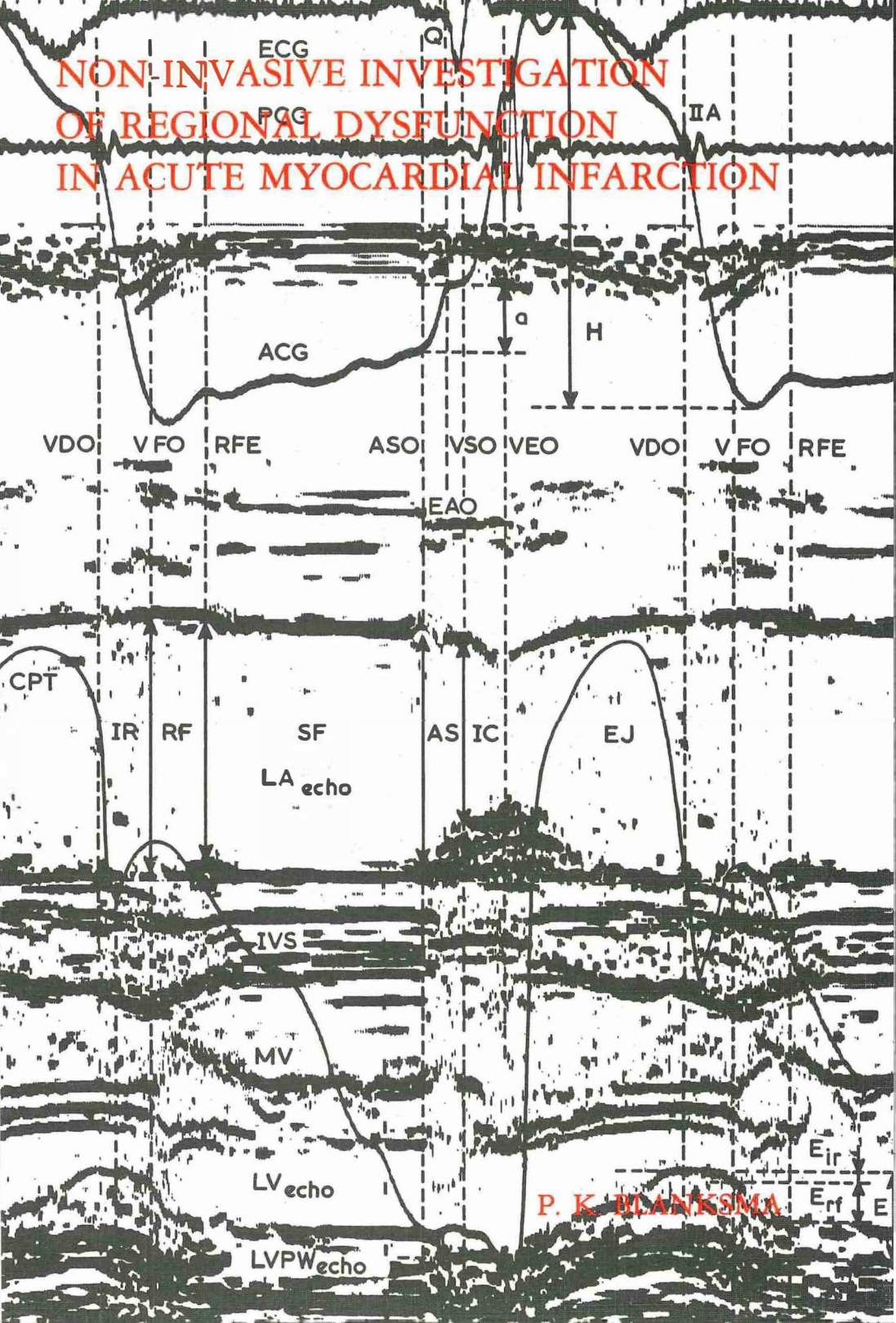
NON-INVASIVE INVESTIGATION OF REGIONAL DYSFUNCTION IN ACUTE MYOCARDIAL INFARCTION



P. K. BLANKSMA

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STELLINGEN

I.

De verhouding tussen de beweging van de achterwand van de linker hartkamer tijdens de isovolumetrische relaxatieperiode en de totale beweging van de achterwand, in dit proefschrift aangeduid als IR-ratio, is een nieuwe, nuttige, tamelijk gemakkelijk door uitwendig onderzoek verkrijgbare, betrouwbare index van regionale dysfunctie in het vroege stadium van het acute myocardinfarct.

II.

De belangrijkste diastolische functiestoornis bij patiënten met een ischaemische hartaandoening is een ongecoördineerd relaxatiepatroon en een daardoor gestoorde snelle vulling van de linker hartkamer.

III.

De belangrijkste diastolische functiestoornis bij patiënten met een hypertrofische cardiomyopathie is een verminderde rekbaarheid van de linker hartkamer.

IV.

De relaxatie van de linker hartkamer moet beschouwd worden als een belangrijke functie van de spierwand van de linker hartkamer, afzonderlijk van en naast de rekbaarheid tijdens de diastole.

V.

De snelheid en omvang van de relaxatie van de linker hartkamer neemt af met het stijgen van de leeftijd.

VI.

Een van de belangrijkste onderwerpen van onderzoek op het gebied van de cardiologie in de komende jaren is de ontwikkeling en bestudering van niet-invasieve methoden van onderzoek, waarbij, door vergelijking van niet-invasieve gegevens met gelijktijdig door hartcatheterisatie verkregen invasieve gegevens, de kwantitatieve waarde van het niet-invasief onderzoek wordt vastgesteld/bepaald.

VII.

Ontwikkeling van methoden van onderzoek van regionale en globale functiestoornissen van de left ventricle bij patiënten met cardiale afwijkingen met behulp van hartcatheterisatie zal een nog nauwkeuriger indicatiestelling voor een nog doelgerichter handelwijze van de chirurgen bij cardiochirurgische therapie mogelijk maken.

VIII.

De noodzakelijke invoering van het gebruik van SI-eenheden op het gebied van de drukmeting kan sterk worden bevorderd door het laten vervaardigen en doen verstrekken van plakstrookjes met een kilopascalmaatverdeling ter bevestiging op alle in gebruik zijnde bloeddrukmeters.

IX.

Uitbreiding van de cardiochirurgische faciliteiten in ons land dient in de eerste plaats te geschieden door uitbreiding van de bestaande centra tot hun optimale omvang en in de tweede plaats, indien nodig, door het stichten van nieuwe centra in die regio's van het land, waar het grootste tekort is aan deze faciliteiten.

X.

Het gebruik van een calcium-ionen-bevattende perfusievloeistof bij de conditionering van het myocard bij open hart operaties heeft minder myocardbeschadiging tot gevolg dan gebruik van een perfusievloeistof die geen calciumionen bevat.

P. Jynge et al., The Journal of Thoracic and Cardiovascular Surgery 1978, 76, 2-15.

XI.

Slechts wanneer binnen de kliniek van de interne geneeskunde aan de afdeling cardiologie voldoende ruimte wordt gelaten voor een zelfstandige ontwikkeling, zullen de aldaar in opleiding zijnde internisten zich in voldoende mate kennis van en inzicht in de diagnostiek en therapie van ziekten van het hart eigen kunnen maken.

XII.

Verbetering van de kwaliteit van de dienstverlening door de huisarts kan in de eerste plaats bereikt worden door een aanzienlijke uitbreiding en intensivering van zijn klinische opleiding, met name in de interne geneeskunde.

XIII.

Het schrijven van een proefschrift is een omslachtige, boeiende, frustrerende, effectieve en voldoening gevende wijze om eigen kennis en inzicht te vergroten.

XIV.

Het formuleren van stellingen behorend bij een proefschrift is een aardige, folkloristische en nutteloze gewoonte.

Stellingen
behorende bij het proefschrift van
P. K. Blanksma

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Groningen 1979

RIJKSUNIVERSITEIT TE GRONINGEN

NON-INVASIVE INVESTIGATION OF REGIONAL DYSFUNCTION IN ACUTE MYOCARDIAL INFARCTION

PROEFSCHRIFT

ter verkrijging van het doctoraat in de geneeskunde
aan de Rijksuniversiteit te Groningen
op gezag van de Rector Magnificus Dr. J. Borgman
in het openbaar te verdedigen op woensdag 12 december 1979
des namiddags te 2.45 uur (precies)

door

PAULUS KORNELIS BLANKSMA

geboren te Sneek

1979
DRUKKERIJ VAN DENDEREN B.V.
GRONINGEN

Promotores: Dr. E. van der Wall
Dr. G. A. Mook
Coreferent: Prof. Dr. J. Nieveen

Het onderzoek, beschreven in dit proefschrift, werd verricht op de afdeling Cardiologie (prof. Dr. J. Nieveen) van de Interne Kliniek (prof. Dr. E. Mandema) van het Academisch Ziekenhuis te Groningen. De echo- en fonocardiografische registraties werden verricht op de afdeling echo- en fonocardiografie (Drs. J. P. M. Hamer) en de hartcatheterisaties binnen de werkgroep hartcatheterisatie en angiocardiografie. Verder werkten aan de totstandkoming van dit proefschrift mee:

manuscript	:	mevr. A. E. Gaarenstroóm-Arriens
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Aan allen, die op welke wijze dan ook mij geholpen hebben bij de voorbereiding van dit proefschrift, in het bijzonder aan mijn beide promotores, betuig ik mijn oprechte dank.

Het verschijnen van dit proefschrift werd mede mogelijk gemaakt door steun van de Nederlandse Hartstichting.

aan mijn ouders
aan Hilda
Cor
Erik-Jan
Hans

CONTENTS

LIST OF SYMBOLS AND ABBREVIATIONS

A_{as}	= change in left atrial diameter during atrial systole
ACG	= apexcardiogram, the external recording of the apical impulse
a/D-ratio	= ratio of the a-wave deflection and diastolic deflection of the apexcardiogram
a/H-ratio	= ratio of the a-wave deflection and total deflection of the apexcardiogram
aMVL	= anterior mitral valve leaflet
Ao	= aorta
AS	= atrial systole
ASO	= atrial systole onset
A_{rf}	= change in left atrial diameter during rapid filling of the left ventricle
CPT	= carotid pulse tracing
D/H-ratio	= ratio of diastolic deflection and total deflection of the apexcardiogram
E	= total excursion of the left ventricular posterior wall echo
E_{ir}	= excursion of the left ventricular posterior wall echo during isovolumic relaxation
E_{rf}	= excursion of the left ventricular posterior wall echo during rapid filling
ECG	= electrocardiogram
echo	= echocardiogram
EF	= ejection fraction
EJ	= left ventricular ejection
IC	= isovolumic contraction
IR-ratio	= index of incoordinate relaxation or index of regional dysfunction: ratio of the excursion of the left ventricular posterior wall echocardiogram during isovolumic relaxation and its total excursion (E_{ir}/E x 100)
IR	= isovolumic relaxation
IVS	= interventricular septum
LA	= left atrium
$LDH_{1\ 2}max$	= index of enzymatic infarct size: maximum plasma concentration of the first and second fraction of lactodehydrogenase after the infarction
LV	= left ventricle
LVPW	= left ventricular posterior wall
MV	= mitral valve
p	= pressure
P	= probability of not-significance
Δp_{as}	= pressure rise during atrial systole
PCG	= phonocardiogram
p_{lvbd}	= minimum left ventricular pressure
p_{lved}	= left ventricular end-diastolic pressure
Q	= initial deflection of the QRS-complex of the electrocardiogram
r	= correlation coefficient
RF	= rapid filling of the left ventricle
RF-ratio	= ratio of the excursion of the left ventricular posterior wall echo during rapid filling and its total excursion (E_{rf}/E x 100)
RFE	= end of rapid filling
RFW	= rapid filling wave of the apexcardiogram
RV	= right ventricle
SEE	= standard error of estimate, standard deviation from the regression line
SF	= slow filling
SR	= spontaneous relaxation: isovolumic relaxation plus rapid filling
SR-ratio	= ratio of the excursion of the left ventricular posterior wall echo during spontaneous relaxation and its total excursion (E_{sr}/E x 100)
SR-ratio/T_{sr}	= velocity of the posterior wall motion during spontaneous relaxation
$1/Tc$	= index of contraction velocity
$1/Tc_{(ACG)}$	= *idem*, derived from the apexcardiogram

$1/T_{C(LVP)}$ = *idem*, derived from the left ventricular pressure curve
T_e = left ventricular ejection time (LVET)
T_{ems} = electromechanical systole
T_{ems}^* = idem, corrected for heart rate
T_{ir} = isovolumic relaxation time
T_{pe} = pre-ejection time or period (PEP)
$1/T_R$ = index of relaxation velocity
$1/T_{R(ACG)}$ = *idem*, derived from the apexcardiogram
$1/T_{R(LVP)}$ = *idem*, derived from the left ventricular pressure curve
T_{rf} = rapid filling time
T_{sr} = spontaneous relaxation time
v_{CE} = velocity of contractile element shortening
VDO = onset of ventricular diastole
VEO = onset of ventricular ejection
VFO = onset of ventricular filling
v_{max} = maximum velocity of contractile element shortening, extrapolated to zero load
VSO = onset of ventricular systole
IIA = first high frequency vibration of the aortic component of the second heart sound

Chapter 1

INTRODUCTION

Ischemic heart disease is one of the most important causes of disability and death in Western countries (77, 197). Almost 50000 people died of atherosclerotic disease (171) in the Netherlands in 1976, of which more than 50 percent succumbed to myocardial infarction. Death resulting from myocardial infarction is mainly due to three causes: arrhythmias, cardiac tamponade and pump failure. Pump failure occurs mainly in the acute phase of myocardial infarction; during hospitalisation it is the main cause of death (60, 63, 65). However, in the first two or three years after an infarction, pump failure can still play an important role because of continuing left ventricular dysfunction (82, 98, 136, 145). Therapeutic management of arrhythmias is continuous to grow more effective, and with the aid of modern methods of arrhythmia monitoring and antiarrhythmic treatment mortality, at least in hospital, has been reduced. Pump failure and cardiac tamponade are therefore becoming relatively more important as causes of death. The results of treatment of pump failure in acute myocardial infarction are disappointing, probably because, as yet, no known form of treatment of serious pump failure has been effective. The final outcome of pump failure in acute myocardial infarction is mainly determined by infarct size, which also influences the occurrence of life-threatening arrhythmias. For instance, when the total cumulative infarct size exceeds 40 percent of the myocardium, the patient mostly dies of cardiogenic shock (118). The purpose of the present study was to try to obtain information about infarct size and left ventricular function in patients with acute myocardial infarction. For this we studied 17 infarct patients and 28 normal individuals, using non-invasive methods: echocardiography, apexcardiography and the measurement of systolic time intervals.

In studying mechanical dysfunction of the left ventricle in acute myocardial infarction, a distinction can be made between dysfunction of the left ventricle as a whole, *i.e. global dysfunction,* and dysfunction of a part of the myocardium, *i.e. regional dysfunction.* Left ventricular dysfunction can be studied during the different periods of the cardiac cycle, *i.e.* the phases of *contraction, relaxation and filling.* In

myocardial infarction, left ventricular dysfunction is primarily regional, since it is caused by loss of function of a part of the ventricular wall, the infarcted area. On the other hand global dysfunction may also occur. Furthermore, it is well known that disorders of contraction, relaxation and filling may be present in acute myocardial infarction. Pump failure in acute myocardial infarction thus may be due to regional and/or global dysfunction.

Methods for the detection, and especially the quantification, of pump failure are not yet fully developed. Apart from the fact that as yet there is no consensus of opinion about how to define and measure cardiac function, most quantities which are used to describe cardiac function cannot be measured easily in patients with recent myocardial infarction. These quantities may also be called indices of ventricular function.

To describe *regional dysfunction* of the left ventricle, no generally accepted index is known. Usually the percentage of the ventricular wall that contracts abnormally is used as an index of regional dysfunction. This percentage is estimated from a left ventricular cineangiogram or from a radioisotope scintigram. It is the percentage of the ventricular cavity outline that moves abnormally. The extent of abnormality in the wall movement can be described qualitatively as hypokinesis (less movement than normal), akinesis (no movement during contraction) and dyskinesis (movement in the opposite direction as compared to normal). This thesis describes a new index, obtained from the echocardiogram of the posterior wall of the left ventricle, which provides a quantitative estimation of regional dysfunction, the IR-ratio (IR = isovolumic relaxation). This is the ratio of the excursion of the left ventricular posterior wall during the isovolumic relaxation period and its total excursion. In particular, the posterobasal part of the ventricular wall has been chosen because this part can be easily visualized and is usually not involved in the infarction. The movement of the unaffected part of the ventricular wall during isovolumic relaxation is considered to reflect the extent of change in the shape of the left ventricle. This change of shape is directly related to that during contraction, and thus to the size of the infarct (see also chapter 2, figs. 1, 2 and 3). In normal persons the IR-ratio is almost zero (0 - 10%) whereas in infarct patients it appears to be related to infarct size (20 - 60%).

To describe *global ventricular function,* indices are derived from pressure curves (invasive) or external pulse tracings (non-invasive). For the evaluation of *systolic function* measurements are taken from the isovolumic contraction part or the ejection part of these curves. The indices related to the isovolumic contraction period are based on the models of myocardial contraction of A.V. Hill and its modifications (14: page 50, 199: page 235). Recently, the validity of these models has been questioned, and experimental evidence has been presented showing that the instantaneous pressure-volume ratio and its maximum value at the end of systole are better indices of systolic function (159). However, this index is difficult to measure, especially in infarct patients, and cannot be obtained non-invasively. In this thesis an index related to systolic function is described, which was derived from the isovolumic contraction part of the apexcardiogram, the external recording of the apical impulse. It is called *1/Tc* here, and it is a measure of the maximum rate of rise of the apexcardiogram during isovolumic contraction. It is similar to the maximum rate of rise of the left ventricular pressure during isovolumic contraction. An index related to ejection is the ejection fraction, which is defined as the ratio of stroke volume and end-diastolic volume. Yet another index is the velocity of circumferential fiber shortening, which is defined as the rate at which midventricular circumference shortens during ejection. However, in the presence of regional dysfunction, these indices cannot be measured with the help of the methods of our investigation, so they were not applied in our study. Systolic time intervals measured according to Weissler (182, 184) are also related to systolic function.

Diastolic function consists of relaxation and filling. Indices of relaxation may be the rate of change of pressure, dimension or wall thickness of the left ventricle after closure of the aortic valve. In our study the value of several indices, derived from the apexcardiogram, the echocardiogram of the left ventricular posterior wall and of the left atrium were tested. There is much controversy concerning indices describing ventricular filling. Differentiation can be made between indices describing the initial, rapid filling phase and describing the rest of diastole: the slow filling phase and the filling during atrial contraction. Rapid filling is mainly dependent on the rate of relaxation. Ventricular filling also depends on diastolic compliance,

which may be measured most appropriately during the second part of diastole. It may *e.g.* be measured as the ratio of the volume change and the pressure change during atrial systole. For the non-invasive quantitative estimation of this compliance we used an index obtained from measurements from the echocardiogram and the apexcardiogram. From the echocardiogram the change in diameter of the left atrium during atrial systole (A_{as}) was measured, reflecting a change in volume. From the apexcardiogram the relative amplitude during atrial systole (a/H-ratio) was measured, reflecting a change in pressure according to our findings. The ratio $A_{as} \div a/H$ was called compliance-ratio.

Measurements concerning ventricular function may be done *invasively* during cardiac catheterisation by means of which accurate data may be obtained (12, 43, 127, 160). In the last one or two decades the development of several *non-invasive* methods, which are applicable to infarct patients, has received increasing attention because these methods are not harmful to the patient and are easily repeatable (8, 9, 26, 64, 68, 72, 74, 80, 83, 85, 86, 89, 91, 128, 134, 140, 144). As mentioned before, three non-invasive methods have been used in our study, because they yield supplementary information and can easily be combined, *viz.* echocardiography, apexcardiography and the measurement of systolic time intervals. These methods are described below.

An *echocardiogram* is a recording of the movements of cardiac structures made by means of reflected ultrasound. Essentially, two techniques are used: the M-mode echocardiography, in which a single beam of ultrasound is used, only representing movements of those structures lying in one line with the transducer, and two-dimensional systems, which give a moving picture of a transsectional plane of the heart. We have used only M-mode echocardiography. Until recently, ejection fraction and velocity of circumferential fiber shortening (19, 41, 44, 79, 92, 156, 162, 183), were calculated by means of this technique, because correlations had been found with angiocardiographically obtained indices. Now, these calculations have been abandoned, especially in the case of patients with coronary artery disease. As could be expected, in these patients the correlations of echocardiographically and angiocardiographically obtained indices have been found to be poor. In ischemic heart disease the main

ventricular dysfunction consists of a change of shape of the left ventricle, whereas calculations based on M-mode recordings are just based on the assumption that no change of shape occurs during contraction.

Gibson *et al.* (50, 51, 52, 167, 169, 170) however, have developed a method, now more generally applied (79) of visualizing regional dysfunction with the help of M-mode echocardiography. After digitizing the signal, they plot, with the aid of a computer system, echocardiographic left ventricular diameter and wall thickness against left ventricular pressure or the apexcardiogram. In fact the idea behind the IR-ratio originated from Gibson's work (51).

Some investigators report, that an impression of segmental wall motion can be gained with the help of a two-dimensional echocardiographic system (34). This was already achieved by Heikilla and Nieminen (61, 62, 116), using M-mode echocardiography. Corya *et al.* (24, 25, 28, 29, 40) detected abnormal wall motion with another M-mode technique (condensed scanning). None of these authors, however, estimated regional dysfunction quantitatively.

Echocardiography can also be used to estimate volume changes of the left atrium. Several authors (18, 67, 198) have found a good correlation between atrial diameter measured from a M-mode recording with angiocardiography. The angiocardiographical measurements were obtained according to the methods of Arvidsson (6), Dodge *et al.* (31), and Sauter *et al.* (142). There is also a good correlation with measurements from two-dimensional echocardiographic systems (143). Strunk *et al.* (158) and Akgun *et al.* (2) found a good correlation between the movements of the aortic posterior wall (so, the left atrial anterior wall) and angiocardiographically measured atrial diameter and volume changes. They found that the left atrial posterior wall usually showed no movement. Pratt (125) found a correlation between aortic posterior wall excursion and stroke volume. As left atrial and left ventricular volume changes are equal but opposite during diastole (112), the volume changes during diastole of the left ventricle may also be estimated by measuring left atrial diameter changes. In infarct patients this can usually not be done from direct measurements of left ventricular diameter changes because of regional dysfunction.

The *apexcardiogram* is the external recording of the apical

impulse. The form of the apexcardiogram resembles a left ventricular pressure curve; there is a rapid systolic rise and a rapid decline at the end of systole. In the diastolic part the rapid and slow filling and the atrial contraction, causing the a-wave, can usually be recognized easily. As early as 1962 Benchimol and Dimond described an increase of the a/H-ratio (ratio of the a-wave deflection and total deflection) of the apexcardiogram in patients with myocardial infarction and during an anginal attack. This was related to an increase in end-diastolic pressure in these patients (11, 30). Later, this was confirmed (99, 151, 165). Kesteloot and coworkers (7, 187) stressed the importance of the apexcardiogram as a reflection of ventricular function and demonstrated the similarity with ventricular pressure changes. According to them the apexcardiogram is even more similar to the wall stress curve, calculated from left ventricular pressure, diameter and wall thickness.

The measurement of *systolic time intervals* was introduced by Weissler *et al.* (182, 184) and has recently been reviewed by Lewis *et al.* (90). The measurements are obtained from simultaneous recordings of an electrocardiogram, a carotid pulse tracing, and a phonocardiogram. The time intervals include the total mechanical systole (Q -IIA or T_{ems}), the left ventricular ejection time (LVET or T_e), and the pre-ejection period or time (PEP or T_{pe}). For clinical use, they are corrected for heart rate. The ratio of pre-ejection time and ejection time (T_{pe}/T_e) also appears to be a valuable quantity and it proved to be independent of heart rate. The measurements have also been applied in myocardial infarction and angina pectoris (1, 38, 71, 89, 99, 156, 183). Lewis *et al.* (88) found in patients with acute myocardial infarction a correlation between the electromechanical systole and urinary excretion of catecholamines (correlation coefficient $r = 0.88$). The ratio of pre-ejection time and ejection time (T_{pe}/T_e) is increased in patients with an old infarct. It correlates with cardiac index and stroke volume ($r = -0.81$) (88). There is also a correlation with ejection fraction ($r = -0.76$) (89). T_{pe}/T_e is influenced also by other factors, *e.g.* valvular disease. Therefore, when patients with different cardiac disorders are taken together, there is no correlation ($r = -0.35$) (1).

The purpose of the investigation described in this thesis may be summarized as follows.

1. Evaluation of a new echocardiographic index of regional dysfunction (IR-ratio).
2. Evaluation of apexcardiographic indices of contraction velocity and relaxation velocity, derived from the isovolumic parts of the apexcardiogram.
3. Application of these and other non-invasive measurements in patients with acute myocardial infarction.
4. Enlargement of the insight into the mechanisms of regional dysfunction of the left ventricle in acute myocardial infarction.

The investigation was performed as follows. In 17 patients with acute myocardial infarction and 28 normal individuals, nearly simultaneous recordings were made of the electrocardiogram, the phonocardiogram, the carotid pulse tracing, the apexcardiogram, and the echocardiograms of the mitral valve, the left atrial anterior and posterior walls, and the left ventricular posterior wall. Because no important change in the heart rate occurred between the recordings, time intervals measured in one recording could be used for the measurements from the other recordings.

The group of 28 normal individuals served as a control group and consisted of 18 patients without cardiac abnormalities and 10 healthy individuals. The results obtained with this group constituted the normal range of the measured quantities and indices. These results were correlated with age. Whenever a significant correlation with age was found, it was taken into consideration in the case of the patient group. Most of the indices which were measured have been already mentioned above. The measurements in the patient group were taken at three instances: in the first week after the infarction, after two weeks, and after two months. The echocardiographic index of regional dysfunction, the IR-ratio, was compared with infarct size as estimated from the maximal value of the first and second fraction of the serum lactodehydrogenase ($LDH_{1+2}max$). As indices of global ventricular function the indices of velocity of contraction and of relaxation were measured from the apexcardiogram. These were compared with the IR-ratio and with the enzymatic infarct size ($LDH_{1+2}max$). A separate study was done in a group of 19 cardiac, but non-infarct patients. During cardiac catheterisation simultaneous recordings of the apexcardiogram and left ventricular pressure were made. The indices of velocity of contraction and of relaxation were

measured from the pressure tracing in the same way as from the apexcardiogram, and compared with those obtained from the apexcardiogram. They were also compared with the maximum rate of rise of the left ventricular pressure (*dp/dt (max)*). In the infarct patients several other indices related to global ventricular function were measured. They can be subdivided into indices related to diastole (*i.e.* to relaxation, rapid filling, and atrial systole) and to ventricular systole. As indices related to relaxation we measured the above mentioned index of relaxation velocity, derived from the apexcardiogram ($1/T_R$), and the mean velocity of the left ventricular posterior wall from the echocardiogram during relaxation (SR-ratio/T_{ir}) as a measure of relaxation velocity of the unaffected ventricular wall. As indices related to rapid filling the movement of the left ventricular posterior wall (RF-ratio) and the change in diameter of the left atrium during rapid filling (A_{rf}) were taken. Also the time duration of the two periods into which relaxation may be divided, isovolumic relaxation time (T_{ir}) and rapid filling time (T_{rf}) was measured. As indices related to atrial systole the a/H-ratio obtained from the apexcardiogram was taken as a measure of the pressure rise during atrial systole, while the change in diameter of the left atrium was obtained from the echocardiogram as a measure of volume change during atrial systole. The ratio of these two quantities is the compliance-ratio as already mentioned before. Finally the systolic time intervals, the electromechanical systole, corrected for heart rate(T_{emis}*), and the ratio of pre-ejection time and ejection time (T_{pe}/T_e) and the index of contraction velocity from the apexcardiogram ($1/T_C$) were obtained as measures of systolic function. These indices were also compared with the IR-ratio and the enzymatic infarct size (LDH_{1+2}max) in order to try to get a better insight into the pathophysiological mechanisms that play a role in acute myocardial infarction.

