"THE APPLICATION OF SERIAL ELECTROPHYSIOLOGICAL TESTING IN THE MANAGEMENT OF PATIENTS WITH VENTRICULAR ARRHYTHMIAS."

by

© ALAN P. RAE

B.Sc., M.B.Ch.B., M.R.C.P.(UK)

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Department of Medical Cardiology,
Royal Infirmary, Glasgow.

Likoff Cardiovascular Institute,
Hahnemann University Hospital,
Philadelphia.

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SUMMARY

The lethal potential of ventricular tachyarrhythmias is well recognised and because of the ineffectiveness of empirically prescribed therapy a directed approach to the treatment of these arrhythmias is mandated. The aim of the studies in this thesis was to further define the applicability of serial electrophysiological testing for the determination of effective antiarrhythmic therapy in patients with these arrhythmias.

In Chapter 1, the potential mechanisms for the development of ventricular tachyarrhythmias and their relation to the use of programmed stimulation are discussed. The prognostic impact of ventricular arrhythmias is reviewed. The therapeutic options are described and the classification of antiarrhythmic drugs is explained. The different management strategies for the prescription of antiarrhythmic therapy are discussed. The historical development and rationale for electrophysiological testing is described.

The methodology and equipment required for this approach is described in Chapter 2. In particular, the stimulation protocol employed in all studies in this thesis is explained.

The induction of ventricular tachyarrhythmia in response to the stimulation protocol is dealt with in

Chapter 3. The varying impact of different factors including the type of underlying heart disease in the patient population being studied and the different components of the stimulation protocol are described. The comparability of the results with those reported from other laboratories confirms the utility of the stimulation protocol. The controversial aspect of sensitivity, specificity and reproducibility of programmed stimulation is discussed.

In Chapter 4, the techniques for tachycardia termination and the effectiveness of pacing modalities are described. The effect of cycle length and antiarrhythmic therapy on pacing termination are discussed.

The concordance between the response to electrophysiological testing with both intravenous and oral formulations of procainamide is dealt with in Chapter 5. The advantages of testing intravenous therapy were offset by the observation that noninducibility with intravenous procainamide was not predictive of noninducibility with oral procainamide. The results from this study confirm that retesting on oral therapy is required even if the intravenous agent is shown to be effective.

The use of serial electrophysiological drug testing to identify effective therapy in patients with ventricular tachyarrhythmias related to coronary artery disease is described in Chapter 6. Overall drug efficacy, efficacy of individual regimens and the effect of the type of

induced arrhythmia on drug response are detailed. The long-term effectiveness of antiarrhythmic regimens identified as successful by electrophysiological testing is confirmed using both the accepted stimulation end-point of noninducibility and the more relaxed end-point of 15 or less repetitive responses.

In Chapter 7, similar results confirming the predictive value of serial drug testing were obtained for patients with ventricular tachyarrhythmias related to cardiomyopathy.

The effect of the combination of amiodarone plus the Type 1 agent procainamide on arrhythmia inducibility is discussed in Chapter 8. The main benefit of the addition of procainamide was on the haemodynamic impact of the induced arrhythmia which may provide a degree of protection from sudden death.

Using multivariate statistical techniques the determinants of the response to serial electrophysiological drug testing were analysed in Chapter 9. Patients with poor left ventricular function were less likely to respond to medical therapy, and suppression of arrhythmia induction was more difficult in patients with induced sustained ventricular tachycardia than in patients with either ventricular fibrillation or nonsustained ventricular tachycardia. During follow up, if recurrence of arrhythmia occurred, it was more likely to be as sudden death if the patients had cardiac failure, and the induced arrhythmia in

the discharge drug study was not symptomatically tolerated. The major independent variable which predicted recurrence of arrhythmia during follow-up was failure of serial electrophysiological drug testing to identify a successful therapy.

In Chapter 10, the predictive value of the response to procainamide is discussed. Failure of procainamide to suppress arrhythmia inducibility predicts failure of other agents in patients with induced sustained ventricular tachycardia but not in patients with either ventricular fibrillation or nonsustained ventricular tachycardia. The implications of these observations in the evaluation of antiarrhythmic drug efficacy are discussed.

In Chapter 11, the use of programmed stimulation to reveal the potential for drug related worsening of arrhythmias is described. The different proarrhythmic responses and their potential clinical value are discussed and the lack of predictability of these responses is investigated.

Important unresolved problems in the clinical application of electrophysiological testing for the management of patients with ventricular tachyarrhythmias are discussed in Chapter 12.

CHAPTER 1

INTRODUCTION AND HISTORICAL REVIEW

Ventricular tachyarrhythmias account for the major proportion of the 100,000 sudden deaths which occur in the United Kingdom per year.

In the last 15 years, there have been tremendous advances in our understanding of the underlying mechanisms for ventricular arrhythmias and with technological development, the methodologies for the detection and quantification of these arrhythmias have been refined. This has provided the basis for a more logical and rational approach to the management of patients with these potentially lethal tachyarrhythmias.

1.1 MECHANISM OF VENTRICULAR ARRHYTHMIAS

Both experimental and clinical studies suggest that ventricular arrhythmias may be due to several electrophysiologically distinct mechanisms. For many years, these arrhythmias were attributed to either automaticity or reentry[1]. Recently a third mechanism, triggered activity, has been demonstrated and its relevance to clinically occurring arrhythmias suggested[2,3].

In the normal heart, certain pacemaker cells, for

example in the sinus and AV nodes, manifest automaticity. During the phase of repolarisation, such cells do not remain at their resting negative potential but spontaneously depolarise. The dominant pacemaker maintains control of the lower pacemakers by the phenomenon of overdrive suppression which is due to both depolarisation of the lower pacemaker cells before the spontaneous phase 4 depolarisation reaches threshold and a dampening effect on the rate of this depolarisation. Failure of the dominant pacemaker may therefore lead to the development of ventricular "escape" rhythms. Although these type of arrhythmias are related to normal automaticity, more frequently, ventricular arrhythmias are due to abnormal automaticity. In an abnormal electrophysiologic milieu, myocardial cells which do not normally manifest automaticity may develop the potential for automaticity due to a reduction in the resting negative diastolic potential, permitting spontaneous depolarisation[4,5]. This latter mechanism probably accounts for the ventricular arrhythmias related to myocardial ischaemia and those occurring in the early phase of myocardial infarction[1,6]. These two types of automaticity may differ in their response to overdrive stimulation. As noted previously, cells with normal automaticity demonstrate overdrive suppression whereas with abnormal automaticity, such suppression may not be evident[7].

The second mechanism underlying ventricular arrhythmias is reentry[1]. This is a disturbance of impulse conduction and for its development certain electrophysiological conditions are required, viz: two electrophysiologically distinct pathways, with unidirectional block in one pathway and slowed conduction in the other. Under these conditions, the impulse blocked in the first pathway may be conducted sufficiently slowly down the second pathway such that it reaches the distal point of the first pathway at a time when it has recovered from refractoriness, thus permitting reciprocation of the impulse and the potential for establishment of a sustained arrhythmia. This mechanism is considered to account for the majority of chronic recurrent ventricular tachyarrhythmias particularly in patients with previous myocardial infarction where the necessary electrophysiological substrate can be provided by the presence of ischaemically damaged or infarcted tissue[8,9,10]. Development of reentry can be initiated by the introduction of premature stimuli or pacing techniques which can create the unidirectional block and slowed conduction required. As will be discussed later, this forms the basis for the clinical electrophysiological approach to the management of ventricular arrhythmias.

Triggered activity is a form of automaticity which, in contrast to the de novo initiation of an impulse due to normal and abnormal automaticity, requires a stimulus to

initiate the primary depolarisation[11]. Two forms of triggered activity have been identified with a differing temporal relationship to the initiating action potential. Early after-depolarisations occur before full re-polarisation of the cell has taken place and consist of oscillatory potentials which can depolarise adjacent cells[11]. This rhythmic discharge has been observed particularly in Purkinje fibres with delay in action potential repolarisation and may correlate with the clinical situation of torsade de pointes due to QT prolongation. Delayed afterdepolarisations occur at the end of the repolarisation phase of the action potential. Although this type of oscillatory potential may be noted in certain cells under normal conditions, they are most marked in Purkinje fibres exposed to toxic concentrations of digitalis. Their development is thought to be due to the increase of calcium within the cell. Arrhythmias which develop in the clinical situation of digitalis toxicity are thought to be due to this mechanism[2].

Since the initiation of triggered activity is dependent on cellular depolarisation, arrhythmias related to this mechanism can be manipulated by premature stimulation and pacing. This response, however, tends to differ from arrhythmias related to a reentrant mechanism.

Evidence from both experimental and clinical electro-physiological studies which tend to favour reentry rather than triggered activity for the majority of chronic

ventricular tachyarrhythmias include:

1) The reproducible initiation and termination of ventricular tachycardia by premature stimulation[12,13].

2) The inverse relationship between the coupling interval of a premature stimulus and the first beat of the initiated tachycardia[14-17].

3) The low incidence of initiation by pacing compared to premature stimulation[1].

4) Demonstration that ventricular tachycardia can be entrained by ventricular pacing[18].

5) The high frequency of termination of tachycardia by ventricular pacing compared to the development of overdrive acceleration[19,20].

6) The finding that verapamil which has been shown to terminate triggered activity is not particularly effective in terminating clinically occurring ventricular tachycardia[17].

These various criteria, however, are only consistent with our present understanding of these mechanisms and although it appears that triggered activity plays only a minor role in chronic ventricular arrhythmias, its precise place in the genesis of these arrhythmias is not yet fully determined[3].

1.2 SIGNIFICANCE OF VENTRICULAR ARRHYTHMIAS

Simple ventricular ectopy occurs both in normal individuals and in patients with heart disease[21,22]. More complex ectopy, including repetitive forms and nonsustained ventricular tachycardia is almost always associated with underlying heart disease[23,24].

In addition to the type of ectopy, the frequency of ectopy is related to the presence or absence of heart disease. Although the ectopic frequency is higher in older age[25], it is considerably more frequent in patients with underlying structural heart disease.

Prognostically, simple ventricular ectopy does not appear to confer an increased risk of sudden death in patients without underlying heart disease[26,27,28]. In direct contrast, complex and frequent ventricular ectopy in the presence of structural heart disease carries a significant increase in this risk[23].

Most studies have evaluated the prognostic implication of complex ectopy in patients with myocardial infarction. Ruberman et al.[29] demonstrated that complex ectopy was associated with an increased risk of sudden death and that this ectopy was an independent risk factor. Similar findings were obtained by Moss et al.[30] and Lichtlen et al.[31]. Califf et al.[32], in a group of patients undergoing cardiac catheterisation for chronic coronary artery disease, noted, not only the association of ventricular

arrhythmias and subsequent mortality but in addition showed a significant association between these arrhythmias and impaired ventricular function. Subsequently, two large post myocardial infarction studies have shown that the mortality was much higher in patients with the combination of complex ectopy and left ventricular dysfunction[33,34]. In the study by Bigger and coworkers an increased risk of sudden death has been observed with an ectopic frequency of >1 VPC/hour[33,34]. More recently this group has reported the significance of nonsustained ventricular tachycardia as a risk factor[35].

The role of ventricular arrhythmia in the aetiology of sudden cardiac death was suggested by the work of Cobb and his colleagues who found that, in survivors of out-of-hospital cardiac arrest, electrocardiographic evidence of acute myocardial infarction was present in only about 30% of patients [36]. The Aspirin Myocardial Infarction Study (AMIS) provided further evidence, demonstrating that in patients dying within 24 hours, 83% of these deaths were due to cardiac arrhythmias [37]. Recently, similar findings have been observed in patients with dilated cardiomyopathy[38,39].

Ambulatory monitoring in patients at the time of sudden cardiac death has shown that the majority of these are due to ventricular tachyarrhythmias[40] and in the reported cases of ventricular fibrillation, ventricular tachycardia preceded the terminal fibrillatory event[40,41].

Patients who have already experienced a sustained tachyarrhythmia remain at high risk of subsequent arrhythmic events. Several studies have suggested that for sustained ventricular tachycardia the annual mortality may be as high as 40%[42,43]. The majority of these patients have underlying heart disease and in particular have dyskinetic ventricular segments due to myocardial fibrosis/aneurysm. Similar mortality figures have been noted for patients who have been resuscitated from out-of-hospital cardiac arrest when the event was not associated with acute myocardial infarction[36].

Although ventricular arrhythmias during the acute phase of myocardial infarction are common[44], prognostically they are of less significance than those occurring in the late phase[45-49]. The acute phase arrhythmias, as discussed previously, are due to the development of abnormal automaticity secondary to a changing electrophysiological milieu at the cellular level. This is in contrast to the chronic reentrant mechanism operative in the later phase arrhythmias. The management strategies for ventricular arrhythmias in acute myocardial infarction therefore, are considerably different from those required for the chronic recurrent arrhythmias discussed in this thesis[47].

1.3 HAEMODYNAMIC EFFECTS OF VENTRICULAR ARRHYTHMIAS

Ventricular arrhythmias may produce a spectrum of

symptomatic effects related to their haemodynamic consequences. The impact on cardiac performance is dependent not only on the direct effect of the arrhythmia itself but is also related to the underlying ventricular function. Ventricular arrhythmias, which may be tolerated or even unappreciated by the patient with a "normal" heart, may have severe deleterious consequences in patients with reduced cardiac function and impaired cardiac reserve.

Several different interdependent factors account for the haemodynamic sequelae. In tachyarrhythmias, shortening of the R-R interval is a result of a reduction in the duration of the diastolic filling time with relative preservation of systolic time. This reduction in diastolic filling time results in a decrease in end-diastolic volume with consequent reduction in cardiac output as determined by the Starling curve. A further consequence of the shortened diastolic filling time is that coronary blood flow may be impaired particularly if there is associated obstructive coronary artery disease. Although changes in heart rate invoke certain compensatory mechanisms, these may also be significantly compromised in patients with impaired myocardial function. Optimum cardiac function requires synchronisation of atrial and ventricular contraction [50,51]. Impairment of this sequencing with loss of the atrial contribution to ventricular filling may therefore be an important component of the resultant haemodynamic response. In addition,

coincidental atrial contraction against a closed tricuspid valve may produce a "negative atrial kick" and venous regurgitation[52]. Disturbance of synchronised inter-ventricular contraction may also be of importance especially in patients with poor left ventricular function[53].

The symptoms perceived by patients with ventricular arrhythmias are very variable, ranging from palpitation to syncope and sudden death. Patients with isolated ventricular ectopic beats may be aware of an unpleasant sensation although the ectopics themselves produce no overall impact on cardiac function. In contrast, certain patients with sustained ventricular tachycardia may remain relatively asymptomatic for many hours except for mild palpitation. In some cases this haemodynamic stability of ventricular tachycardia has prevented the correct diagnosis of the arrhythmia.

1.4 TREATMENT OF VENTRICULAR TACHYARRHYTHMIAS

Bigger and Morganroth have proposed a clinical and prognostic classification for ventricular arrhythmias, sub-dividing into benign, potentially malignant and malignant[54,55]. Benign arrhythmias were considered to be simple ectopy in patients without underlying heart disease for whom no antiarrhythmic therapy was indicated for prognostic reasons. Potentially malignant arrhythmias

included more complex ectopy associated with structural heart disease especially with impaired ventricular function. In this subdivision, therapy was indicated on the basis of the high risk of subsequent sudden death. Patients who had already experienced a malignant ventricular tachyarrhythmia required an aggressive management approach to prevent the high incidence of recurrence of a potentially lethal event.

General Principles

Irrespective of whether ventricular arrhythmias require treatment for symptoms or for prognostic purposes, attention must be paid to the treatment and correction of provocative factors and underlying disease states if present. These factors include hypokalaemia and acidosis. Discontinuation of cardioactive agents including caffeine and nicotine in addition to concomitant drug therapy such as the sympathomimetic amines should be considered. The association of drugs (eg. type I antiarrhythmic agents and tricyclic antidepressants) which lengthen the QT interval with the potential for the development of polymorphous ventricular tachycardia (torsade de pointes) is well recognised.

Methods of Treatment

Several different modalities can be employed for the acute and long term treatment of ventricular tachy-arrhythmias:

1) antiarrhythmic drug therapy

2) pacing techniques including premature stimulation[56,57]

3) internal cardioverter[58,59]

4) automatic implantable cardioverter/ defibrillator[60,61,62]

5) surgery including encircling endocardial ventriculotomy and subendocardial resection[59,60,61,62]

For most patients, first-line treatment is the prescription of antiarrhythmic therapy. Alternative modalities are considered if the medical approach is ineffective or inappropriate. The studies discussed in this thesis relate to the use of antiarrhythmic drugs for patients with ventricular tachyarrhythmias and the application of these other options is not addressed further.

1.5 ANTIARRHYTHMIC DRUG THERAPY FOR VENTRICULAR TACHYARRHYTHMIAS

Potential mechanisms of effect

As discussed previously, several mechanisms have been implicated in the development of ventricular arrhythmias. The suppressive effects of different antiarrhythmic agents can be explained by differing modifications to these mechanisms.

