 years, one replacement per week is

necessary in a clinic of 100 pacemaker patients, occupying one hospital bed continuously throughout the year.

In the future the range of stimulation methods will be wide enough to meet all clinical situations necessitating a choice from these various methods. Further advances may result from combinations and modifications of existing methods; in due time a P-wave triggered, R-wave blocked pacemaker will be feasible. However more complicated pacemakers depend on development in electronics and sources of power.

The important comparison of the results with transthoracic and transvenous electrodes is now being made in many clinics. However each type of electrode has its specific advantages, and therefore the alternative will remain although one type may be favoured.

All these advances result in a progressive increase in the number of pacemaker patients. Extracorporal analysis of implanted pacemakers requires further development, but at present offers effective monitoring, allowing timely intervention in pacemaker failure. This provides a basis of confidence from which the patient can resume his place in society. An international pacemaker-monitoring system is desirable in the future, so that other clinics may take over the emergency care of a patient, who is far from his own centre. It is important that each patient should carry his essential pacemaker data wherever he goes; we issue a pacemaker passport for this purpose. Within limits such a standardised monitoring system is already in operation in the Netherlands.

The 'Artificial Pacemaker' introduced by Hyman has undergone much development and has now become a generally accepted form of electrotherapy. This manuscript has traced this development and tried to anticipate further improvement.

Summary

Electrical stimulation of human organs, including the heart, was first investigated more than 150 years ago. This thesis reports the development of electrical cardiac stimulation from a medico-physical angle, and special attention is given to the various facets of the artificial cardiac pacemaker and its use in heart-block resulting from lesions of the conduction system.

The scope of the manuscript is first outlined, followed by a discussion of the anatomy and physiology of the conduction system. Particular reference is made to its blood supply, as coronary artery disease is one of the most important causes of heart block. This leads to a full discussion of the aetiology in which not only structural leasions of the conduction tissue are considered, but also the importance and frequency of excessive vagal tone, electrolyte imbalance and drug toxicity.

The clinical presentation of heart block is described and is followed by a consideration of therapy with sympathomimetics (Epinephrine, Norepinephrine and in particular Isoproterenol) and corticosteroids on an aetiological basis. The effect of such therapy is mostly symptomatic, depends on the aetiology and decreases with time. Surgical treatment of heart block by vagotomy or homo- or autotransplantation of the sino-auricular node does not give good results, and leaves physical therapy with an electrical pacemaker as the third therapeutic possibility.

The first successful post-mortem stimulation of the human heart was achieved by Vassali, Giulio and Rossi in Turin at the end of the 18th century. This was followed by many more attempts by numerous investigators with varying success. But it was not until 1932 that Hyman in New York developed an effective cardiac stimulator for clinical use. Hyman conceived his 7,2 kg apparatus, as a substitute for the natural cardiac pacemaker and called it the 'artificial cardiac pacemaker'.

Advances in the field of electronics enabled improvements to be made in this pacemaker and after 1950 development of various types of pacemakers and electrodes became rapid.

Ten different methods of stimulation are described, distinguishing stimulator sites (external or implantable), methods of impulse transmission (direct or indirect), types of electrode (skin, oesophageal, transthoracic, transvenous and 'humoral') and types of stimulator (asynchronous, P-wave triggered or R-wave controlled). Discussion of the relative advantages and disadvantages of each method is based on published and own experience.

The methodology of the animal research is reported. Surgical ligation of the Bundle of His to induce heart block was performed in dogs through a thoracotomy incision. Various types of electrodes, conduction leads and stimulators were investigated in these animals, the most important parameter being the stimulation threshold. The results are used in discussion of the individual components of the stimulation unit. The apparatus developed for threshold measurement and cardiac monitoring is described and discussed: the Cardiotest is used to measure the stimulation threshold and the effective resistance of the electrode circuit; the Vasophon monitors peripheral pulsation; the Autocardiotest, a combination of both Cardiotest and Vasophon, offers the possibility of automatic threshold measurement; the Vasoalarm is the Vasophon with an alarm system; the Monitor is used for a simple direct check of some implanted stimulators.