Chapter 2 describes the metabolic changes which take place in the myocardium in ischemia and infarction, and the consequences of regional dysfunction for the mechanical function of the left ventricle. A schematic representation is given of the wall movements in regional dysfunction explaining why the IR-ratio may be taken as a measure of regional dysfunction. In chapter 3, apexcardiography is discussed with a review of the literature. Here, the comparative

invasive-non-invasive study in 19 patients during cardiac catheterisation is described with the results. The way in which global ventricular function may be estimated from measurements from the apexcardiogram is discussed. Chapter 4 gives the clinical data of the infarct patients and the group of normals and the methods used in the examination of the patients. The way in which the measurements and calculations are performed are also given in detail. In chapter 5 the results of the measurements and the calculations of the correlations between the different quantities and indices are presented. Finally, chapter 6 gives the discussion and the conclusions of the investigation.

Chapter 2

REGIONAL DYSFUNCTION OF THE LEFT VENTRICLE IN ACUTE MYOCARDIAL INFARCTION

2.1. *Metabolic changes in ischemia and infarction of the myocardium*

In the absence of valvular disorders or congenital defects, left ventricular function is mainly determined by myocardial function. Before discussing the way in which left ventricular function may be disturbed by ischemia and infarction, we will first describe the way in which myocardial activity may be influenced by the metabolic changes accompanying ischemia and infarction.

In the last few years it has become apparent from a number of investigations, that in ischemia of the myocardial cell an intracellular acidosis arises readily (14, 66, 75). The acidosis is chiefly the result of accumulation of lactic acid in the cells, as a result of anaerobic glycolysis. H^{+} ions inhibit the anaerobic energy metabolism and at the same time show in three ways a competitive antagonism with Ca^{2+}-ions. Firstly Ca^{2+}-ions are involved in the activation of the actin-myosine interaction, which is necessary for the contraction. H^{+} ions can be bound by troponine-C at the same site as Ca^{2+}, thus inhibiting the actin-myosine interaction. Secondly there is a competition of H^{+} ions with Ca^{2+}-ions during the slow inward current via the cell membrane. In this way intracellular acidosis causes a contraction disorder (66, 84, 191) in the ischemic region. Finally H^{+} ions inhibit the re-uptake of Ca^{2+}-ions in the sarcoplasmic reticulum at the end of the contraction, due to which a relaxation disorder can occur (14, 75).

Prolonged and severe ischemia often involves adrenergic stimulation of the heart (200). The combination of ischemia and adrenergic stimulation can exhaust the intracellular stores of energy-rich phosphates (adenosine triphosphate and creatine phosphate). In this way cell necrosis can finally develop (23, 42, 81, 105, 180, 181), which is accompanied by intracellular edema. Through this the stiffness of the infarcted area increases (4, 119, 196).

The adrenergic stimulation that takes place when an infarction develops, increases the velocity of contraction and relaxation and thus stimulates *global function* of the left ventricle. It is presumed that this effect occurs because cyclic AMP, the intracellular effector of the

sympathetic stimulation, augments the absorption of Ca^{2+} in the sarcoplasmic reticulum. As a result, the quantity of Ca^{2+}-ions which is released in the next contraction is greater. In addition Ca^{2+}-influx via the cell membrane increases. An increase in the intracellular energy consumption also occurs. The results of this may be that the existing ischemia becomes worse and the size of the infarct increases. Existing *regional dysfunction* may also increase in this way. Thus adrenergic stimulation improves the global function of the infarcted left ventricle and impairs the regional function. The net effect will depend on the size and the stage of development of the infarct (12, 149).

2.2. *The influence of ischemia and cell necrosis on the mechanical function of the left ventricle*

By cardiac performance we understand here the external work of the left ventricle. Cardiac performance is determined by 1. extracardiac factors, 2. factors determining contraction, 3. factors determining filling, and 4. heart rate. These factors will be briefly discussed.

With extracardiac factors preload and afterload are meant. There is a mutual influence between the heart and the peripheral vascular bed. The degree of filling of the peripheral vessels partly determines the volume of the left ventricle at the beginning of the contraction (preload). The pressure in the arterial system and the impedance of the peripheral vascular bed form the load of the left ventricle during the contraction (afterload).

Factors determining contraction are contractility and co-ordination of contraction. The performance of the heart depends on the intrinsic instantaneous functional level of the myocardium or contractility (see chapter 3) and the degree of co-ordination of contraction or regional function. Systolic functional disturbance of the left ventricle can therefore be global (contractility disorder) or regional (co-ordination disorder). The way in which regional dysfunction can be of influence on the contraction of the left ventricle, has been examined by means of a model study by Elings *et al.* (35). They report that when a part of the heart muscle has a decreased contractility, the development of wall tension lags behind that of the rest of the myocardium, so that at a certain moment this part of the

myocardium is stretched by the unaffected part. There is a non-uniform development of wall tension. In this way the normal, on cross-section almost circular shape of the ventricle, becomes irregular during contraction. So, during contraction there is a change of shape, which disappears during relaxation.

The factors determining the filling of the left ventricle are relaxation, diastolic compliance of the left ventricle and force of atrial contraction. Relaxation may be described as the process of decline of wall stress that begins after the end of contraction. It is an elastic recoil causing a rapid decline in pressure in the ventrice, sometimes lower than the pressure outside the heart *i.e.* below zero. The elastic recoil is caused by the fact that the endsystolic muscle length is shorter than the relaxed length, and myocardial muscle, because of its elastic properties, has the tendency to take on its relaxed length spontaneously (49, 70, 122, 135, 192). In patients with ischemic heart disease it has been shown that the velocity of relaxation is lower than normal. This has also been shown in papillary muscle experiments and in animals with experimental ischemia (45, 55, 56, 57, 94, 100, 103, 120, 132, 168). It may be suggested that this reduced velocity of relaxation is caused by a global relaxation disturbance in which the rate of increase in length and the rate of the decline of wall stress have both decreased. A regional relaxation disturbance could also exist. In this case a decreased rate of decline in pressure in the left ventricle goes along with different changes of length in different parts of the myocardium (see chapter 6). Gibson *et al.* (50, 51, 52, 167, 169, 170), Ruttley *et al.* (138) and Alam *et al.* (3) demonstrated that especially in patients with myocardial ischemia, *i.e.* with a regional functional disorder, there exists an incoordinate pattern of relaxation. An incoordinate pattern of relaxation has also been demonstrated in other patients (53, 141, 155). Gibson found an inward movement and an increase in thickness of the wall during isovolumic relaxation of the malfunctioning parts of the myocardium. During isovolumic relaxation ventricular volume does not change. Then an outward movement with a reduction of wall thickness of the rest of the myocardium must take place. This was also demonstrated in the study mentioned above (51). So in patients with regional dysfunction the shape of the left ventricle must change during isovolumic relaxation. Figures 1 and 2 demonstrate the movements of the ventricular wall

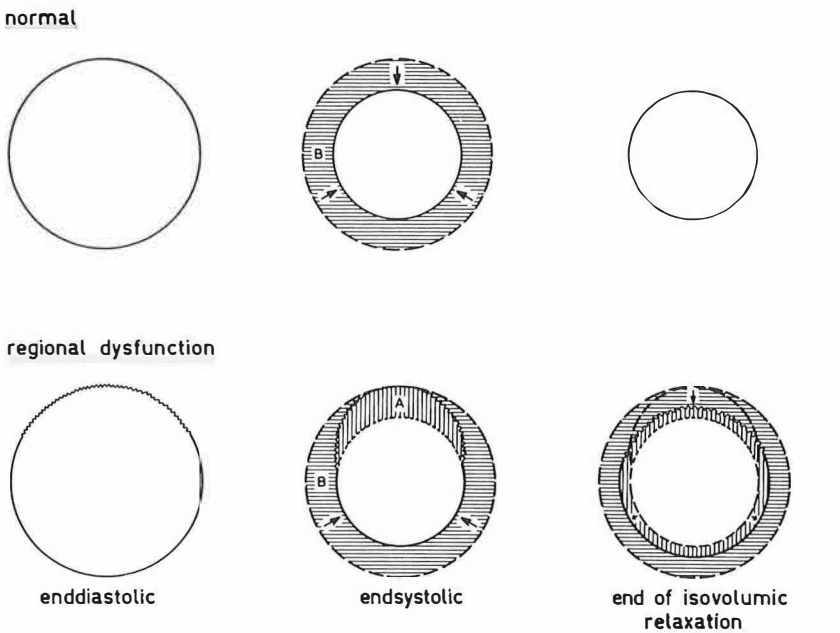


Fig. 1. Schematic drawing of outlines of the left ventricular cavity, illustrating normal and incoordinate pattern of contraction and relaxation of the left ventricle. Upper panel the normal, lower panel the incoordinate contraction and relaxation (regional dysfunction). During incoordinate contraction a change takes place in the shape of the left ventricle, which reverses during relaxation. As a result, the end-systolic volume increases with volume A as compared to normal. This is indicated by vertical bars. At the end of isovolumic relaxation (lower panel) the volume indicated with vertical bars is the same as in the end-systolic situation (lower panel), middle), because between these two situations no volume change occurs.

during the cardiac cycle. Normally (fig. 1, upper panel; fig. 2, patient A), a concentric contraction takes place, while during the isovolumic relaxation hardly any change of shape occurs. In regional dysfunction (fig. 1, lower panel; fig. 2, patient B), a part of the ventricular wall lags behind during contraction. End-systolic volume is therefore greater than normal; in fig. 1 this increase in volume is labelled as

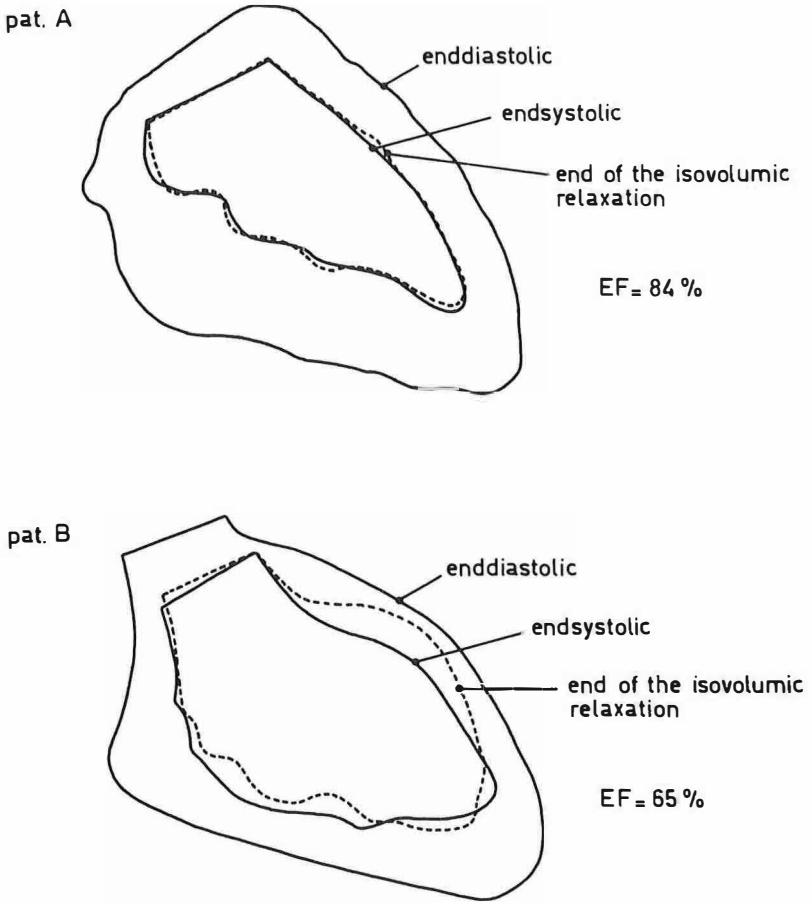


Fig. 2. Outlines of the left ventricular cavity obtained from cineangiocardiograms (30° right anterior oblique projection) in a patient without coronary artery disease (patient A) and in a patient with obstructive coronary artery disease of the inferior wall (patient B). The latter shows an inward movement of the affected region during the isovolumic relaxation period; in patient A there is no significant wall movement during this period. The isovolumic relaxation period in patient A was 40 ms, in patient B it was 140 ms. The ejection fraction (EF) in both patients was normal. The left ventricular posterior wall is not shown in this projection.

volume A. During the isovolumic relaxation a change of shape takes place, because the ventricular wall takes on a concentric shape. The unaffected part of the ventricular wall moves outwards. The extent of this movement depends on volume A and therefore on the size of the affected area. As can be seen in the lower panel of fig. 1: the area indicated with vertical bars in the situation at the end of isovolumic

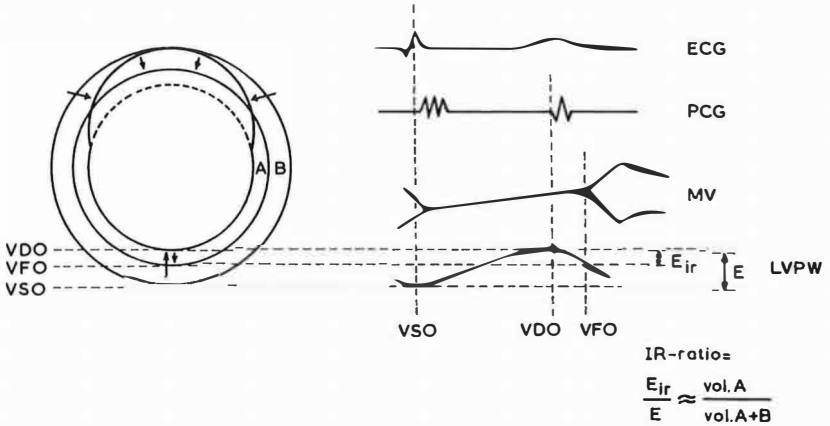


Fig. 3. Schematic drawing of left ventricular cross-section (compare fig. 1) illustrating the relation of incoordinate relaxation with electrocardiogram (ECG), phonocardiogram (PCG), mitral valve echocardiogram (MV) and left ventricular posterior wall echocardiogram (LVPW). VSO = ventricular systole onset, VDO = ventricular diastole onset, VFO = ventricular filling onset. The time from VDO to VFO is the isovolumic relaxation time. The volumes A and B are the same as in fig. 1. Calculation of the IR-ratio is performed as indicated: E_{ir} = excursion of the LVPW during isovolumic relaxation, E = total excursion of the LVPW. The short arrows indicate the wall movement during isovolumic relaxation, the longer arrows indicate wall movement during contraction.

relaxation is the same as volume A in the end-systolic situation. Therefore the ratio of the excursion of the well-functioning ventricular wall during isovolumic relaxation (E_{ir}) and the total excursion (E) must be related to the ratio of volume A and volume A+B (fig. 3). The ratio E_{ir}/E is indicated as IR-ratio.

The relaxation process takes place during the isovolumic relaxation and rapid filling; these two periods together are called spontaneous relaxation period here. The beginning of the filling of the ventricle is determined by the moment at which the pressure in the left ventricle falls below the pressure in the left atrium. Rapid filling, therefore, will begin earlier as the velocity of the fall in pressure in the left ventricle (so the velocity of relaxation) becomes greater. The end of the rapid filling is determined by the end of the relaxation. Consequently, not only the rate of filling during the rapid filling period, but also the duration of the rapid filling is determined by the velocity of relaxation. The change in pressure in the left ventricle during the rapid filling period seems to be determined by two factors: the relaxation process of the left ventricular wall and the

rate of filling of the left ventricle. At the beginning of the rapid filling period relaxation preceeds the filling and the pressure will drop still further. At the end of this period the filling continues because of blood inertia, while the relaxation is almost complete and the pressure and the wall stress rise again. The latter has the effect that the difference in pressure between the left atrium and the left ventricle that existed during the initial phase of the rapid filling period, is equalized, and the rate of the filling decrease, which signifies the end of the rapid filling period.

Some publications (27, 59, 68, 139, 152) point to a disturbance in the rapid filling in ischemic heart disease. The maximum rate of early diastolic filling of the left ventricle, as determined from measurements using radioisotopes, is clearly below normal. Also the increase of ventricular volume during rapid filling, as a fraction of the total filling, is smaller than normal (68, 139). The same results were found by means of echocardiography by Decoodt (27). Hammermeister *et al.* found the same with the help of quantitative angiocardiography (59). The duration of the rapid filling period was shortened according to Sylvestre *et al.*, who used the apexcardiogram (152). This indicates that in patients with ischemic heart disease the maximum rate of filling and the total volume change during the rapid filling period are disturbed. From the results of the work of Gibson *et al.* mentioned above (50, 51, 52, 167, 169, 170), it must be assumed that this is caused by a relaxation disturbance. During isovolumic relaxation the shape of the left ventricle changes as a consequence of which isovolumic relaxation lasts longer than normal.

After relaxation a rest period for the ventricle follows which begins with the slow filling period. During this period there exists only a slight difference in pressure between the left atrium and the left ventricle. The rate of the filling during slow filling will depend on diastolic compliance of the left ventricle. The filling of the left ventricle during atrial systole depends on the force of atrial contraction and the diastolic compliance of the left ventricle. The rise in pressure in the left ventricle during atrial systole (a-wave) is a measure for the force of atrial contraction. Diastolic compliance is measured as the ratio of change in volume and change in pressure during atrial systole. It is the reciprocal of the slope of the straight line which can be drawn through the points of the volume-pressure

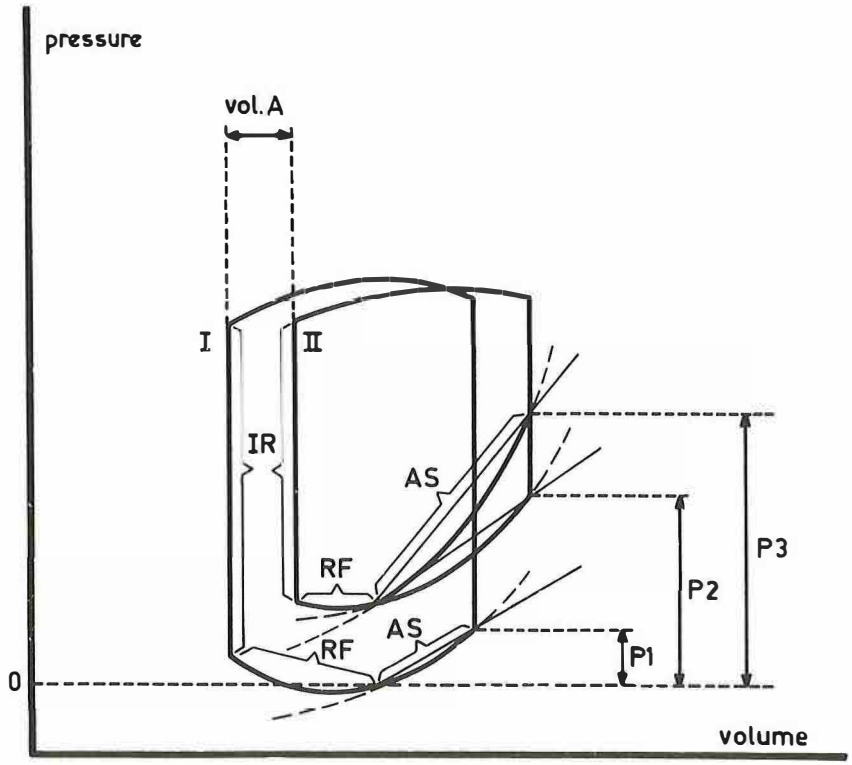


Fig. 4. Schematic volume-pressure lines of the normal left ventricle (I) and the left ventricle with regional dysfunction (II), with and without decreased left ventricular compliance. Volume A is the same as in fig. 1. Diastolic compliance is measured as the reciprocal of the slope of the straight lines through the points of the volume-pressure line, corresponding to beginning and end of atrial systole (AS). The end-diastolic pressure is indicated as p_1 (normal situation), p_2 (regional dysfunction with normal compliance), p_3 (regional dysfunction with decreased compliance). In II isovolumic relaxation (IR) proceeds slower and lasts longer, rapid filling (RF) is diminished and atrial activity is increased. The whole diastolic volume-pressure line is shifted to higher pressure and volume values.

line corresponding to beginning and end of atrial systole (fig. 4). Extensive studies have been made of the relation of volume and pressure during ventricular diastole and the influence on this of ischemic changes in the heart muscle (33, 46, 54, 93, 94, 119, 196). When in patients with coronary sclerosis ischemia develops, the volume-pressure line as a whole moves to higher pressure (94). In animal experiments short-lived ischemia caused no change in the compliance of the left ventricle (119, 196). It appears from Mann's investigation (94) that in ischemia the early diastolic pressure is

higher than normal, but that the slope of the late diastolic volume-pressure line is normal. Possibly the relaxation disturbance in ischemia causes an upward shift of the volume-pressure line, without change of the compliance of the left ventricle. The end-diastolic pressure and volume of the left ventricle are increased (fig. 4, p_2). It is generally accepted that at *infarction* the diastolic volume-pressure line of the left ventricle moves upwards (higher pressure) and becomes steeper (fig. 4). This is also found in animal experiments (4, 46, 100). In some patients with an infarct at a certain stage however the volume-pressure line may move to the right (larger end-diastolic volume) (12). A reduced compliance is a third cause for a high diastolic pressure in the left ventricle in patients with an infarct (fig. 4, p_3). Finally there is some evidence, that the pericardium and the right ventricle play a role in the rise of the diastolic pressure in ischemia and infarction (54).

Chapter 3

THE APEXCARDIOGRAM AND THE GLOBAL LEFT VENTRICULAR FUNCTION

3.1. *The apexcardiogram*

The apexcardiogram was recorded to estimate global left ventricular function non-invasively. The apexcardiogram (fig. 5) is

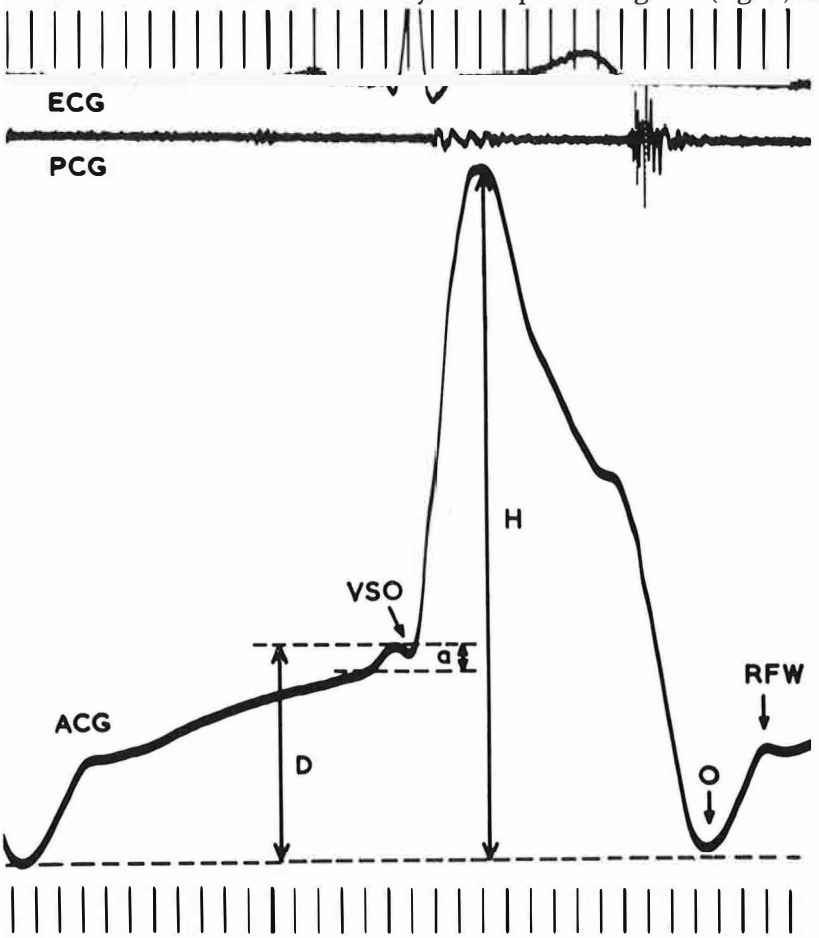


Fig. 5. Normal apexcardiogram (ACG) recorded simultaneously with the electrocardiogram (ECG) and the phonocardiogram (PCG); a = a-wave, due to atrial contraction, D = diastolic deflection, H = total deflection, VSO = ventricular systole onset (upstroke point), RFW = rapid filling wave, O = lowest point of the curve. Time lines 40 ms.

the external recording of the apical impulse. For the recording of this, different types of transducers are used. In the first place there are transducers which are connected via an air-filled tube with a funnel-shaped pickup or a capsule according to Marey, which is placed on the chest wall. The movements of the chest wall are then conducted via pressure changes in the air in the connecting tubing to a pressure transducer. The pressure transducer may contain a piezoelectric crystal or strain gauges. A piezoelectric crystal generates electrical energy when subjected to pressure *changes*. Thus, when a sustained pressure is applied to the crystal, the generated signal falls to the baseline with a certain time constant. Depending on the time constant, the recorded signal is more or less distorted. The transducers used for invasive blood pressure recording usually contain strain gauges. These can also be used for external pulse recording. These transducers have an "infinite time constant", which means that the generated signal of a sustained impulse does not fall to the baseline, and that the recorded signal is not distorted. In the second place, there are transducers which can be placed directly on the chest wall, *e.g.* the Hewlett-Packard APT-16 transducer. The movements of the chest wall are then transmitted directly to the pressure transducer. The APT-16 transducer contains a differential inductance transformer, which has also an "infinite time constant".

Several authors have tried to find a relation between the apexcardiogram and the mechanical activity of the heart. The relation of the apexcardiogram to the intraventricular pressure has been studied, as also the relation with its wall stress. Aubert *et al.* (7) made simultaneous recordings of the apexcardiogram, the left ventricular pressure and a left ventricular echocardiogram in dogs. Using the Laplace relation, they calculated, with the aid of a computer system, wall stress from left ventricular internal diameter, wall thickness and pressure. During the isovolumic periods there is by definition no change of volume. Therefore during these periods there should be no difference between changes in pressure and wall stress. Aubert *et al.* (7) found that the ejection part of the apexcardiogram agreed better with wall stress than with left ventricular pressure.

When the apexcardiogram and the wall stress curve are compared, there are small differences (7). These differences might be explained when it is assumed that impulse effects of ejection and filling of the

left ventricle could also influence the form of the apexcardiogram. Impulse effects might be caused by acceleration and deceleration of blood flowing in and out the left ventricle. This is illustrated in fig. 6.