In arrhythmias related to automaticity,

antiarrhythmic drugs may a) suppress the spontaneous phase 4 depolarisation, or b) separate the maximum diastolic potential from the depolarisation threshold level by either reducing further the maximum diastolic potential or raising the threshold. In addition to modifying impulse generation, the automatic impulse propagation can be blocked by depressing conduction or prolonging refractoriness of the adjacent myocardium.

Since the development of reentry requires a critical balance in the electrophysiological milieu, interrupting the reciprocating wavefront can be produced by influencing either conduction and/or refractoriness in the circuit. Block in conduction in the antegrade pathway would obviously isolate the potential substrate whereas acceleration of conduction in the pathway may cause the impulse to reach the retrograde pathway at a time when it is still refractory and therefore extinguish the wave of excitation. Increase in the refractoriness of the retrograde pathway could also prevent retrograde impulse conduction.

Triggered activity is dependent on cycle-length and therefore modifications in heart rate may suppress this arrhythmic mechanism. The amplitude of early after-depolarisations increase with lengthening of the cycle length of stimulation in contrast to delayed after-depolarisations whose amplitude decreases. An increase in heart rate would therefore tend to suppress

early after-depolarisations and a decrease in heart rate suppress delayed after-depolarisations. In addition, since after-depolarisations are dependent on the plateau phase of the action potential, antiarrhythmic agents which either decrease the inward calcium current maintaining this phase or increase the current with shortening of repolarisation will tend to prevent the initiation of triggered activity.

Antiarrhythmic agents in general do not have specific isolated effects but tend to have several potential actions which may or may not be dose-dependent.

Classification of Antiarrhythmic Agents

The most widely accepted classification for antiarrhythmic agents is based on their predominant electrophysiological effect on the cellular action potential as proposed by Vaughan Williams[67].

Subsequently, this classification has undergone several modifications to include additional classes of antiarrhythmic drugs[68,69,70].

Table 1.1 illustrates the modified Vaughan Williams classification as proposed by Morganroth[54].

Class I Antiarrhythmic Agents

The main action of class I agents is depression of the fast inward sodium current responsible for the upstroke of the myocardial action potential (phase 0). Within this

CLASS	DESCRIPTION	EXAMPLE
1A	MODERATE DEPRESSION OF PHASE 0 DEPOLARISATION; PROLONGED REPOLARISATION	QUINIDINE, PROCAINAMIDE, DISOPYRAMIDE
1B	WEAK DEPRESSION OF PHASE 0 DEPOLARISATION; SHORTENED REPOLARISATION	LIGNOCAINE, TOCAINIDE, MEXILETINE, APRINDINE
1C	STRONG DEPRESSION OF PHASE 0 DEPOLARISATION; LITTLE EFFECT ON REPOLARISATION	FLECAINIDE, ENCAINIDE, INDECAINIDE, PROPAFENONE
II	B-ADRENOCEPTOR BLOCKERS	PROPRANOLOL, PINDOLOL, METOPROLOL, ATENOLOL, TIMOLOL, NADOLOL
III	PROLONGED REPOLARISATION	AMIODARONE, SOTALOL, BETHANIDINE
IV	CALCIUM CHANNEL BLOCKERS	VERAPAMIL, DILTIAZEM

TABLE 1.1 Antiarrhythmic Drug Classification

EMPIRICAL	DIRECTED
EMPIRICAL PRESCRIPTION	EXERCISE TESTING
DRUG LEVEL MONITORING	HOLTER MONITORING
	ELECTROPHYSIOLOGICAL TESTING.

TABLE 1.2 Approach to treatment of ventricular arrhythmias

class, there is a further subdivision based on the relative potency of the depression of phase 0 and effects on repolarisation.

Class IA

Class IA agents include quinidine, procainamide and disopyramide. These drugs exert a concentration-dependent depressant effect on the velocity of phase 0 (V max.) of atrial and ventricular tissue[71,72,73] and modify the depolarisation threshold potential. Automaticity is further decreased by depression of phase 4 depolarisation. Class IA agents also prolong the duration of the action potential and the effective refractory period[71,72], although in the case of disopyramide this direct action is modified by its anticholinergic effect which tends to counteract this prolongation[74].

Class IB

In contrast, the Class IB agents, lignocaine, mexiletine and tocainide tend only to have a minor effect on V max. of the action potential and no effect on the resting membrane potential of cardiac tissue[75,76,77]. A further differing feature from the Class IA compounds is that these agents shorten the duration of the action potential and the refractory period although the former effect predominates with a resultant relative prolongation of refractoriness.

Class IC

Flecainide, encainide and propafenone are classified as 1C compounds on the basis of their profound depression of phase 0 of the action potential and only minimal effects on action potential duration[70,78,79].

Class II Antiarrhythmic Agents

The Class II agents comprise the beta-adrenoceptor blocking drugs whose main antiarrhythmic effect is to modify catecholamine-induced responses. Although propranolol also possesses local anaesthetic action, at beta-adrenoceptor blocking doses, it does not change V max. or the resting membrane potential.

Class III Antiarrhythmic Agents

The predominant electrophysiological feature of Class III agents is significant prolongation of the action potential with prolongation of repolarisation and refractoriness.

Amiodarone possesses potent Class III activity in all cardiac tissue[80]. In addition, amiodarone has been shown to interact with thyroid metabolism and have a non-competitive sympathetic antagonism. Recently studies have suggested that it may also possess a type I effect with depression of phase 0 [81], and in myocardial ischaemia it is this antiarrhythmic effect which may predominate[82].

Other Class III agents include sotalol which also has

beta-adrenoceptor blocking activity and bretylium which possesses antifibrillatory and sympatholytic properties.

Class IV Antiarrhythmic Agents

The Class IV drugs verapamil and diltiazem both demonstrate slow calcium channel antagonism. The action potential of pacemaker cells is calcium dependent and polarisation is due to the movement of the slow inward current, although as has been noted recently, sodium ions may also be involved in this process. In such slow-response cells, these Class IV drugs depress V max. and the amplitude of the action potential due to reduction in the conductance of the slow channel[83]. Verapamil has also been shown to depress triggered activity due to delayed after-depolarisation[17,84].

Recently a fifth class has been suggested with the characteristic antiarrhythmic effect being impedance of chloride ion trans-membrane flux[85].

1.6 APPROACH TO TREATMENT OF VENTRICULAR TACHYARRHYTHMIAS

With the availability of a large number of antiarrhythmic agents with differing pharmacological actions, and the malignant potential of ventricular tachyarrhythmias, the approach to their utilisation is extremely important (Table 1.2).

Empirical Approach

For many years the standard approach has been empirical, that is, prescription of an antiarrhythmic agent, the efficacy of which is determined by the subsequent recurrence or nonrecurrence of the index arrhythmia. Although in practical terms convenient for the physician, when treating patients with potentially lethal arrhythmias, the major disadvantage of this approach is very obvious, since the first manifestation of lack of efficacy of the therapy may be sudden death. An extension of the empirical approach is the adjustment of dosage of the agent on the basis of the plasma/serum drug level to bring the level within a "therapeutic range"[86]. The major limitation of the use of "therapeutic" levels is the fact that such values may not directly correlate with efficacy and may be more applicable to the identification of toxicity. Furthermore the range is derived from pooled data and therefore may be less valid when related to the individual. In patients with ventricular tachyarrhythmias, the recurrence rate employing an empirical approach is of the order of 30-40%.

Directed Approach

The rationale for a directed approach to the prescription of antiarrhythmic therapy relies on the identification of an endpoint in the individual patient against which the efficacy of drug therapy can be assessed. This approach recognises and takes into consideration not

only the individual's response to the drug therapy but, as importantly, provides a prospective evaluation of the protection afforded by the therapy. The optimum directed approach requires the reproducible development of the spontaneous arrhythmia in its clinical setting.

Exercise Testing

In patients with exercise-induced ventricular arrhythmias, formal exercise testing can be employed to identify both the arrhythmia and its subsequent suppression by effective therapy. Woefel et al., in a study of 11 patients with reproducible ventricular tachycardia on exercise testing, identified effective therapy for 10 patients, 9 of whom remained free of arrhythmia over a mean follow up period of 18 months[87]. These arrhythmias were thought to be related to delayed after-depolarisations[3]. Recently, I was involved in a study of patients with exercise-induced ventricular tachycardia which demonstrated that these arrhythmias were not related to myocardial ischaemia or increased circulating catecholamine levels, but were more probably due to an enhancement of the sensitivity to normal catecholamine levels[88]. In this group of patients betaadrenoceptor blocker therapy was demonstrated to be particularly effective.

These arrhythmias, however, form only a very small proportion of patients with recurrent ventricular arrhythmias, and for most patients exercise testing alone is inadequate for direction of therapy.

Holter Monitoring

With the recognition that ventricular ectopic beats may trigger the onset of a sustained arrhythmia, suppression of ventricular ectopy has been used as an end-point for drug efficacy. Holter monitoring or telemetric trendscription permits a quantitative assessment of the frequency and density of ventricular ectopic beats and provides a means of determining the degree of suppression by antiarrhythmic therapy. Unfortunately, complete suppression of ventricular ectopy is difficult to achieve and the problem is further compounded by the spontaneous variability of ventricular ectopic activity which therefore necessitates extended periods of monitoring before a direct drug effect can be established [89,90].

In relation to the association between ectopic beats and sustained arrhythmias, it has been demonstrated that there may be a dichotomy between drug suppression of sustained arrhythmias and ventricular ectopy[91,92]. Furthermore, validation of the postulate that suppression of ectopy indicates protection against lethal arrhythmia has not yet been achieved. Conversely, in some patients in whom medical or surgical therapy has prevented arrhythmia recurrence, ventricular ectopy persists[93].

A more practical end-point for Holter directed therapy has been proposed by Lown and colleagues, and recently long term follow-up of patients has provided evidence for the efficacy of this approach[94,95]. This

group considered that complete suppression of more complex forms of ectopy was more achievable than complete suppression of all forms. In this approach, which employs combined Holter and exercise procedures, the aim of therapy is total abolishment of nonsustained ventricular tachycardia and R-on-T ventricular ectopic beats, reduction in paired ectopic beats by at least 90% and reduction of the total ectopic count by at least 50%. The patients undergo both acute intravenous loading and extended monitoring during subsequent oral testing. Multiple drug studies are employed. Although this approach does appear to identify long term successful therapy, it is complex, costly and requires a long in-patient stay. Such testing is applicable to patients with high levels of ambient ventricular ectopy but not to patients subject to spontaneous occurrences of sustained ventricular tachyarrhythmias but with otherwise low frequencies of ventricular ectopic activity.

1.7 DEVELOPMENT OF THE ELECTROPHYSIOLOGICAL APPROACH

Clinical cardiac electrophsyiology has its origins in the 18th and 19th century. The first stimulation of living tissue using electricity has been attributed to Sulzer in 1752[96] when he touched his tongue with a bimetal strip. In 1775 Abilgard [97] demonstrated the lethal nature of electricity on a chicken using an electric current from

a Leyden flask. The concept of "bio-electricity" or "animal-electricity" was suggested from the experiments of Galvani on his frog-muscle preparation[98], although this was disputed by Volta who considered that the electrical generation in a bimetal strip was independent of the biological system to which it was connected. Verification of the concept was provided by de Nobili[99] using a "galvanometer" to record electrical currents and Matteucci[100] who demonstrated stimulation of the nerve from one nerve-muscle preparation by the muscle from a second. The development of electrophysiology as a scientific entity was due in major part to the German physiologist Emil du Bois-Reymond who provided the basic insights into the stimulation of electrical generation in muscle and nerve[101]. He demonstrated the "injury current" in muscles and showed that the transverse section of a nerve was electronegative in relation to the intact surface. In 1799, Alexander von Humboldt described the action of electricity on the spontaneous beat of the exposed heart of different animals[102]. Such fundamental studies provided Kollicker and Muller, in 1856, with the means of demonstrating the electrical activity of the heart with a galvanometer[103]. Recordings of the action current within the heart were obtained by Nuel in 1873[104] and photographic records of this were produced by Marey[105] using a modification of the Lipmann capillary electrometer.

In a series of pioneering experiments, Englemann

systematically defined the excitability and activity of the heart including the propagation of the wave of contraction in the ventricles, the electromotive properties of the resting heart and the electrical changes during repolarisation[106,107]. Electrical activity during fibrillation in the isolated dog heart was recorded by Fredericq in 1887[108].

Electromotive changes in the human heart were first recorded by Waller[109] and in 1895 Einthoven described the human electrocardiogram[110]. Subsequently, Einthoven developed the string galvanometer for routine recording of the electrocardiogram[111]. Definition of the components of the electrocardiogram in relation to the propagation of the electrical impulse through the heart was provided by the extensive research of Lewis[112].

Direct recording of intracavitary electrograms was first reported in 1945 by Lenegre and Maurice[113]. Developments in recording techniques permitted registration of these potentials in all the chambers of the heart[114-117].

Although the integration of the AV conducting system had been described in 1906 by Taware[118], the His bundle electrogram was first recorded in 1958 by Alanis, Gonzalez and Lopez in the isolated canine heart[119]. His bundle recordings in man were obtained using an electrode catheter in 1960[120], but it was not until 1969 that Scherlag and coworkers described the standard electrode catheter

technique for His bundle recording[121]. Subsequently, electrode catheter recording of electrograms from the sinus node[122] and accessory pathways[123] have been obtained.

In comparison to the development of intracardiac recording techniques, the application of electricity to the induction and termination of arrhythmias is more recent. Despite the demonstration of induction of ventricular fibrillation by electrical currents in 1899 by Prevost and Battelli[124], the seminal studies by Wiggers on the vulnerable period and fibrillation threshold and the electrical stimulation of the heart in asystole by Hyman[125] in the 1930s, developments in this area essentially start in the early 1950s[126]. Reentry as a mechanism of tachyarrhythmia was proposed initially by Mines [127]. The presence of a potential substrate for reentry was reported in 1956 by Moe and coworkers[128] and subsequently in 1963 the initiation and termination of supraventricular tachycardia was demonstrated in a canine model[129]. The seminal study by Durrer et al.[130] in 1967 demonstrated that supraventricular tachycardia could be initiated and terminated by the introduction of premature beats in patients with Wolff-Parkinson-White syndrome. Evidence for a reentrant basis for the majority of paroxysmal supraventricular tachycardias was provided by Bigger and Goldreyer using a systematic approach with programmed stimulation and His bundle recording[131]. These techniques were translated to patients with ventricular tachycardia in

1972 by Wellens et al.[12] who also suggested that the mechanism underlying this arrhythmia was reentry[15]. A macroreentrant mechanism was described by Akhtar and coworkers in 1976 with the demonstration of the "V3 phenomenon" or bundle branch reentrant beat[132], although clinically occurring tachycardia of this type is very uncommon [133,134]. The microreentrant basis for the majority of ventricular tachycardias in patients with underlying coronary artery disease was demonstrated in a series of studies from Josephson, Horowitz and coworkers using programmed stimulation for the induction and termination of ventricular tachycardia, and epicardial/endocardial mapping techniques to identify the presence of delayed conduction[16,135,136,137]. From such investigations this group developed the subendocardial approach to the resection of the "site of origin" of ventricular tachycardia.

These studies provided the basis for the widespread application of programmed stimulation techniques to the evaluation of ventricular tachycardia. The use of electrophysiological testing in patients with out-of-hospital cardiac arrest was reported by Ruskin et al.[138] who demonstrated that a ventricular tachyarrhythmia could be initiated in high proportion of these patients. These initial observations have been confirmed by other groups[139,140,141]. Subsequently the utility of this approach has been described in other conditions associated

with ventricular tachyarrhythmias including arrhythmogenic right ventricular dysplasia[142,143] and dilated cardiomyopathy[144,145].

Similarly, programmed ventricular stimulation has been employed to determine whether a ventricular tachyarrhythmia might be the causative factor in patients with syncope of undetermined origin[146,147,148] and more recently its use as a means of identifying high-risk patients post myocardial infarction[149-155] has been investigated.

On the premise that, in patients with inducible arrhythmias, an antiarrhythmic agent which prevented re-induction of the arrhythmia would be effective in the longterm, serial electrophysiological drug testing was developed, initially for supraventricular tachycardia[156] and subsequently for ventricular tachycardia[42,43,157].

Since these initial studies, the therapeutic application of serial electrophysiological drug testing has been evaluated in patients with ventricular tachyarrhythmias in a wide range of different clinical settings[158-161].

The studies in this thesis further develop the use of this form of directed treatment approach to the management of patients with ventricular tachyarrhythmias.

CHAPTER 2

METHODOLOGY

All studies were performed in a dedicated electrophysiological laboratory used exclusively for electrophysiological investigation.

2.1 ELECTROPHYSIOLOGICAL EQUIPMENT

The major components of the equipment employed consisted of 1) multichannel electrophysiological recorder; 2) multichannel storage oscilloscope; 3) multichannel magnetic tape recorder; 4) junction box; and 5) programmable stimulator. The arrangement and connections of these various components are shown schematically in Figure 2.1.