Research on the influence of polarity on the electrodes showed that with a unipolar system the current threshold is determined by the heart electrode, both with cathodal and anodal stimulation, and that lower current and voltage thresholds are found with cathodal stimulation. With a bipolar system the current threshold is equal to the cathodal current threshold of the negative electrode of the unipolar system except where the anodal current threshold of the positive electrode is lower. This may occur when the negative electrode is much larger or when there is excessive tissue reaction around it, e.g. an inflammatory process. In such circumstances, the positive electrode determines the current threshold of a bipolar system. It was also observed that bipolar voltage thresholds did not correlate with unipolar voltage thresholds and that the current threshold does not depend on electrode position, either on or in the heart, provided that the electrodes are situated on intact myocardium.

Electrodes are classified as epicardial, intramural and endocardial stimulation electrodes and indifferent electrodes. The advantages and

disadvantages of the various designs of each are analysed with particular reference to electrolysis, tissue reaction around the electrodes and thrombus formation in endocardial stimulation. The electrode circuit is discussed.

Analysis of the current threshold shows that it is determined by the electrically active cardiac tissue around the electrode, thus with a given stimulation system and polarity the current threshold depends on the shape and dimensions of the electrode, the tissue reaction around it and the excitability of the surrounding intact myocardium. Using a constant current the greatest current density is achieved with an electrode as small as possible, but such an electrode is not yet the most favourable, because it gives a high electrical resistance in the electrode circuit, shown experimentally. This ohmic resistance consists of the resistance of the conduction leads and electrodes, the resistance of the electrode-tissue transition zones, which is approximately inversely proportional to the electrode dimensions, and the resistance of the tissues between the electrodes.

Resistance measurements also showed that current threshold changes are not necessarily accompanied by changes in the resistance in the electrode circuit as the electrode tissue reactions have little influence on the ohmic resistance in the circuit. The Cardiotest can be used to determine the effective resistance of the electrode circuit, whereas the real ohmic resistance can be calculated from the voltage and current of the impulse. The effective resistance proves to be greater than the real ohmic resistance as a result of the polarization at the electrodes during the stimulation impulse. This polarization causes an e.m.f., which is opposed to the impulse voltage and increases during the impulse, thus producing an increasing effective resistance in the circuit. Polarization voltage ultimately achieves a maximum, which depends on the type of electrode and the surrounding tissue, and the rate at which this is achieved, is determined by the current density at the electrode surface.

As the voltage threshold is not only determined by the stimulation electrode, but also by the rest of the electrode circuit, it depends on the effective resistance of the circuit which varies with the impulse current. Thus the voltage threshold is not a useful parameter in comparative studies and the same applies to energy thresholds.

The concept of the operational value of a stimulation unit is described. The operational value for current respectively voltage is that current respectively voltage which is administered to the tissues by a functioning pacemaker. A distinction is drawn here, between current pacemakers,

where the operational current remains constant during the impulse and the operational voltage depends on this current and the impedance of the circuit, and voltage pacemakers where the operational current depends on the impedance and the voltage across the circuit. Intermediate types between voltage and current pacemakers are possible. The relation between the stimulation threshold and the operational value gives an indication of the margin of safety. This is expressed as the relative threshold (stimulation threshold/operational value), which is used in choosing between electrode combinations in an individual patient and gives an indication of the safety margin throughout the course of long-term stimulation on a particular electrode combination, records being made at each stimulator replacement.

Impulse transmission from the stimulator to the stimulating electrode is considered under direct transmission with transthoracic and transvenous electrodes and indirect transmission by means of inductive coupling. Conduction leads and stimulation catheters themselves are discussed.

The stimulator, itself, is then considered in detail. Investigations into the optimal impulse form showed that of 5 wave forms the rectangular impulse gave the lowest current threshold and the triangular impulse the lowest charge threshold; the optimal impulse duration appeared to be between 1 and 2.5 msecs. when the parameters of charge threshold, the energy threshold and the safety margin are used. The impulse frequency is examined with reference to its haemodynamic effect and battery life, the optimum lying between 60 and 75 ppm. Some pacemakers allow frequency variation after implantation, which is sometimes desirable, either by percutaneous adjustment or by magnetic relay switching to a second frequency of $\pm$ 95 ppm. Pacemaker manufacture, based on these criteria, is discussed and reference is also made to the electronic circuit, sources of power, insulation and electrode connections.

The operation of basic pacemaker circuits, pulse forming (blocking oscillator and multivibrator) and output circuits (voltage and current), is described with such modifications as the current limited voltage pacemaker. The development and operation of P-wave triggered and R-wave controlled pacemakers are discussed.