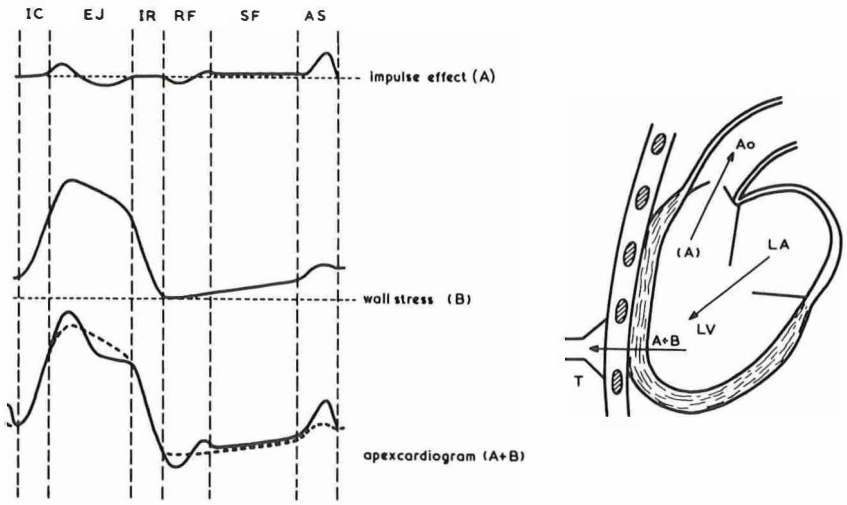


Fig. 6. Schematic drawing of the origin of the apexcardiogram. The apexcardiogram is considered to be the result of changes in force exerted by the heart on the chest wall. Two components may be distinguished: impulse effects, caused by blood entering and leaving the left ventricle (A) and changes in wall stress (B). IC = isovolumic contraction, EJ = ejection, IR = isovolumic relaxation, RF = rapid filling, SF = slow filling, AS = atrial systole, Ao = aorta, LA = left atrium, LV = left ventricle, T = pickup of the apical impulse transducer.

The supposed impulse effects are shown in the left panel, upper curve (A), the wall stress is shown in the middle curve (B). The sum of both curves is then the apexcardiogram. During the isovolumic periods (IC and IR) there are no impulse effects.

Several investigators (36, 95, 96, 133, 151, 161, 175, 177, 187, 190) have compared simultaneously recorded apexcardiograms and left ventricular pressure curves. They found that the upstroke points at the onset of ventricular systole and the lowest points of both curves occur nearly simultaneuosly (161, 190). Also the shape of the isovolumic contraction parts (175, 187) was nearly the same. The diastolic parts agreed less than the isovolumic parts. The a/H-ratio (ratio of the a-wave deflection and total deflection, see fig. 5) of the apexcardiogram correlates with the amplitude of the a-wave of the left ventricular pressure curve. Voigt and Friesinger found a

correlation coefficient $r = 0.81$ (177). When the a/H-ratio was compared with end-diastolic pressure, Voigt and Friesinger found only a poor correlation ($r = 0.45$). There was no correlation between the a/D-ratio (ratio of the a-wave deflection and diastolic deflection, see fig. 5) and the end-diastolic pressure. Van der Wall (178) found in patients with hypertrophic cardiomyopathy a linear correlation between the a/H-ratio and the end-diastolic pressure. Rios and Massumi (133) compared left ventricular end-diastolic pressure with D/H-ratio (ratio of diastolic deflection to total deflection, see fig. 5). In patients with different diagnoses they found a good correlation ($r = 0.87$).

3.2. *The global left ventricular function*

The instantaneous functional level of the myocardium, contractility, can be defined as that variable quality of the myocardium, which together with preload and afterload determines cardiac performance. Contractility determines also the relation between contractile force, shortening velocity and length of the muscle fibers. By cardiac performance we understand here the external cardiac work (chapter 2). As there is no shortening of the myocardium during isovolumic contraction, an attempt has been made to determine a contractility index from the pressure change during this period. Wall tension and pressure change proportionally in this period, because ventricular diameter and wall thickness hardly change. It is possible to derive that the velocity of pressure rise divided by the pressure is proportional to the shortening of the contractile element (14, 75, 199):

$$(1) \qquad \frac{dp}{dt} /p = k \,.\, v_{CE}$$

where p = left ventricular pressure, v_{CE} = velocity of contractile element shortening and k = constant. Analogous to the force-velocity relation, p (for force) can be plotted against $\frac{dp}{dt} /p$ (for velocity). Extrapolation of this value to zero load yields the maximum value of contractile element shortening v_{max}. In the book by Yang *et al.* (199) 12 indices are mentioned, some of which are similar to v_{max}.

They are all corrected for preload. v_{max} seems one of the best to determine contractility, but this index can only be obtained from a high fidelity pressure signal of the left ventricle. Besides, it did not come up to the expectations concerning reliability and reproducibility (121, 126, 153). Lately it has been demonstrated that the contractility indices, even those corrected for preload, are still influenced by preload and afterload. Therefore they are not a proper representation of the intrinsic functional level of the myocardium (14, 75, 199). Yet these indices seem clinically useful, especially when they can be obtained in a simple and non-invasive way.

3.3. *Comparison of the apexcardiogram and left ventricular pressure curve*

To compare the apexcardiogram with the left ventricular pressure curve, an investigation was made, in which both curves were recorded simultaneously during cardiac catheterisation. A total of 25 patients with different diagnosis were examined. In 18 patients the similarity of both curves was examined by comparing isovolumic contraction and relaxation indices. In 22 patients amplitude ratios obtained from the apexcardiogram were compared with pressure values.

3.3.1. *Methods*

The apexcardiogram was recorded with an APT-16 Hewlett-Packard transducer, which has an "infinite time constant" (see 3.1.). Recording of the left ventricular pressure curve was done with a cathethertip-manometer (type Millar, PC-350, PC-370 or PC-471), with simultaneous recording of its first derivative. In 7 patients pressure was recorded using a fluid-filled cathether and a Statham P23Db pressure transducer. Immediately preceding or following left ventricular pressure recording, aortic pressure was recorded with the same catheter. The upstroke points of the apexcardiogram and the left ventricular pressure curve, which were coincident, were taken as onset of the isovolumic contraction period. The upstroke point of the aortic pressure curve was taken as end of the isovolumic contraction period. The pre-ejection period, *i.e.* the time between the onset of the Q-wave of the ECG and the upstroke of the aortic pressure curve, was measured and plotted in the record of ECG, apexcardiogram and left

ventricular pressure. This is shown in figure 7. Horizontal lines were drawn through both curves at the beginning and at the end of the isovolumic contraction period, and the tangent in the point of inflection was drawn. From the point of intersection of the tangent and the upper horizontal line, a perpendicular was dropped on the lower horizontal line. The time between the points of intersection of the tangent and of the perpendicular with the lower horizontal line is called $T_{C(ACG)}$ (C = contraction). The slope of the tangent is:

(2) $$\frac{dA}{dt}(max) = \frac{A^*}{T_{C(ACG)}}$$

or:

(3) $$\frac{\frac{dA}{dt}(max)}{A^*} = \frac{1}{T_{C(ACG)}}$$

where A = deflection of the apexcardiogram, related to the upstroke point, A^* = the deflection during isovolumic relaxation. The same operation can be carried out on the left ventricular pressure curve (fig. 7):

(4) $$\frac{dp}{dt}(max) = \frac{p^*}{T_{C(LVP)}}$$

or:

(5) $$\frac{\frac{dp}{dt}(max)}{p^*} = \frac{1}{T_{C(LVP)}}$$

The index $1/T_{C(LVP)}$ is similar to other contractility indices obtained from measurements during the isovolumic contraction period. Correlation between $1/T_{C(ACG)}$ and $1/T_{C(LVP)}$ was calculated. From the left ventricular pressure curve and the apexcardiogram relaxation velocity indices were also calculated. The parts of the curves during the isovolumic relaxation period were treated in the same way as described for the isovolumic contraction period. The onset of isovolumic relaxation coincides with the aortic component of the 2nd heart sound. The lowest point of the curves (the O-point, see fig. 5) was taken as the end of isovolumic relaxation.

In 22 patients left ventricular end-diastolic pressure and the

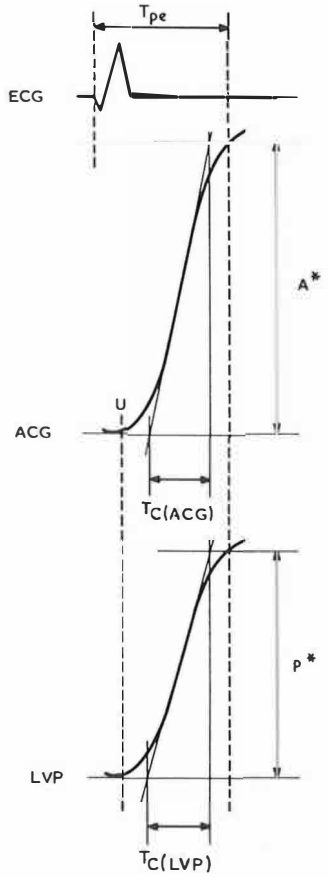


Fig. 7. Schematic drawing of the apexcardiogram (ACG) and the left ventricular pressure curve (LVP) during isovolumic contraction. ECG = electrocardiogram, T_{pe} = pre-ejection period, derived from the ECG and a previously recorded aortic pressure curve, U = upstroke points of the simultaneously recorded apexcardiogram and left ventricular pressure curve, A* = change of deflection of the apexcardiogram during the isovolumic contraction, p* = pressure change during the isovolumic contraction. The construction of the time intervals $T_{C(ACG)}$ and $T_{C(LVP)}$ is shown. The reciprocal of these time intervals is used as index of left ventricular contraction velocity.

pressure rise during atrial contraction were measured. Also the a/H-ratio and the a/D-ratio (ratio of a-wave deflection and diastolic deflection) of the apexcardiogram (fig. 5) were calculated.

3.3.2. *Results*

Table 1 gives the result of the measurements of the indices of

isovolumic contraction and isovolumic relaxation. Figure 8 shows a fair correlation between $1/T_{C(LVP)}$ and $1/T_{C(ACG)}$ ($r = 0.97$). The regression line almost coincides with the line of identity. When patients with aortic stenosis were discarded, a good agreement was also found between $dp/dt(max)$ and $1/T_{C(ACG)}$ ($r = 0.79$, fig. 9). Table 1 and figure 10 give the results of the measurements of $1/T_{R(ACG)}$ and $1/T_{R(LVP)}$ ($r = 0.84$). The relation between left ventricular end-diastolic pressure and a/H-ratio is given in table 2 and figure 11. Only when the minimal diastolic pressure is below 5 mmHg, there appears to be a good agreement between these two quantities ($r = 0.87$).

Table 1. Comparison of the isovolumic contraction and relaxation indices of the left ventricular pressure curve and the apexcardiogram.

				isovolumic contraction			isovolumic relaxation	
patient	sex	age (years)	diagnosis	$1/T_{C(LVP)}$ (s^{-1})	$1/T_{C(ACG)}$ (s^{-1})	$dp/dt(max)$ (mm Hg.s^{-1})	$1/T_{R(LVP)}$ (s^{-1})	$1/T_{R(ACG)}$ (s^{-1})
4	m	20	HOCM	25	26	1400	19	14
6	m	54	AI AS	21	23	1680	16	14
7	m	39	AS	24	21	1350	29	24
8	f	20	MI	28	26	1680	39	30
9	m	36	MI	21	22	1120	13	14
10	m	46	AS AI	21	22	1880	17	16
11	m	55	CA	16	14	840	17	14
12	m	52	CA	18	19	1520	10	10
14	f	36	CCM	17	17	830	19	13
15	m	52	AS	12	13	1480	17	15
16	m	34	AS MI	17	16	1540	12	14
			post-VES:	19	20	2000	—	—
19	f	37	AI MI	19	21	—	14	14
20	f	25	AI	24	25	2080	21	13
21	m	39	AS	26	27	1180	31	19
22	m	31	CCM	14	16	960	—	—
23	m	29	AS	12	13	1200	—	—
24	f	56	AS	17	17	1450	20	10
25	m	33	AS AI	15	15	1610	18	18

AS = aortic stenosis
AI = aortic insufficiency
CA = cardiac aneurysm
CCM = congestive cardiomyopathy
MI = mitral insufficiency
HOCM = hypertrophic obstructive cardiomyopathy
post-VES = post ventricular extrasystolic beats

In tables 1 and 2 the same numbers have been used for the same patients.

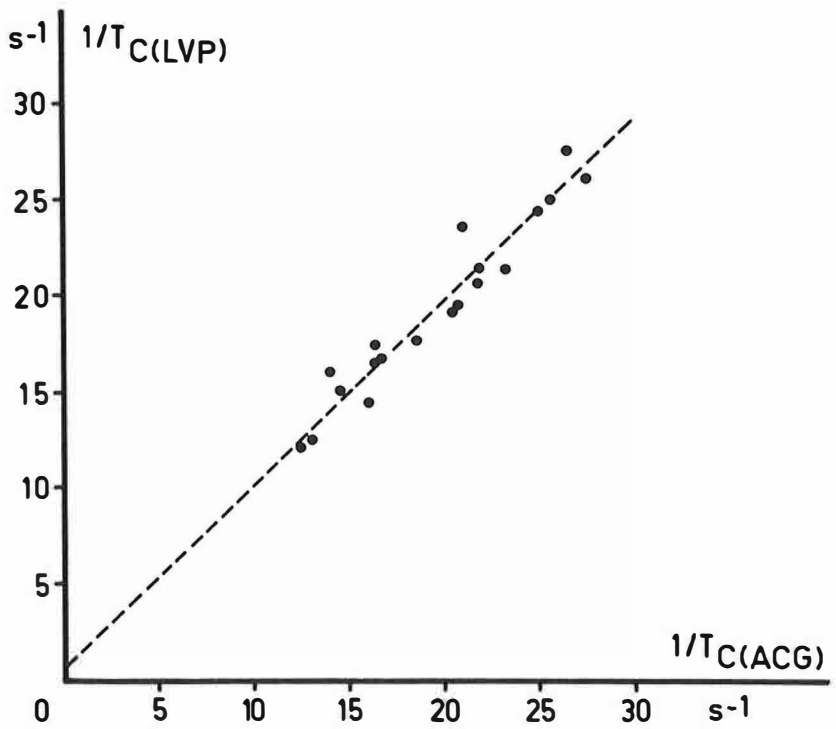


Fig. 8. Relation between the contraction velocity index of the apexcardiogram $1/T_{C(ACG)}$ and of the left ventricular pressure curve $1/T_{C(LVP)}$. Correlation coefficient $r = 0.97$, $n = 19$, $1/T_{C(LVP)} = 0.97 \cdot 1/T_{C(ACG)} + 0.26\ s^{-1}$, SEE (standard error of estimate) $= 1.18\ s^{-1}$.

Figure 12 shows the relation between the a/H-ratio and the pressure rise during atrial contraction ($r = 0.78$). The a/D-ratio appeared not to correlate with any of the other variables.

3.3.3. *Discussion*

The comparison of the indices of isovolumic contraction and relaxation velocity of the apexcardiogram and the left ventricular pressure curve show close agreement. These indices resemble preload- and afterload corrected contractility indices of isovolumic contraction as described by Mason *et al.* (97) and as reviewed by Yang *et al.* (199). The index $1/T_{C(ACG)}$ may therefore be used as a non-invasive contractility index, which may be compared to other indices,

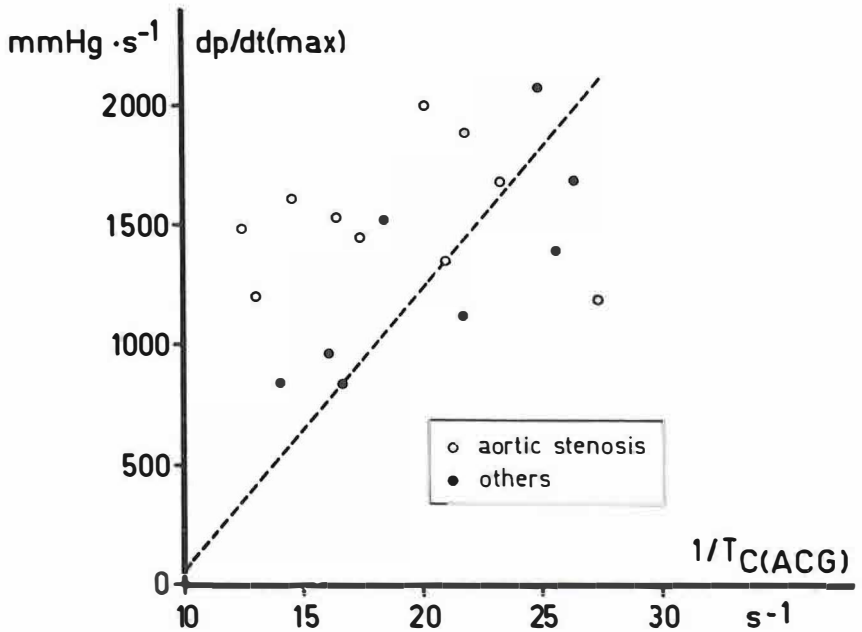


Fig. 9. Relation between the contraction velocity index $1/T_{C(ACG)}$ and the $dp/dt(max)$. Patients without aortic stenosis: $r = 0.79$, $n = 9$, $dp/dt(max) = 73.2 \cdot 1/T_{C(ACG)} - 195$ mmHg s^{-1}.

e.g. $\frac{dp}{dt}/p\ (max)$ (101).

In the same way $1/T_{R(ACG)}$ may be used as an index of relaxation velocity. There is less agreement between the relaxation velocity indices obtained from the apexcardiogram and the left ventricular pressure curve than between the contraction velocity indices. This may be explained by the fact that it was not possible to determine the end of the isovolumic relaxation period (the moment of mitral valve opening) exactly, because no simultaneous records of pressure and the echocardiogram of the mitral valve have been made. The moment of minimal diastolic pressure was therefore taken as the end of isovolumic relaxation. However, this moment does not coincide with the real end of the isovolumic relaxation period; from echocardiographic recordings it can be shown that this point occurs about 20 - 60

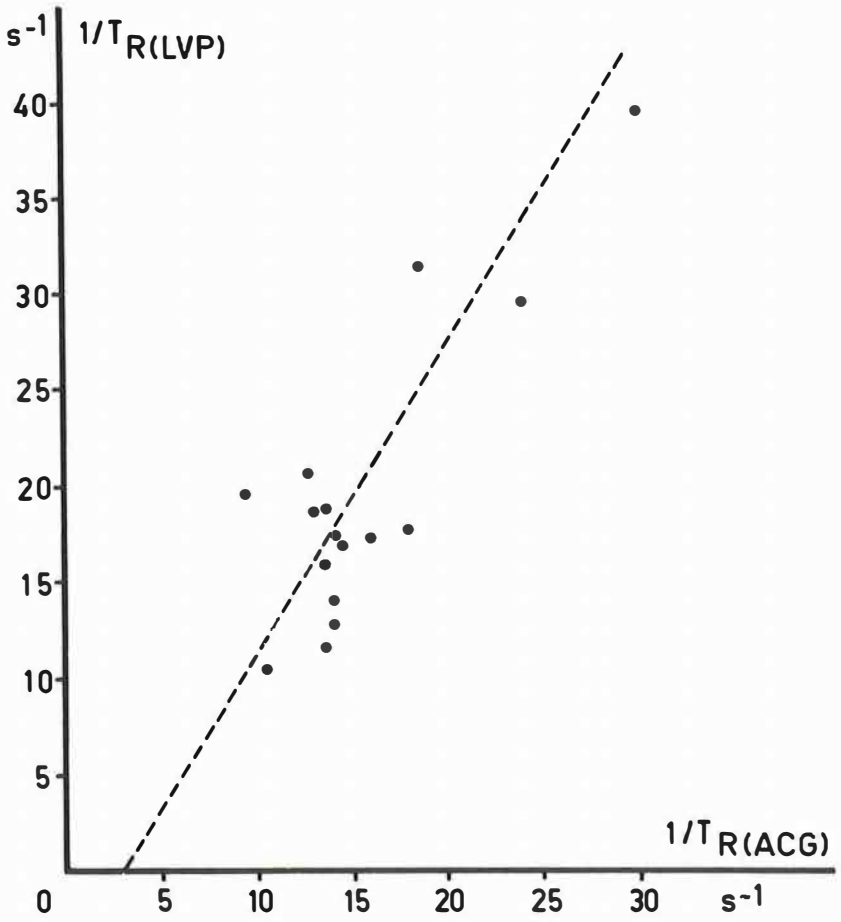


Fig. 10. Relation between the relaxation velocity index of the apexcardiogram $1/T_{R(ACG)}$ and the left ventricular pressure curve $1/T_{R(LVP)}$. $r = 0.84$, $n = 16$, $1/T_{R(LVP)} = 1.26 \cdot 1/T_{R(ACG)} - 0.32\ s^{-1}$, SEE = 4.2 s^{-1}.

ms later (see *e.g.* fig. 16). Consequently the duration of the isovolumic relaxation period, which is on the average about 60 ms, may be overestimated considerably. The relaxation velocity index described here resembles the ratio of maximal rate of decline of left ventricular pressure and end-systolic pressure, which, according to Mathey (100), is a sensitive index for a relaxation disturbance.

Concerning the diastolic indices, the findings are the same as described in the literature (36, 133, 177, 178), *viz.* a fair agreement

Table 2. Comparison of diastolic measurements of the left ventricular pressure curve and the apexcardiogram.

patient	sex	age (years)	diagnosis	p_{lvbd} (mm Hg)	p_{lved} (mm Hg)	Δp_{as} (mm Hg)	a/H (%)	a/D (%)
1	m	34	AS	0	24	—	18.9	55.3
2	f	32	MS AI	0	6	5	7.9	53.4
3	m	42	AS AI	6	26	11	11.4	33.8
4	m	20	HOCM	3	23	9	21.5	50.6
5	m	36	AS AI	3	11	3	4.5	44.6
6	m	54	AI AS	6	15	9	12.2	67.4
7	m	39	AS	9	20	—	6.1	43.9
8	f	20	MI	1	7	0	5.7	28.1
9	m	36	MI	—2	7	5	8.2	30.7
10	m	46	AS AI	7	17	14	12.1	53.8
11	m	55	CA	13	26	10	20.6	68.0
12	m	52	CA	12	20	7	8.7	54.7
13	m	32	PC	2	13	6	6.5	36.1
		during	R.A.P.	1	1	0	0	0
15	m	52	AS	16	29	19	16.8	58.9
17	m	55	Ch.R.	2	9	5	9.5	—
18	f	30	MS AI	1	16	4	8	47.6
20	f	39	AI	7	15	7	18.6	92.5
21	m	39	AS	11	29	12	16	48.9
22	m	31	CCM	19	32	10	10.6	38.8
23	m	29	AS	14	26	9	7.6	31.1
24	f	56	AS	6	31	20	32.7	78.6
25	m	33	AS AI	2	12	5	6.6	36.5

AS = aortic stenosis
AI = aortic insufficiency
CA = cardiac aneurysm
Ch.R. = chordal rupture
CCM = congestive cardiomyopathy
MI = mitral insufficiency
MS = mitral stenosis
PC = constrictive pericarditis
HOCM = hypertrophic obstructive cardiomyopathy
R.A.P. = right atrial pacing 120/min.
p_{lvbd} = minimum diastolic pressure
p_{lved} = enddiastolic pressure
Δp_{as} = pressure rise during atrial systole
a/H = ratio of a-wave and total wave of the apexcardiogram
a/D = ratio of a-wave and diastolic wave

In tables 1 and 2 the same numbers have been used for the same patients.

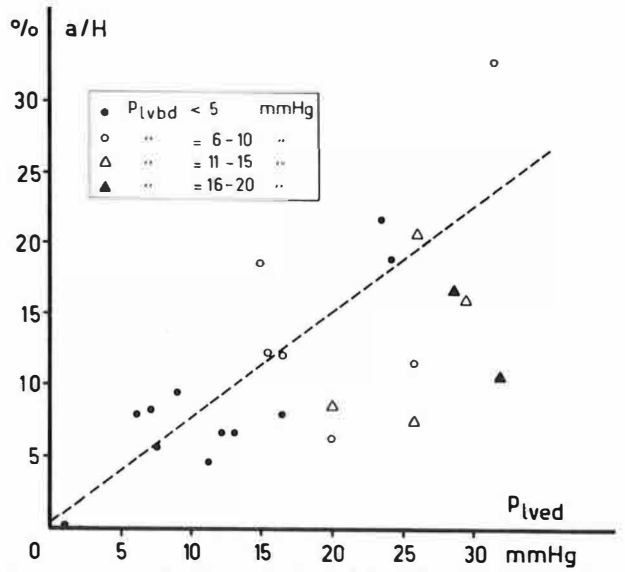


Fig. 11. Relation between the left ventricular end-diastolic pressure p_{lved} and the a/H-ratio of the apexcardiogram. When minimal diastolic pressure $p_{lvbd} < 5$ mmHg, $r = 0.87$ (n = 11, a/H-ratio = $0.75 \cdot p_{lved} + 0.1$, $P < 0.0005$. When $p_{lvbd} > 5$ mmHg, $r = 0.33$ (n = 12, N.S.), all patients: $r = 0.66$ ($n = 23$).

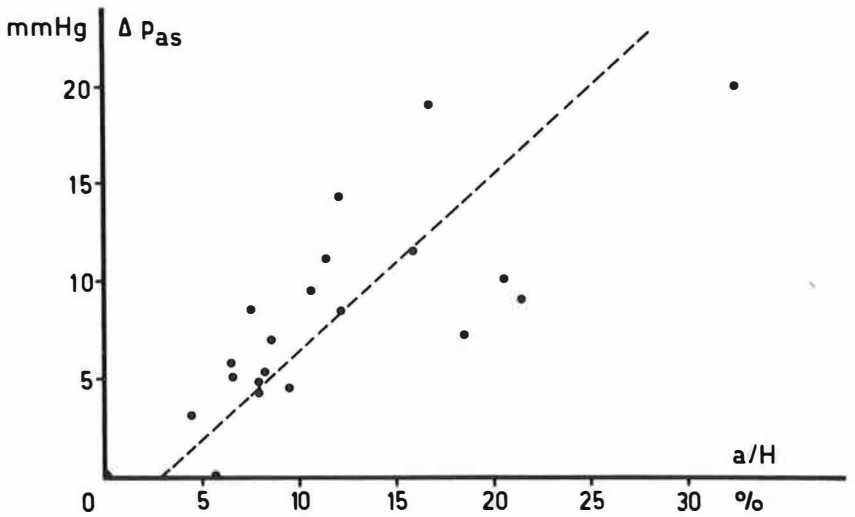


Fig. 12. Relation between the pressure rise during atrial contraction (Δp_{as}) and the a/H-ratio of the apexcardiogram in patients with various cardiac disorders as listed in table 2. $r = 0.78$, $n = 21$, $\Delta p_{as} = 0.92 \cdot a/H$-ratio — 2.7, SEE = 5 mmHg, $P < 0.00005$.

between the a/H-ratio and left ventricular pressure rise during atrial contraction. In patients with hypertrophic cardiomyopathy the a/H-ratio, expressed in percentages, and end-diastolic pressure, expressed in mmHg, is almost the same (van der Wall, 178), (see also table 2, patient 4). In other patients there is no direct relation between the a/H-ratio and the end-diastolic pressure (table 2, fig. 11).