1) Multichannel Electrophysiological Recorder

The multichannel recording system employed (Electronics for Medicine: VR16) had 12 E.C.G./intracardiac signal modules which could be switched depending on the array of surface and intracardiac signals to be displayed. The intracardiac signals were amplified and bandpass filtered in the frequency range of 30 - 500Hz which permitted optimum definition of the intracardiac electrograms

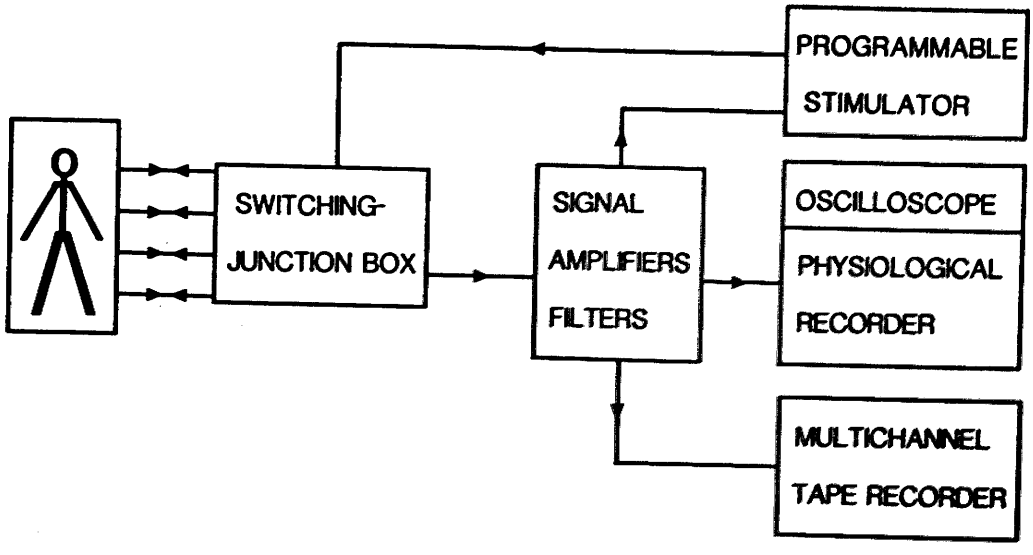

Fig. 2.1 Schematic diagram of the electrophysiological equipment employed.

particularly the His bundle electrogram. The surface electrocardiographic leads and intracardiac electrograms were simultaneously displayed on a multichannel oscilloscope at a speed of 75 mm./sec. which allowed satisfactory separation of the electrograms.

Hard copy real-time recordings were obtained on either an 8-channel or 16-channel ink-jet recorder (Siemens-Elema Mingograf) at paper speeds of 100 - 250 mm./sec.

2) Multichannel Storage Oscilloscope

Integration of the storage oscilloscope, synchronised to the intracardiac signal permitted recording and interpretation of the response to the premature stimuli between the drive train sequences.

3) Multichannel Tape Recorder

All signals were recorded on continuous magnetic analogue tape. Since initiation of arrhythmias is unpredictable and could also occur spontaneously during the course of the study, this facility allowed retrieval of such recordings throughout the duration of the study. In addition, these recordings could be edited before hard copy illustrations on photographic paper were made.

4) Junction Box

The electrode catheters inserted in the patient were connected via sterilised cables to the junction box attached to the catheterisation table. This multielectrode box allowed choice of electrode array for both pacing and intracardiac signal sensing.

5) Programmable Stimulator

The programmable stimulator was a Bloom DTU-101 optically isolated constant current stimulator equipped with 6 stimulus channels and 4 output channels. This unit can deliver up to 5 extrastimuli to all output channels with the digital timing unit allowing continuous pacing at cycle lengths from 1 - 9,999 ms. in 1 ms. increments. The coupling intervals of the extrastimuli can also be set in the same range. The extrastimuli can be synchronised to any of the spontaneous surface or intracardiac electrograms or to the paced output.

In addition the Bloom stimulator generates a time marker pulse.

2.2 CATHETERISATION PROCEDURE

The electrophysiologic studies were performed with the patients in the fasting post-absorptive state. Routine premedication was not administered. If indicated intravenous boluses of diazepam were given during the study.

In addition to the surface electrocardiographic leads, two large patch defibrillator pads (R-2 Corporation) were applied to the chest wall to permit defibrillation remote from the patient.

Multielectrode catheters with a 1 cm. interelectrode spacing (USCI) were inserted into the femoral veins, under

local anaesthesia, using the modified Seldinger technique. If femoral venous access was unobtainable, the brachial or subclavian veins were employed. The standard arrangement for the evaluation of patients with ventricular tachyarrhythmias was the insertion of three catheters which were positioned under fluorscopic guidance; a 7F tripolar catheter placed across the tricuspid valve annulus to record the His bundle electrogram and two 6F quadripolar catheters placed in the high right atrium and at the right ventricular apex (Figure 2.2). In studies requiring stimulation of the left ventricle (see below) a quadripolar catheter was inserted retrogradely via the right or left femoral artery.

After positioning the catheters, heparin was administered to prevent the development of venous thrombosis, initially as a bolus of 2,000 iu followed by an infusion, at a rate of 1,000 iu/hour.

During the procedure, systemic blood pressure was monitored either by cuff sphygmomanometry or by direct intraaortic pressure recording.

2.3 RECORDING ARRAY

For the two quadripolar catheters, the distal two electrodes were used for pacing with the proximal electrode pair used for sensing the bipolar intracardiac signal. A bipolar electrogram was also recorded from the tripolar His

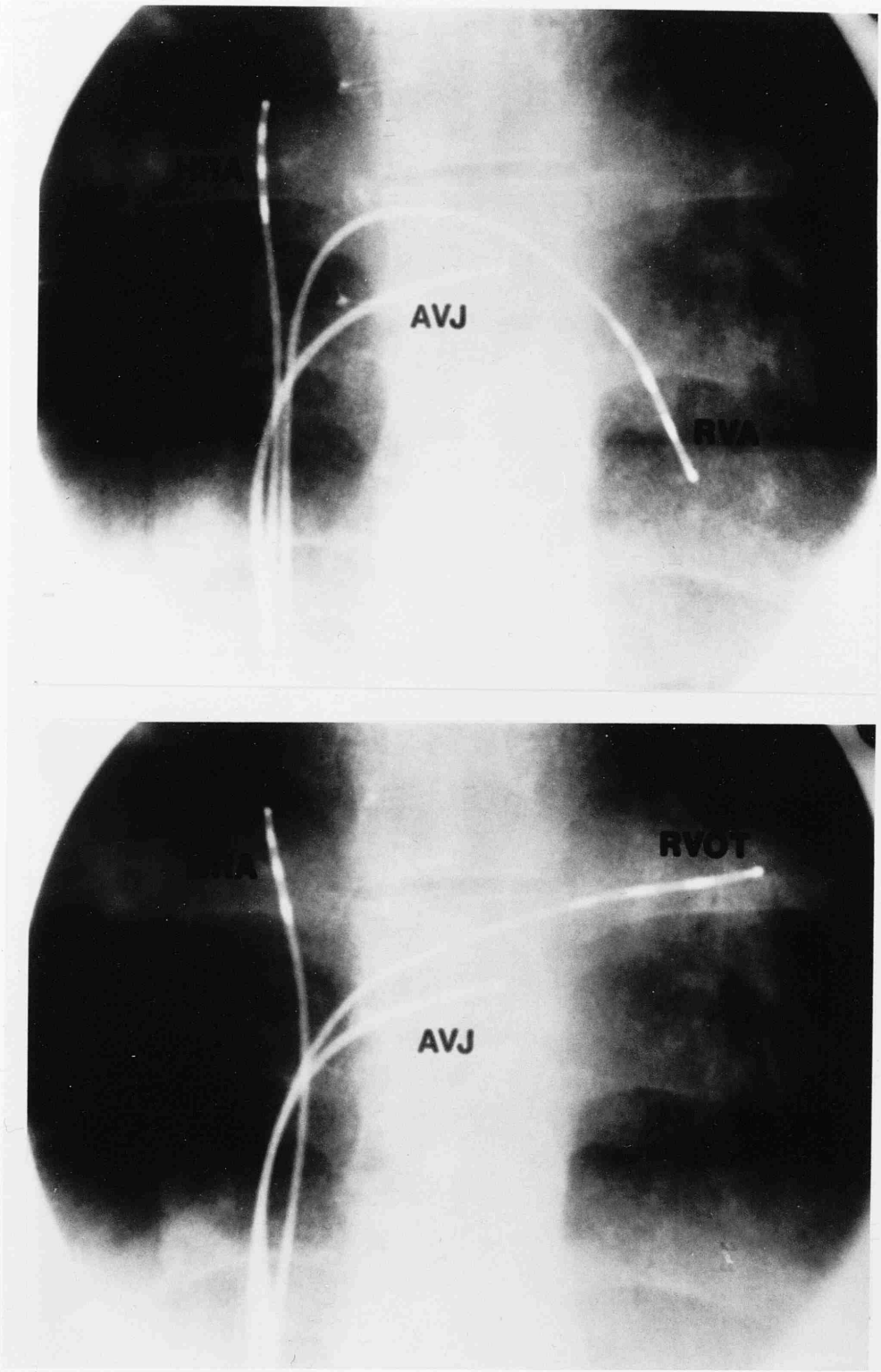

Fig. 2.2 Standard catheter positions.

HRA - high right atrium
AVJ - atrioventricular junction
RVA - right ventricular apex
RVOT - right ventricular outflow tract

bundle catheter, the electrode pair being selected to obtain the optimum His bundle electrogram. The intracardiac signals were recorded simultaneously with the surface electrocardiographic leads I, aVF and V1 which are approximately orthogonal. For analysis of AV conduction intervals, recordings were made at 250 mm./sec. with recordings performed during pacing and programmed stimulation at 100 mm./sec.

A typical recording is shown in Figure 2.3. The upper time mark is at 1 second intervals with the lower time marks at 1000, 100 and 10 msec. intervals.

2.4 PROGRAMMED STIMULATION PROTOCOL

The same stimulation protocol was applied in all patients studied. Since the results of electrophysiological testing are dependent on the stimulation protocol applied and, although advocated there is, as yet, no accepted standardised protocol, uniformity of the stimulation protocol for each laboratory is mandatory to permit inter-patient comparison. The stimulation protocol employed in these studies was developed by Dr. L.N. Horowitz at the University of Pennsylvania. This protocol conforms to that recommended by the North American Society of Pacing and Electrophysiology[162].

Stimulation was performed at a pulse duration of 1

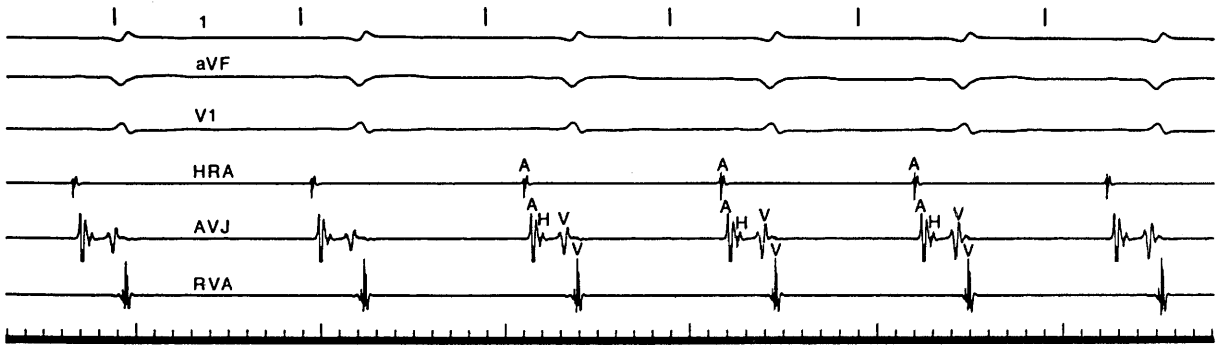

Fig. 2.3 Standard recording array.

HRA - high right atrium
AVJ - AV junction
RVA - right ventricular apex

A - atrial electrogram
H - His bundle electrogram
V - ventricular electrogram

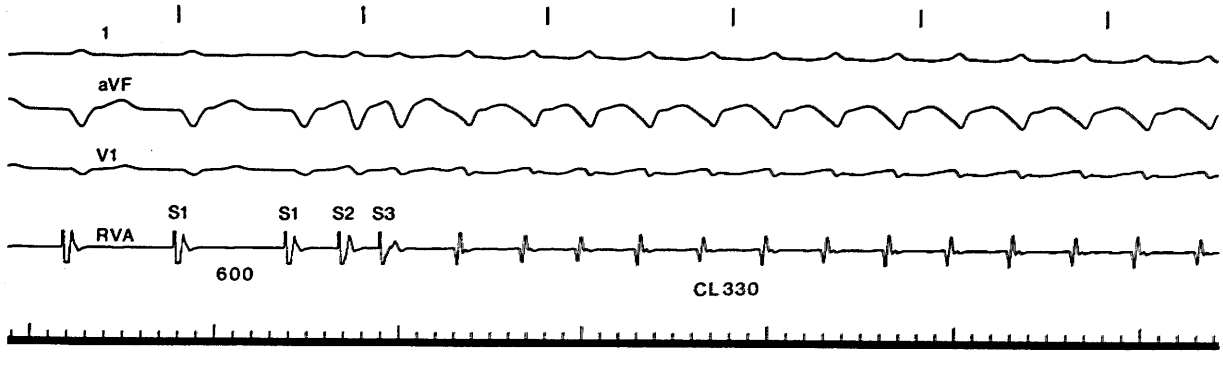

Fig. 2.4 Standard recording array for programmed ventricular stimulation.

Annotations as in Fig. 2.3

S1 S1 - drive cycle
S2 - first extrastimulus
S3 - second extrastimulus

msec. with a stimulation strength of twice diastolic threshold. The use of a pulse amplitude of twice diastolic threshold is routine practice in many laboratories. In a canine study[163], an increase in current strength was shown to facilitate the induction of ventricular tachyarrhythmias by permitting the introduction of extrastimuli at shorter coupling intervals, the results from clinical studies however are variable. In two studies, the yield of induced arrhythmias has been higher with five times diastolic threshold[164] and 20mA[150] compared to twice diastolic threshold. In contrast, Morady et al.[165] demonstrated that although an increased yield was obtained with a current strength of 10mA, in 20% of patients arrhythmias were not inducible at the higher strength although an arrhythmia was induced at twice diastolic threshold. One concern with the use of higher pulse amplitudes, is the possibility of an increased induction of nonclinical arrhythmias[166].

BASELINE STUDY

The protocol can be divided into two parts for discussion purposes: programmed atrial stimulation and programmed ventricular stimulation. Baseline studies were performed in the drug-free state after discontinuation of previous antiarrhythmic therapy for at least five half-lives of the agent.

Programmed Atrial Stimulation

The stimulation protocol in the baseline study included assessment of sinus nodal, atrial, AV nodal and His-Purkinje conduction in addition to the inducibility of ventricular tachyarrhythmias. This evaluation was performed both to determine inducibility of ventricular arrhythmias by atrial stimulation and identification of co-existent conduction defects which might influence subsequent selection of antiarrhythmic therapy, indicate the need for insertion of a back-up permanent pacemaker to allow prescription of such therapy.

After measurement of baseline surface electrocardiographic intervals (PR, QRS, QT and JT) the standard intracardiac AV conduction intervals were measured, including PA, AH, HV and Q-RVA[167].

The normal values for the laboratory are shown in Table 2.1.

Sinus nodal function was evaluated by measurement of the sinoatrial conduction time (Narula method[168]) and sinus node recovery time. For the latter, atrial pacing was performed at multiple cycle lengths starting at a cycle length just shorter than the basic sinus cycle length down to a cycle length of 300 msec. The maximum sinus node recovery time was the longest interval from the last paced atrial complex to the first normal atrial complex at any paced cycle length. For the laboratory, the normal value for the sinus node recovery time is 1.3 x sinus cycle

INTERVAL	NORMAL VALUES (mec)
PA	30 - 55
AH	60 - 125
HV	35 - 55
His bundle	10 - 25

TABLE 2.1 Normal baseline intracardiac conduction intervals

length + 101 msec. a corrected sinus node recovery time (maximum sinus node recovery time - basic sinus cycle) < 550 msec. Presence of escape beats and secondary pauses were also noted.

Atrial, AV nodal, His-Purkinje function: In addition to the baseline intervals AV conduction was evaluated by the response to atrial pacing at multiple cycle lengths and the measurement of functional, relative and effective refractory periods by the extrastimulus method[167]. Single atrial extrastimuli were introduced in late diastole during sinus rhythm and atrial paced cycle lengths of 600 msec. and 450 msec. The coupling interval was shortened by 10 - 20 msec. till atrial refractoriness was obtained.

Programmed Ventricular Stimulation

Retrograde AV function was similarly assessed by incremental ventricular pacing and ventricular extra-stimulation [167].