In considering the clinical application of the electrical cardiac pacemaker, the indications for pacing are discussed and the procedure for pacemaker insertion is described. Patient follow-up is covered in detail with particular reference to the new method of photo analysis for stimulation unit

assessment, as well as pulse and ECG monitoring and X-ray techniques.

In photo analysis the pacemaker impulse is displayed on an oscilloscope screen using standard ECG (Einthoven) leads. The wave form is photographed and analysis may then be made of the shape, duration, amplitude and slope of the impulse. As a result of these measurements, it was possible to detect timely the development of defects in stimulation, especially with unipolar voltage and current limited voltage pacemakers, allowing operative intervention with still satisfactory stimulation in most cases. Moreover, using this technique, defects can be localized in the stimulator itself (e.g. battery voltage or electronic circuit) or in the electrode circuit (e.g. increased resistance, imminent fracture of a conduction lead or insulation defects), allowing the appropriate intervention to be made. The technique is described fully and examples of defect patterns are given.

Attention is drawn to the danger of connection of more than one mains powered monitoring or stimulation apparatus to a patient.

The future possibilities of electrical cardiac stimulation are discussed.

No attempt has been made in this manuscript either from personal investigations or from a study of the literature to advocate a standard stimulation methods. It is intended, however, to enable the reader from the description of the great variety of possibilities, to choose for each patient, the optimal method of application of this new electrotherapeutic measure – the artificial cardiac pacemaker.

Samenvatting

De electrische prikkelbaarheid van organen van het menselijk lichaam werd reeds meer dan 150 jaar geleden onderzocht. Eén van deze organen was het menselijk hart. Dit proefschrift tracht de ontwikkeling van de electrische hartstimulatie weer te geven, benaderd vanuit een medisch-physisch standpunt. Speciale aandacht wordt daarbij besteed aan de verschillende facetten van de kunstmatige gangmaker van het hart, die zijn toepassing vindt bij patienten met een hartblock ten gevolge van een gestoord geleidingssysteem.

Na een overzicht van de indeling van dit manuscript in het eerste hoofdstuk, worden in hoofdstuk II de anatomie en physiologie van het geleidingssysteem besproken. Onder meer wordt de vascularisatie van het geleidingssysteem geanalyseerd, daar aandoeningen van de coronairvaten één van de belangrijkste oorzaken van het hartblock vormen. Dit blijkt uit het tweede deel van hoofdstuk II, waar de aetiologie van het A-V block wordt behandeld. Naast de structurele beschadigingen van het geleidingssysteem, waaronder bovengenoemde oorzaak wordt gerangschikt, worden nog abnormale parasympaticus invloed, storingen in de electrolyt-huishouding en intoxicaties onderscheiden. Deze oorzaken komen echter minder frequent voor.

Na een bespreking van de klinische kenmerken van het A-V block worden in het laatste deel van hoofdstuk II de verschillende therapeutische mogelijkheden besproken. De medicamenteuze therapie maakt, afhangend van de aetiologie, onder meer gebruik van sympatico-mimetica (Epinephrine, Norepinephrine, Ephedrine en vooral Isoproterenol) en corticosteroïden. Het effect van de behandeling, die dikwijls symptomatisch is, is afhankelijk van de aetiologie en neemt in verloop van de tijd af. Ook pogingen om met chirurgische ingrepen (vagotomie en homo- of autotransplantatie van de sinusknoop) het hartblock te be-

strijden geven geen goed resultaat te zien. Aan de derde therapeutische mogelijkheid, de physische therapie in de vorm van de elektrische gangmaker, zijn de volgende hoofdstukken gewijd.

De eerste succesvolle stimulering van het menselijk hart werd, postmortem, bereikt door Vassali, Giulio en Rossi in Turijn aan het einde van de 18e eeuw. In de daaropvolgende tijd werden door verschillende onderzoekers meer of minder geslaagde pogingen ondernomen, zoals in hoofdstuk III wordt beschreven. Het duurde tot 1932 voordat Hyman in New York een apparaat ontwikkelde waarmee bij patienten het hart effectief gestimuleerd kon worden. Aangezien hij dit apparaat als een vervanging van de natuurlijke gangmaker van het hart beschouwde noemde Hyman zijn 7,2 kg zware toestel 'de kunstmatige gangmaker van het hart'.