Chapter 4

PATIENTS AND METHODS

4.1. *Patients*

In the case of 17 patients out of the 32 originally selected for this study, comparative measurements could be made. All patients had acute transmural myocardial infarction. They had not had an infarction before and showed the characteristic signs of an acute myocardial infarction, *i.e.* new q-waves in the electrocardiogram, changes in the QRS-loop of the vectorcardiogram, and a typical rise of enzyme levels. The patients had sinus rhythm at the time of

Table 3. Data of the examined infarct patients.

patient	sex	age (years)	infarct location	medication	further diagnosis
1	m	55	ant.	Diu,Mex,Thi	CARA, D.M.
2	m	62	inf.	Mpr	
3	m	51	inf.	Apr,I D	
4	m	49	inf.	Apr,I D	
5	m	51	inf.	Apr	Hyp
6	m	68	ant.sept.	Apr	
7	m	74	inf	Dig,Ins	D.M.
8	m	74	ant.sept.	Dis	
9	m	71	ant.		
10	m	57	inf.lat.		
11	m	66	ant.	Dis,Dig	
12	m	75	ant.	Ver	
13	m	66	ant.lat.	Dis,Dig,Diu	CVA
14	m	59	ant.sept.,-lat.	Dig	
15	m	79	ant.sept.		
16	m	46	post.lat.	Apr	
17	m	40	inf.	Apr	

Medication:
Diu = diuretic
Mex = mexiletine
Thi = thiazinamium
Mpr = metoprolol
Apr = alprenolol
ID = isosorbide dinitrate
Dig = digoxine
Ins = insuline
Dis = disopyramide
Ver = verapamil

further diagnoses:
CARA = chronic non-specific lung disease
D.M. = diabetes mellitus
Hyp = hypertension
CVA = cerebrovascular disease

examination; they had no left ventricular conduction disorders like left bundle branch block or left anterior hemiblock, and no valvular disease. The data of the patients are summarized in table 3.

Another group of 18 patients was selected to serve as a control group. They fulfilled four critieria: they had no clinical signs of cardiovascular disease, they had no abnormalities on the echo- and phonocardiogram, they did not take cardiac medication, such as digitalis, antiarrhytmics or beta-blocking agents, and they did not have malignant disease. These patients are referred to as graphically normal patients. Their data are enumerated in table 4. A group of 10 healthy volunteers was also examined. These were hospital staff members, 23 to 59 years old, who had a normal electrocardiogram, no cardiac complaints and no cardiac abnormalities at physical examination. Finally, 10 infarct patients were examined twice by two independent observers to obtain data about the reproducibility of the measurements.

4.2. *Methods*

Thirteen patients were examined three times: 1. on the 5th to 7th day after the infarction, immediately after discharge from the

Table 4. Data of graphically normal patients.

patient	sex	age (years)	reason for the investigation
1	f	24	innocent murmur
2	f	27	innocent murmur
3	f	31	slight mitral valve prolaps without click or murmur
4	f	20	innocent murmur
5	m	51	atypical angina; coronary angiography: normal
6	f	49	innocent murmur
7	m	51	orthostatic syndrome
8	f	46	innocent murmur
9	f	56	innocent murmur
10	f	70	pericardial cyst
11	m	40	insign. mitral valve prolaps
12	m	49	innocent murmur
13	m	28	innocent murmur
14	f	55	innocent murmur
15	m	47	family investigation for cardiomyopathy
16	m	34	family investigation for cardiomyopathy
17	f	44	innocent murmur
18	m	14	innocent murmur

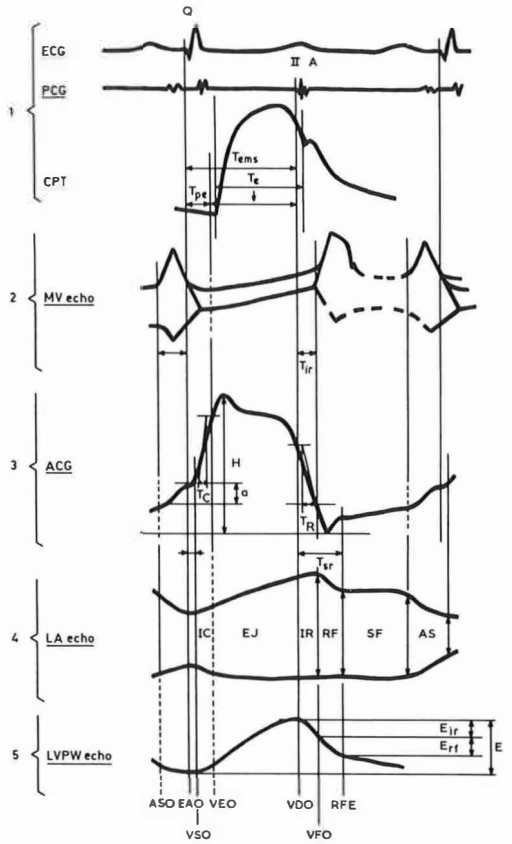


Fig. 13. Schematic representation of the recording of electrocardiogram (ECG), phonocardiogram (PCG), carotid pulse tracing (CPT), echocardiogram of the mitral valve (MV-echo), apexcardiogram (ACG), and echocardiograms of the left atrium (LA-echo) and left ventricular posterior wall (LVPW-echo). Q = initial deflection of the q-wave of the ECG (onset of electrical activation, EAO); IIA = moment of the first high frequency vibrations of the aortic component of the second heart sound (onset of ventricular diastole, VDO); T_{ems} = electromechanical systole (time from EAO to VDO); T_e = ejection time (time from CPT upstroke to incisura); T_{pe} = pre-ejection time (PEP, T_{ems} minus T_e); VEO = onset of ventricular ejection; ASO and VFO are read off the MV echo: ASO = onset of atrial systole, VFO = onset of ventricular filling; T_{ir} = isovolumic relaxation time (time from VDO to VFO); H = total deflection of the apexcardiogram; a = a-wave amplitude; VSO = onset of ventricular systole (corresponds to upstroke point of the ACG); RFE = end of rapid filling (corresponds to rapid filling wave of ACG, see fig. 5); T_C and T_R: see fig. 7; T_{sr} = time of spontaneous relaxation; IC = isovlumic contraction, EJ = ejection, IR = isovolumic relaxation, RF = rapid filling, SF = slow filling, AS = atrial systole; E = total excursion of the LVPW echo, E_{ir} = excursion during isovolumic relaxation, E_{rf} excursion during rapid filling.
Recordings 1-5 were made successively within 0.5 h. In this period, heart rate did not show a change of more than 10 min^{-1}.

coronary care unit, 2. a week later on the 12th to 14th day and 3. about two months after the infarction. In some cases the study was not complete as a result of the clinical condition of the patient; in one case because the patient died before the third examination could take place. In the case of 4 patients the examination was only done on the 5th to 7th day.

The examination consisted of successive recording of the carotid pulse tracing, the echocardiogram of the mitral valve, the apexcardiogram and the echocardiogram of the left atrium and the left ventricular posterior wall. All these recordings were made together with a standard lead electrocardiogram and a phonocardiogram (fig. 13). These 5 registrations were made within half an hour. It appeared to be impracticable to make the registrations simultaneously. During the examination, however, heart rate did not show a change of more than 10 beats per minute. Therefore, the variation in the length of the time intervals due to variation of heart rate was negligible. A change in heart rate of 10 beats per minute, for instance, changes the pre-ejection period with 4 ms, according to the Weissler equation (182, 184). This is within the error of measurement. Consequently, a time interval measured in one record could be transported to another.

The standard lead electrocardiogram with the greatest deflection (lead II or III) was recorded; in the same patient the same lead was used in all three examinations. The phonocardiogram was recorded in the second left intercostal space near the sternum, using a suction cup microphone and an amplifier with an input impedance of 1 M Ω and 15 dB attenuation at 100 Hz as compared to 600 Hz. The apexcardiogram and carotid pulse tracing were recorded using a funnel shaped pickup connected via an air filled PVC-tubing with a Cambridge transducer, which contained a piezoelectric crystal. The transducer-amplifier assembly had a time constant of 0.5 s (see chapter 3.1.). This is shorter than the recommended minimum value of 2.5 s (73). However, for the indices used in this study, there appeared to be no significant differences in the results of the measurements, as compared with the results obtained when a Marey capsule was connected to a Statham P23Db pressure transducer, which had an infinite time constant. The apexcardiogram was recorded from the most lateral impulse, the patient lying in left

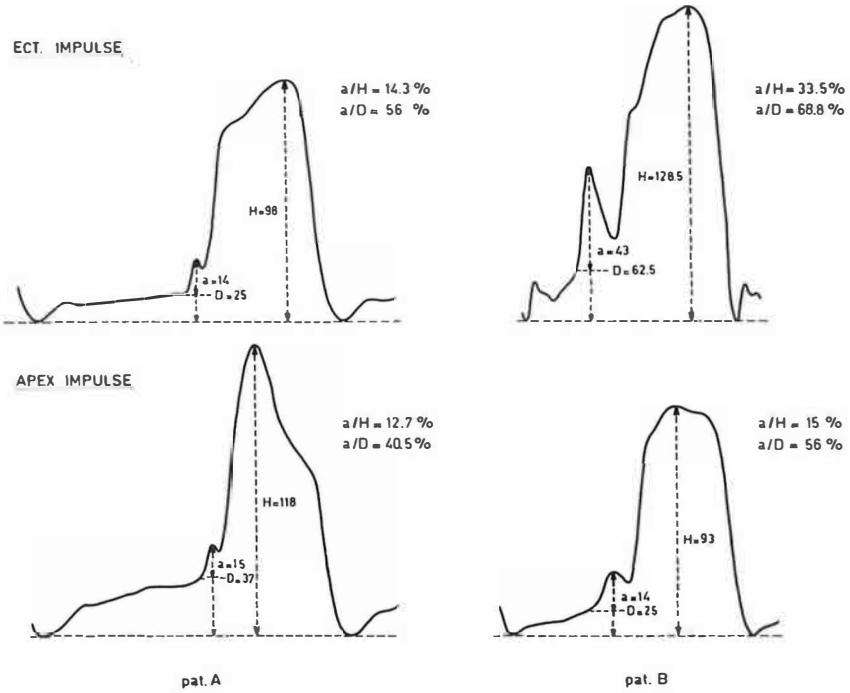


Fig. 14. Waveforms of the true apex impulse and the medially situated ectopic infarct impulse, obtained in two patients with an anterior infarction. The ectopic impulse has a rising systolic plateau and a higher a/H-ratio and a/D-ratio as the true apex impulse, registered in the same patient.

lateral position. Patients with anterior wall infarction sometimes appeared to have two quite different impulse waveforms (fig. 14). The impulse recorded medially seems to be the impulse of the infarct region itself. It has a rising "hypertrophic" plateau and a higher a/H-ratio. Care was taken to avoid registration of this ectopic impulse. All curves were recorded in the endexpiratory phase. To ensure optimal registration the patients were lying in left lateral position, with the same posture during all examinations. The left arm was positioned next to the head, the right arm along the body. The head of the patient was positioned a little higher than the body, the back was supported by a pillow. This way the patients could lie comfortably, and muscle vibrations which could disturb the registration were avoided as much as possible. The echocardiograms were recorded with the examiner sitting at the left side of the patient as described by Feigenbaum *et al.* (20, 41). A 2.25 MHz transducer was used, focussed

at 7.5 cm, and connected to an Ekoline echocardiograph. The echocardiogram of the mitral valve was recorded in the usual way with the transducer perpendicular on the chest wall in the 4th left intercostal space parasternally. Whenever a better recording could be obtained with the transducer in a perpendicular position elsewhere on the chest wall, it was made there. Care was taken that the same recording was made in the same way each time the patient was examined. The pulse curves were recorded with the examiner and the patient in the same position. When recording the left ventricular echocardiogram, special care was taken to obtain a good picture of a normally moving part of the posterior wall. The left atrium was recorded, with the transducer tilted to a position upwards and to the right of the mitral valve. Care was taken to obtain a good recording of the left atrial anterior and posterior wall, in such a way that these structures were represented as uninterrupted lines in the echocardiogram. Depending on the ease in obtaining good recordings, the examination lasted 10 to 30 minutes.

The amplifiers of the different signals (electrocardiogram, phonocardiogram, pulse curves, and echocardiogram) were connected to a Cambridge fiberoptic recorder with photographic registration at a paper speed of 100 mm/s.

4.3. *Measurements and calculations*

4.3.1. *Carotid pulse tracing*

From the carotid pulse tracing (fig. 15), left ventricular ejection time (T_e), electromechanical systole (T_{ems}) and pre-ejection time (T_{pe}) were measured according to Weissler (182, 184). The ratio of pre-ejection time and ejection time (T_{pe}/T_e) was calculated. The electromechanical systole was corrected for heart rate (T_{ems}*).

4.3.2. *Apexcardiogram*

From the apexcardiogram (fig. 16), the following indices were calculated: a/H-ratio (the ratio of the amplitude of the a-wave to total amplitude), the index of contraction velocity $1/Tc$, and the index of relaxation velocity $1/T_R$. The calculation of these indices has already been described in chapter 3 and is illustrated in fig. 7. The isovolumic contraction period is defined by the upstroke of the apexcardiogram

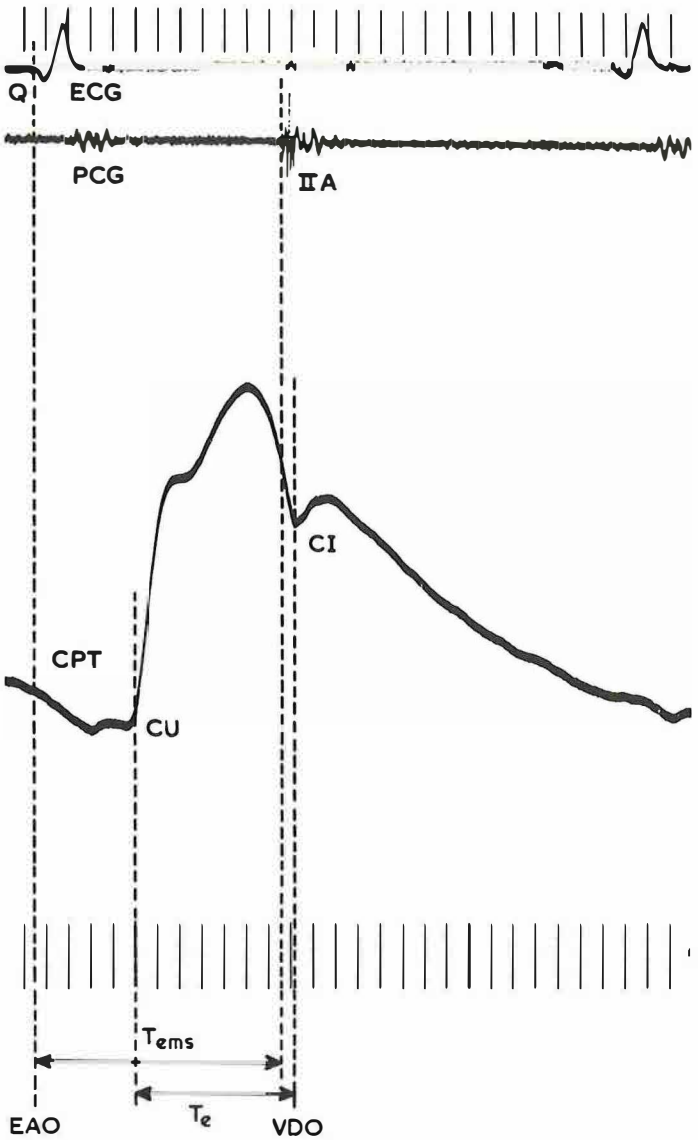


Fig. 15. Recording of the electrocardiogram (ECG), phonocardiogram (PCG), and carotid pulse tracing (CPT). CU = upstroke, CI = incisura. The Q of the ECG marks the electrical activation onset (EAO), the aortic component of the second heart sound (IIA) the ventricular diastole onset (VDO). Ejection time (Te) and electromechanical systole ($Tems$) are measured as indicated. Time lines 40 ms.

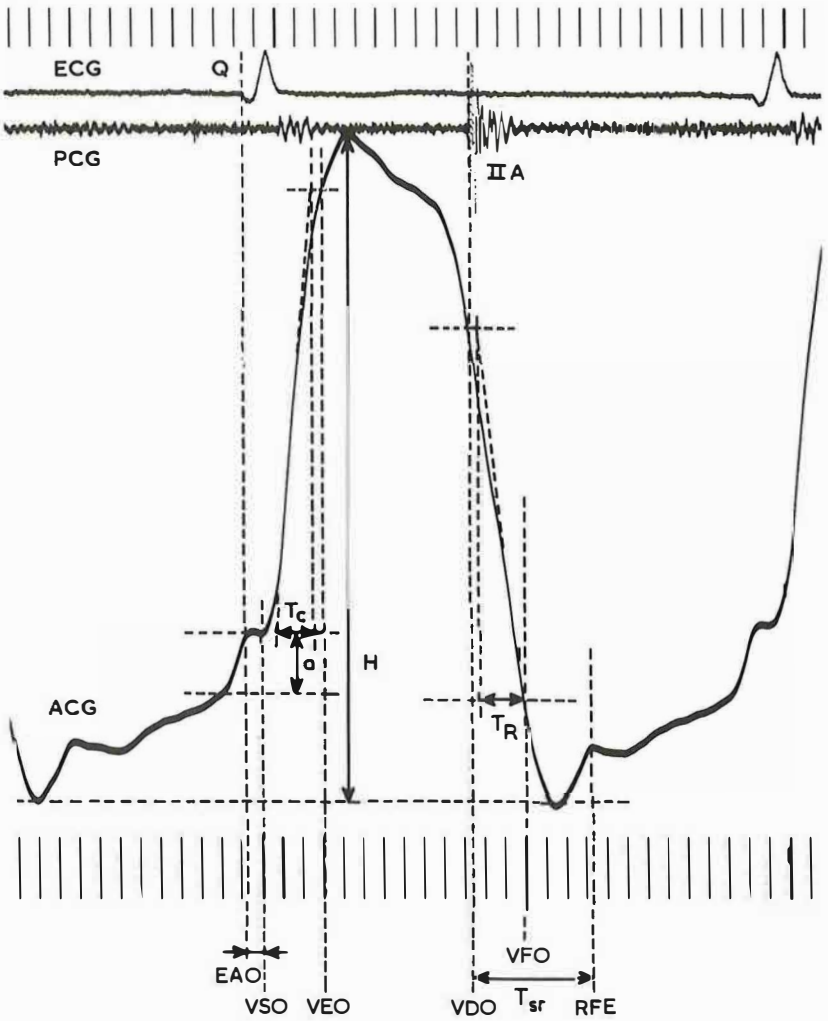


Fig. 16. Recording of the electrocardiogram (ECG), phonocardiogram (PCG), apexcardiogram (ACG). *Tc* = time interval related to isovolumic contraction. *TR* = time interval related to isovolumic relaxation; for construction see chapter 3 and fig. 7. *a* = amplitude of the a-wave, *H* = total amplitude, EAO = electrical activation onset, VSO = ventricular systole onset, which is defined by the upstroke point. VDO = ventricular diastole onset, defined by IIA, VFO = ventricular filling onset, RFE = rapid filling end, which is defined by the peak of the rapid filling wave. Spontaneous relaxation time is the time from VDO to RFE. Time lines 40 ms.

(VSO, fig. 13) and the end of the pre-ejection period (VEO). The isovolumic relaxation period begins at the second heart sound (IIA, VDO) and ends with the mitral valve opening (VFO), read off the mitral valve echo. It should be noted that for the measurements described in chapter 3, the lowest point of the apexcardiogram was taken as the end of the isovolumic relaxation period. The time interval from the Q-wave of the ECG to the upstroke of the ACG (EAO - VSO: also called electromechanical delay) was measured. This time interval was used for measurements from the left atrial echocardiogram. This was also the case with the spontaneous relaxation time, beginning at IIA (or VDO) and ending at the peak of the rapid filling wave (or RFE). In some patients T_c could not be measured because of a notch in the apexcardiogram during isovolumic contraction, caused by mitral valve closure.

4.3.3. *Echocardiogram of the mitral valve*

The echocardiogram of the mitral valve (fig. 17) has been made to determine the onset of flow through the mitral valve at the beginning of rapid filling and again at the beginning of atrial systole. The time interval VDO-VFO (from the aortic component of the second heart sound to the onset of the early diastolic rapid anterior motion of the anterior mitral valve leaflet) was measured. This is the isovolumic relaxation time (T_{ir}). Furthermore, the time interval ASO - EAO (onset of the late diastolic rapid anterior motion of the anterior mitral valve leaflet to the Q-wave of the ECG) was measured. The sum of the time ASO - EAO and the time EAO - VSO, obtained from the apexcardiogram, is the atrial contraction time (see left atrial echocardiogram).

4.3.4. *Echocardiogram of the left atrium*

The echocardiogram of the left atrium (figs. 18 and 19) was used to determine the filling pattern of the left ventricle in terms of atrial diameter changes (2, 157, 158). The left atrial diameter was measured at the moments VFO, RFE, ASO and VSO (fig. 13). These moments were determined from the apexcardiogram and the echocardiogram of the mitral valve (4.3.2., 4.3.3.). They correspond with changes of motion of the left atrial anterior wall (fig. 18 in a normal person and

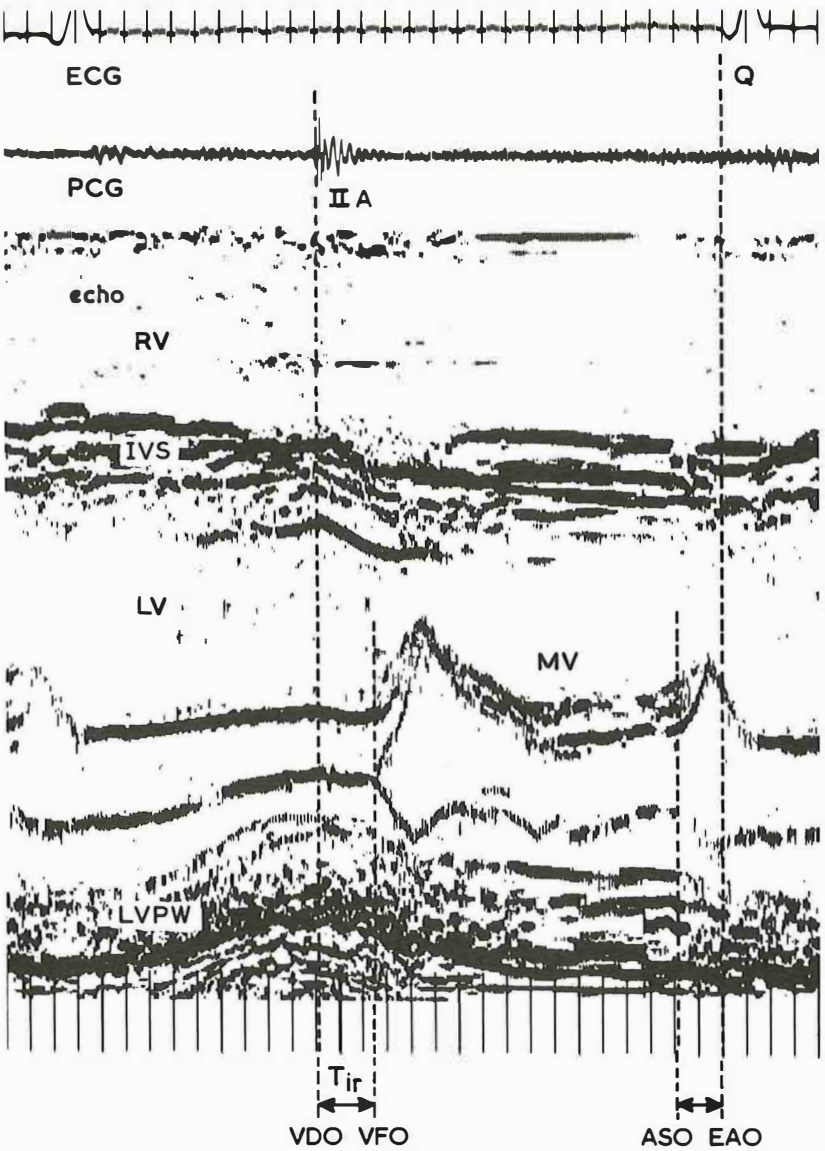


Fig. 17. Recording of electrocardiogram (ECG), phonocardiogram (PCG), and echocardiogram of the mitral valve (echo). RV = right ventricle, IVS = interventricular septum, LV = left ventricle, MV = mitral valve, VDO = ventricular diastole onset, VFO = ventricular filling onset, ASO = atrial systole onset, EAO = electrical activation onset. Isovolumic relaxation time (T_{ir}) is the time from VDO to VFO. Time lines 40 ms.

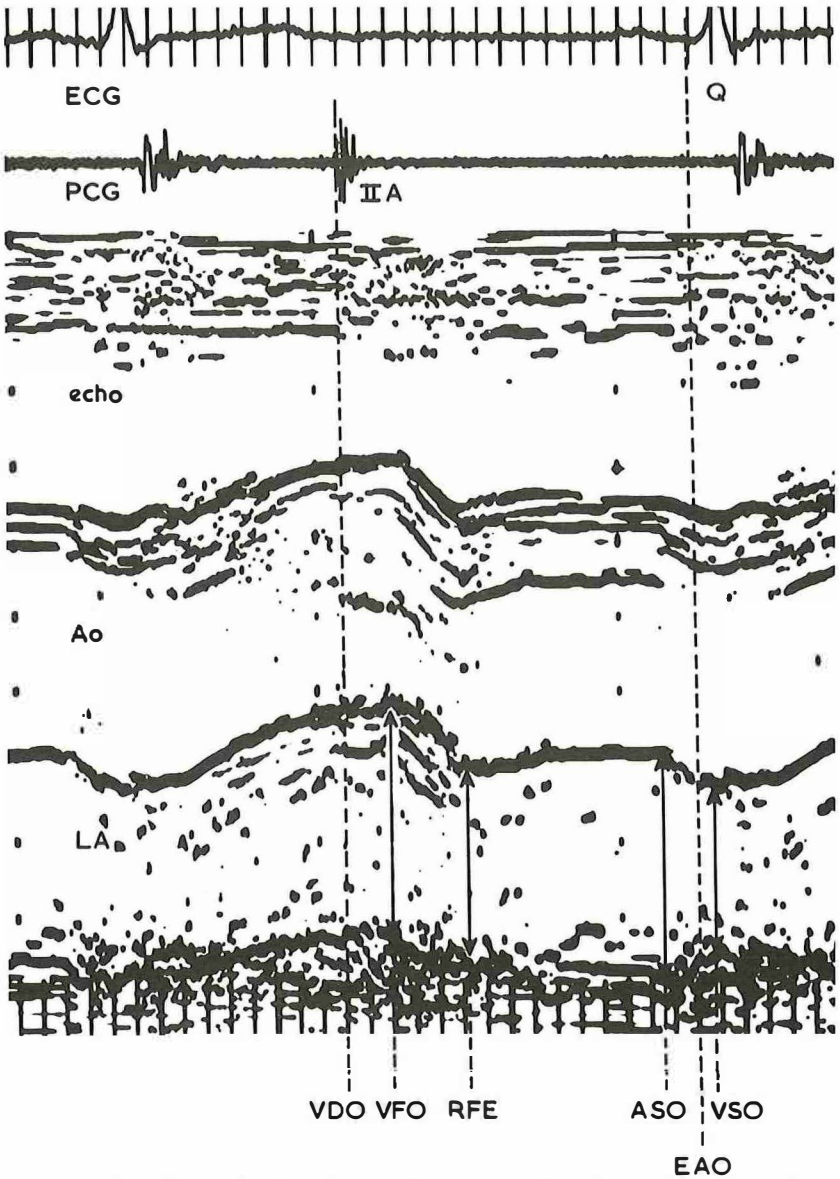


Fig. 18. Recording of the electrocardiogram (ECG), phonocardiogram (PCG), echocardiogram of the left atrium (echo) in a normal person. Ao = aorta, LA = left atrium, VDO = ventricular diastole onset, VFO = ventricular filling onset, RFE = rapid filling end, ASO = atrial systole onset, EAO = electrical activation onset, VSO = ventricular systole onset. Left atrial dimension is measured at the moments VFO, RFE, ASO and VSO. These moments are derived from the mitral valve echocardiogram and the apexcardiogram. Time lines 40 ms.