The ventricular stimulation protocol included the introduction of single, double and triple ventricular extrastimuli during sinus rhythm and ventricular paced cycle lengths of 600 msec. and 450 msec. Occasionally nonstandard paced cycle lengths were employed. If the resting heart rate was around 100 bpm - a paced cycle length of 550 msec. was used to produce constant capture. The extrastimuli were introduced after eight beats of sinus rhythm or ventricular pacing (S1-S1). If no retrograde VA conduction was present and antegrade sinus capture occurred

which perturbed the drive train, simultaneous ventricular and atrial pacing was performed. The first extrastimulus (S2) was positioned late in diastole. The extrastimulus coupling interval (S1-S2) was shortened by decrements of 10 - 20 msec. till ventricular refractoriness occurred. The coupling interval of the first extrastimulus (S1-S2) was then set at 50 - 100 msec. longer than the refractory period and a second extrastimulus introduced (S3). The S2 - S3 interval was shortened till S3 failed to capture at which point the S1 - S2 interval was shortened until S3 again captured. This cycle was repeated until S2 failed to capture. Introduction of a third extrastimulus (S4) followed the same procedure with shortening of the coupling interval S3 - S4 till S4 failed to capture and then shortening S2 - S3 and subsequently S1 - S2. The protocol was performed until S2 failed to capture. The stimulation protocol end-point was the induction of a sustained arrhythmia.

If no sustained arrhythmia was induced with three ventricular extrastimuli during sinus rhythm and two paced cycle lengths at the right ventricular apex, the catheter was repositioned at the right ventricular outflow tract and the complete protocol repeated. In patients with a documented sustained arrhythmia or who had suffered an out-of-hospital cardiac arrest requiring cardiopulmonary resuscitation left ventricular stimulation, employing the same protocol, was performed at one or two left ventricular

sites.

The use of burst ventricular pacing for arrhythmia induction was employed in the protocol initially but was subsequently discontinued.

In patients in whom a sustained arrhythmia was induced, reproducibility of induction was confirmed by repeat stimulation, unless DC cardioversion was required for termination.

The ventricular stimulation protocol employed is similar to that used by other groups. Although one laboratory has advocated the use of a changing drive cycle of eight beats prior to the introduction of extrastimuli[169], most laboratories employ a constant cycle, eight beat drive train. Selection of paced cycle lengths of 600 msec. and 450 msec. permitted the use of two sufficiently separate cycle lengths without pacing the heart too rapidly which might provoke myocardial ischaemia in patients with underlying coronary artery disease and therefore influence arrhythmia induction.

The technique for introduction of extrastimuli is also common to many laboratories. A slightly different approach is employed by some groups[42,170]. In this technique, the coupling interval of the first extrastimulus is decreased until ventricular refractoriness is reached, it is then increased by 10 to 20 msec. until consistent capture is achieved and the second extrastimulus is introduced 100 to 150 msec. longer than the S1 - S2

interval and the procedure repeated. In clinical practice, no differences in inducibility with the two methods of scanning diastole with extrastimuli are apparent[171].

The rationale for the number of extrastimuli used and different sites of stimulation are discussed in Chapter 3.

The use of isoprenaline infusion to facilitate induction of ventricular tachyarrhythmias was not employed in these studies although it has been advocated to increase the sensitivity of the stimulation protocol[172].

On the initiation of ventricular tachycardia, a stopwatch was started and attempts at termination were not performed if the patient was haemodynamically stable until the tachycardia had persisted for 30 seconds to confirm the sustained nature of the tachyarrhythmia. Termination of sustained arrhythmia was performed by pacing or extrastimulation techniques or if cardiovascular collapse had ensued, DC cardioversion. If the tachycardia was haemodynamically stable and well tolerated, termination was initially attempted by the introduction of single and subsequently double ventricular extrastimuli. If this was unsuccessful or the tachycardia rate was rapid, burst ventricular pacing was performed to terminate the arrhythmia. If termination attempts with this mode failed, burst pacing was repeated at higher current strengths. In refractory cases, overdrive ventricular

pacing with the introduction of single ventricular extrastimuli was performed. Arrhythmia termination is discussed further in Chapter 4.

2.5 SERIAL DRUG STUDIES

In most cases, the first drug study was performed during the baseline study after reproducible arrhythmia induction had been demonstrated.

In subsequent follow-up studies, the patient underwent a limited electrophysiological study only to determine arrhythmia inducibility unless significant sinus node or AV conduction impairment had been identified in the baseline study. One or two quadripolar catheters were inserted. In general if no retrograde VA conduction had been present in the baseline study, the second catheter was positioned in the right atrium to permit simultaneous atrial and ventricular stimulation, thus preventing antegrade sinus capture. In some patients, a single catheter was inserted via an antecubital or subclavian vein and in these cases a Berkovitz-Castellanos hexapolar catheter was used. The same ventricular stimulation protocol as used in the baseline study was employed. The full protocol was completed if no sustained arrhythmia was induced, irrespective of the mode of induction of the baseline arrhythmia. Left ventricular stimulation was performed in follow-up studies, only if it had been required for arrhythmia induction in the baseline study.

2.6 DEFINITION OF TERMS

Uniform definitions for induced arrhythmias were applied in all studies.

Sustained Ventricular Tachycardia was defined as ventricular tachycardia that lasted longer than 30 seconds or that required termination before 30 seconds because of the development of cardiovascular collapse.

Ventricular Fibrillation was considered to be the initiated arrhythmia if within 3 seconds after the initiation of a sustained arrhythmia, typical chaotic ventricular activitity was present in any surface electrocardiographic lead.

Nonsustained Ventricular Tachycardia was defined as a spontaneously terminating ventricular tachycardia that was at least 6 complexes but shorter than 30 seconds in duration.

2.7 ANTIARRHYTHMIC DRUG REGIMENS

Selection of antiarrhythmic drug regimens was based on the patient's history of previous exposure to antiarrhythmic therapy. A history of hypersensitivity, allergy or pro-arrhythmic response to a drug precluded its use. History of clinical ineffectiveness, however, did not prevent further trial of the agent unless the ineffectiveness correlated with serum drug levels within

the accepted therapeutic range.

The drug regimens were evaluated at either the maximally tolerated dose, or the maximal dose allowed in investigational protocols.

Drug studies were performed after a steady-state level was obtained. For oral therapy this usually required 2 - 3 days administration before follow-up study was performed, except in the case of amiodarone when study was performed after 10 - 14 days loading. If an intravenously administered regimen was successful, repeat testing of the regimen after oral administration was performed to confirm suppression of arrhythmia inducibility. As far as possible, the dosage of the oral medication was adjusted to obtain a drug level comparable with the level obtained during the intravenous study.

When drugs were used in combination, the same dosages were used except for the combination of amiodarone and intravenous procainamide, in which the dose of procainamide was limited to 1000 mg. (see Chapter 8).

In all cases, blood was withdrawn for drug level measurement either at the time of arrhythmia induction or if no arrhythmia was induced, at the completion of the protocol.

The antiarrhythmic agents and the dosage employed are listed in Table 2.2.

PROCAINAMIDE
1,000 - 2,000 mg. i.v. (50 mg/min then 4 - 8 mg/min)
750 - 2,000 mg. p.o. sustained release preparation every 6 hours

QUINIDINE
342 - 648 mg. (gluconate) p.o. every 8 hours

DISOPYRAMIDE
100 - 300 mg. p.o. every 6 - 8 hours

MEXILETINE
5 mg/kg i.v. (10 mg/min) then 4 mg/min
150 - 300 mg. p.o. every 8 hours

AMIODARONE
1,000 mg/day p.o. for 7 days then 800 mg/day for 7 days

BETHANIDINE
1,500 mg/day p.o.

FLECAINIDE
100 - 200 mg. p.o. every 12 hours

INDECAINIDE
60 - 100 mg. i.v. (15 mcg/kg/min)
50 - 100 mg. p.o. every 8 hours

TOCAINIDE
400 - 800 mg. p.o. every 8 hours

BEPRIDIL
400 - 600 mg. p.o. daily

PHENYTOIN
1,000 mg/day p.o. for 2 days then 300 mg/day

LIDOCAINE
225 mg. i.v. (15 mg/min) then 4 mg/min

(i.v. = intravenously p.o. = orally)

TABLE 2.2 Antiarrhythmic agents and dosages employed in drug studies

CHAPTER 3

APPLICATION OF THE ELECTROPHYSIOLOGICAL STIMULATION PROTOCOL

The reproducible induction of a ventricular tachyarrhythmia provides the basis for the application of electrophysiological testing to the management of patients with these arrhythmias. The diagnostic yield from programmed stimulation is dependent on the stimulation protocol employed. As discussed in Chapter 2, there is no standardisation or uniformity in the stimulation protocol among different laboratories and it was therefore important to analyse the response to the protocol employed in this thesis and to determine the impact of different factors on arrhythmia induction.

The stimulation protocol described in Chapter 2 was applied in all studies.

For discussion purposes, the patient population has been analysed in two groups. The first group of patients comprises those with previously documented ventricular tachyarrhythmias and the second group comprises patients with syncope of undetermined origin in whom a disturbance of rhythm had not been confirmed as the aetiological cause prior to study.

In the former group both the induction of arrhythmias and the presence of associated conduction abnormalities

have been analysed.

PATIENTS WITH VENTRICULAR TACHYARRHYTHMIAS

3.1 PATIENTS

Electrophysiological testing was performed on a total of 385 patients referred with a history of ventricular tachyarrhythmias. A history of at least one episode of documented sustained ventricular tachycardia was present in 153 patients, 99 patients had experienced a cardiac arrest requiring cardiopulmonary resuscitation (not related to acute myocardial infarction) and 133 patients had symptomatic nonsustained ventricular tachycardia. Coronary artery disease documented by 1) history of previous myocardial infarction, 2) presence of reversible myocardial ischaemia by exercise testing, 3) presence of segmental wall motion abnormalities by 2-D echocardiography or radionuclide angiography, or 4) coronary angiography, was present in 273 patients. Cardiomyopathy or valvular heart disease was present in 90 patients (termed non-coronary disease) and in 22 patients, no structural heart disease was identified (although cardiac biopsy was not performed) these latter patients being considered to have primary electrical disease.

3.2 RESULTS

In the 385 patients, a ventricular tachyarrhythmia was

induced in 256 (67%) of the patients. Sustained ventricular tachycardia was induced in 180 patients (47%), ventricular fibrillation in 23 patients (6%) and nonsustained ventricular tachycardia in 53 patients (14%).

3.3 Effect of Presenting Arrhythmia (Fig. 3.1)

In 153 patients with a history of sustained ventricular tachycardia, a ventricular arrhythmia was induced in 129 (84%) of the patients which was significantly higher than the induction rate of 62% for patients with cardiac arrest (62 of 99 patients) ($p<0.001$) and the induction rate of 49% of patients with nonsustained ventricular tachycardia (65 of 133 patients) ($p<0.001$). There was no statistical difference between the latter two groups.

The presenting arrhythmia was also a determinant of the type of arrhythmia induced by programmed stimulation. Sustained ventricular tachycardia was induced more often in patients with a history of sustained ventricular tachycardia (76%) than in patients with cardiac arrest (30%) or patients with nonsustained ventricular tachycardia (25%) ($p<0.0001$). Ventricular fibrillation was induced in 14% of patients with cardiac arrest compared to 2% in patients with sustained ventricular tachycardia ($p<0.001$) and 5% in patients with nonsustained ventricular tachycardia. Induction of nonsustained ventricular tachycardia was observed in 19% of patients with nonsustained ventricular tachycardia and 18% of patients with cardiac arrest compared to only a 6% induction rate in

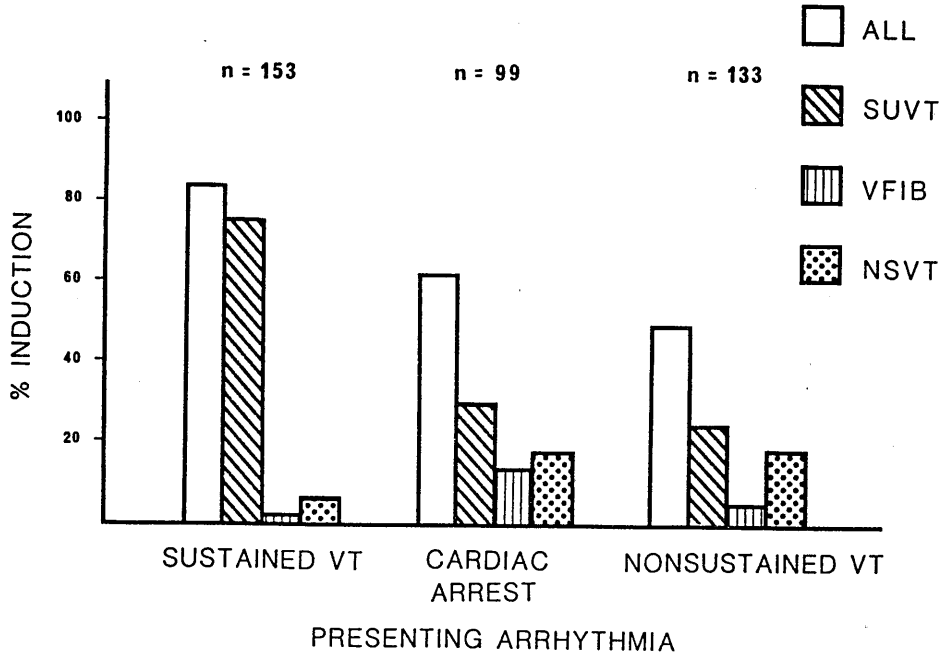

Fig. 3.1 Effect of presenting arrhythmia on induction of ventricular tachyarrhythmias

SUVT = sustained ventricular tachycardia
VFIB = ventricular fibrillation
NSVT = nonsustained ventricular tachycardia

patients with sustained ventricular tachycardia ($p<0.01$).

3.4 Effect of Underlying Heart Disease

To determine the impact of the type of underlying heart disease on arrhythmia induction, the results were analysed in relation to the presence of coronary disease, noncoronary disease and primary electrical disease. Overall, a ventricular arrhythmia was induced in 196 of 273 (72%) patients with coronary disease, 47 of 90 (52%) patients with noncoronary disease and 13 of 22 (61%) patients with primary electrical disease (Fig. 3.2). These differences however did not reach statistical significance. Similarly, there were no significant differences when the induction rates were analysed further in relation to presenting arrhythmia. In patients with a history of sustained ventricular tachycardia, a ventricular arrhythmia was induced in 113 of 131 (85%) patients with coronary disease, 16 of 19 (84%) patients with noncoronary disease and 3 of 4 (75%) patients with primary electrical disease. For patients with cardiac arrest the induction rates were 64% (44 of 69 patients), 53% (10 of 19 patients) and 60% (6 of 10 patients) respectively. In patients with nonsustained ventricular tachycardia the rates were 53% (39 of 73 patients), 40% (21 of 52 patients) and 50% (4 of 8 patients) respectively.

In contrast, the type of underlying heart disease did influence the type of arrhythmia induced (Fig. 3.3).

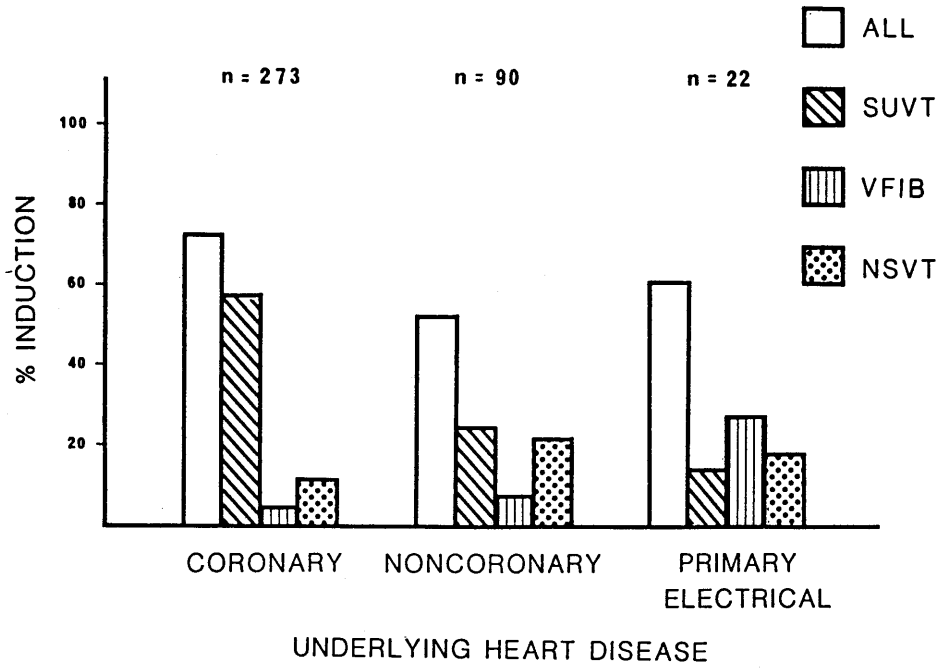

Fig. 3.2 Effect of underlying heart disease on induction of ventricular tachyarrhythmias.