Mede door de vooruitgang op het gebied der electronica slaagde men erin het principe van deze gangmaker in steeds vervolmaakter versies toe te passen. Deze ontwikkeling nam vooral na 1950 een grote vlucht. Dit leidde tot de ontwikkeling van verschillende gangmakers en electroden.

In hoofdstuk IV worden 10 verschillende stimuleringsmethoden door ons onderscheiden, welke ontstonden door verschillen in het stimuleringsapparaat (uitwendig of implanteerbaar), de impulsoverdracht (direct of indirect), de eigenlijke stimulering (huid-, oesophagus-transthoracale-, transveneuze- en humorale electroden) en de stimuleringsprincipes (asynchrone, P-top getriggerde en R-top gestuurde stimulering). Van elke methode worden het principe, het dierexperimenteel onderzoek en de klinische toepassing behandeld, waarbij tot slot van elke methode de voor- en nadelen ten opzichte van de andere methoden worden besproken.

De analyse van de stimuleringsmethoden was het resultaat van literatuur studie en de resultaten van het eigen dierexperimenteel- en patientenonderzoek. De opzet van het dierexperimenteel onderzoek wordt in hoofdstuk V behandeld. Voor dit onderzoek werd gebruik gemaakt van proefdieren (honden), waarbij via een hemi-thoracotomie een hartblock werd gemaakt door ligering van de bundel van His. Bij deze dieren werden verschillende typen electroden, geleidingsdraden en stimulatoren onderzocht, waarbij onder meer de stimuleringsdrempel als parameter fungeerde. Voor het bepalen van de parameters en voor het controleren van de hartactiviteit werden een aantal apparaten ontworpen, die in het laatste deel van het hoofdstuk worden behandeld. Onder meer worden besproken de Cardiotest, voor de bepaling van de stimuleringsdrempel en de effectieve weerstand van het electrodencircuit; de Vasophon, voor

de controle van de perifere pulsaties; de Autocardiotest, een combinatie van beide voorgaande apparaten met de mogelijkheid van automatische drempelmetingen; de Vasoalarm, een combinatie van de Vasophon en een waarschuwingsapparaat en tenslotte de Monitor, voor een eenvoudige en rechtstreekse controle van bepaalde geimplanteerde stimulatoren. De resultaten van deze onderzoekingen worden in de volgende hoofdstukken besproken.

De eigenlijke electrode vormt het onderwerp van hoofdstuk VI. Onderzoek naar de invloed van de polariteit van de electroden leerde dat bij monopolaire stimulering de drempel voor de stroom (uiteraard) bepaald wordt door de hartelectrode, zowel bij kathodale als bij anodale stimulering, waarbij de kathodale stimulering lagere drempelwaarden voor de stroom en spanning levert. Verder blijkt dat bij bipolaire stimulering de drempel voor de stroom gelijk is aan de kathodale drempel voor de stroom van de negatieve electrode bij monopolaire stimulering, behalve in die gevallen waar de anodale stroom-drempel van de positieve electrode lager is, zoals in het geval van een veel grotere negatieve electrode of als zich rond de negatieve electrode een relatief grotere weefselreactie, bijvoorbeeld een ontsteking, heeft ontwikkeld. De positieve electrode bepaalt dan de stroomdrempel van de bipolaire stimulering. Verder bleek dat de bipolaire drempel voor de spanning niet is gecorreleerd met één van de monopolaire drempelspanningen. Als derde punt werd gevonden dat de stroomdrempel niet afhangt van de plaats van de electroden op het hart, mits de electroden in intact hartspierweefsel werden aangebracht.

In het derde deel van hoofdstuk VI worden de verschillende electroden besproken, volgens de indeling epicardiale, intramurale en endocardiale stimuleringselectroden en indifferente electroden. De voor- en nadelen van de verschillende uitvoeringen worden geanalyseerd, waarbij in het laatste deel van de paragraaf de electrolyse, de weefselreacties rond de electroden en de thrombusvorming bij endocardiale stimulering apart worden behandeld.