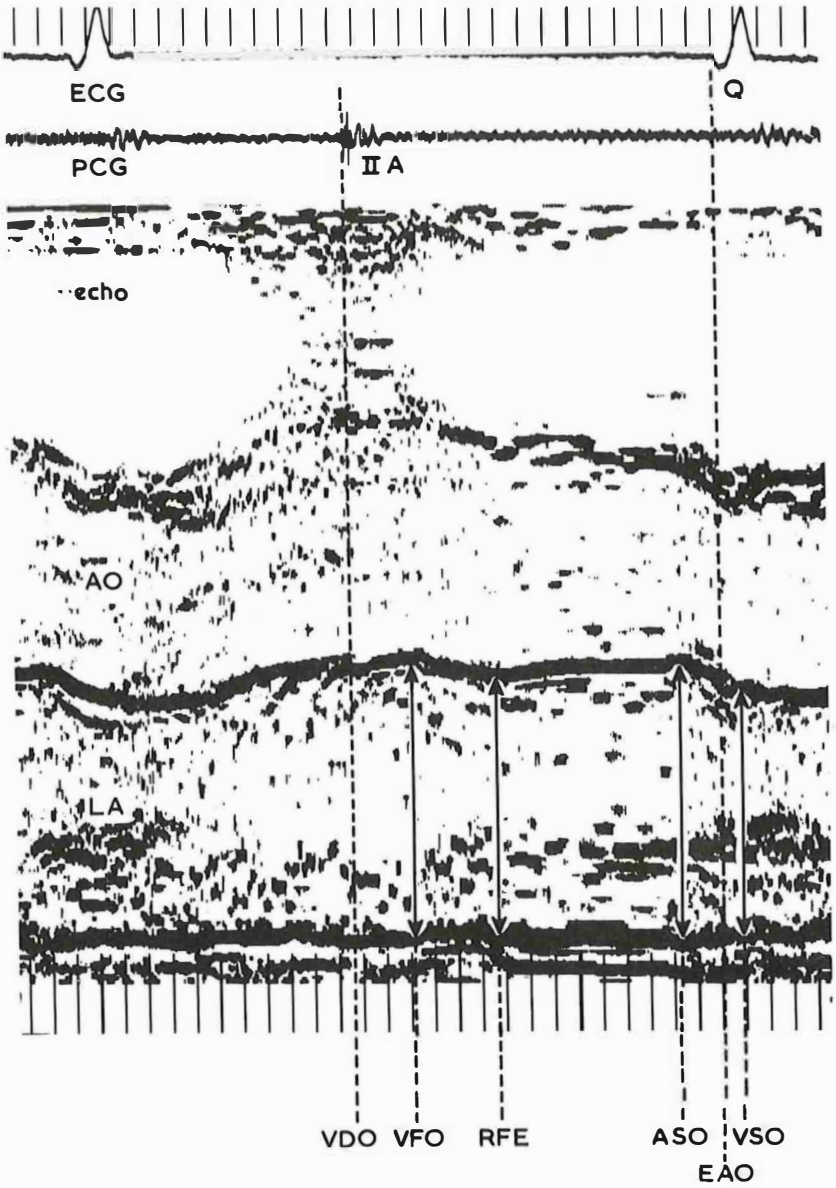


Fig. 19. Recording of the left atrial echocardiogram in an infarct patient. Abbreviations as in fig. 18. The isovolumic relaxation period is longer and the dimension change of the left atrium during the rapid filling period is smaller as compared to normal (fig. 18). In this case the posterior left atrial wall does not move at all. Time lines 40 ms.

fig. 19 in an infarct patient). The left atrial diameter change during rapid filling (A_{rf}) and during atrial systole (A_{as}) was determined.

The diastolic ventricular compliance or "compliance-ratio" was calculated as the ratio of A_{as} and the a/H-ratio of the apexcardiogram. The former is related with volume change, the latter with pressure change during atrial systole (chapter 3, fig. 12).

4.3.5. *Echocardiogram of the left ventricle*

From the echocardiogram of the left ventricle (fig. 20 and 21), the ratio of the excursion of the posterior wall echo during isovolumic relaxation and its total excursion was calculated: IR-ratio = E_{ir}/E (chapter 2, fig. 2). Also, the ratio of the excursion of the posterior wall echo during rapid filling and its total excursion was calculated (RF-ratio = E_{rf}/E, index of left ventricular volume change during rapid filling). The ratio of the excursion during spontaneous relaxation (isovolumic relaxation plus rapid filling) and total excursion is thus the sum of the IR-ratio and the RF-ratio (SR-ratio = E_{sr}/E). The velocity index of the posterior wall during spontaneous relaxation (SR-ratio/T_{sr}) was also calculated. Where the SR-ratio has been expressed as a fraction and T_{sr} has been expressed in seconds, SR-ratio has been expressed in s^{-1}.

4.4. *Statistical methods*

For all measurements, when possible, the mean value of five successive beats was taken. Calculations with regard to correlations, and calculations of significance of differences, were performed with usual methods and formulas; the Student-t test was used for paired data and the analysis of variancé for multiple data. Calculations were performed with a Texas-Instruments TI-58 pocket calculator with statistical module. The formulas have been derived from Geigy's Wissenschaftlichte Tabelle (48).

To test the reproducibility of the measurements of the IR-ratio, $1/Tc$, and $1/T_R$, 10 patients were examined twice by two independent observers. The registrations were also processed by these two observers. Three correlations were calculated: 1. between the results of the measurements done by the two observers from the same registration (measurement variability); 2. between the results of the measurements done by the same observer from the two registrations

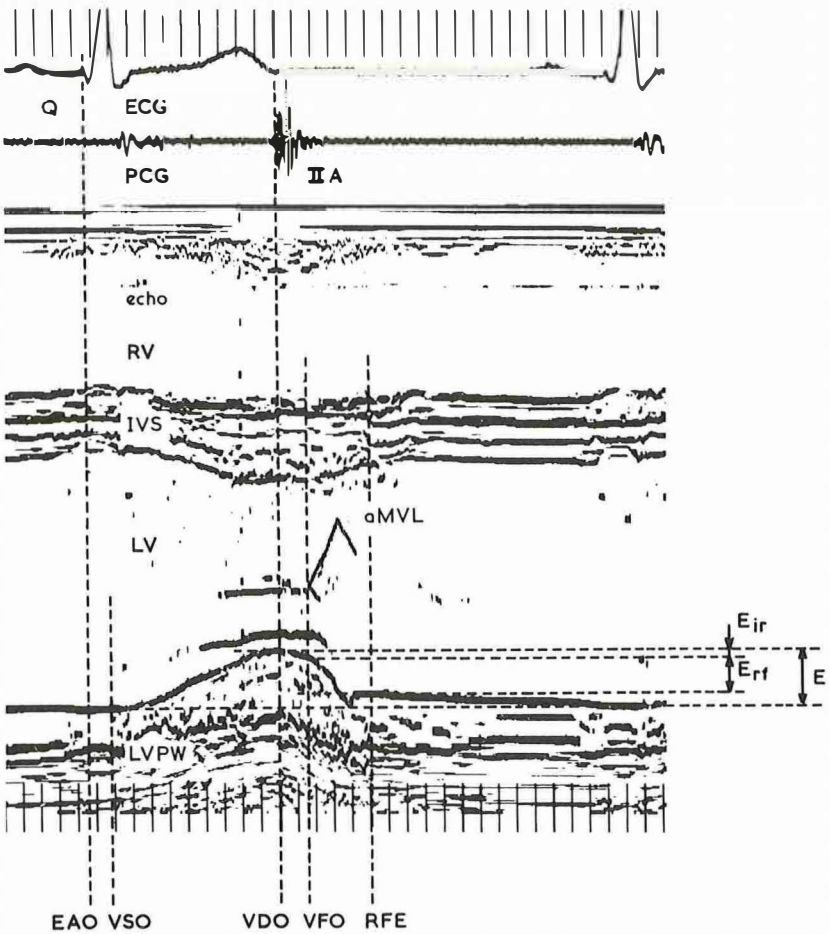


Fig. 20. Recording of the electrocardiogram (ECG), phonocardiogram (PCG), left ventricular posterior wall echocardiogram (echo) in a normal person. RV = right ventricle, IVS = interventricular septum, LV = left ventricle, LVPW = left ventricular posterior wall, aMVL = anterior mitral valve leaflet, EAO = electrical activation onset, VSO = ventricular systole onset, VDO = ventricular diastole onset, VFO = ventricular filling onset, RFE = rapid filling end, E_{ir} = excursion during isovolumic relaxation, E_{rf} = excursion during rapid filling, E = total excursion of the left ventricular posterior wall. Time lines 40 ms.

obtained in each patient (recording variability); 3. between the results of the measurements by each observer from his own registration (interobserver variability). The measurements and calculations were performed without either observer knowing, which

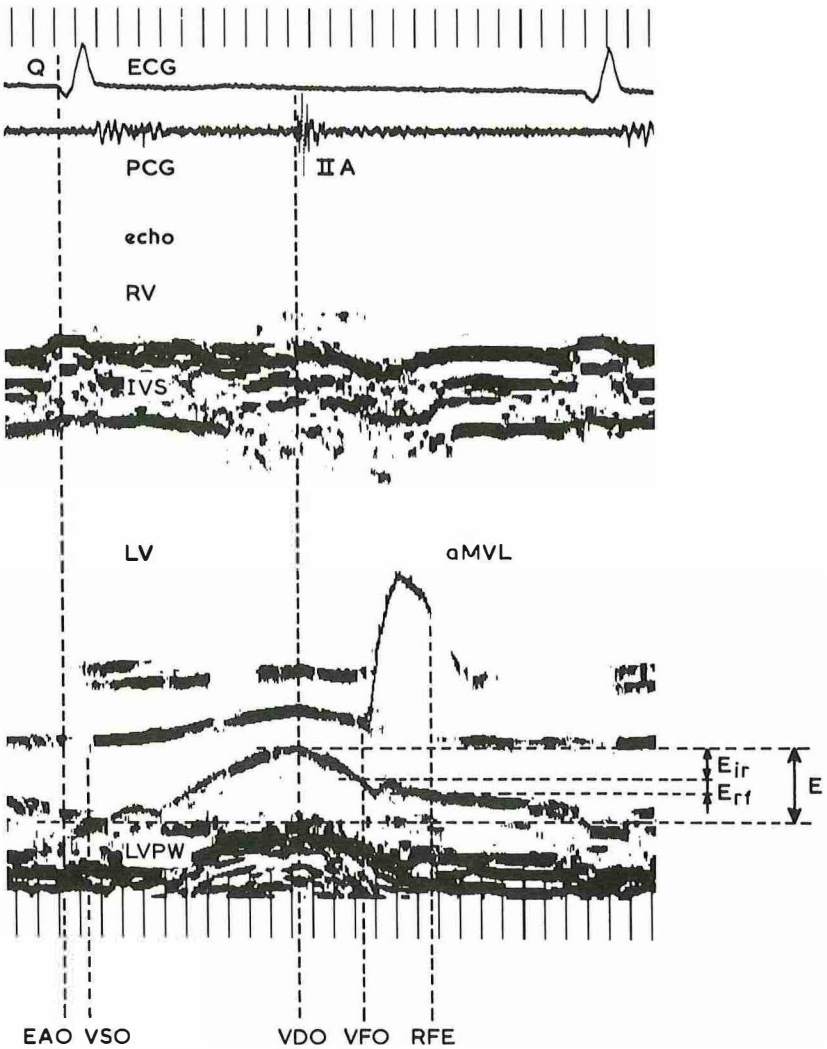


Fig. 21. Recording of the left ventricular posterior wall in an infarct patient. Abbreviations as in fig. 20. As compared to normal (fig. 20), the isovolumic period is longer, the excursion during this period is larger and the excursion during rapid filling is smaller. Time lines 40 ms.

patient the recording belonged to and by which observer the recording was made.

4.5. *Determination of enzymatic infarct size*

Infarct size was estimated by means of daily determinations of the serum concentrations of lactodehydrogenase and the percentage of the first and second fraction of it. The maximum value of the serum level of the first two fractions of lactodehydrogenase ($LDH_{1+2}max$) was taken as a measure of enzymatic infarct size. The normal value of LDH_{1+2} is 154 ± 34 U.

Chapter 5

RESULTS

5.1. *Reproducibility of the measurements*

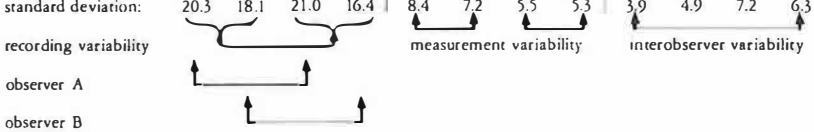
The results of the reproducibility test are presented in table 5. The two observers A and B performed measurements of the IR-ratio, $1/Tc$, and $1/T_R$ on all recordings made by the same two observers. In this way from every patient 4 values were obtained for all 3 indices. In the upper part of the table the results of these measurements are shown. The results of the reproducibility calculations for the above mentioned indices are shown in the lower part of the table. Firstly the correlations are shown between the results of the two recordings, made from the same patients (recording variability), 1. according to observer A, 2. according to observer B and 3. according to the average values obtained by the two observers. Secondly the correlations are presented between the measurements by observer A and by observer B on the same recordings (measurement variability). Finally the correlations are given between the results of the measurements of observer A on his own recordings and the results of observer B on his recordings from the same patients (interobserver variability). Also the standard errors of estimate are given. Regarding the IR-ratio the correlations are rather good. With respect to $1/Tc$ and even more to $1/T_R$ there is a striking difference in the reproducibility of the measurements made by observer A as compared to those made by observer B. The measurements by observer B are much less reproducible than those of observer A, who made all the other measurements of the investigation, described in this thesis. There were no statistically significant differences between the mean values obtained in the same patients (IR-ratio: $P < 0.1$, $1/Tc$: $P < 0.5$, $1/T_R$: $P < 1$).

5.2. *Results in the normals*

Two groups of normals were examined: patients in whom no cardiac abnormalities were found (group a) and a group of ten healthy volunteers (group b). The results of both groups are shown in table 6. No significant differences appear to exist between the two groups. Because of age differences between the normal groups and the group

Table 5. Results of the reproducibility test.

index:	IR-ratio (%)				$1/Tc$ (s^{-1})				$1/T_R$ (s^{-1})			
curves recorded by observer:	A		B		A		B		A		B	
measurements made by observer:	A	B	A	B	A	B	A	B	A	B	A	B
	51	41	58	37	21.6	19.5	18.6	27.0	12.5	11.4	12.8	12.5
	48	43	29	32	—	—	—	—	—	—	37.5	34.0
	16	14	13	20	18.8	16.7	18.7	17.5	21.4	16.5	21.3	16.5
	12	12	33	24	32.3	23.2	21.0	19.2	17.5	16.9	20.4	24.3
	47	19	28	21	42.4	24.0	—	—	25.7	27.3	—	—
	06	07	02	0	—	—	—	—	19.9	15.0	13.5	16.3
	20	17	29	14	26.6	23.9	23.1	19.0	15.4	17.4	12.4	12.8
	−12	−21	−12	−14	23.6	21.1	21.6	22.3	24.1	23.4	22.4	15.7
	01	06	−04	−06	37.1	40.4	34.4	31.3	21.5	16.7	22.8	17.8
	24	21	06	12	21.1	20.8	19.4	17.3	18.5	12.9	20.5	19.5
mean:	21.3	15.9	18.2	14.0	27.9	23.7	22.4	21.9	19.6	17.9	20.4	18.8
standard deviation:	20.3	18.1	21.0	16.4	8.4	7.2	5.5	5.3	3.9	4.9	7.2	6.3



IR-ratio:			
recording variability:			
observer A:	r = 0.81	SEE = 13%	n = 10
observer B:	r = 0.86	SEE = 8	n = 10
mean of A and B:	r = 0.83	SEE = 11	n = 10
measurement variability:	r = 0.89	SEE = 10	n = 20
interobserver variability:	r = 0.89	SEE = 10	n = 10
$1/Tc$:			
recording variability:			
observer A:	r = 0.91	SEE = 2.8 s^{-1}	n = 7
observer B:	r = 0.72	SEE = 3.7	n = 7
mean of A and B:	r = 0.88	SEE = 2.4	n = 7
measurement variability:	r = 0.64	SEE = 6.0	n = 15
interobserver variability:	r = 0.55	SEE = 4.5	n = 7
$1/T_R$:			
recording variability:			
observer A:	r = 0.75	SEE = 3.0 s^{-1}	n = 8
observer B:	r = 0.05	SEE = 3.8	n = 8
mean of A and B:	r = 0.18	SEE = 4.3	n = 8
measurement variability:	r = 0.85	SEE = 3.2	n = 18
interobserver variability:	r = 0.33	SEE = 4.7	n = 8

of the infarct patients, the indices obtained in the normal groups were correlated with age. The correlation of $1/Tc$ with age is poor ($r = -0.45$, fig. 22). The relaxation velocity index $1/T_R$ correlates better with age ($r = 0.76$, fig. 23). The same is true for the isovolumic

relaxation time (T_{ir}, $r = 0.65$, fig. 24), the index of left ventricular volume change during rapid filling (RF-ratio, $r = -0.47$, fig. 25), the mean velocity of left ventricular posterior wall motion during rapid filling (SR-ratio/T_{ir}, $r = -0.58$, fig. 26), and the change in diameter of the left atrium during rapid filling (A_{rf}, $r = -0.51$, fig. 27). The index of incoordinate relaxation (IR-ratio), the change in diameter of the left atrium during atrial systole, the a/H-ratio, and the compliance-ratio appeared not to correlate with age. For the indices with a significant correlation with age, the mean and standard deviation belonging to the mean age of the infarct patients was calculated. These values were used as normal values and are indicated in the figures presenting the data of the infarct patients.

From the correlations with age, it appears that relaxation is clearly an age-dependent phenomenon. The end-diastolic phenomena, like the changes in pressure and volume during atrial systole (A_{as} and the a/H-ratio) and the compliance-ratio, however, are not age-dependent. Theoretically, the IR-ratio should be zero in normals. However, in normals there is also a slight change of shape of the left ventricle during the isovolumic periods (138). There may also be a slight change in position of the left ventricle with respect to the thoracic wall during the isovolumic periods. Therefore the IR-ratio is in most normal cases not zero. A maximum value of 17 percent was found in the normal group. Correlations with heart rate were also calculated, but these were not significant.

5.3. *Results in the infarct patients*

The results obtained in the infarct patients are presented in table 7. The IR-ratio obtained at the first examination appeared to correlate with the enzymatic infarct size or $LDH_{1+2}max$ (chapter 4.2.7.). The correlation coefficient $r = 0.86$ ($n = 16$, SEE = 182 U, fig. 28). However, the IR-ratios obtained in the following examinations were quite different (fig. 29). A correlation with infarct size as expressed by $LDH_{1+2}max$ no longer existed. The results of the three examinations were compared: in 6 patients the IR-ratio had its lowest value at the second examination, in 2 patients in the first and in 2 patients in the third examination. The data of the other patients are not complete. The other indices measured were correlated with the IR-ratio and with the enzymatic infarct size (table 8). The table

Table 6. Results in the case of the normals.

a. graphically normal patients

pat.	sex	age (years)	heart rate (min^{-1})	Relaxation and rapid filling: IR-ratio (%)	T_n (ms)	T_m (ms)	RF-ratio (%)	A_m (mm)	SR-ratio/T_n (s^{-1})	$1/TR$ (s^{-1})	Atrial systole: A_a (mm)	a/H-ratio (%)	compl. ratio (mm/%)	Ventricular contraction: $1/T_c$ (s^{-1})
1	f	24	62	—	64	150	—	4.7	—	—	3.6	—	—	—
2	f	27	82	—	37	135	—	6.3	—	33	4.2	—	—	24
3	f	31	64	10	60	111	46	6.2	3.3	25	3.3	5.0	0.66	18
4	f	20	68	0	44	141	76	6.7	4.1	23	5.3	6.3	0.84	21
5	m	51	78	—	83	164	39	4.5	2.6	—	2.8	—	—	—
6	f	49	72	—	80	126	—	2.1	—	17	7.9	—	—	17
7	m	51	65	—	—	—	—	8.1	—	—	3.1	—	—	—
8	f	46	67	15	85	—	64	4.4	3.7	15	4.0	—	—	17
9	f	56	74	—	60	113	—	5.1	—	17	0.7	11.1	0.06	26
10	f	70	70	—	100	79	—	—	—	15	—	—	—	19
11	m	40	71	14	67	155	65	8.0	3.5	23	3.8	—	—	19
12	m	49	70	5	55	157	61	—	3.1	—	—	—	—	—
13	m	28	58	16	64	130	55	8.7	3.7	20	3.6	—	—	23
14	f	55	62	—	57	—	—	5.0	—	—	3.7	7.6	0.49	22
15	m	47	50	—	—	—	—	—	—	—	—	—	—	25
16	m	34	67	2	57	152	49	9.3	2.5	23	8.0	—	—	21
17	f	44	56	—	—	—	—	—	—	—	—	4.5	—	22
18	m	14	84	2	29	144	66	12.1	3.9	50	3.6	—	—	29

b. healthy volunteers

19	m	31	64	17	63	163	59	8.1	3.4	29	2.6	8.9	0.29	—
20	m	40	65	1	95	154	40	7.0	1.6	30	6.3	10.7	0.59	—
21	m	27	64	1	35	145	78	6.7	4.3	29	2.4	4.8	0.50	—
22	m	31	69	8	36	145	69	8.2	4.3	39	5.7	5.8	0.98	25
23	m	40	65	2	69	136	65	7.4	3.3	19	3.9	3.0	1.30	—
24	m	28	70	7	52	162	69	5.7	3.6	29	4.9	3.0	1.63	28
25	m	23	73	6	57	121	69	6.1	4.2	24	4.9	5.9	0.61	24
26	m	24	60	4	61	—	—	4.5	—	—	4.1	—	—	—
27	m	59	60	13	81	—	—	3.6	—	15	7.1	9.5	0.74	24
28	m	28	60	9	78	131	53	9.7	4.1	18	8.1	5.8	1.4	27
mean value:*				7.3	84	139	44	4.2	2.3	15.4	4.4	6.7	0.78	19.9
standard deviation:*				5.6	14	21	10	2.0	0.6		1.9	2.7	0.45	3.2
correlation with age r:					0.65		—0.47	0.51	—0.58	0.76				—0.45
significance $P <$				N.S.	0.001	N.S.	0.05	0.005	0.01	0.001	N.S.	N.S.	N.S.	0.05

* For the indices with a significant correlation with age the mean and standard deviation, belonging to the mean age of the infarct patients (62.3 y) are presented.

gives correlation coefficients and the *P*-values of each correlation, together with the numbers of the figures representing the individual data. Indices related to ventricular diastole (relaxation and rapid filling, atrial systole) correlated better with the IR-ratio and $LDH_{1+2}max$ than the indices related to ventricular contraction

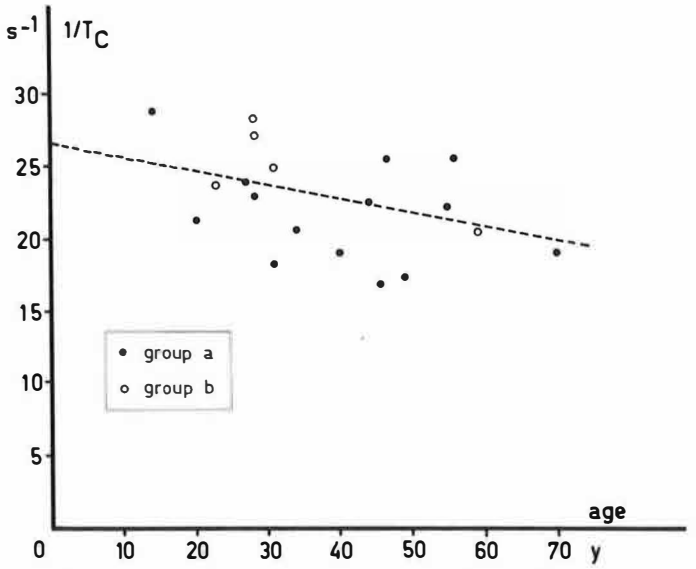


Fig. 22. Relation between the index of contraction velocity *1/Tc* and age in normals: $r = -0.45$, $n = 19$, $y = 26.6 - 0.11\,x$, SEE = 3.2 s^{-1}. Group a: graphically normal patients; group b: healthy volunteers.

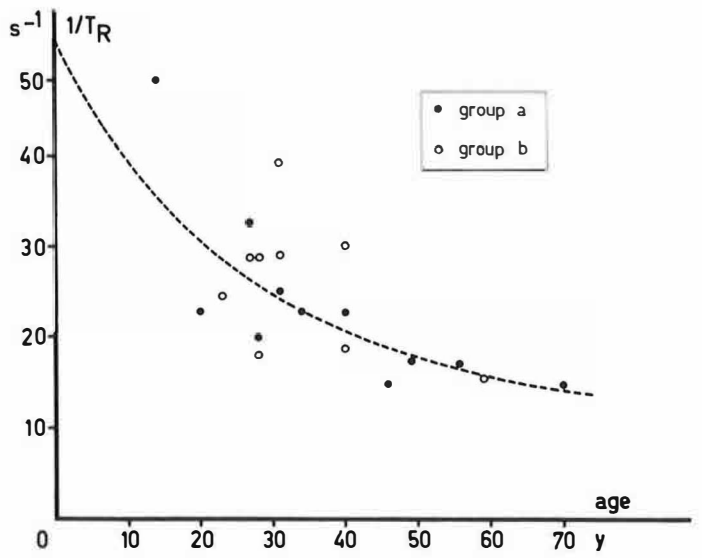


Fig. 23. Relation between the index of relaxation velocity *1/TR* and age in normals: $r = 0.76$, $n = 20$, $y = 1/(0.018 + 0.0007\,x)$. Group a and b: see fig. 22.