Abbreviations as in Fig. 3.1

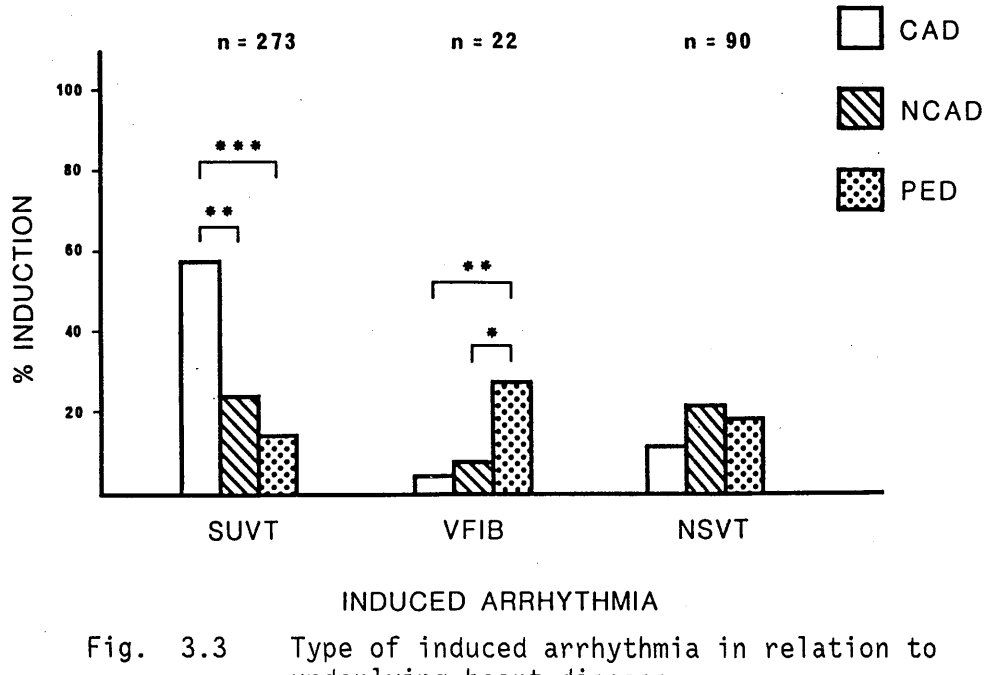

Fig. 3.3 Type of induced arrhythmia in relation to underlying heart disease.

CAD - coronary artery disease
NCAD - noncoronary disease
PED - primary electrical disease

* $p < 0.01$

*** $p < 0.0001$

Sustained ventricular tachycardia was induced in 57% of patients with coronary disease compared to 24% of patients with noncoronary disease ($p<0.001$) and 14% of patients with primary electrical disease ($p<0.0001$). Ventricular fibrillation was induced in 27% of patients with primary electrical disease which was higher than in patients with coronary artery disease (4%) ($p<0.001$) or noncoronary disease (7%) ($p<0.01$). There was no significant difference in the rate of induction of nonsustained ventricular tachycardia in the three groups.

To determine whether the type of coronary disease was important the 273 patients with underlying coronary artery disease were further subdivided into patients with coronary artery disease but no previous infarction (angina group), patients who had sustained a myocardial infarction within six weeks prior to electrophysiological testing (recent-infarction group) and patients with myocardial infarction more than three months prior to testing (remote-infarction group). There were 37 patients in the angina group, 30 patients in the recent- infarction group, and 206 patients in the remote-infarction group. A ventricular arrhythmia was induced in 13 (35%), 16 (53%) and 167 (81%) of the patients in the three groups respectively (Fig. 3.4). There was no difference in the induction rates in the angina group and the recent-infarction group but these rates were significantly lower than that obtained for the remote-infarction group

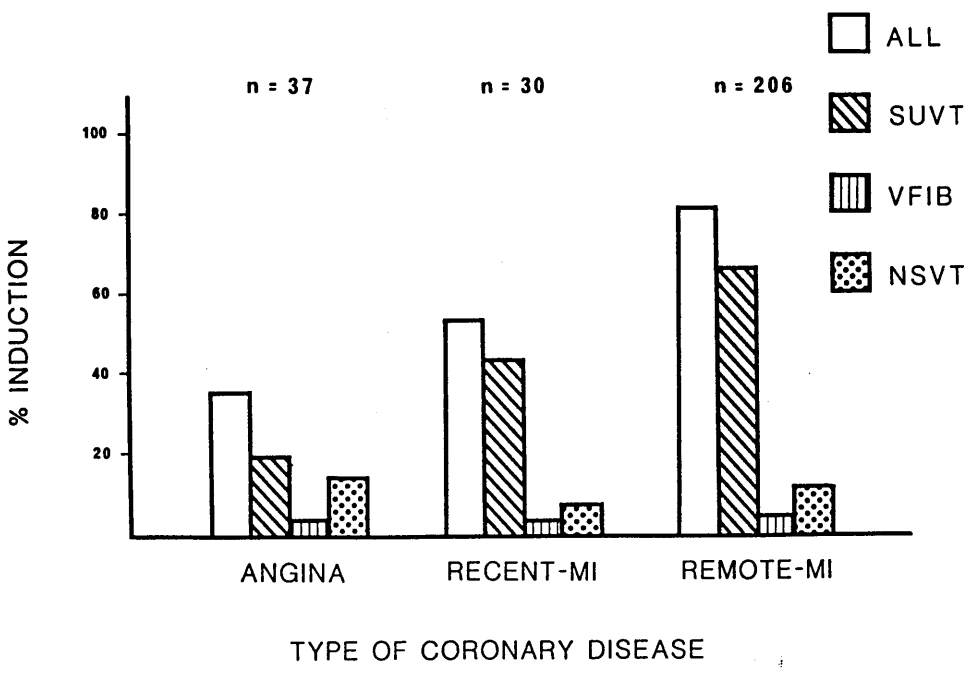

Fig. 3.4 Effect of type of coronary disease on induction of ventricular tachyarrhythmias.

Abbreviations as in Fig. 3.1

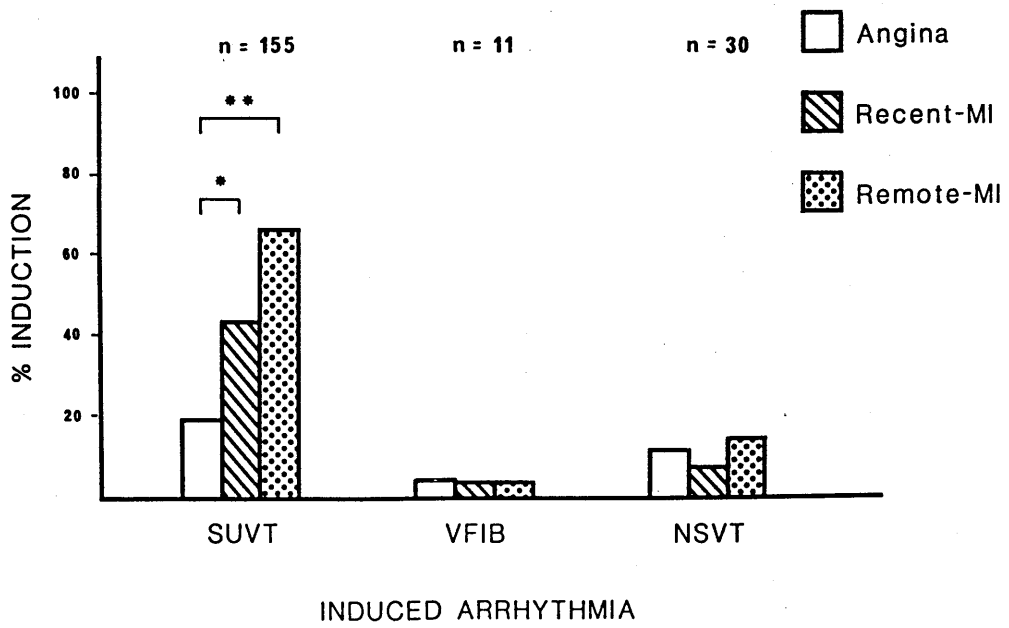

Fig. 3.5 Type of induced arrhythmia in relation to type of underlying coronary disease.

* $p < 0.05$

** $p < 0.0001$

($p<0.0001$) and ($p<0.005$) respectively.

In patients presenting with a history of sustained ventricular tachycardia, a ventricular arrhythmia was induced in 5 of 12 (42%) patients with angina, 12 of 17 (71%) patients with recent-infarction and 96 of 102 (94%) patients with remote-infarction, the latter being significantly higher than for the former groups ($p<0.001$) and ($p<0.01$), respectively. Higher induction rates were also observed for the remote- infarction group in patients presenting with cardiac arrest and nonsustained ventricular tachycardia (75% and 63% respectively) compared to the angina group (40% and 20%) and the recent- infarction group (43% and 17%).

In relation to the type of arrhythmia induced, sustained ventricular tachycardia was induced more frequently in the remote-infarction group (66%) than in the recent-infarction group (43%) ($p<0.05$) or the angina group (19%) ($p<0.0001$) (Fig. 3.5). No such differences were observed for ventricular fibrillation (4%, 3% and 3% respectively) and nonsustained ventricular tachycardia (11%, 7% and 14% respectively).

3.5 Effect of Different Components of Stimulation Protocol

a) Cycle Length of Drive Train

Three standard drive trains for introduction of extrastimuli were employed, sinus rhythm, and ventricular paced cycle lengths of 600 msec. and 450 msec. In 22

cases, a nonstandard cycle length was employed usually either 550 msec. or 500 msec. For the purposes of this analysis, these results were included in the results for the closer drive train cycle length (i.e. 600 msec. or 450 msec. respectively). Overall, ventricular arrhythmia induction occurred during sinus rhythm in 5% of patients, during a ventricular paced cycle length of 600 msec. in 52% of patients and during a ventricular paced cycle length of 450 msec. in 43% of patients.

b) Site of Stimulation

In the 256 patients with inducible ventricular arrhythmias 4 (2%) were inducible with high right atrial pacing and atrial extrastimuli. In each of these four cases, the same ventricular arrhythmia was also inducible with a single ventricular extrastimulus at the right ventricular apex. With the ventricular stimulation protocol employed, 80% of the patients were inducible at the right ventricular apex and 18% required stimulation at the right ventricular outflow tract. In patients with sustained ventricular tachycardia or cardiac arrest left ventricular stimulation was performed and a ventricular arrhythmia was induced in a further 2% with this technique. Examples of arrhythmia induction are shown in Fig. 3.6.

c) Number of Extrastimuli

With the hierarchical system for the introduction of extrastimuli, the induction rates in this section have been analysed in respect of the number of patients exposed to

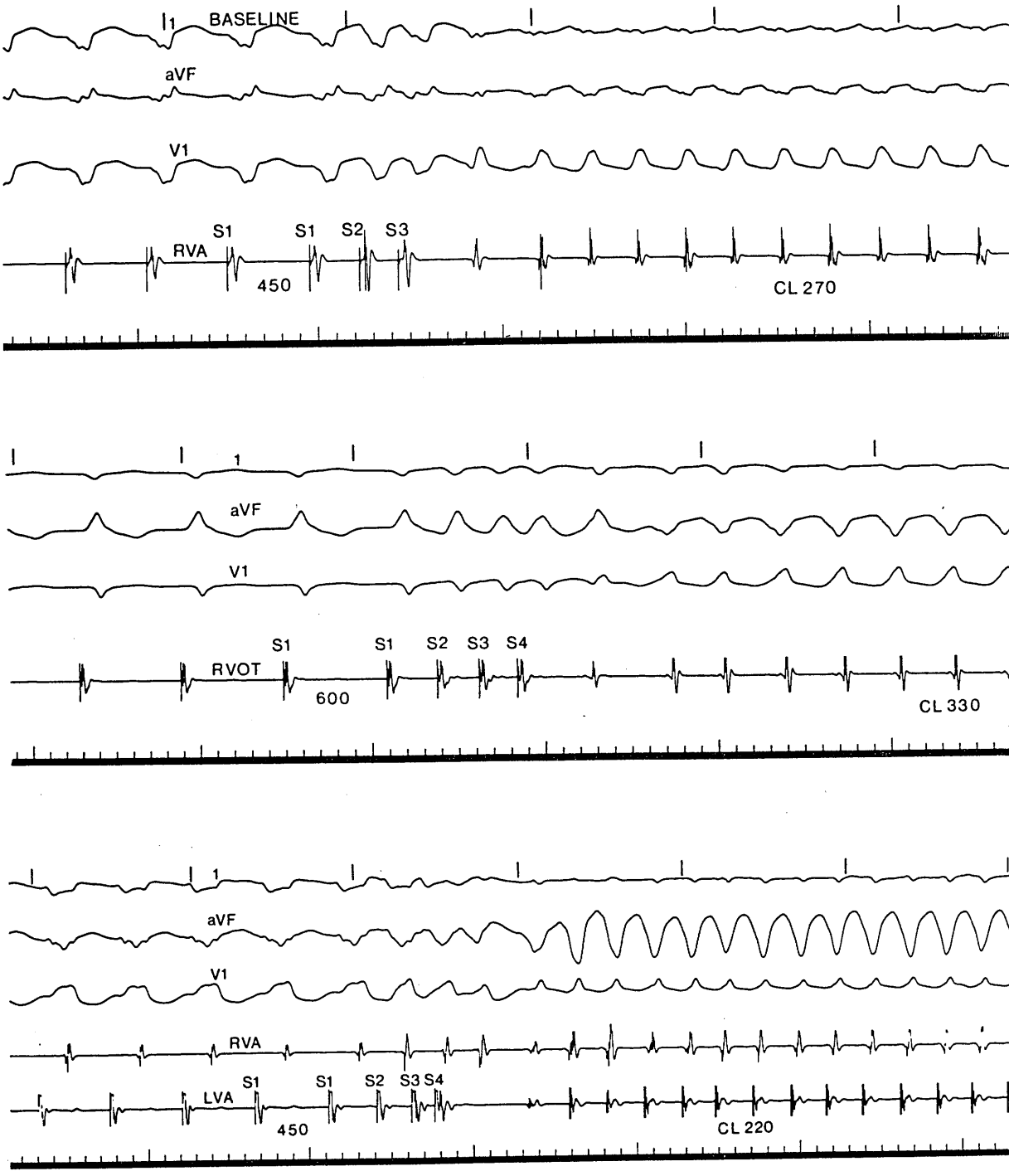

Fig. 3.6 Induction of tachycardia at different ventricular sites; upper panel: right ventricular apex, middle panel: right ventricular outflow tract, lower panel: left ventricle.

that number of extrastimuli and not to the total number of patients studied, since, if a tachycardia was induced with single extrastimuli, attempts at induction with double or triple extrastimuli were not performed. Furthermore, with this protocol, triple extrastimuli were introduced at the right ventricular apex before single and double extrastimuli at the right ventricular outflow tract and therefore an accurate evaluation of the sensitivity for arrhythmia induction related to the number of extrastimuli required is precluded. With these limitations, for the 256 patients with inducible ventricular arrhythmias, arrhythmia induction was obtained with single extrastimuli in 26 (10%) patients, double extrastimuli in 94 (37%) and triple extrastimuli in 136 (53%) patients.

In patients with a history of sustained ventricular tachycardia, single extrastimuli induced a ventricular arrhythmia in 22 of 153 (14%) patients which was significantly higher than for patients with cardiac arrest (2 of 99 patients) ($p<0.005$) and patients with nonsustained ventricular tachycardia (2 of 133 patients) ($p<0.005$) (Fig. 3.7). A similar pattern was observed for double extrastimuli with induction rates of 42%, 19% and 16% respectively ($p<0.01$ and $p<0.001$). For triple extrastimuli, there was no difference between patients with sustained ventricular tachycardia and cardiac arrest (71% and 59%) but both were higher than the 37% induction rate for nonsustained ventricular tachycardia ($p<0.001$ and

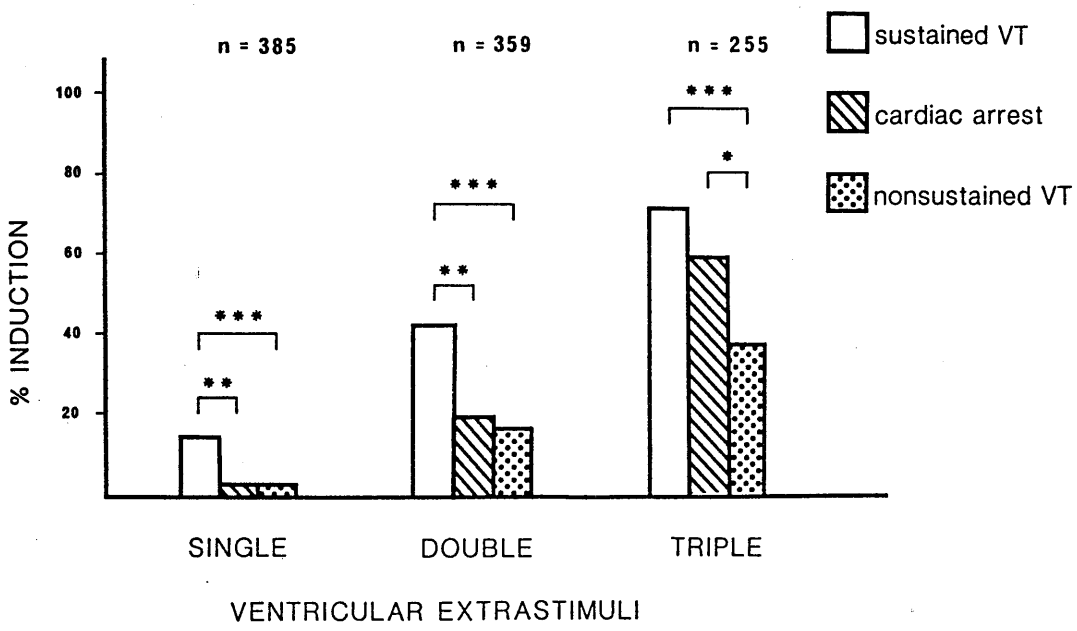

Fig. 3.7 Number of ventricular extrastimuli required for induction in relation to the presenting arrhythmia

* P<0.05
** P<0.01
*** P<0.001

$p<0.05$ respectively).