In het laatste deel van hoofdstuk VI wordt het electrodencircuit besproken. Analyse van de stroomdrempel leert dat deze wordt bepaald door de stroomdichtheid in het intacte hartspierweefsel rondom de electrode, waaruit volgt dat bij een bepaalde stimuleringswijze en polariteit, de stroomdrempel afhangt van de vorm en afmetingen van de electrode, de weefselreactie rond de electrode en de prikkelbaarheid van het intacte hartspierweefsel. Hoewel bij constante stroom de grootste stroomdichtheid bij een zo klein mogelijke electrode wordt bereikt,

is een dergelijke electrode toch niet optimaal, daar hij een grote electrische weerstand in het electrodencircuit oplevert. Dit blijkt uit de weerstandsbepalingen in het electrodencircuit. Deze Ohmse weerstand is opgebouwd uit de weerstand van de geleidingsdraden en electroden, de weerstand van het overgangsgebied electrode-lichaamsweefsel en de weerstand van het transportgebied tussen beide electroden. De tweede weerstand is bij benadering omgekeerd evenredig met de afmetingen van de electrode.

Uit de weerstandsmetingen volgde verder dat een verandering van de stimuleringsdrempel voor de stroom niet gepaard hoeft te gaan met een weerstandsverandering in het electrodencircuit, aangezien de weefselreactie rond de electrode vrijwel geen invloed heeft op de Ohmse weerstand van het electrodencircuit. Behalve de Ohmse weerstand, die berekend kan worden uit de spannings- en de stroomimpuls, kan men met behulp van de Cardiotest ook de effectieve weerstand van het electrodencircuit bepalen. Deze substitutieweerstand blijkt groter te zijn dan de reële Ohmse weerstand, hetgeen een gevolg is van de polarisatie welke tijdens de stimuleringsimpuls aan de electroden optreedt. Deze polarisatie, die in hoofdstuk VI wordt besproken, resulteert in een e.m.k. tegengesteld aan de impulsspanning, die gedurende de impuls toeneemt, waardoor de effectieve weerstand in het electrodencircuit toeneemt. De polarisatiespanning bereikt tenslotte practisch een maximum, dat afhangt van de aard van de electrode en het omringende weefsel, waarbij de snelheid waarmee het maximum wordt bereikt bepaald wordt door de stroomdichtheid aan het electrodenoppervlak.

De spanningsdrempel, die niet alleen door de stimuleringselectrode maar ook door de rest van het electrodencircuit wordt bepaald, hangt onder meer af van de effectieve weerstand in het electrodencircuit. Aangezien deze effectieve weerstand varieert bij verschillende impulsstromen vormt de spanningsdrempel geen goede parameter voor een vergelijkend onderzoek naar de prikkelbaarheid. Hetzelfde geldt voor de stimuleringsdrempel voor de energie. Beide stimuleringsdrempels en de invloed van wijzigingen in het electrodencircuit daarop worden in hoofdstuk VI besproken.

Behalve de stimuleringsdrempels onderscheiden we ook de werkwaarde van een stimuleringseenheid. Onder de werkwaarde voor de stroom resp. spanning worden die stroom resp. spanning verstaan welke door een functionerende pacemaker aan het weefsel worden toegediend. In dit opzicht dient onderscheid gemaakt te worden tussen stroompacemakers, waarbij de werkwaarde voor de stroom constant blijft gedurende

de impuls en waarbij de werkspanning afhankelijk is van deze stroom en de weerstand in het circuit en spanningspacemakers, waarbij de werkstroom afhangt van de effectieve weerstand in het electrodencircuit en de in het circuit (nog) beschikbare spanning. Tussen beide pacemakertypen zijn overgangsvormen mogelijk. De verhouding tussen de stimuleringsdrempel en de werkwaarde levert een indicatie op over de veiligheidsmarge. Wij drukken deze uit in de relatieve drempel welke gelijk is aan het quotient van stimuleringsdrempel en werkwaarde. Deze relatieve drempel vormt een indicatie voor de keuze van de stimuleringscombinatie indien meerdere electroden zijn aangebracht en geeft verder een inzicht in het verloop van de veiligheidsmarge bij langdurige stimulering indien de waarden steeds worden vastgelegd bij b.v. vervanging van de pacemaker.

Het zevende hoofdstuk is gewijd aan de impulseoverdracht van de stimulator naar de stimuleringselectrode. De directe impulsoverdracht met transthoracale of transveneuze electroden en de indirecte impulseoverdracht met inductieve koppeling worden behandeld, waarbij tevens de verschillende geleidingsdraden en stimuleringscatheters worden besproken.