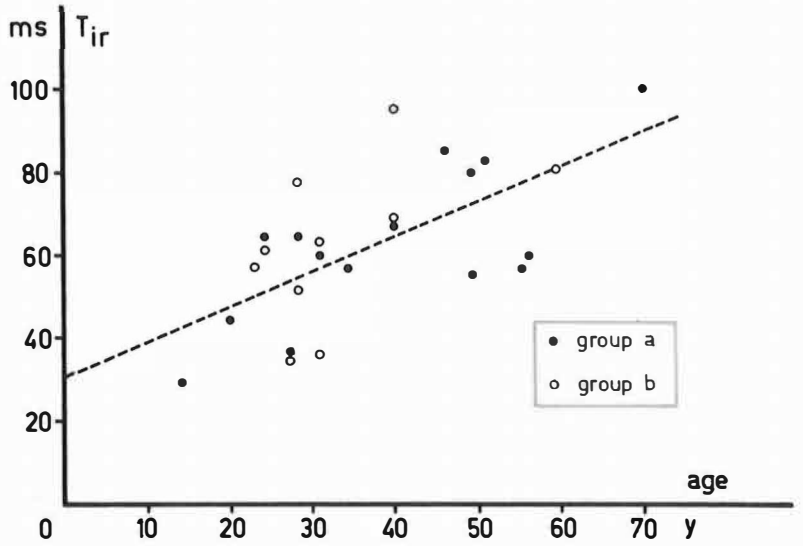


Fig. 24. Relation between the isovolumic relaxation time T_{ir} and age in normals: $r = 0.65$, $n = 25$, $y = 31 + 0.85\ x$, SEE = 14 ms. Group a and b: see fig. 22.

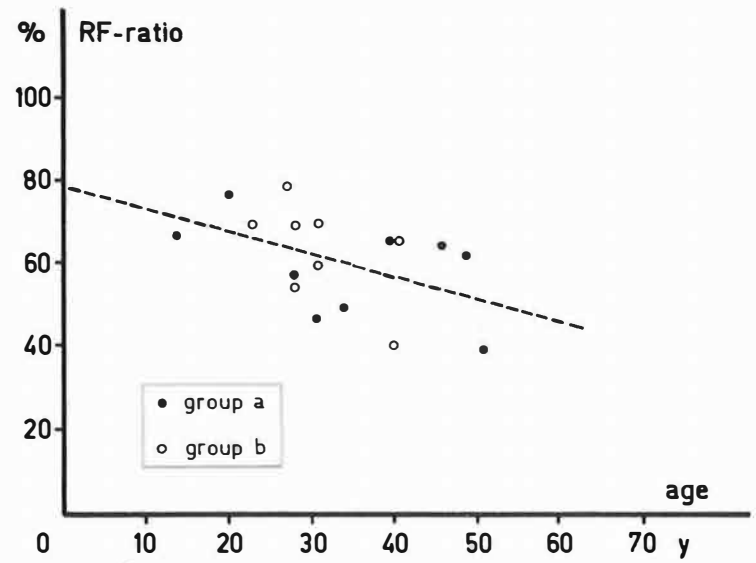


Fig. 25. Relation between the index of rapid filling of the left ventricle RF-ratio and age in normals: $r = -0.47$, $n = 17$, $y = 78 - 0.0054\ x$, SEE = 10%. Group a and b: see fig. 22.

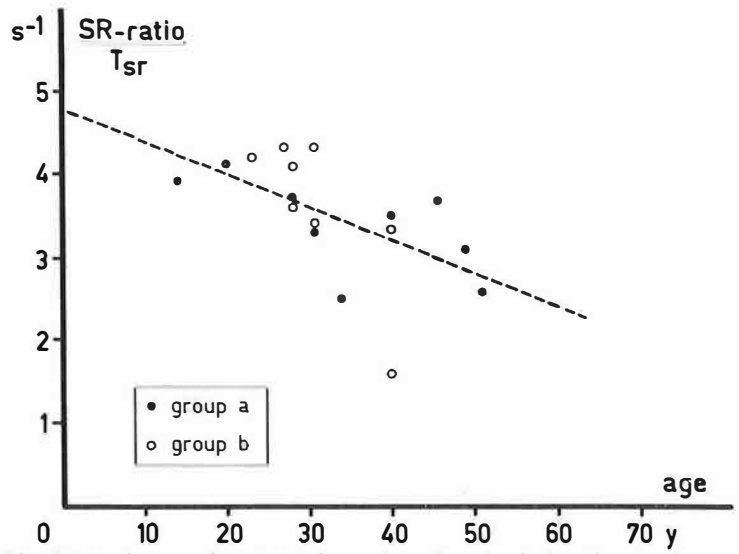


Fig. 26. Relation between the velocity of posterior wall motion during relaxation SR-ratio/T_{sr} and age in normals: $r = -0.58$, $n = 17$, $y = 4.9 - 0.041\,x$, SEE = 0.6 s^{-1}. Group a and b: see fig. 22.

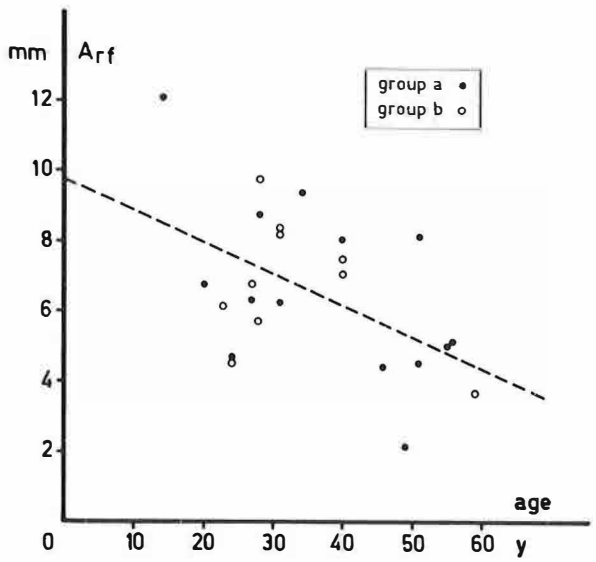


Fig. 27. Relation between the left atrial diameter change during rapid filling of the left ventricle A_{rf} and age in normals: $r = -0.51$, $n = 24$, $y = 9.8 - 0.089\,x$, SEE = 0.2 mm. Group a and b: see fig. 22.

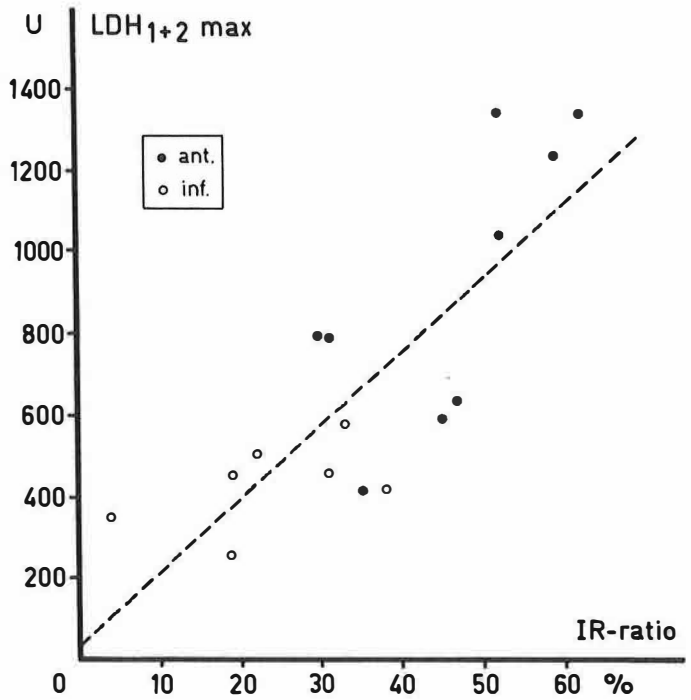


Fig. 28. Relation between the index of incoordinate relaxation IR-ratio as measured in the first week after infarction and enzymatic infarct size $LDH_{1+2}max$: linear correlation: $r = 0.81$, $y = 39.7 + 18.0\,x$, SEE = 210 U, quadratic correlation: $r = 0.86$, $n = 16$, $y = 283 + 0.26\,x^2$, SEE = 182 U. ant. = anterior infarction, inf. = inferior and lateral infarction.

(isovolumic contraction and ejection). Out of the latter indices only the ratio of pre-ejection time to ejection time (T_{pe}/T_e) shows a moderate correlation with the IR-ratio ($r = 0.46$). The isovolumic relaxation time correlates only with the IR-ratio, not with $LDH_{1+2}max$. The rapid filling time and the left atrial diameter change during rapid filling have a negative correlation with the IR-ratio and $LDH_{1+2}max$. The index of left ventricular volume change during rapid filling (RF-ratio) also shows a negative correlation with the IR-ratio and a small, negative correlation with $LDH_{1+2}max$. The left ventricular posterior wall velocity during relaxation (SR-ratio/T_{sr}), *i.e.* the relaxation velocity index of the unaffected part of the ventricular wall, correlated positively with the IR-ratio and $LDH_{1+2}max$. However, the global relaxation velocity index $1/T_R$ shows a negative correlation.

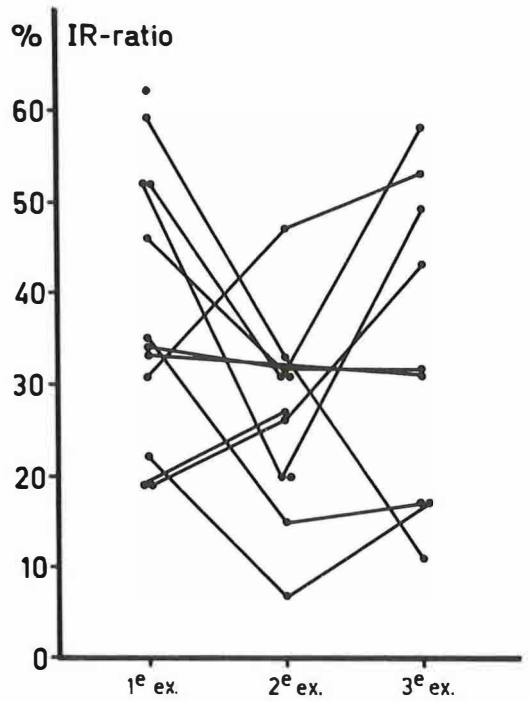


Fig. 29. The index of incoordinate relaxation IR-ratio in the first week after infarction (1e ex.), in the second week after infarction (2e ex.), and two months after the infarction (3e ex.).

The correlation between the indices related to atrial systole or ventricular end-diastole and the IR-ratio depends on the moment of examination, but the correlation between these indices and $LDH_{1+2}max$ is not dependent of the moment of examination. At the second and third examination there is a positive correlation between the change in left atrial diameter during atrial systole (A_{ai}) and the IR-ratio, while there is no correlation with $LDH_{1+2}max$. At the first examination a correlation was found between the a/H-ratio of the apexcardiogram and the IR-ratio, while the a/H-ratios of all three examinations together correlate with $LDH_{1+2}max$. The compliance-ratio shows a negative correlation with the IR-ratio at the first examination, a positive correlation at the second examination and no correlation at the third examination. There is a poor negative correlation between the compliance-ratio of all examinations and $LDH_{1+2}max$.

Table 7. Results of the measurements in the infarct patients.

				Relaxation and rapid filling							Atrial systole			Ventricular contraction		
pat.	exam.	heart rate	$LDH_{H_2}max$	IR-ratio	T_{ir}	T_{rf}	RF-ratio	A_{rf}	SR-ratio/T_{sr}	$1/T_R$	A_{as}	a/H-ratio	compl. ratio	$1/T_C$	T_{ems}*	T_{pc}/T_c
		(min^{-1})	(U)	(%)	(ms)	(ms)	(%)	(mm)	(s^{-1})	(s^{-1})	(mm)	(%)	(mm/%)	(s^{-1})	(ms)	
1	1	88	1329	62	126	48	13	0.7	4.3	—	2.7	19.0	0.14	30.6	551	0.64
	2	—		—	—	—	—	—	—	—	—	—	—	—	—	—
	3	—		—	—	—	—	—	—	—	—	—	—	—	—	—
2	1	48	246	19	85	208	22	5.9	1.4	—	5.4	14.5	0.37	22.2	554	0.46
	2	45		27	111	185	46	5.9	2.5	—	3.6	11.6	0.31	21.6	546	0.34
	3	—		—	—	—	—	—	—	—	—	—	—	—	—	—
3	1	66	473	19	79	186	23	—	1.6	24.4	—	15.9	—	30.9	513	0.42
	2	54		26	92	177	38	3.6	2.4	13.8	5.2	11.7	0.44	28.0	521	0.36
	3	60		43	112	177	35	2.9	2.7	14.9	11.3	4.9	2.3	25.5	515	0.52
4	1	—	869	—	—	—	—	—	—	—	—	—	—	—	—	—
	2	59		20	61	135	63	7.1	4.2	18.2	3.7	12.5	0.30	—	509	0.30
	3	—		—	—	—	—	—	—					—	—	—
5	1	57	448	34	116	107	31	3.0	2.9	11.6	6.1	10.6	0.58	19.3	532	0.42
	2	58		32	99	172	61	3.9	3.4	12.7	3.3	8.1	1.25	14.7	550	0.63
	3	56		32	105	140	25	3.9	2.3	10.8	4.4	8.0	0.55	14.0	566	0.52
6	1	73	1034	52	104	116	39	0	4.1	11.5	7.5	19.3	0.39	24.8	502	0.39
	2	69		31	93	149	41	0.9	3.0	12.6	5.2	19.3	0.34	21.2	534	0.49
	3	—		—	—	—	—	—	—	—	—	—	—	—	—	—
7	1	58	572	33	102	131	47	1.4	3.4	12.6	7.3	9.1	0.80	19.7	503	0.45
	2	—		—	—	—	—	—	—	—	—	—	—	—	—	—
	3	66		31	104	118	35	1.2	3.0	11.6	7.0	13.0	0.54	18.1	526	0.44
8	1	72	402	35	95	132	61	4.1	4.2	10.6	3.4	7.7	0.44	19.5	536	0.50
	2	61		15	107	156	61	2.7	4.0	37.9	3.9	23.0	0.17	31.0	533	0.33
	3	58		17	107	156	30	3.4	1.8	15.1	7.4	8.0	0.93	30.0	530	0.36

9	1	73	780	31	98	134	39	1.3	2.8	14.0	4.1	10.8	0.42	22.6	513	0.49
	2	66		47	127	115	21	4.3	2.8	11.0	10.0	10.8	1.22	20.9	526	0.40
	3	74		53	132	108	10	2.4	2.6	10.4	9.2	15.8	0.58	19.7	548	0.52
10	1	68	492	22	72	133	48	5.5	3.4	15.4	5.2	9.1	0.57	22.5	539	0.40
	2	64		7	58	133	60	—	2.9	17.2	—	9.1	—	20.0	549	0.36
	3	66		17	57	161	50	5.9	3.1	17.5	5.3	17.0	0.31	20.0	563	0.37
11	1	68	795	30	—	—	—	—	—	—	—	—	—	—	—	—
	2	—		—	—	—	—	—	—	—	—	—	—	—	—	—
	3	—		—	—	—	—	—	—	—	—	—	—	—	—	—
12	1	84	1229	59	82	76	10	0.6	4.4	16.9	3.6	21.2	0.17	25.1	546	0.47
	2	82		33	72	98	17	0.6	2.9	25.9	4.3	22.1	0.19	29.3	541	0.42
	3	89		11	51	107	—	1.4	—	—	2.0	20.0	0.10	24.3	546	0.42
13	1	88	1329	52	93	106	13	0.3	3.3	13.2	5.4	30.6	0.18	21.9	511	0.48
	2	88		20	66	156	65	1.4	3.6	21.1	4.5	31.0	0.14	26.2	513	0.48
	3	99		49	78	74	14	1.7	4.1	18.4	5.7	41.5	0.14	32.5	530	0.45
14	1	61	580	46	105	120	32	0.5	3.5	13.1	6.7	14.4	0.46	24.9	501	0.42
	2	65		31	104	143	25	3.1	2.3	14.9	8.5	14.9	0.57	—	512	0.40
	3	66		58	110	136	29	2.4	3.5	12.4	9.6	28.2	0.55	32.9	511	0.39
15	1	82	637	47	—	—	—	—	—	—	—	—	—	—	—	—
	2	—		—	—	—	—	—	—	—	—	—	—	—	—	—
	3	—		—	—	—	—	—	—	—	—	—	—	—	—	—
16	1	86	421	38	—	—	—	—	—	—	—	—	—	—	—	—
	2	—		—	—	—	—	—	—	—	—	—	—	—	—	—
	3	—		—	—	—	—	—	—	—	—	—	—	—	—	—
17	1	44	350	4	—	—	—	—	—	—	—	—	—	—	—	—
	2	—		—	—	—	—	—	—	—	—	—	—	—	—	—
	3	—		—	—	—	—	—	—	—	—	—	—	—	—	—
mean:				33	94	134	36	2.7	3.1	15.7	5.7	16.0	0.52	23.8	530	0.44
standard deviation:				15	21	35	17	2.0	0.8	5.9	2.3	8.2	0.45	5.1	18	0.08
difference from normal $P<$				0.001	0.05	N.S.	0.05	0.005	0.001	N.S.	0.05	0.001	0.05	0.001	0.001	0.001

Table 8. Correlation of the measured indices with the indices of incoordinate relaxation (IR-ratio) and enzymatic infarct size ($LDH_{1+2}max$).

	Indices	IR-ratio	$LDH_{1+2}max$
relaxation and rapid filling	isovolumic relaxation time (T_{ir})	$r = 0.58$ $P<0.001$ fig. 30	N.S.
	rapid filling time (T_{rf})	$r = -0.59$ $P<0.001$ fig. 31	$r = -0.70$ $P<0.001$
	index of left ventricular volume change during rapid filling (RF-ratio)	$r = -0.63$ $P<0.001$ fig. 32	$r = -0.36$ $P<0.05$
	left atrial diameter change during left ventricular rapid filling (A_{rf})	$r = -0.50$ $P<0.01$ fig. 33	$r = -0.63$ $P<0.001$
	velocity of posterior wall motion during relaxation (SR-ratio/T_{ir})	$r = 0.42$ $P<0.05$ fig. 34	$r = 0.52$ $P<0.005$
	relaxation velocity index ($1/T_R$)	$r = -0.45$ $P<0.05$ fig. 35	N.S.
atrial systole	left atrial diameter change during atrial systole (A_{as})	1st ex. N.S. 2nd and 3rd ex. $r = 0.69$ $P<0.001$ fig. 36	N.S.
	index of left atrial contractile force (a/H-ratio of the ACG)	1st ex. $r = 0.62$ $P<0.05$ 2nd and 3rd ex. N.S. fig. 37	$r = 0.69$ $P<0.001$ fig. 38
	compliance-ratio $\left(\frac{A_{as}}{a/H}\right)$	1st ex. $r = -0.66$ $P<0.05$ 2nd ex. $r = 0.72$ $P<0.05$ 3rd ex. N.S. fig. 39	$r = -0.43$ $P<0.001$ fig. 40
isovolumic contraction	contraction velocity index ($1/T_C$)	N.S. fig. 41	N.S.
ejection	rate-corrected electro-mechanical systole (T_{emi}^*)	N.S. fig. 42	N.S.
	ratio of pre-ejection time to ejection time (T_{pe}/T_e)	$r = 0.46$ $P<0.05$ fig. 43	N.S.

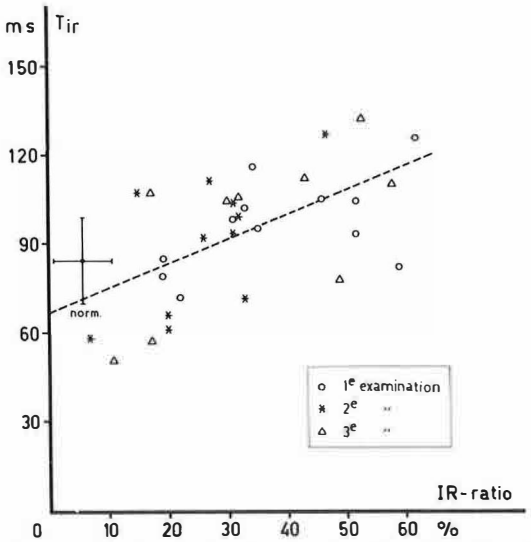


Fig. 30. Relation between the isovolumic relaxation time T_{ir} and the IR-ratio. The normal values for the mean age of the infarct patients (62.3 y) are indicated at the left ($T_{ir} = 84 \pm 14$ ms, IR-ratio $= 7.3 \pm 5.6\%$). $r = 0.58$, $n = 32$, $y = 0.83\ x + 66$.

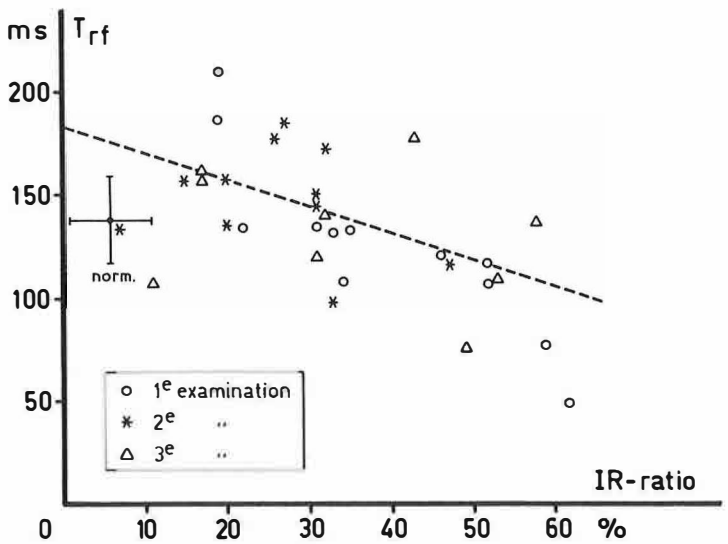


Fig. 31. Relation between the rapid filling time T_{rf} and the IR-ratio. The normal values are indicated at the left ($T_{rf} = 139 \pm 21$ ms, IR-ratio $= 7.3 \pm 5.6\%$). $r = -0.59$, $n = 32$, $y = 180 - 1.39\ x$.

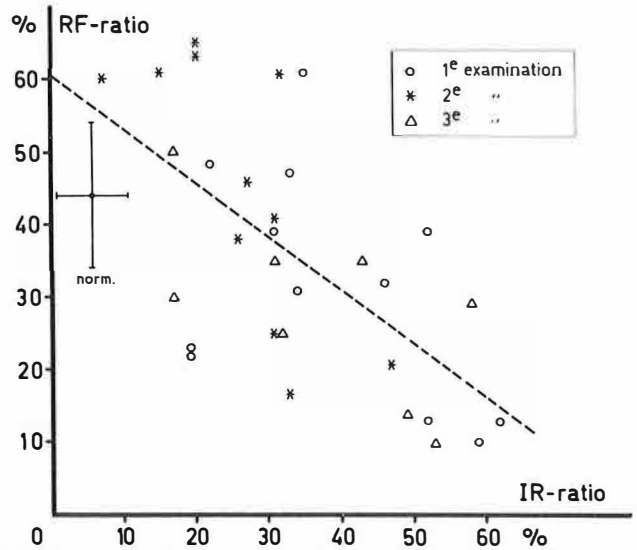


Fig. 32. Relation between the index of rapid filling of the left ventricle RF-ratio and the IR-ratio. The normal values for the mean age of the infarct patients (62.3 y) are indicated at the left (RF-ratio = 44 ± 10%, IR-ratio = 7.3 ± 5.6%). $r = -0.63$, $n = 31$, $y = 61 - 0.74\,x$.

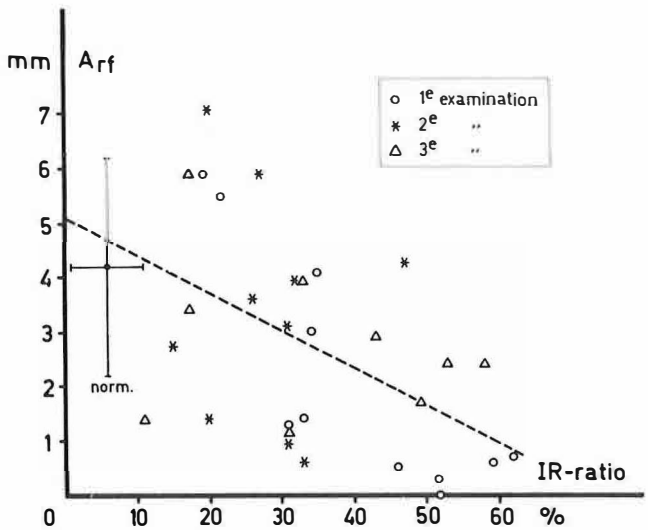


Fig. 33. Relation between the left atrial diameter change during rapid filling of the left ventricle A_{rf} and the IR-ratio. The normal values for the mean age of the infarct patients (62.3 y) are indicated at the left ($A_{rf} = 4.2 \pm 2.0$ mm, IR-ratio = 7.3 ± 5.6%). $r = -0.50$, $n = 30$, $y = 5.1 - 0.069\,x$.

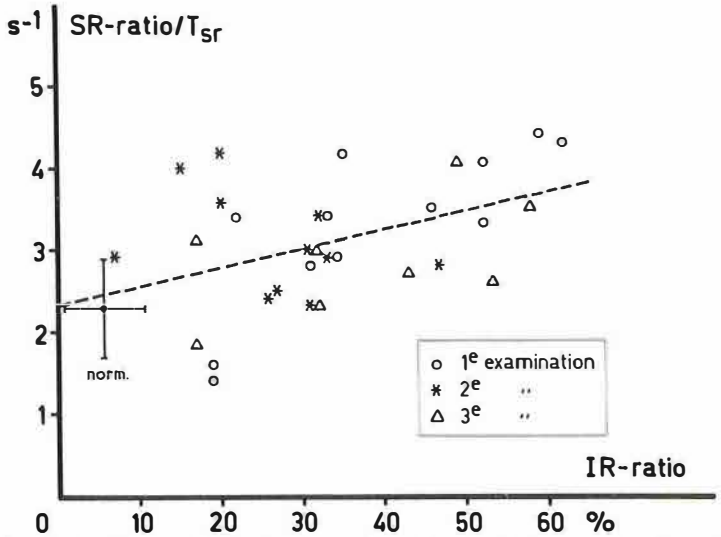


Fig. 34. Relation between the velocity of posterior wall motion during relaxation SR-ratio/T_{sr} and the IR-ratio. The normal values for the mean age of the infarct patients (62.3 y) are indicated at the left (SR-ratio/T_{sr} = 2.3 ± 0.6 s^{-1}, IR-ratio = 7.3 ± 5.6%). $r = 0.42$, $n = 31$, $y = 0.23 + 0.0023\ x$.

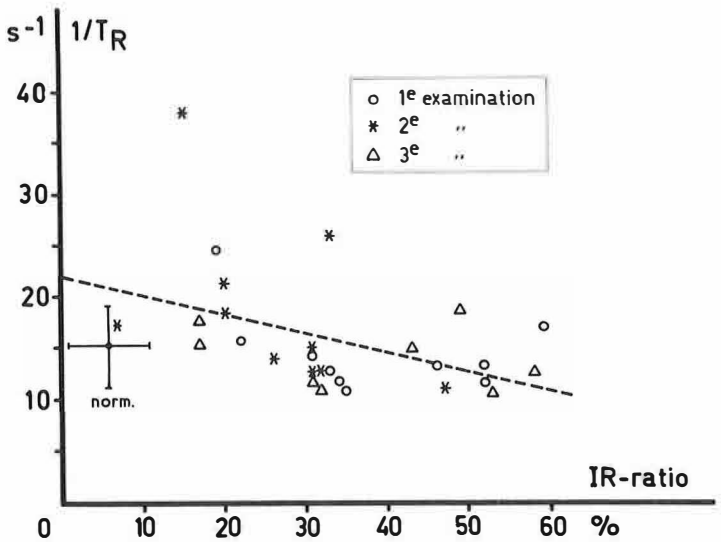


Fig. 35. Relation between the index of relaxation velocity $1/T_R$ and the IR-ratio. The normal values for the mean age of the infarct patients (62.3 y) are indicated at the left ($1/T_R$ = 15.4 (13.5 — 17.8 s^{-1}), IR- ratio = 7.3 ± 5.6%). $r = -0.45$, $n = 28$, $y = 22.0 - 0.19\ x$.