As a percentage of the number of induced arrhythmias there was a trend towards induction of sustained ventricular tachycardia with fewer extrastimuli compared to ventricular fibrillation and nonsustained ventricular tachycardia. Single extrastimuli induced sustained ventricular tachycardia in 21 of 180 (12%) patients, ventricular fibrillation in 1 of 23 (4%) patients and nonsustained ventricular tachycardia in 1 of 53 (2%) patients although these differences were only significant in respect of sustained versus nonsustained ventricular tachycardia ($p<0.05$). Examples of arrhythmia induction with single, double and triple ventricular extrastimuli are shown in Fig. 3.8.

3.6 Associated Conduction Abnormalities

Programmed atrial stimulation was performed in the baseline study to evaluate both arrhythmia inducibility and in particular sinus nodal function and AV conduction. For technical reasons a comprehensive study could not be performed in all cases. Of the 385 patients, sinus nodal function could not be evaluated in 46 patients, AV nodal conduction in 40 patients and His-Purkinje conduction in 21 patients.

For the purposes of this analysis, significant

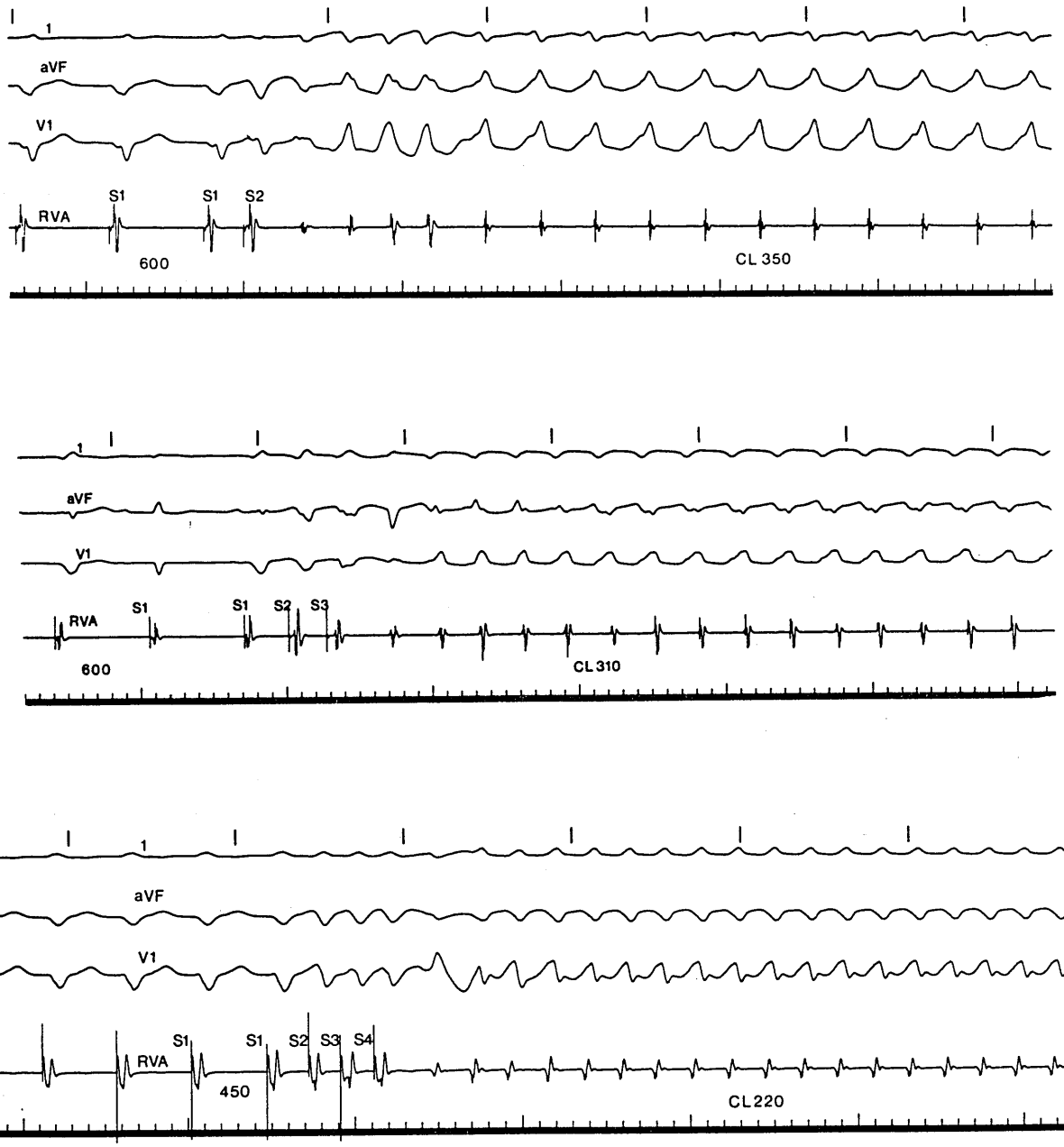

Fig. 3.8 Induction of ventricular tachycardia by one extrastimulus (upper panel), two extrastimuli (middle panel) and three extrastimuli (lower panel).

abnormalities of conduction were defined as:

a) Sinus nodal function - sinus node recovery time > 1400 msec. and corrected sinus node recovery time > 550 msec.

b) AV conduction - basal AH > 125 msec. and development of AV nodal block at an atrial paced cycle length >500 msec.

c) His-Purkinje conduction - basal HV interval $\geq$ 70 msec.

Although adoption of these definitions limits the sensitivity of the evaluation, it was considered that less strict criteria would not necessarily be clinically important.

Overall, at least one conduction disturbance was identified in 87 (24%) of the patients who had at least one component of the conduction system evaluated. Sinus node dysfunction was found in 15 (4%) of the patients, disturbance of AV nodal conduction in 18 (5%) of the patients and disturbance of His-Purkinje conduction in 70 (19%) of the patients.

Interestingly, despite the relatively strict nature of the criteria, implantation of a permanent pacemaker as part of the management of the patient's arrhythmia was required in only 8 (2%) of the patients; 2 patients with sinus node dysfunction, 1 patient with AV nodal conduction impairment, 4 patients with disturbance of His-Purkinje conduction and

1 patient with a combination of sinus node dysfunction and disturbance of HisPurkinje conduction.

3.7 INDUCTION OF VENTRICULAR TACHYARRHYTHMIAS IN PATIENTS WITH SYNCOPE OF UNDETERMINED ORIGIN

Programmed electrical stimulation was also performed in patients with syncope of undetermined origin. The patient population consisted of 117 patients with recurrent syncope. By definition, these patients had no identifiable neurological or structural cardiac abnormality to account for their symptomatic events. The full stimulation protocol was performed in all patients including up to triple ventricular extrastimuli at two right ventricular sites. Left ventricular stimulation was not performed in these patients.

Employing the same criteria for a significant conduction abnormality as documented above, and including the diagnosis of carotid sinus hypersensitivity as the reproducible development of a period of asystole of at least 3 seconds in response to carotid sinus massage, at least one electrophysiological abnormality was identified in 64 (55%) of the patients. In 6 patients more than one abnormality was present. The abnormalities identified are listed in Table 3.1.

A ventricular tachyarrhythmia was induced in 33 (28%) of the patients. In all but one of these patients, underlying heart disease was present; coronary artery

ABNORMALITY	NUMBER OF PATIENTS
SINUS NODE DYSFUNCTION	8 (7%)
CAROTID SINUS HYPERSENSITIVITY	11 (9%)
AV NODAL CONDUCTION IMPAIRMENT	6 (5%)
HIS PURKINJE CONDUCTION IMPAIRMENT	9 (8%)
AV NODAL REENTRANT TACHYCARDIA	3 (3%)
ATRIAL FIBRILLATION	2 (2%)
SUSTAINED VENTRICULAR TACHYCARDIA	11 (9%)
NONSUSTAINED VENTRICULAR TACHYCARDIA	14 (12%)
VENTRICULAR FIBRILLATION	8 (7%)
NO ABNORMALITY	53 (45%)

TABLE 3.1 Electrophysiological abnormalities identified in patients with syncope of undetermined origin

disease in 25 patients and dilated cardiomyopathy in 7 patients. Sustained ventricular tachycardia was induced in 11 patients, ventricular fibrillation in 8 patients and nonsustained ventricular tachycardia in 14 patients. Sustained ventricular tachycardia was induced with double extrastimuli in 3 patients and triple extrastimuli in 8 patients. The pattern of induction for ventricular fibrillation and nonsustained ventricular tachycardia was similar, with double extrastimuli in 3 patients and triple extrastimuli in 5 patients and double extrastimuli in 3 patients and triple extrastimuli in 11 patients respectively. The duration of nonsustained ventricular tachycardia ranged from 6 to 100 complexes (mean = 34 $\pm$ 29) and the morphology was unimorphic in 6 patients and polymorphic in 8 patients.

3.8 DISCUSSION

The induction of ventricular tachyarrhythmias by programmed stimulation techniques is obviously determined by many interdependent factors. These factors relate either to variables which are inherent to the patient population under study such as the presenting arrhythmia or the type of underlying heart disease or to the more controllable variables of the stimulation protocol. With respect to the latter, since there is no standard stimulation protocol, comparison of results of induction of

ventricular arrhythmias between different groups may be difficult.

Effect of Presenting Arrhythmia

The differences in induction rates in relation to the presenting arrhythmia observed in this study are in accord with those reported by other laboratories. In most studies of patients presenting with sustained ventricular tachycardia, a ventricular arrhythmia was induced in more than 80% of patients [13,173,174,175]. In comparison, in patients with out-ofhospital cardiac arrest, arrhythmia induction occurred in 60 to 80% of the patients [138-140]. Similarly, lower results have been reported in patients with nonsustained ventricular tachycardia compared to sustained ventricular tachycardia. In 4 studies, induction rates ranging from 38 to 65% were observed [13,173,176,177]. As will be discussed later, the response of patients with nonsustained ventricular tachycardia to programmed stimulation is more dependent on the population studied and the stimulation protocol employed than the former groups.

Effect of Underlying Heart Disease

Induction of ventricular arrhythmias also depends on the type of underlying heart disease. In the present study, there was a trend towards a higher frequency of induction in patients with coronary artery disease compared

to patients with cardiomyopathy or primary electrical disease. A similar trend was observed by Prystowsky et al.[178]. The impact of underlying heart disease is emphasised further by the differential rates of induction in relation to the type of coronary artery disease. Patients with remote-infarction have the highest incidence of arrhythmia induction and the observed rate of 81% is similar to previous reported series[13,173]. This presumably reflects the presence of an endocardial scar in this patient group which provides the ideal substrate for the development of a reentrant arrhythmia. Indeed the highest induction rate obtained in this analysis (94%) was in patients with a history of sustained ventricular tachycardia and previous myocardial infarction. This is almost identical to that observed by Brugada et al.[179]. It is important to note that, in most large series evaluating the application of programmed stimulation, the majority of patients studied have a history of previous myocardial infarction. Although not addressed in the studies in this thesis, programmed stimulation has been employed to induce ventricular arrhythmias in other types of heart disease including patients with the long QT syndrome[158], mitral valve prolapse[159], hypertrophic cardiomyopathy[160,161] and arrhythmogenic right ventricular dysplasia[142,143] with variable results.

Patients with primary electrical disease form only a small proportion of patients studied. Prystowsky et

al.[178] reported an induction rate of 53% in 46 patients investigated. The diagnosis of primary electrical disease however is a diagnosis by exclusion and in a recent study, endomyocardial biopsy has demonstrated features of early cardiomyopathy in these patients[180] and therefore results obtained in a series not undertaking this investigation, including the present, may be difficult to interpret.

Effect of Different Components of Stimulation Protocol

a) Cycle Length of Drive Train

Selection of the cycle lengths of the drive train in the stimulation protocol has been discussed in Chapter 2. Induction of ventricular arrhythmias by extrastimuli introduced during sinus rhythm was very low at 5% which is similar to previously published reports[178]. The benefits of employing a ventricular paced drive train may be due to a shortening of ventricular refractoriness related to a more rapid rate[181] or reversal of the wave front of activation during ventricular pacing facilitating penetration of the reentrant circuit[182]. The use of more than one cycle length for the drive train has also been shown to increase the yield of arrhythmia induction[183,184].

Because of the low yield using sinus rhythm, the electrophysiological protocol used in our laboratory has now been modified to the use of the ventricular drive trains before sinus rhythm which has reduced the duration

of the procedure in many cases.

b) Site of Stimulation

The use of multiple sites of stimulation is employed in most stimulation protocols. Induction of ventricular tachycardia by atrial stimulation occurred in only 2% of cases which is similar to that reported by Prystowsky and Zipes[174]. Wellens et al.[185] observed an incidence of 13% for induction by atrial stimulation. The higher rate in this latter study presumably reflects the patient population since in these studies, including the present, the tachycardia could also be induced by single ventricular extrastimuli in all cases.

The relative rates of induction observed in relation to the three stimulation sites employed in this study are in accord with previous reports. Doherty et al.[186] noted an increased yield of 58% using a second right ventricular site. Brugada and Wellens[175] have suggested that increasing the aggressiveness of the stimulation at the right ventricular apex is a more effective means of inducing ventricular tachycardia than changing the site of stimulation. This is however at variance with the study from Doherty and co-workers[187]. Furthermore, Prystowsky et al.[188] have observed that tachycardias inducible at the right ventricular outflow tract but not at the apex have certain specific characteristics.

The use of multiple sites may also reduce the need for triple extrastimuli. Morady et al.[189] observed that this induction mode was not required in 53% of patients when double extrastimuli were delivered at two right ventricular sites.

The requirement for left ventricular stimulation is also related to the extent of stimulation within the right ventricle. Robertson et al.[190] reported that 11% of patients with sustained ventricular tachycardia required left ventricular stimulation when single and double extrastimuli were employed in the right ventricle. In contrast, with triple extrastimuli, the additional yield in the left ventricle was only 2%[189]. In addition, the need for left ventricular stimulation may depend on the presenting arrhythmia. Buxton et al.[191] reported that 19% of patients presenting with out-of-hospital cardiac arrest required stimulation at this site despite the use of a stimulation protocol including triple extrastimuli at two right ventricular sites.

c) Number of Extrastimuli

The number of extrastimuli employed in the stimulation protocol is probably the most important determinant of sensitivity and specificity of the response to programmed stimulation. With increasing number of extrastimuli there is an increased yield of arrhythmias induced but at the penalty of a reduction in specificity of the test[175,189,

191-194. In addition to the increased yield a further advantage of the use of more extrastimuli is the reduced need for left ventricular stimulation as noted above. Mann et al.[192] reported that the use of three and four extrastimuli increased the arrhythmia induction rate from 37% to 65% in patients with spontaneous sustained ventricular tachycardia but at the cost of an increased induction of nonclinical tachycardia from 19 to 37%. Brugada et al.[193] evaluated the use of up to 4 extrastimuli in 52 patients without suspected ventricular arrhythmias. With an end-point for the stimulation protocol of 6 or more beats, a ventricular arrhythmia was induced in 31 (60%) of the patients. In contrast, the use of only up to double extrastimuli appears to be associated with a higher specificity[13,173]. It is interesting to note that Echt et al.[183] found that the number of extrastimuli employed was more important for the induction of ventricular tachycardia than the number of cycle lengths of the drive train used.

Type of Induced Arrhythmia

The type of arrhythmia induced is also an important factor in relation to the specificity of the stimulation protocol. The most specific end-point for programmed stimulation is the reproducible induction of sustained monomorphic ventricular tachycardia which is identical to the clinically occurring tachycardia. Not infrequently, however, the morphology of the induced tachycardia is

different but most investigators would still consider that this represented a satisfactory end-point, and was a specific response[13,173,194]. The significance of polymorphic nonsustained ventricular tachycardia and ventricular fibrillation is more controversial especially when induced with aggressive stimulation protocols [191-195]. These arrhythmias can be induced in patients without documented arrhythmias in 13 to 51%[192,195]. In patients however, who have previously manifested these arrhythmias, the specificity of these responses is presumably higher. A further problem arises in interpreting the specificity, if these arrhythmias are the only arrhythmias induced in patients who have documented sustained tachycardia. It is not known whether such induction denotes a satisfactory reproducible endpoint for subsequent drug evaluation. Furthermore, although a nonclinical tachycardia, by definition, does not resemble previously spontaneously occurring arrhythmias, the possibility of clinical manifestation in the future remains speculative.

The sensitivity and specificity of programmed stimulation adopts even greater importance when this technique is applied to prospectively identify patients at risk of developing arrhythmias in the postmyocardial infarction phase. Greene et al.[196] suggested that the induction of multiple repetitive responses by a single extrastimulus was predictive of subsequent sudden death, further studies[197,198,199] however have not supported this

concept and it is apparent that repetitive responses are a very nonspecific feature. To date the prognostic value of electrophysiological testing remains controversial and the results from several studies have been very variable[149-155]. The application of electrophysiological testing in this situation is not addressed in this thesis.