Het laatste deel van de stimuleringseenheid, de eigenlijke stimulator vormt het onderwerp van hoofdstuk VIII. Bij een onderzoek naar de optimale impulsvorm blijkt uit een 5-tal impulsvormen de rechthoekpuls de laagste stroomdrempel en de driehoekpuls de laagste ladingsdrempel op te leveren. De optimale impulsduur blijkt tussen 1–2,5 msec te liggen, uitgaande van een drietal parameters nl. de ladingsdrempel, de energiedrempel en de veiligheidsmarge. De impulsfrequentie wordt geanalyseerd aan de hand van de haemodynamische verhoudingen en de levensduur van de batterijen. De basisfrequentie blijkt dan 60-75 imp/min. te zijn, waarbij sommige pacemakers de mogelijkheid van een, in bepaalde gevallen wenselijke, frequentievariatie of een tweede extern inschakelbare frequentie van ± 95 imp/min. bezitten.

In het tweede deel van hoofdstuk VIII worden de factoren, welke bij de fabricage van de pacemaker, uitgaande van bovengenoemde normen, van belang zijn, besproken. Achtereenvolgens worden behandeld het electronisch circuit, verschillende vormen van energievoorziening, de isolatie en de aansluiting van de electroden.

Het derde en laatste deel van hoofdstuk VIII behandelt de samenstelling en werking van de verschillende basis pacemaker circuits en de variaties daarop aan de hand van diagrammen. Onder meer worden het pulsvormend-circuit (blocking oscillator en multivibrator) en het uitgangs-

circuit (spannings- en stroomcircuit) behandeld en hun modificaties, waaronder de stroombegrensde spanningspacemaker. Als laatste worden de ontwikkeling en de werking van de P-top getriggerde en de R-top gestuurde pacemaker besproken.
Het voorlaatste hoofdstuk is gewijd aan de klinische toepassing van de electrische gangmaker van het hart. Na een uiteenzetting van de indicatiestelling en de werkwijze bij implantatie van een pacemaker, wordt het belangrijkste deel van het hoofdstuk besteed aan de controle van de pacemaker patient. Behalve het klinische onderzoek van de patient zelf, worden de mogelijkheden van controle van de stimuleringseenheid behandeld. Op dit gebied bestaan naast de polscontrole, ECG analyse en de soms toepasbare Rö controle grote mogelijkheden in de nieuwe photo analyse.

Bij deze laatste methode worden de pacemakerimpulsen met behulp van de normale ECG afleiding volgens Einthoven zichtbaar gemaakt op een oscillograaf. Deze impulsen worden vervolgens photografisch vastgelegd. Uit het verloop van de impulsvorm, waarbij o.m. de impulsduur, -amplitude en -helling worden bepaald, is het vooral bij monopolaire spannings- en stroombegrensde spanningspacemakers mogelijk gebleken zich ontwikkelende defecten in de stimulering tijdig te herkennen. Deze defecten kunnen zowel gelocaliseerd zijn in de stimulator zelf (ladingstoestand van de batterijen, werking van de electronisch circuit) als in het electrodencircuit (verhoogde weerstand, dreigende draadbreuk, isolatie defecten) en bleken in de meeste gevallen met de methode tijdig bij een nog intacte stimulering te herkennen. De werkwijze en voorbeelden van de voorkomende defecten worden uiteengezet. Aan het slot van hoofdstuk IX wordt nog gewezen op het gevaar van het aansluiten van meerdere bewakings- en stimuleringsapparaten aan één patient.

Het boek besluit met een korte beschouwing over de mogelijkheden van de electrische therapie in de toekomst.

Aan het slot van deze samenvatting dient te worden opgemerkt, dat het niet de bedoeling is geweest in dit manuscript aan de hand van eigen onderzoekingen en literatuurstudie een standaard stimuleringsmethode en stimuleringseenheid aan te wijzen. Veeleer is getracht een inzicht te geven in de electrische stimulering van het hart, om de lezer, aan de hand van de besproken grote verscheidenheid van toepassingsmogelijkheden zijn eigen keuze te laten maken, om zodoende voor iedere patient tot een optimaal gebruik te komen van dit nieuwe electrotherapeuticum, de kunstmatige gangmaker van het hart.

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