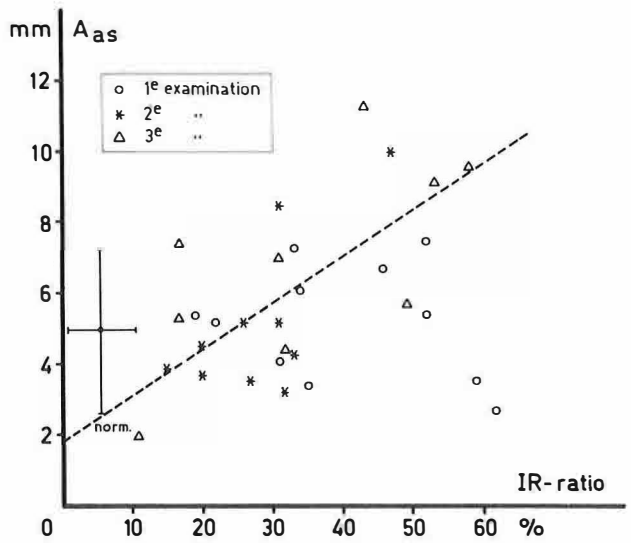


Fig. 36. Relation between the left atrial diameter change during atrial systole A_{as} and the IR-ratio. The normal values are indicated at the left ($A_{as} = 4.4 \pm 1.9$ mm, IR-ratio $= 7.3 \pm 5.6\%$). $r = 0.69$, $n = 19$, $y = 1.8 + 0.13\ x$.

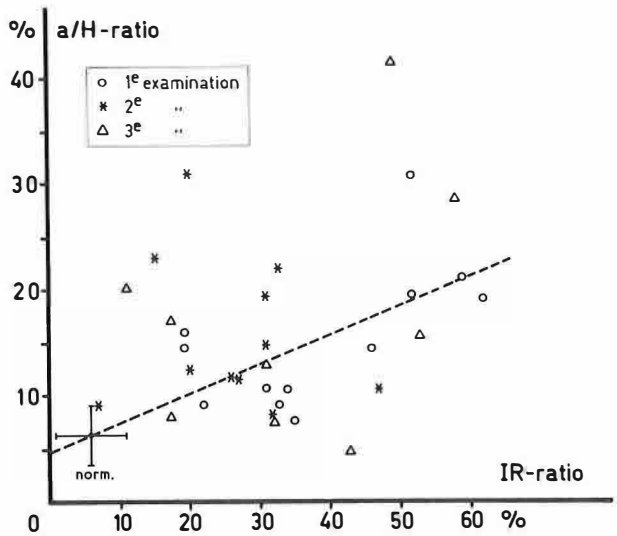


Fig. 37. Relation between the index of left atrial contractile force a/H-ratio and the IR-ratio. The normal values are indicated at the left (a/H-ratio $= 6.7 \pm 2.7\%$, IR-ratio $= 7.3 \pm 5.6\%$). The correlation is only present at the first examination: $r = 0.62$, $n = 12$, $y = 4.8 + 0.27\ x$.

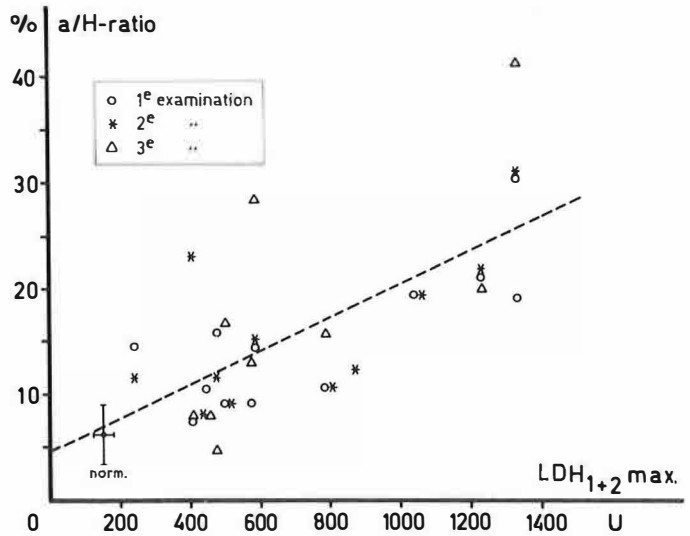


Fig. 38. Relation between the index of left atrial contractile force a/H-ratio and enzymatic infarct size LDH_{1+2}max. The normal values are indicated at the left (a/H-ratio = 6.7 ± 2.7%, LDH_{1+2}max = 154 ± 34 U). $r = 0.69$, $n = 32$, $y = 4.5 + 0.016\ x$.

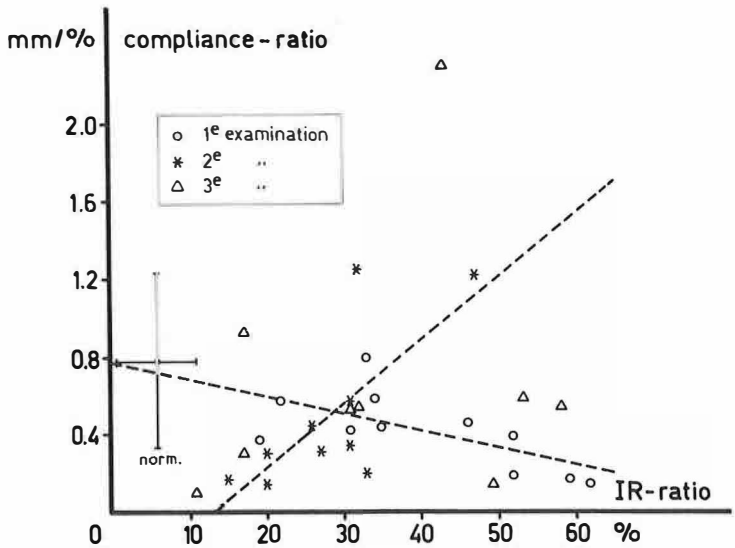


Fig. 39. Relation between the compliance-ratio and the IR-ratio. The normal values are indicated at the left (compliance-ratio = 0.78 ± 0.45 mm/%, IR-ratio = 7.3 ± 5.6%). Only in the first two examinations correlations are found: 1e examination: $r = -0.66$, $n = 11$, $y = 0.78 - 0.009\ x$, 2e examination: $r = 0.72$, $n = 10$, $y = -0.44 + 0.033\ x$.

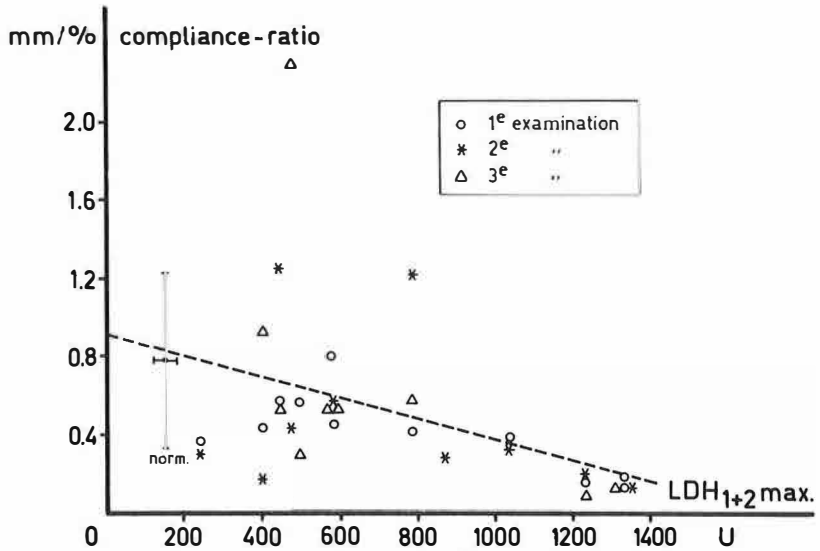


Fig. 40. Relation between the compliance-ratio and enzymatic infarct size $LDH_{1+2}max$. The normal values are indicated at the left (compliance-ratio = 0.78 ± 0.45 mm/%, $LDH_{1+2}max$ = 154 ± 34 U). $r = -0.43$, $n = 30$, $y = 0.91 - 0.00053\ x$.

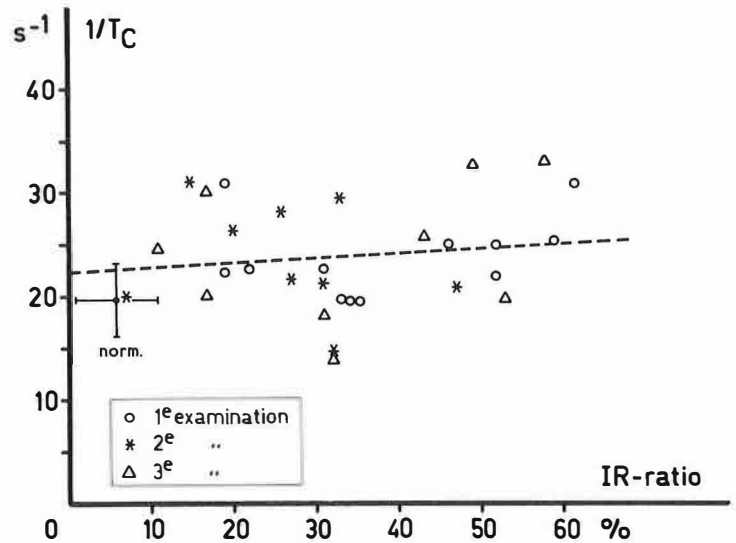


Fig. 41. Relation between the index of contraction velocity $1/Tc$ and the IR-ratio. The normal values for the mean age of the infarct patients (62.3 y) are indicated at the left ($1/Tc$ = 19.9 ± 3.2 s^{-1}, IR-ratio = 7.3 ± 5.6%). $r = 0.14$, $P < 0.5$ (N.S.).

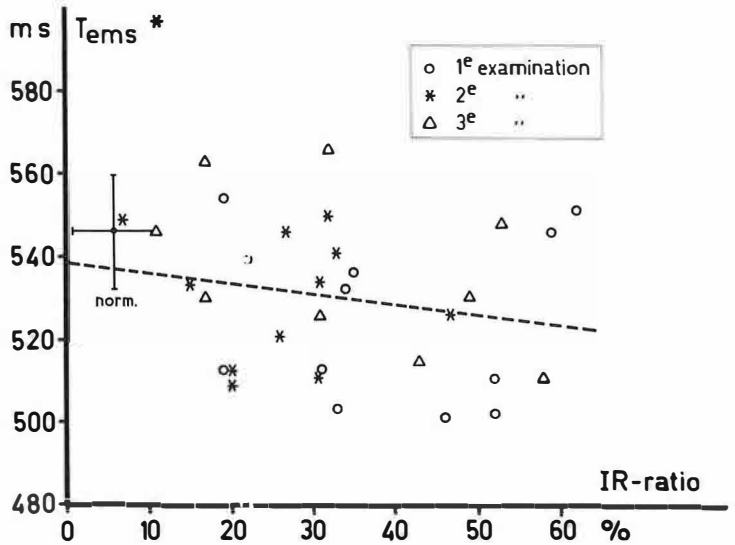


Fig. 42. Relation between the electromechanical systole, corrected for heart rate, T_{ems}* and the IR-ratio. The normal values are indicated at the left (T_{ems}* = 547 ± 14 ms (according to Weissler), IR-ratio = 7.3 ± 5.6%). $r = -0.20$, $P < 0.5$ (N.S.).

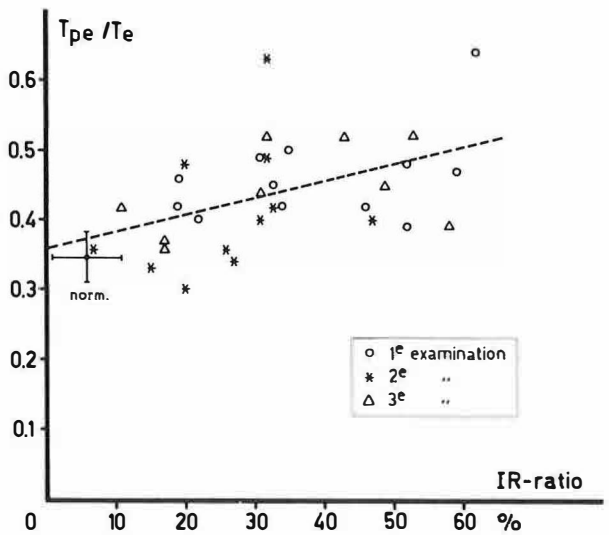


Fig. 43. Relation between the ratio of pre-ejection time and ejection time T_{pe}/T_e and the IR-ratio. The normal values are indicated at the left (T_{pe}/T_e = 0.345 ± 0.036 (according to Weissler), IR-ratio = 7.3 ± 5.6%). $r = 0.46$, $n = 32$, $y = 0.36 + 0.0024\,x$.

Chapter 6

DISCUSSION

Infarct size may be estimated from the rise in serum levels of some enzymes. The total amount of discharged enzyme can be calculated from the course of the plasma enzyme concentration during the first days after infarction and the plasma volume (147, 148, 150). If the enzyme concentrations in the myocardium are known, the mass of the infarcted muscle can be calculated. The myocardial fraction of creatine phosphokinase (CPK-MB) is cardiospecific and its usage for this purpose should therefore be preferred (174). A disadvantage of using this enzyme, however, is the necessity of frequent sampling (once per 3 hours), because of its high rate of appearance and disappearance. The myocardial concentration of CPK-MB is low and a small amount is released. The determination of the resulting low serum enzymes is relatively inaccurate, which is another drawback of using this enzyme. The first and second fraction of lactodehydrogenase (LDH_{1+2}), together also characterized as α-HBDH, is somewhat less cardiospecific. It occurs also in the erythrocytes. LDH_{1+2} concentration is therefore also increased in hemolytical syndromes, in which levels up to 3000 U may be found. In the absence of hemolytical disease, however, the determination of LDH_{1+2} can give a fairly good estimation of infarct size, as demonstrated by Witteveen *et al.* (69, 194, 195) and by Erhardt (37). Advantages are: a high concentration of the enzyme in the myocardium, of which more is released than of CPK-MB, and a slow disappearance from the plasma. There is a good correlation of the maximum value of plasma concentration LDH_{1+2} determined once or twice daily with infarct size as determined from autopsy findings (37). Because of the advantages of the LDH_{1+2} max determination in comparison with the use of CPK-MB, LDH_{1+2} max was chosen for the estimation of enzymatic infarct size in this study.

Besides information about infarct size from enzyme determinations, it is necessary to have information about the mechanical dysfunction of the heart in the acute phase of myocardial infarction. The main purpose of the present study was to evaluate non-invasive methods to estimate regional dysfunction and infarct size from

echocardiography and pulse curves. An investigation was made in (originally) 32 infarct patients. At the earliest possible moment after the infarction echocardiograms and pulse curves were recorded. At the time of the investigation it was not yet possible to make the recordings in the coronary care unit. Therefore the first examination could be done not earlier than on the 5th to 7th day, the day on which the patients were discharged from the CCU. Because it could be expected that in the period after the infarction changes would occur in the cardiac function, the examination was repeated twice, after one week and after two months.

The 32 patients, originally selected did not all appear to be suitable for the study: 6 patients used a dose of beta-blocking agents producing bradycardia and/or hypotension. This medication appeared to affect the measurements considerably. These patients were therefore excluded. Another 5 patients could not be examined in the first week as a result of their clinical condition, which did not allow them to be transported from the CCU to the department of echo- and phonocardiography. Finally, in 4 patients with a posterior or large inferior infarction it appeared not to be possible to obtain a reliable echocardiographic recording of the left ventricular posterior wall. In the remaining 17 patients measurements could be made. It is not to be expected that if more patients had been examined higher correlation coefficients would have been found. However, the significance of the correlations might have been better.

In these 17 patients a nearly simultaneously (within half an hour) registration was done of electrocardiogram, phonocardiogram, carotid pulse tracing, apexcardiogram and echocardiogram of the mitral valve, the left ventricular posterior wall and the left atrium. These recordings yielded supplementary information. Because heart rate did not change significantly between the recordings, time intervals measured in one recording could be used for the measurements in the other recordings. Indices related to ventricular systole (isovolumic contraction and ejection) and ventricular diastole (relaxation and filling) were measured.

Out of these indices the IR-ratio agreed fairly well with LDH_{1+2} max. The IR-ratio was measured from the echocardiogram of the unaffected posterior wall of the left ventricle. It is the ratio of the excursion during isovolumic relaxation and total excursion. In

chapter 2 the mechanism relating IR-ratio and infarct size has been explained. The movement of the unaffected left ventricular posterior wall during isovolumic relaxation is related to a change of shape, and the change of shape is related to the size of the infarct (or malfunctioning region). The recording of the movements of the posterior wall of the left ventricle was chosen, because this part of the ventricular wall is rarely affected and because it may easily be visualized on an echocardiogram. In this study 4 of the 32 patients originally selected had a posterior or a large inferior infarction. In these cases it was not possible to visualize the posterior wall, because the posterior wall was part of the infarcted area or was close to it; when the wall segment to be recorded is near the infarcted area it is very difficult to visualize it on an M-mode echocardiogram. In that case the angle between the wall segment and the ultrasonic beam changes during the cardiac cycle (fig. 44). Throughout the cardiac

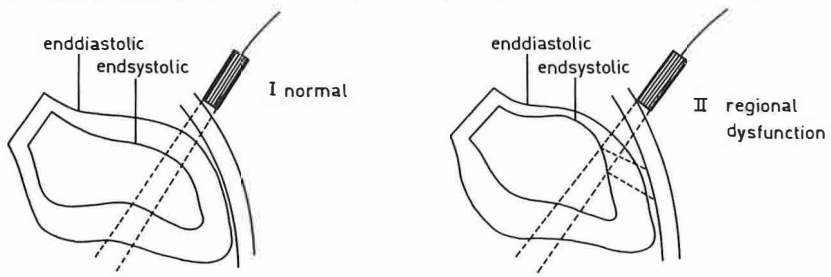


Fig. 44. Schematic drawing of left ventricular cavity outlines in relation to the direction of the echotransducer explaining visualisation difficulties in regional dysfunction. In the normal case (I) the shape of the ventricular cavity does not change and the echo beam may be directed perpendicularly to the wall. In the case of regional dysfunction (II) the wall near the affected area changes its position during the heart cycle and is not all the time perpendicular to the ultrasonic beam.

cycle the ultrasound is then reflected in different directions, making continuous recording of the endocardium impossible.

The accuracy of the measurement of the IR-ratio depends on the quality of the echocardiogram and the accuracy in the determination of the isovolumic relaxation time. The accuracy is thus partly subject to the limitations of M-mode echocardiography. However, only the ratio of two excursions of the posterior wall had to be detected. The accuracy in the determination of the isovolumic relaxation period depends on the phonocardiogram and the mitral valve echo. The beginning of isovolumic relaxation is rather well defined, *viz.* by the

first high frequency vibrations of the second heart sound. The end of the isovolumic relaxation is determined by the mitral valve opening. The exact moment of mitral valve opening may be difficult to establish. The movements of the mitral valve are rather complicated. Much investigation has been made into the relation of echocardiographic mitral valve movements and hemodynamic and cineangiocardiographic measurements (39, 78, 87, 106, 124, 137). From this it may be concluded that the onset of early diastolic rapid anterior motion of the mitral valve coincides rather accurately with the onset of flow through the mitral valve. From the reproducibility test (table 5) it may be concluded that the measurement of the IR-ratio can be made with sufficient accuracy.

When the heart as a whole does not move during the isovolumic phase of relaxation and when there is no regional dysfunction, the IR-ratio should be zero (see fig. 1). In normal cases (table 6) values between 0 and 17 percent were found. This means that also in normal cases there may be some movement of the posterior wall of the left ventricle: either the heart as a whole may move or there may be a small change in shape.

In only one of the infarct patients, on the 5th to 7th day after the infarction, a normal IR-ratio was found (table 7, patient no. 17). In this patient, however, LDH_{1+2} max was also low, 350 U; normally 154 ± 34 U is found. In all the other infarct patients, on the 5th - 7th day after the infarction, the IR-ratio was larger than 17%. In two patients, nos. 2 and 3, the IR-ratio was 19%. These patients had also a low LDH_{1+2} max.

The course of the IR-ratio as obtained at the three examinations is shown in fig. 29. At the 2nd examination, about 2 weeks after the infarction, the IR-ratio was on the average lower than at the first as well as the third examination. This could be explained by changes in the compliance of the infarcted area. It may be imagined that the lower the compliance (or the higher the stiffness) of the infarcted area, the greater is the extent of change in shape during the isovolumic relaxation, and the higher the velocity at which the change of shape takes place. Thus the lower the compliance, the larger the IR-ratio should be. From the data shown in fig. 29 it must then be concluded that one week and two months after an infarction the compliance of the infarcted area is lower than two weeks after the

infarction. This agrees with what may be concluded from histological observations. The fact is that one week after the infarction, intracellular edema is seen in the infarcted area, with increased stiffness (see also chapter 2). After two weeks this edema again disappears. After two months fibrosis of the infarcted area can be observed, which again causes an increase in stiffness. The results of the measurements of the compliance-ratio at the 1st and 2nd examination are consistent with this; at the first examination there was a negative correlation between the IR-ratio and the compliance-ratio (the larger the IR-ratio, the smaller the compliance-ratio), while at the second examination a positive correlation was found. The data of the third examination did not show a significant relation. It should be borne in mind that the compliance-ratio is an index of global ventricular function; it is not only dependent on the compliance of the infarcted area, but also on the size of the infarct.

Other indices were obtained from pulse curves and the echocardiogram of the left atrium. The reliability of measurements from pulse curves, especially from the apexcardiogram, is determined by the time constant of the recording system. Except in the experiments described in chapter 3, the system used for the recording of apexcardiogram and carotid pulse tracing had a time constant of 0.5 s. This is shorter than the recommended minimum value of 2.5 s (73). However, for the indices used in this study (a/H-ratio, $1/Tc$ and $1/TR$), there appeared to be no significant difference in the results of the measurements as compared with the results obtained when a Marey capsule was connected to a Statham P23Db pressure transducer, with an infinite time constant. Others (73) have also demonstrated that the a/H-ratio is hardly influenced by the time constant of the system. The slow parts of the systolic and diastolic plateau are influenced when the time constant is less than 1 s (76, 188). As obtained from the apexcardiogram, the reproducibility of $1/Tc$, and that of $1/TR$ even more, is greatly dependent on the skill of the observer. This can be seen from table 5, which gives the results of the reproducibility study. Observer B had little experience in doing these measurements on the apexcardiogram. Further investigation is necessary to improve the practicability of the measurements of these indices, for instance by simultaneous recording of the apexcardiogram with its first derivative. With more experience

however, the measurements were fairly well reproducible and appeared to correlate well with measurements on the left ventricular pressure curve (chapter 3). They might therefore be regarded as indices of contraction and relaxation velocity.

The systolic time intervals have been used to study left ventricular function in myocardial infarction (88, 89, 182, 184). These times intervals, measured non-invasively from carotid pulse tracing, electrocardiogram and phonocardiogram, agree with those obtained invasively, according to Moene *et al.* and van der Werf *et al.* (16, 103, 108, 109, 182, 184, 186).

Measurements on the echocardiogram of the left atrium are reliable (67), provided that well defined delineations of the left atrial anterior and posterior wall can be obtained. This appeared to be possible in all our patients and normal individuals. There is some evidence that diastolic changes in left atrial diameter reflect volume changes of the left ventricle during this period (2, 18, 67, 125, 158, 198). However, it has not been established how accurately the left ventricular volume changes can be predicted from left atrial diameter changes. This limits the use of these measurements in the individual patient. Our findings in the normal individuals show large variations.

Indices from the echocardiogram, the apexcardiogram and systolic time intervals were measured to see if they would give more information about the pump function and more insight into the different pathophysiological relations of regional dysfunction, especially during ventricular diastole. Some indices are "old", *i.e.* they have already been used for some time for the evaluation of cardiac function. The duration of the total electromechanical systole, corrected for heart rate (T_{ems}*), and the ratio of pre-ejection time and ejection time (T_{pe}/T_e) have been applied in patients with acute myocardial infarction (89, 90). According to Lewis a marked shortening of T_{ems}* up to 485 ms is found in acute myocardial infarction. This would be a direct effect of increased adrenergic tone (88). Normally T_{ems}* is 547 ± 14 ms. In 7 out of 13 infarct patients, we found values lower than 533 ms and there was no correlation of T_{ems}* with the enzymatic infarct size or with the IR-ratio. The ratio T_{pe}/T_e is related to ejection fraction (88); the smaller the ejection fraction, the larger the T_{pe}/T_e. It may be expected that infarct patients have a smaller ejection fraction than normal. This has indeed been found by

Bertrand (12). T_{pe}/T_e is normally 0.345 ± 0.036, thus between 0.31 and 0.38. Almost all infarct patients had values higher than 0.38. However, there was no correlation with enzymatic infarct size, and the correlation with the IR-ratio was poor. It appears from our data, therefore that T_{em1}* and T_{pe}/T_e do not give useful information in patients with acute myocardial infarction.

According to Benchimol and Dimond the a/H-ratio of the apexcardiogram is increased in patients with acute myocardial infarction. It is related to end-diastolic pressure. Normally the a/H-ratio should be lower than 15%. In our group of normals it was always below 11%. In the patient group much higher values were found. There is some correlation with enzymatic infarct size and with the IR-ratio obtained one week after the infarction.