Patients with Syncope of Undetermined Origin

In patients with syncope of undetermined origin, for whom an arrhythmic etiology has not been identified by noninvasive testing, programmed stimulation has been recommended[200]. The results of such testing have been very variable ranging from 18-68%[146,147,148,200,201]. The discrepancies in these observations are due to differences in the patient population, in particular in relation to the presence of structural heart disease. The results obtained in the present study are similar to those reported by Hess et al.[148]. More pertinent to the present discussion is the role of this technique in identifying a ventricular tachyarrhythmia as the underlying etiology. The interpretation of arrhythmia inducibility however may be very difficult. Since no documentation of previous arrhythmias to account for syncope is available, the specificity of the response to programmed stimulation is paramount. As noted previously, the induction of polymorphic nonsustained ventricular tachycardia and ventricular fibrillation may merely reflect the

aggressiveness of the stimulation protocol employed. However this has to be balanced by the possibility that, in some patients, these arrhythmias may be causative. In the present study, polymorphic nonsustained tachycardia and ventricular fibrillation was induced in 16 patients and in 11 of these triple extrastimuli were required. The specificity of arrhythmia induction in these latter patients in relation to their history of syncope may therefore be questionable.

Reproducibility of Arrhythmia Induction

A major limitation of the present analysis of arrhythmia induction is the fact that a prospective evaluation of the reproducibility of the stimulation protocol was not performed. Mcpherson et al.[202] observed a reproducibility of 88% in patients undergoing repeat baseline studies over a three day period. This group also reported that reproducibility fell with arrhythmia induction requiring triple extrastimuli. In contrast, Bigger et al.[203] found no change in inducibility in relation to the number of extrastimuli employed and Kudenchuk et al.[204] reported that non-reproducibility with three and four extrastimuli was not significantly greater than when two extrastimuli were used. Short-term reproducibility was also investigated by Duff et al.[205] who concluded that replacement of the catheter between studies (compared to the catheter being left in-situ) enhanced this

response. Re-insertion of the stimulation catheter between studies is routine practice in the studies performed in this thesis. Evaluation of longer term reproducibility was performed by Schoenfeld et al.[206]. This group reported that reproducibility was excellent in patients with coronary artery disease but was significantly lower in patients without coronary artery disease. Interestingly, in this latter study, some patients with sustained ventricular tachycardia in the first study had nonsustained tachycardia in the second study and vice-versa. Furthermore, the morphology of the induced arrhythmia was not necessarily identical. This observation has obvious implications with respect to what is an acceptable end-point for stimulation in patients with documented arrhythmias.

CONCLUSIONS

The results from this study confirm that the response to programmed stimulation employing the stimulation protocol used in this thesis is comparable to that reported from other laboratories. The impact of different determinants on arrhythmia induction in relation to the patient population studied and the limitations of a protocol involving triple extrastimuli are discussed.

CHAPTER 4

TERMINATION OF VENTRICULAR TACHYCARDIA

The ability to repeatedly terminate ventricular tachycardia, safely and effectively, is an important factor in the utility of electrophysiological testing in the management of patients with ventricular arrhythmias. Although DC cardioversion is the most effective procedure for tachycardia termination, its repeated application is obviously limited.

Several studies have demonstrated that pacing modalities can terminate sustained ventricular tachycardia in over 60% of cases[16,20,42,207,208]. The various techniques for termination have included premature stimulation, pacing entraiment, burst pacing and overdrive pacing plus premature stimulation.

This analysis was performed to determine the effectiveness of termination of ventricular tachycardia by pacing techniques in relation to the tachycardia rate and the impact on tachycardia termination by antiarrhythmic therapy.

4.1 PATIENTS AND METHODS

The patient population consisted of 180 consecutive

patients undergoing electrophysiological study and in whom a sustained ventricular tachycardia was induced in the baseline study. There were 162 men and 18 women with a mean age of 62 ± 11 years. Underlying heart disease included coronary artery disease in 160 patients, cardiomyopathy or valvular heart disease in 15 patients and primary electrical disease in 5 patients. The ejection fraction, as measured by radionuclide ventriculography ranged from 7 to 75% (mean = 30 ± 16%).

After induction of tachycardia, attempts at termination by pacing techniques were attempted. Selection of modality depended on the rate of the tachycardia and haemodynamic response to the tachycardia. In general, premature stimulation was performed during slower and well tolerated tachycardias and burst pacing employed in these only if premature stimulation was ineffective or accelerated the tachycardia. In faster, haemodynamically more unstable tachycardias, burst pacing was employed initially. Failure to terminate the tachycardia necessitated DC defibrillation.

In 146 patients, sustained ventricular tachycardia remained inducible during 363 subsequent drug studies, and the effects of pacing termination in relation to concurrent antiarrhythmic therapy were analysed in this subgroup of patients. The agents employed are listed in Table 4.1.

Sustained ventricular tachycardia was defined as ventricular tachycardia of greater than 30 seconds in

REGIMEN	NO. OF STUDIES	REGIMEN	NO. OF STUDIES
PROCAINAMIDE	75	QUINIDINE + MEXILETINE	32
QUINIDINE	38	AMIODARONE + PROCAINAMIDE	25
MEXILETINE	35	PROCAINAMIDE + MEXILETINE	14
AMIODARONE	92	AMIODARONE + MEXILETINE	6
FLECAINIDE	15	PROCAINAMIDE + PHENYTOIN	4
INDECAINIDE	10	QUINIDINE + PHENYTOIN	3
PIRMENOL	4	QUINIDINE + LIGNOCAINE	1
DISOPYRAMIDE	3	AMIODARONE + QUINIDINE	1
LIGNOCAINE	3	DISOPYRAMIDE + MEXILETINE	1
BETHANIDINE	1		

TABLE 4.1 Drug regimens employed

duration or tachycardia requiring termination within 30 seconds because of the development of cardiovascular collapse.

Acceleration of the tachycardia by pacing techniques was defined as a reduction in the cycle length of the tachycardia by at least 50 msec.[208].

4.2 RESULTS

By study design all patients had inducible sustained ventricular tachycardia in the baseline study. Ventricular tachycardia was induced by single extrastimuli in 20 patients, double extrastimuli in 70 patients and triple extrastimuli in 90 patients. The induced tachycardia cycle length ranged from 140 to 539 msec. (mean = 271 $\pm$ 66 msec.).

Ventricular tachycardia was terminated by pacing modalities in 105 (58%) of the patients. Premature stimulation was effective in 9 (5%) of the patients and burst pacing in 96 (53%) of the patients. The mean cycle length for the burst pacing was 50 $\pm$ 37 msec. shorter than the tachycardia cycle length. Cardioversion was required for termination in 75 (42%) of the patients. Examples of pacing termination are shown in Fig. 4.1.

The effectiveness of pacing modalities was dependent on the cycle length of the tachycardia. The mean cycle length of the tachycardias for which pacing modalities were

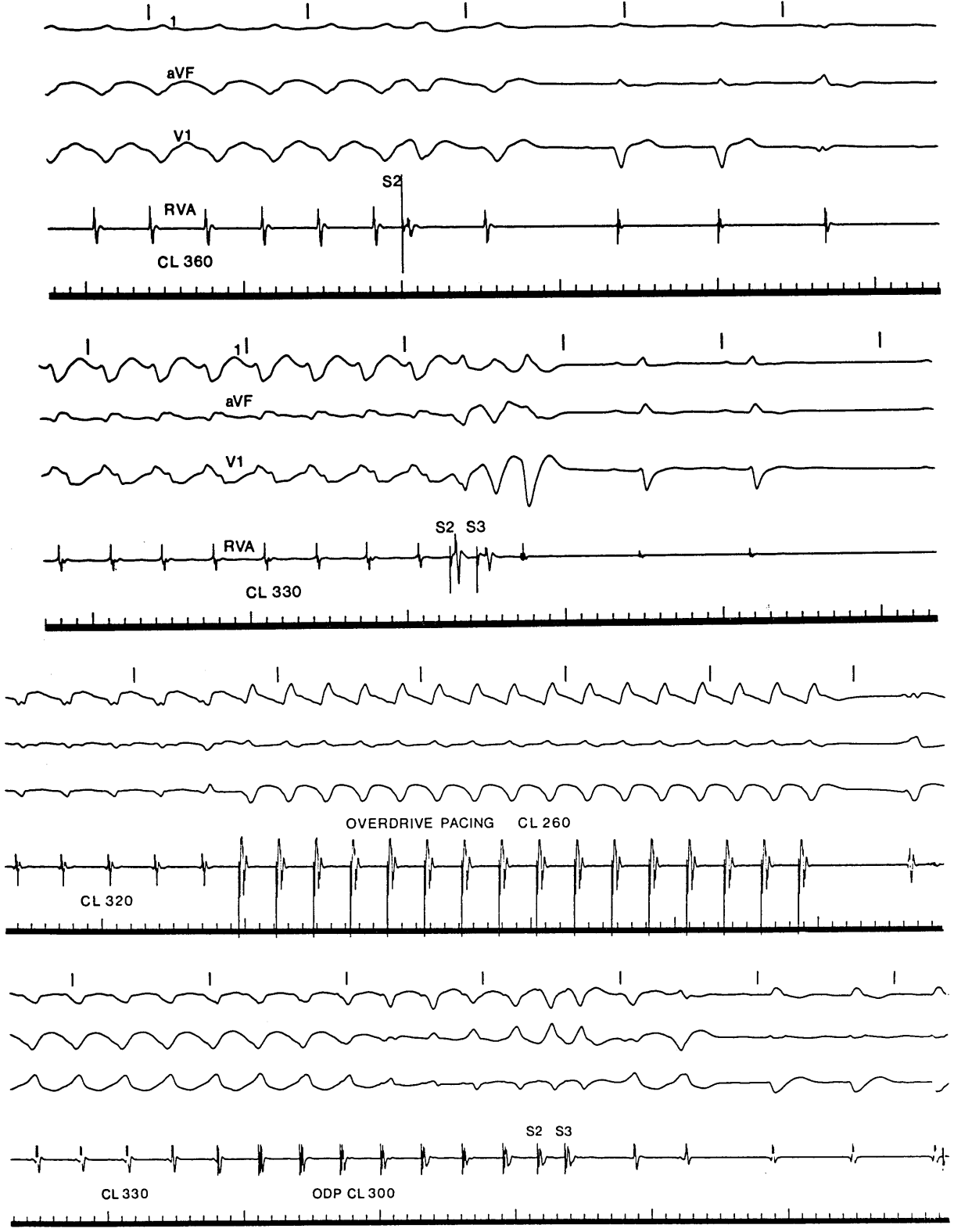

Fig. 4.1 Examples of termination of tachycardia by different pacing modalities: single ventricular extrastimuli, double ventricular extrastimuli, overdrive pacing and combination of overdrive pacing and double ventricular extrastimuli.

effective was 380 ± 60 msec. for premature stimulation and 299 ± 57 msec. for burst pacing ($P<0.005$). The mean cycle length of the tachycardias which required DC cardioversion was significantly shorter than for pacing termination at 223 ± 37 msec. ($P<0.001$).

The success of pacing termination in relation to tachycardia cycle length was analysed further (Table 4.2). Cardioversion was required for all tachycardias with a cycle length less than 200 msec., in contrast to the 100% success obtained for pacing modalities in tachycardias with a cycle length of 350 msec. or longer. Between cycle lengths of 201 and 349 msec. there was an increase in the frequency of pacing success with a decrease in the tachycardia rate (Fig. 4.2). Over this range of cycle lengths, the need for cardioversion was not dependent on the baseline left ventricular function (as measured by the global ejection fraction) (Table 4.3). Acceleration of the tachycardia by attempts at pacing termination occurred in 29 (16%) of patients. In 11 of these patients, although the tachycardia was accelerated, the tachycardia was still terminated by burst pacing at a shorter cycle length. The mean cycle length of tachycardias which were accelerated was 256 ± 45 msec. Examples of tachycardia acceleration due to attempts at pacing termination are shown in Fig. 4.3.

TACHYCARDIA CYCLE LENGTH (msec.)	TOTAL NO. OF EPISODES	PACING TERMINATION SUCCESS
<200	15	0
201 - 249	62	16 (26%)
250 - 299	44	34 (77%)
300 - 349	41	37 (90%)
350 - 399	8	8 (100%)
>400	10	10 (100%)

TABLE 4.2 Pacing termination in relation to cycle length of tachycardia

TACHYCARDIA CYCLE LENGTH (msec.)	METHOD OF TERMINATION	EJECTION FRACTION (%)	
200 - 249	PACING	28 ± 13	N.S.
	CARDIOVERSION	30 ± 15	
250 - 299	PACING	26 ± 14	N.S.
	CARDIOVERSION	30 ± 15	
300 - 349	PACING	30 ± 16	N.S.
	CARDIOVERSION	30 ± 14	

TABLE 4.3 Termination of ventricular tachycardia in relation to ventricular function