Nearly all of the measured indices of relaxation and rapid filling in normals appeared to be related to age (table 6, figs. 23 - 27). Only the IR-ratio and the rapid filling time T_{rf} did not show a correlation with age. The isovolumic relaxation time (T_{ir}) was longer and the rate of relaxation ($1/T_R$) was smaller with increasing age (figs. 23 and 24). T_{ir} and T_R are obviously related to each other (see fig. 13). During relaxation there is a spontaneous decline in wall stress and in ventricular pressure. Muscle fiber length increases as a result of elastic recoil. The process takes place not only during the isovolumic phase but also during rapid filling. Relaxation is a spontaneous process, the occurrence of which is an intrinsic property of the ventricular wall functioning normally. This is illustrated *e.g.* in the infarct patients with delayed mitral valve opening. In patients 1, 5 and 6 for instance, the isovolumic relaxation time (T_{ir}) is prolonged and the rapid filling time (T_{rf}) is shortened. T_{ir} shows a positive correlation with the IR-ratio in all patients together (fig. 30). T_{rf} shows a negative correlation with the IR-ratio and the enzymatic infarct size (fig. 31). There is more delay in the onset than in the end of rapid filling. In normals the index of left ventricular volume change during rapid filling (RF-ratio) and the left atrial diameter change during rapid filling of the left ventricle (A_{rf}) show a negative correlation with age (figs. 25 and 27). Thus with increasing age the volume change of the left ventricle and that of the left atrium seem to decrease. In the infarct patients the movement during rapid filling of the left ventricular wall (RF-ratio) and of the left atrial wall (A_{rf}) are

diminished (figs. 32 and 33). The RF-ratio and A_{rf} show a negative correlation with the IR-ratio and the enzymatic infarct size (LDH_{1+2} max). (figs. 32 and 33). This may be explained as follows. Normally the rapid filling of the left ventricle depends on the wall movement during relaxation. In infarct patients the initial part of this wall movement occurs during the change in the shape of the left ventricle preceding mitral valve opening, which was described in chapter 2 (figs. 1 and 3). Therefore, after mitral valve opening the extent of the movement of the ventricular wall and thus also the volume change during rapid filling is less than normal. The relation of the rate of relaxation and of the volume change during rapid filling with age may be explained as follows. According to Winegrad (192) the elastic recoil accompanying relaxation depends on the elasticity of intercellular microfilaments. These elastic microfilaments probably show a decrease in number and in function with increasing age, which may cause a decline in rate and extent of relaxation.

In the infarct patients the relaxation velocity of the normal ventricular wall as measured from the velocity of movement of the posterior wall echo (SR-ratio/T_{sr}) is on the average higher than in the normal group. There is a small correlation between the SR-ratio/T_{sr} with the IR-ratio and enzymatic infarct size (fig. 34). The relaxation velocity of the ventricle as a whole, as expressed by $1/T_R$ shows a small, negative correlation with the IR-ratio (fig. 35). Because of an impaired rapid filling of the left ventricle, left atrial volume preceding atrial contraction may be increased. Also the minimum diastolic pressure of the left ventricle may be higher as a result of incoordinate relaxation (93, 94); see also fig. 4, chapter 2. According to the Starling effect of the left atrium, the force of left atrial contraction may be increased. This corresponds to an increased a/H-ratio. In the infarct patients the a/H-ratio was clearly higher than in normal cases. However, only the results of the first examination showed a correlation between the a/H-ratio and the IR-ratio (fig. 37). The correlation between the a/H-ratio and enzymatic infarct size (LDH_{1+2} max) was slightly better and more significant (fig. 38). Increased force of left atrial contraction should increase the volume change during contraction. The echocardiographic left atrial diameter change during atrial contraction (A_{ar}), however, was at the first and second examination only slightly greater than normal. At

the third examination A_{at} was much greater. Left ventricular filling during atrial systole may also depend on the left ventricular end-diastolic compliance which according to the compliance-ratio, was lower one and two weeks after the infarction, than two months after the infarction. In the first two weeks after the infarction the atrial contribution to ventricular filling probably could not yet compensate for the decrease during rapid filling. Stroke volume would therefore also be decreased. After two months, however, left atrial contraction may have been improved.

The index of contraction velocity $1/Tc$ was higher in the infarct patients. This may be due to an increase in end-diastolic volume (increase in preload) or to adrenergic stimulation. The pathophysiologic changes following acute myocardial infarction have been summarized in fig. 45. Myocardial infarction causes incoordinate

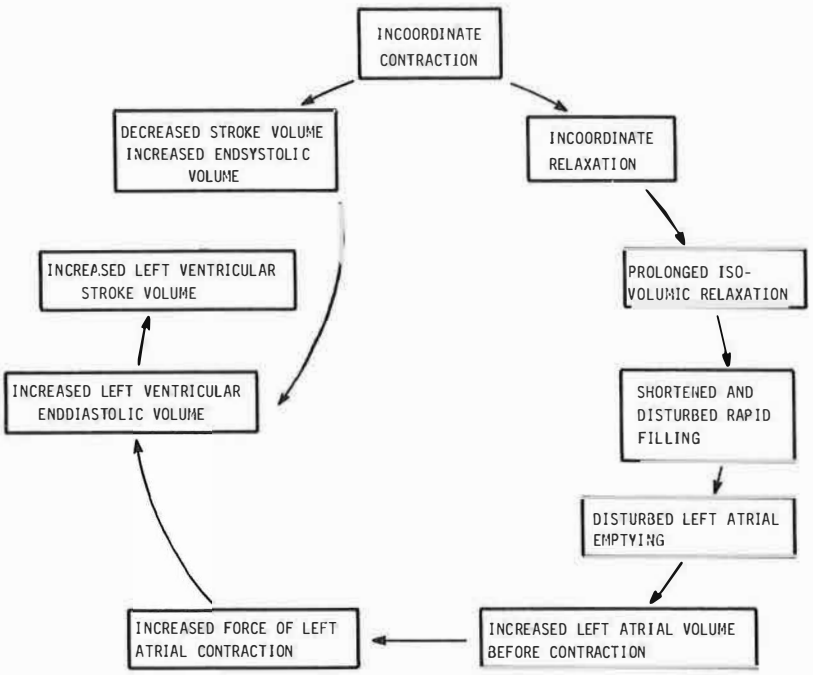


Fig. 45. Schematic diagram of the pathophysiological changes following acute myocardial infarction.

contraction and incoordinate relaxation. Incoordinate contraction causes an increase in end-systolic volume. Prolonged incoordinate

relaxation disturbs the mechanism by which rapid filling occurs. In this way left atrial volume preceding left atrial contraction is larger than normal. This causes an increased force of atrial contraction, which may increase left ventricular end-diastolic volume. By the Starling mechanism of the left ventricle, stroke volume, which had been diminished by the incoordinate contraction, may again be increased. Also when at infarction left ventricular stroke volume decreases more than right ventricular stroke volume, mean left atrial pressure will increase. This causes an increased filling of the left ventricle and so an increase of its end-diastolic volume. So it is possible that in regional dysfunction in myocardial infarction pump function is fully compensated, whereas incoordinate relaxation and an abnormal filling pattern of the left ventricle can still be demonstrated. This is accompanied by an increased end-systolic and end-diastolic volume. Therefore, regional dysfunction can be detected more easily by examination of relaxation and rapid filling than otherwise.

Measurement of the IR-ratio could be used in the early stage of myocardial infarction for monitoring therapy to reduce infarct size. Betablocking agents (5, 10, 13, 32, 107, 110, 111, 117, 123, 129, 135, 163, 164, 172, 173, 179, 193) have been found to reduce infarct size and thus regional dysfunction. Calcium antagonists might have the same action (113, 114, 115, 130, 154, 185). Vasodilation therapy could ameliorate or worsen regional dysfunction depending on the hemodynamic situation (17, 21, 22, 104, 146, 149, 189). Catecholamines are used when there is pump failure (166). The IR-ratio meets most of the demands which could be made on a suitable index of infarct size. According to Braunwald (15) the ideal technique to assess the efficacy of interventions for infarct size reduction should be: 1. non-hazardous, 2. non-invasive, 3. capable of assessing, and expressing quantitatively the size of the infarct, 4. rapidly applicable, so that treatment can start immediately, 5. relatively simple, easy to apply and inexpensive, so that its usefullness is not restricted to specialized centers and 6. applicable to all patients with myocardial infarction. Only the last two requirements are not completely fullfilled. An echocardiograph is expensive and in some patients with large inferior or posterior infarctions the IR-ratio cannot be measured. However, further investigation in the early stage of

myocardial infarction with the described methods is necessary.

In summary the following conclusions can be made.

1. The IR-ratio appears to be a new, useful and quite easily obtainable and reliable non-invasive index of regional dysfunction in the early stage of acute myocardial infarction.
2. From an apexcardiogram indices of velocity of contraction and relaxation may be derived, which reflect global ventricular function. However, the measurement of these indices may be too complicated for clinical use.
3. Congestive heart failure caused by myocardial infarction is not only due to decreased left ventricular diastolic compliance but also due to incoordinate relaxation, which in turn is closely related to incoordinate contraction. The relaxation disorder causes a disturbance in initial rapid filling, which may be compensated by increased atrial activity.
4. Relaxation should be considered as an important function of the left ventricular myocardium, lasting from the end of systole till the end of rapid filling. In normal persons the rate and extent of relaxation are related to age. Relaxation should be considered seperately from and next to diastolic compliance.
5. The most valid and sensitive indices of regional dysfunction can be derived from the relaxation period.

SUMMARY

This thesis describes a non-invasive method by which important data can be obtained about the pump function of the heart in patients with acute myocardial infarction. Disturbance in the pump function of the heart is an increasingly important cause of death and disability in patients with coronary artery disease. Arrhythmias are another important cause of death in these patients, but lately it has been possible to treat these more and more effectively, because more effective drugs and better methods of investigation are available. In chapter 1 this matter is discussed and several methods are described by which the pump function of the heart can be investigated. In patients with acute myocardial infarction it is important to obtain data on global dysfunction: the functional disturbance in the left ventricle as a whole, and regional dysfunction: the functional disturbance in a part of the left ventricular wall. Left ventricular function can be studied during the different periods of the cardiac cycle, *i.e.* the phases of contraction, relaxation and filling. Invasive investigation (cardiac catheterisation) generally gives extensive and reliable results. In the last one or two decades, the development of several non-invasive methods applicable to infarct patients has received increasing attention, because these methods are not harmful to the patient and are easily repeatable. Our investigation was made by registering an echocardiogram (of the left ventricular posterior wall, the mitral valve and the left atrium), an apexcardiogram and a carotid pulse tracing, together with an electrocardiogram and a phonocardiogram. Patients with recent myocardial infarction were examined. The examination has been carried out three times: in the first week, in the second week and two months after the infarction.

In chapter 2 a description is given of the way in which the pump function of the left ventricle gets disturbed as a result of regional dysfunction. Regional dysfunction occurs because of localized stenoses in the coronary arteries, which reduce the circulation of a part of the myocardium. It consists of an abnormal way of contraction and relaxation in which a part of the ventricular wall lags behind the rest. Normally during relaxation an elastic recoil takes place, causing the rapid filling with blood from the left atrium. Two thirds of the ventricular filling normally takes place this way. The remaining third

part of the filling is mainly caused by atrial contraction. Incoordinate contraction, occurring in regional dysfunction, causes a change in the shape of the left ventricle, which disappears during relexation (see fig. 1). This change in the shape of the left ventricle takes place during isovolumic relaxation and causes a movement of the left ventricular posterior wall, which does not occur in normal cases. The movement of the left ventricular posterior wall echo during isovolumic relaxation is expressed as a fraction of its total movement. This fraction is called IR-ratio and is introduced here as a non-invasive index of incoordinate relaxation. This in turn is related to the size of the infarct. The relaxation disorder also causes a disturbance in early diastolic filling. Left atrial contraction therefore has to contribute relatively more to ventricular filling.

Chapter 3 discusses the way in which information about cardiac function may be obtained from the apexcardiogram. For this purpose, a study was made in which simultaneous recordings were made of left ventricular pressure and apexcardiogram during cardiac catheterisation. The study was made in 19 patients with different diagnoses. It appears that the apexcardiogram is similar to the left ventricular pressure curve (or wall stresscurve),especially during the isovolumic periods. From the isovolumic parts of the apexcardiogram, indices can be obtained of contraction velocity and relaxation velocity, which agree to similar indices obtained from the left ventricular pressure curve. There is some agreement between the index of contraction velocity and *dp/dt (max).* Further, the ratio of the a-wave amplitude and total amplitude of the apexcardiogram (*a/H*-ratio) is related to the left ventricular pressure rise during atrial contraction.

Chapter 4 gives the data of the 17 infarct patients and the 28 normal individuals, as well as the methods of the investigation. From the carotid pulse tracing, the electrocardiogram and the phonocardiogram, systolic time intervals were measured, including left ventricular ejection time and the total electromechanical systole. Also the ratio of pre-ejection time and ejection time was calculated. From the recording of the apexcardiogram, the indices of contraction velocity and relaxation velocity, mentioned in chapter 3, and the *a/H*-ratio were measured. From the mitral valve echocardiogram, the onset of flow, at the beginning of rapid filling and again at

the beginning of atrial systole, was determined. From the echocardiogram of the left atrium, the filling pattern of the left ventricle in terms of atrial diameter changes was obtained. From the left atrial diameter change during atrial systole and the a/H-ratio of the apexcardiogram, an index of left ventricular end-diastolic compliance, the compliance-ratio, was calculated. From the echocardiogram of the left ventricular posterior wall, the above mentioned IR-ratio was measured. The IR-ratio was compared with the maximum concentration of the enzyme lactodehydrogenase, 1st and 2nd fraction (LDH_{1+2} max) in the plasma, which is a measure of infarct size. Finally, a reproducibility study was made to test the reliability of the measurements by means of repeated independent observation.

Chapter 5 presents the results of the investigation. From the investigation of the normal individuals it appears that measurements related to relaxation are age-dependent: indices related to relaxation velocity and volume changes during rapid filling are lower with increasing age. In infarct patients the IR-ratio in the first week after infarction correlates with infarct size as expressed by LDH_{1+2} max. Measurements related to relaxation, isovolumic phase and rapid filling appeared to correlate quite well with the IR-ratio. Measurements related to atrial contraction correlated better with LDH_{1+2} max than with the IR-ratio. Indices related to ventricular systole showed hardly any relation to the IR-ratio or LDH_{1+2} max.

In chapter 6 the results of the investigation are discussed. It appears that regional dysfunction in myocardial infarction can indeed be described as proposed in chapter 2. Myocardial infarction causes incoordinate contraction and incoordinate relaxation. Incoordinate contraction causes a decrease in the stroke volume and increase in the end-systolic volume. Incoordinate relaxation causes a disturbance in rapid filling. In this way, left atrial volume preceding left atrial contraction is larger than normal. This results in an increased force of left atrial contraction, which in turn may cause an increase in the end-diastolic volume. Via the Starling mechanism of the left ventricle, this may increase the stroke volume, thus compensating for the consequences of incoordinate contraction. As diastolic compliance is also less than normal, especially in the early stage, this does not always occur.

From the reproducibility study it can be concluded that the measurement of the IR-ratio is sufficiently reliable and sensitive. It may therefore be used as an index of infarct size in the early stage of acute myocardial infarction. Further investigation should be made to establish the value of the IR-ratio in monitoring patients with acute myocardial infarction and in the control of their therapy with e.g. betablocking agents, calcium antagonists, vasodilating drugs and catecholamines.

In summary, the following conclusions can be made:

1. The IR-ratio appears to be a new, useful and quite easily obtainable and reliable non-invasive index of regional dysfunction in the early stage of myocardial infarction.
2. From an apexcardiogram indices of velocity of contraction and relaxation may be derived, which reflect global ventricular function. However, the measurement of these indices may be too complicated for clinical use.
3. Congestive heart failure caused by myocardial infarction is not only due to decreased left ventricular diastolic compliance but also due to incoordinate relaxation, which in turn is closely related to incoordinate contraction. The relaxation disorder causes a disturbance in initial rapid filling, which may be compensated by increased atrial activity.
4. Relaxation should be considered as an important function of the left ventricular myocardium, lasting from the end of systole till the end of rapid filling. In normal persons the rate and extent of relaxation are related to age. Relaxation should be considered seperately from and next to diastolic compliance.
5. The most valid and sensitive indices of regional dysfunction can be derived from the relaxation period.

SAMENVATTING

Dit proefschrift beschrijft een methode, waarmee door middel van uitwendig onbloedig onderzoek, een aantal belangrijke gegevens kunnen worden verkregen over de functie van het hart als pomp bij patiënten die kort tevoren een hartinfarct hebben doorgemaakt. Storingen in de pompwerking van het hart worden steeds belangrijker als doodsoorzaak en als oorzaak van invaliditeit bij patiënten met afwijkingen aan de kransvaten van het hart. De ritmestoornissen die een andere belangrijke doodsoorzaak bij deze patiënten vormen, kunnen namelijk de laatste tijd steeds beter worden behandeld door beter werkzame geneesmiddelen en betere onderzoekmethoden. In hoofdstuk 1 wordt dit besproken. Tevens worden verschillende methoden vermeld met behulp waarvan de pompwerking van het hart kan worden bestudeerd. Het is van belang bij patiënten met een hartinfarct gegevens te verzamelen over de globale dysfunctie van de linker hartkamer, de functiestoornis van de kamer als geheel, en over de regionale dysfunctie, de functiestoornis van een deel van de wand van de linker hartkamer. Verder kan men de functie van het hart in de verschillende fasen van de hartcyclus bestuderen, namelijk in de systole (samentrekking van de hartspier) en in de diastole (de verslapping van de hartspier en de vulling van het hart). Inwendig onderzoek met behulp van hartcatheterisatie levert over het algemeen uitvoerige en betrouwbare gegevens op. Algemeen wordt echter aangenomen dat dit onderzoek teveel risico's met zich mee brengt bij patiënten met een vers hartinfarct. Uitwendige onderzoekmethoden zijn veilig en zonder veel ongemak voor de patiënt uitvoerbaar, maar de gegevens die deze methoden opleveren zijn in uitvoerigheid en betrouwbaarheid beperkter dan die verkregen bij hartcatheterisatie.

Het onderzoek werd uitgevoerd door registratie van echocardiogrammen van de linker hartkamerachterwand, de mitraalklep (tussen linker boezem en linker kamer) en van de linker boezem, een apexcardiogram en een carotispolscurve, gelijktijdig met een electrocardiogram en een fonocardiogram. Met een echocardiogram worden de bewegingen van de hartkleppen en de wand van de linker hartkamer en linker boezem vastgelegd met behulp van ultrageluid. Een apexcardiogram is een uitwendige

registratie van de bewegingen van de hartpunt. Een carotispolscurve is de uitwendige registratie van de pulsaties van de halsslagader. Het electrocardiogram is de registratie van de electrische activiteit van het hart en een fonocardiogram is de registratie van het geluid van het hart, dus de harttonen. Het onderzoek werd gedaan bij patiënten die voor de eerste maal een hartinfarct doormaakten. Driemaal werden registraties gemaakt, in de eerste week, de tweede week, en twee maanden na het infarct.

In hoofdstuk 2 wordt een uiteenzetting gegeven over de wijze waarop de pompwerking van de linker hartkamer wordt gestoord, wanneer een deel van de spierwand niet meer goed functioneert. Dit is het geval bij een storing in de bloedvoorziening van de hartspier door vernauwingen van de kransslagaders. De storing bestaat uit een afwijkende wijze van samentrekking en verslapping. Een gedeelte van de spierwand blijft achter bij de rest. Bij de verslapping van het hart vindt in normale gevallen een elastisch terugveren plaats, waardoor bloed uit de linker voorkamer als het ware wordt aangezogen. Op deze wijze vindt normaliter ongeveer twee derde van de vulling van de linker hartkamer plaats. Het overige deel van de vulling komt hoofdzakelijk tot stand door de samentrekking van de linker boezem. Bij de afwijkende wijze van samentrekking, die het gevolg is van het uitvallen van een deel van de hartspier, vindt een verandering van de vorm van de linker hartkamer plaats, die weer wordt hersteld bij de verslapping (zie fig. 1). Deze vormverandering vindt plaats voordat de vulling van de linker hartkamer begint, op een moment dat alle hartkleppen gesloten zijn. Het volume van het hart blijft tijdens deze periode dus gelijk. We noemen deze periode de isovolumetrische relaxatieperiode. Door meting van de beweging van de achterwand van de linker hartkamer tijdens deze periode uit het echocardiogram (de IR-ratio) is de omvang van de genoemde vormverandering, die op zijn beurt weer samenhangt met de grootte van het infarct, te schatten. De afwijkende verslapping gaat gepaard met een verstoring van de vroege vulling van de linker kamer. Hierdoor wordt het hart tijdens deze periode minder goed gevuld en zal de linker boezem door haar samentrekking een grotere bijdrage moeten leveren aan de vulling. Dit blijkt ook uit de literatuurgegevens.

In hoofdstuk 3 is nagegaan welke informatie over de functie van

het hart is te verkrijgen uit de uitwendige registratie van de pulsaties van de hartpunt, het apexcardiogram. Hiervoor is een onderzoek gedaan, waarbij tijdens hartcatheterisatie van patiënten met verschillende afwijkingen de druk in de linker hartkamer en het apexcardiogram gelijktijdig zijn geregistreerd. Uit dit onderzoek blijkt dat het apexcardiogram overeenkomst vertoont met het verloop van de druk in de linker hartkamer. Met name die gedeelten van de curve die geregistreerd worden gedurende de tijd dat alle hartkleppen gesloten zijn, bij het begin van de samentrekking en de verslapping van de hartkamers, lijken waardevol te zijn. Men kan hieruit een getal vinden dat iets zegt over de snelheid van samentrekking en die van verslapping. Ook het gedeelte van de curve geregistreerd tijdens de samentrekking van de linker voorkamer (de a-top) levert informatie op. De grootte van deze a-top hangt samen met de drukstijging in de linker kamer ten gevolge van de samentrekking van de linker boezem.

Hoofdstuk 4 geeft de gegevens van de 17 infarctpatiënten en de 28 onderzochte normale personen. Tevens wordt de methode van onderzoek besproken. Uit de registratie van de pulsaties van de halsslagader (carotispolscurve) samen met het electrocardiogram en de geluidsregistratie (fonocardiogram) wordt de duur van de uitdrijving van bloed in de aorta berekend. Uit de registratie van de pulsaties van de hartpunt (apexcardiogram) worden de indices voor de snelheid van samentrekking, de snelheid van verslapping en voor de kracht van samentrekking van de linker boezem berekend, zoals aangegeven in hoofdstuk 3. Van het echocardiogram van de mitralisklep wordt het moment van het begin van de vulling van de linker kamer en van de samentrekking van de linker voorkamer gemeten. Uit diameterveranderingen van de linker voorkamer op het echocardiogram wordt de wijze van vulling van de linker kamer beoordeeld en de mate waarin de initiële snelle vulling door de verslapping van het hart en de samentrekking van de linker voorkamer daaraan bijdragen. De relatieve beweging van de achterwand van de linker kamer tijdens de isovolumetrische relaxatieperiode, de IR-ratio, beschreven in hoofdstuk 2, wordt gebruikt als maat voor de omvang van de vormverandering tijdens de verslapping en dus ook tijdens de samentrekking. De IR-ratio wordt vergeleken met de maximale concentratie in het bloed van het enzym

lactodehydrogenase (1e en 2de fractie) na het infarct. Deze zogenaamde $LDH_{1+2}max$ is een maat voor de grootte van het infarct. Tenslotte wordt beschreven hoe de betrouwbaarheid van een aantal metingen is getest door herhaalde onafhankelijke beoordeling.

In hoofdstuk 5 worden de resultaten van het onderzoek beschreven. Uit het onderzoek bij normalen blijkt dat de metingen die iets te maken hebben met het verslappingsproces leeftijdsafhankelijk zijn. De verslapping gebeurt langzamer naarmate men ouder wordt. Bij de infarctpatiënten blijkt de omvang van de vormverandering van de hartkamer tijdens de verslapping, de IR-ratio, direct na het infarct gemeten overeen te komen met de grootte van het infarct, uitgedrukt als $LDH_{1+2}max$. Metingen die betrekking hebben op de verslapping, isovolumetrische fase, snelle vulling en samentrekking van de linker voorkamer, bleken beter overeen te komen met de IR-ratio dan metingen die betrekking hebben op de samentrekking van de linker kamer. De samentrekkingskracht van de linker voorkamer en de rekbaarheid van de kamer tijdens de vulling hangen samen met de grootte van het infarct en veranderen niet veel tijdens het verdere verloop.

In hoofdstuk 6 worden de resultaten van het onderzoek besproken in het licht van wat in hoofdstuk 2 besproken is over de functiestoornis van het hart na een infarct. Men kan uit de resultaten concluderen dat de storing in pompwerking door een hartinfarct inderdaad kan worden beschreven, zoals in hoodstuk 2 wordt voorgesteld. Door een ongecoördineerde wijze van samentrekking van het hart ontstaat een storing in de uitdrijving van het bloed. Hiermee hangt een ongecoördineerde wijze van verslapping samen, waardoor een storing in de vulling ontstaat, met name in de vroege fase. Hoewel het infarct ook een verhoogde weerstand tegen passieve vulling veroorzaakt, wordt de vroege vullingsstoring gecompenseerd door een toegenomen activiteit van de linker boezem, en wel in de loop van de tijd na het infarct in toenemende mate. Een en ander veroorzaakt een hogere druk in de linker hartkamer tijdens de vulling en een groter volume van de linker kamer aan het begin van de samentrekking van de kamer. Daardoor wordt meer bloed uitgedreven tijdens de samentrekking van het hart. Op deze wijze wordt de uitdrijvingsstoornis gecompenseerd, echter met een abnormaal vullingspatroon en een verhoogde samentrekkingskracht

van de linker boezem. Methoden om deze laatste verschijnselen aan te tonen, zijn dus gevoeliger voor het aantonen van een abnormale pompwerking bij patiënten met kransvatafwijkingen dan methoden van onderzoek naar de samentrekking van de linker kamer of de uitdrijving van het bloed uit het hart.

Of de beschreven methoden zich lenen voor onderzoek van de individuele patiënt, hangt samen met de gevoeligheid en de betrouwbaarheid van de methoden. Gezien de resultaten, onder andere van het reproduceerbaarheidsonderzoek, lijkt de meting van de beweging van de achterwand van de linker kamer tijdens de verslapping (IR-ratio) redelijk betrouwbaar en gevoelig te zijn. In de toekomst zal het nodig zijn de beschreven methoden te vergelijken met het resultaat van onderzoek bij hartcatheterisatie. Ook zal geprobeerd moeten worden de nauwkeurigheid van de meetmethoden te verbeteren. Om het inzicht in het verloop van de storingen van de pompwerking van het hart na een infarct te verbeteren, zal het verder nodig zijn, onderzoek op de beschreven wijze, aangevuld met inwendige metingen bij infarctpatiënten in een vroeger stadium te verrichten.

Tenslotte kunnen de volgende conclusies worden geformuleerd.

1. De IR-ratio blijkt een nieuwe, nuttige, tamelijk gemakkelijk door uitwendig onderzoek verkrijgbare, redelijk betrouwbare index van regionale dysfunctie te zijn in het vroege stadium van het acute hartinfarct.
2. Van een apexcardiogram kunnen indices van snelheid van concentratie en van relaxatie worden verkregen, die de globale functie van de linker hartkamer weerspiegelen. De meting van deze indices is echter waarschijnlijk te ingewikkeld voor klinisch gebruik.
3. Hartdecompensatie tengevolge van een hartinfarct wordt niet alleen veroorzaakt door een verminderde rekbaarheid van de linker kamer maar ook door een ongecoördineerde wijze van relaxatie, die op zijn beurt nauw samenhangt met een ongecoördineerde wijze van contractie. De relaxatiestoornis veroorzaakt een verstoring van de vroege snelle vulling, die gecompenseerd kan worden door een toegenomen activiteit van de linker voorkamer.
4. De relaxatie, die duurt van het eind van de kamercontractie tot het

eind van de snelle vulling, moet beschouwd worden als een belangrijke functie van de spierwand van de linker hartkamer. Bij normale mensen hangen de snelheid en de mate van relaxatie samen met de leeftijd. De relaxatie moet afzonderlijk worden bekeken naast de diastolische rekbaarheid.

5. De meest waardevolle en gevoelige indices van regionale dysfunctie zijn die ontleend aan de relaxatieperiode.

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