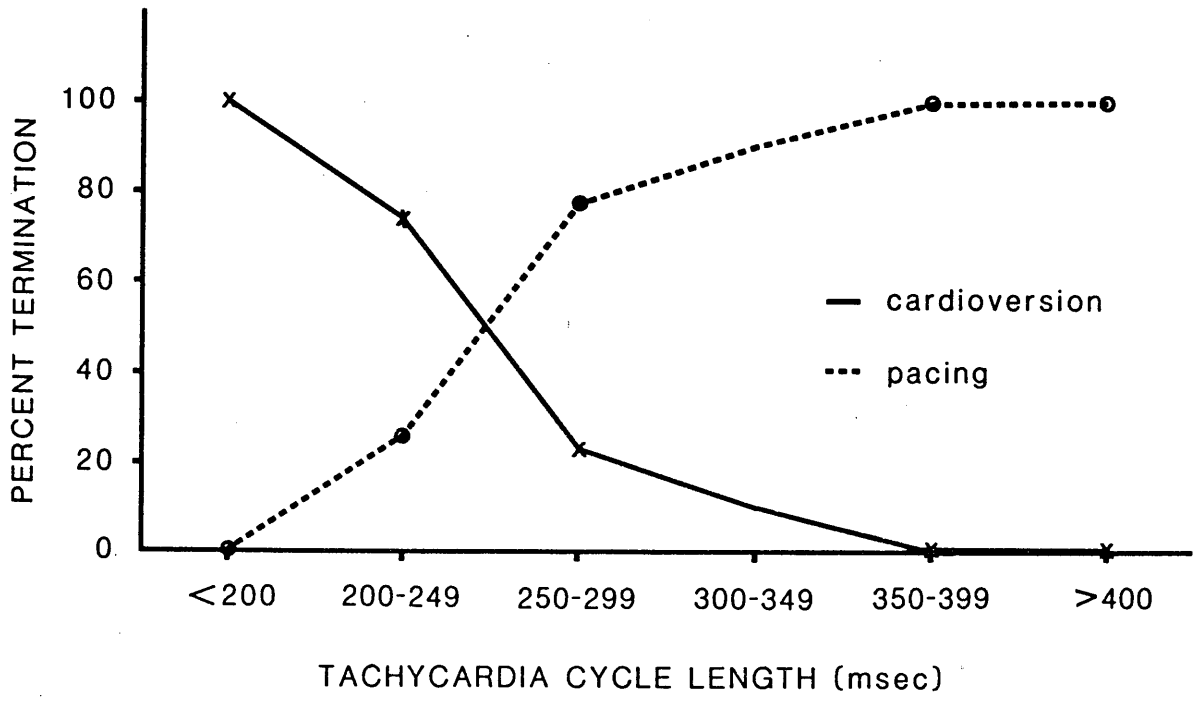

Fig. 4.2 Effect of tachycardia cycle length on the termination of tachycardia

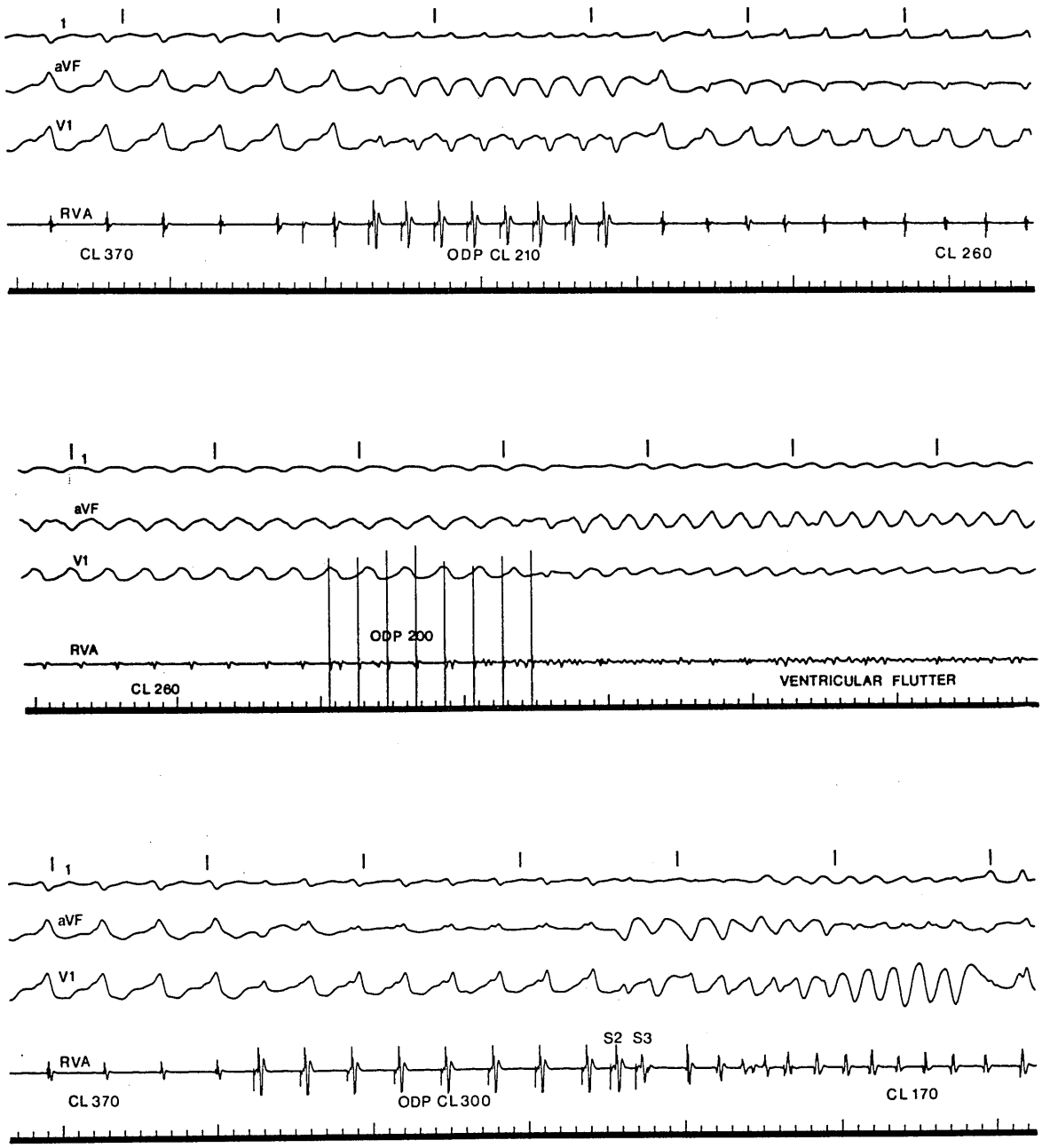

Fig. 4.3 Acceleration of tachycardia due to attempts at pacing termination. Upper and middle panels: overdrive pacing; lower panel: overdrive pacing plus extrastimuli.

Effect of Antiarrhythmic Therapy

In the 146 patients in whom a sustained tachycardia was still inducible on antiarrhythmic therapy, the mean cycle length of the tachycardia was increased from 272 $\pm$ 65 to 349 $\pm$ 78 msec ($p<0.001$) by antiarrhythmic therapy. The success rate for pacing termination increased from 90 (62%) of 146 studies to 270 (74%) of 363 studies ($p<0.05$) (Table 4.4).

The increased success of pacing termination on antiarrhythmic therapy was due to the proportionately larger number of tachycardias with a longer cycle length (Table 4.5). In the baseline study, 66% of the tachycardias had a cycle length less than 300 msec. compared to only 28% in the studies on antiarrhythmic therapy. Within each grouping of tachycardia cycle lengths there was a trend towards an increased requirement for DC cardioversion for termination in patients on antiarrhythmic therapy. This only reached significance, however, for tachycardias with cycle lengths of 250 to 299 msec., where cardioversion was required for 19% of studies in the baseline compared to 53% of studies on antiarrhythmic therapy ($p<0.001$) (Fig. 4.4). Acceleration of tachycardia occurred in 27 (18%) in the baseline study as compared to 47 (13%) on antiarrhythmic therapy.

Pacing Modalities

Since the choice of modality for pacing termination

	BASELINE	ON THERAPY
TOTAL NO. OF STUDIES	146	363
BURST PACING	82 (56%)	226 (62%)
PREMATURE STIMULATION	6 (4%)	44 (12%)
CARDIOVERSION	58 (40%)	93 (26%)

TABLE 4.4 Effect of antiarrhythmic therapy on termination of ventricular tachycardia

TACHYCARDIA CYCLE LENGTH (msec.)	BASELINE	ON THERAPY
<200	0/8	-
201 - 249	15/53 (28%)	4/20 (20%)
250 - 299	29/36 (81%)	35/74 (47%)*
300 - 349	30/33 (91%)	70/92 (76%)
350 - 399	8/8 (100%)	78/87 (90%)
>400	8/8 (100%)	83/90 (92%)

TABLE 4.5 Pacing termination of ventricular tachycardia. Relation of cycle length of tachycardia during antiarrhythmic therapy.

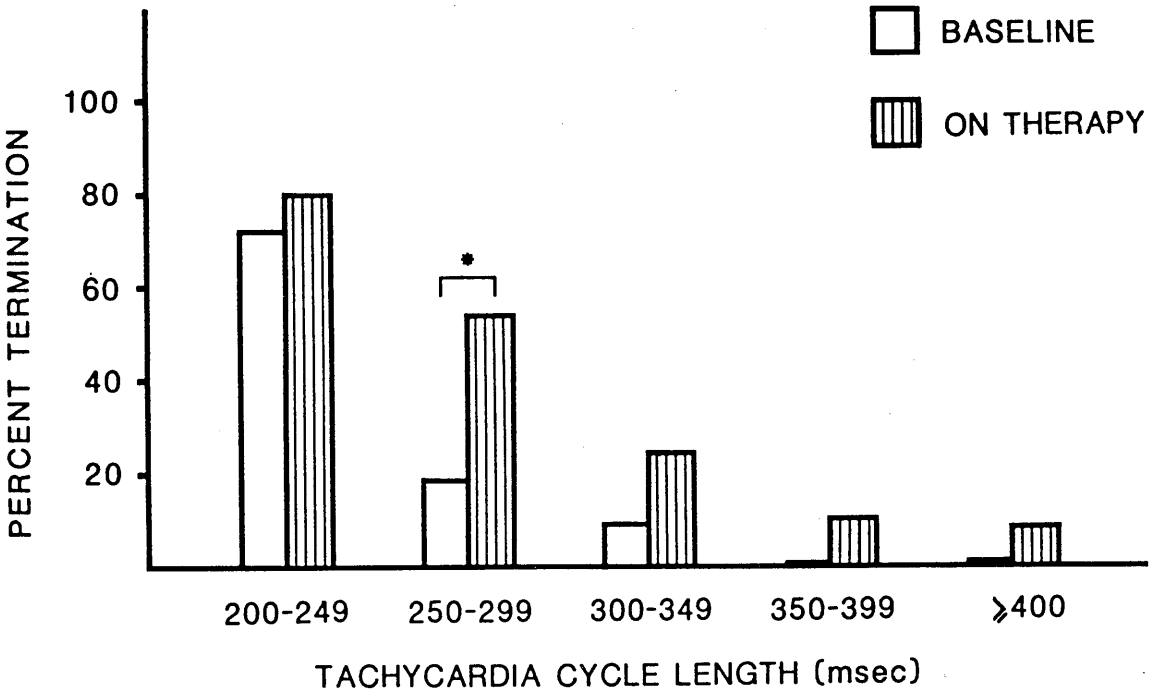

Fig. 4.4 Requirement for cardioversion for tachycardia termination. Effect of antiarrhythmic therapy in relation to tachycardia cycle length.

* $p < 0.001$

depended on the rate of the tachycardia and the patient's haemodynamic response, direct comparison between effectiveness of premature stimulation and burst pacing could not be evaluated. Slowing of the tachycardia rate by drug therapy permitted successful termination of tachycardia in 12% of cases by premature stimulation as compared to 4% in the baseline study. In one of the 6 cases in the baseline study and 7 cases on antiarrhythmic therapy, the premature stimuli were introduced during overdrive pacing of the tachycardia.

4.3 DISCUSSION

In patients with ventricular arrhythmias, the ability to reproducibly induce the clinical arrhythmia has provided a means of identifying effective antiarrhythmic therapy. Application of this technique however would be significantly limited if resort to cardioversion was required for each case. This study confirms other groups' experience of termination of ventricular tachycardia[16,20,42,207,208]. In approximately 60% of cases, ventricular tachycardia can be effectively terminated by pacing techniques. Wellens et al.[209] have previously discussed the factors relating to the ability of pacing techniques to terminate ventricular tachycardia, in particular the cycle length, the size and site of the

reentrant circuit, the distance of the site of stimulation from the circuit and the electrophysiological properties of the intervening tissue. The termination of tachycardia by pacing stimulation requires penetration of the reentrant circuit and collision of the stimulus impulse with the tachycardia wavefront thus abolishing further arcus movement. The width of the termination zone of the reentrant circuit is dependent on the cycle length of the tachycardia. Furthermore, at sites distant from the reentrant circuit, it is more difficult for the premature stimuli to penetrate the circuit during this critical phase of activation of the circuit.

Effect of Tachycardia Rate

The critical factor of tachycardia rate was demonstrated in the study from Fisher et al.[20] with successful termination in 93% of tachycardias with rates less than 250 bpm compared to 17% with faster tachycardias. This observation has been confirmed in subsequent studies[208,209,210,211]. In the present study the success rate of tachycardias with cycle lengths ranging from 201-249 msec. was only 26% compared to 100% success if the cycle length was 350 msec. or longer. A further factor reducing the success rate for pacing techniques in faster tachycardias, is the haemodynamic impact produced. In patients with already compromised left ventricular function, cardiovascular collapse can occur quickly

necessitating the immediate termination of the tachycardia by cardioversion.

Pacing Techniques

A number of different pacing techniques have been employed to terminate ventricular tachycardia induced during electrophysiological testing. The introduction of single premature stimuli is effective in slower tachycardias. Josephson et al.[211] reported a 43% success rate for this mode, although as noted by Naccarelli et al.[208] the tachycardia rate is critical. In their study, a single extrastimulus was effective in 40% of tachycardia with a cycle length > 350 msec. compared to only 12% with cycle lengths < 350 msec. Double extrastimuli and, in particular, burst pacing are more effective termination modalities especially in faster tachycardias. The increased success rate is due to the "peeling back" of refractoriness of the intervening tissue between the site of stimulation and the reentrant circuit, facilitating impulse penetration. The combination of overdrive pacing plus the introduction of premature stimuli has been reported by Gardner et al.[212]. With this method, successful termination of ventricular tachycardia was achieved in 21 of 25 patients in each of whom overdrive pacing and extrastimulation individually at similar cycle lengths and coupling intervals had failed to interrupt the tachycardia.

A further technique for termination is the use of entrainment[18]. Entrainment of a tachycardia is the continuous resetting of a tachycardia with variable fusion and is dependent on tachycardia rate[18], site of stimulation[213] and duration of pacing[18]. Keren et al.[210] have reported a success rate of 27% with this modality.

The benefits of increasing the current strength was demonstrated by Waxman et al.[214]. Single extrastimuli at a current strength of 5-10mA were effective in 11 of 53 episodes of tachycardia which could not be terminated at the standard current strength of twice diastolic threshold. In the present study, stimulus amplitudes of up to 10mA were frequently employed in both extrastimulation and burst pacing attempts although this could not be specifically evaluated.

I have recently been involved in the evaluation of an alternative modification of the pacing stimulus. In a preliminary study[215] using a low energy (mean current amplitude = 7.2 $\pm$ 1.2mA) long duration stimulus (mean pulse duration = 414 $\pm$ 33 msec.) which is longer than the cycle length of the tachycardia (mean cycle length = 377 $\pm$ 25 msec.). Successful termination was achieved in 6 of 9 episodes of ventricular tachycardia. Although not elucidated, as yet, the mechanism underlying this modality may be related to the induction of multiple extrastimuli by the pacing stimulus.

Site of Stimulation

In the present study, the attempts at pacing termination were performed in the right ventricle at the site of initiation of the tachycardia, except in 5 cases where left ventricular stimulation was required. Since most ventricular tachycardias are of left ventricular origin, stimulation in the left ventricle, nearer the reentrant circuit may facilitate pacing termination, although no detailed study of this approach has been reported. The practical difficulties of arterial catheterisation, however, would preclude this as a routine procedure.

Acceleration of Tachycardia

Acceleration of tachycardia by the pacing techniques employed for termination is the major concern limiting the application of permanent antitachycardia pacemakers to patients with ventricular tachycardia. In the study from Fisher et al. [20], although only 4% of attempts at pacing termination produced tachycardia acceleration, at least one episode occurred in 43% of the patients. Mason et al.[42] noted an 11% risk of acceleration which is similar to the results observed in the present study. Acceleration of the tachycardia is dependent on the cycle length of the tachycardia and the type of pacing technique employed. Naccarelli et al.[208] reported a 0% incidence of acceleration with single extrastimuli, 15% with double

extrastimuli and 18% with burst pacing. Unfortunately, with rapid tachycardias, a more aggressive pacing modality is required with a consequent increase in the risk of acceleration [20,42]. The faster the rate of the burst pacing required, the more likely the acceleration of the arrhythmia[20,157]. During attempts at pacing termination, therefore, burst pacing is initiated at cycle lengths initially only 20 to 30 msec. shorter than the cycle length of the tachycardia.

Effect of Antiarrhythmic Therapy

In two previous studies, the impact of antiarrhythmic therapy on pacing termination has been analysed[208,210]. In both studies, antiarrhythmic agents have improved the success rate of termination by increasing the cycle length of the tachycardia. In contrast, in the present study, although there was an increase in the overall number of successful terminations, there was a trend towards an increase in the need for cardioversion in patients on antiarrhythmic therapy. In patients with tachycardia cycle lengths ranging from 200 to 249 msec. this difference was statistically significant. This feature has been observed anecdotaly previously[212]. This adverse aspect may be related to two factors. Firstly the negative inotropic effect of antiarrhythmic therapy may worsen the haemodynamic response of the patient relative to the tachycardia rate and therefore necessitating cardioversion.

Secondly, many antiarrhythmic agents are effective by increasing ventricular refractoriness. Development of entrance block into the reentrant circuit[16] or increased refractoriness of intervening tissue may prevent impulse penetration. Antiarrhythmic therapy, however, does not appear to increase the risk of acceleration.

CONCLUSIONS

The present study confirms the efficacy of pacing techniques for the termination of ventricular tachycardia. If the tachycardia rate is lower than 200 bpm, pacing termination is very likely to be effective. Although antiarrhythmic therapy increases the overall rate of termination by increasing the cycle length of the tachycardia, effects on ventricular function and refractoriness may increase the need for cardioversion in some instances. The risk of acceleration of the tachycardia by attempts at pacing termination although small, continues to limit the long-term application of this technique.

CHAPTER 5

COMPARATIVE RESPONSE OF INTRAVENOUS AND ORAL PROCAINAMIDE DURING ELECTROPHYSIOLOGICAL TESTING

The rationale for serial electrophysiological drug testing is that the modification of arrhythmia induction by drug therapy equates with the long-term effect of that therapy. It has therefore been advocated that drug evaluation studies should be performed only with orally administered agents. Intravenous drug testing, however, provides a more rapid attainment of "therapeutic levels" and because of shorter half-lives, trials of different agents can be performed over an abbreviated timespan. In clinical practice, failure of suppression of arrhythmia induction by intravenous therapy has usually precluded repeat testing of the oral formulation of the drug.

Recently, Marchlinski et al.[216] have suggested that repeat testing with oral procainamide is not required if intravenous procainamide is effective in suppressing arrhythmia induction.

The aim of this study was to evaluate the comparative response between intravenous and orally administered procainamide, and to determine whether intravenous testing predicted the outcome on oral therapy.

5.1 Patients and Methods

The patient population consisted of 19 patients with inducible sustained ventricular tachyarrhythmias (sustained ventricular tachycardia in 18 patients and ventricular fibrillation in 1 patient). There were 17 men and 2 women with ages ranging from 42 to 71 years (mean = 61 ± 9 years). Nine patients had clinically documented episodes of sustained ventricular tachycardia, 5 patients had experienced an out-ofhospital cardiac arrest, 2 patients had syncope and 3 patients had symptomatic nonsustained ventricular tachycardia. Underlying heart disease included coronary artery disease in 16 patients, all of whom had experienced a previous myocardial infarction, 1 patient had dilated cardiomyopathy and 2 patients had no evidence of structural heart disease. The mean ejection fraction for the group as measured by radionuclide ventriculography was 30 ± 17% ranging from 11 to 68%.

The standard stimulation protocol was employed at two sites in the right ventricle. Left ventricular stimulation was not required in this study.

For the purposes of this study non-inducibility was defined as the induction of less than 6 repetitive responses at completion of the entire stimulation protocol.

Procainamide was administered intravenously at a rate of 50 mg/min to the maximum tolerated dose or at least 1000 mg. The total dose was limited by the development of

toxic effects, including hypotension or widening of the QRS complex to >25% of the baseline. After completion of the loading dose, a maintenance infusion of 2 to 8 mg/min was administered for the duration of the study. For oral administration a sustained release preparation of procainamide was prescribed in a dosage ranging from 1000 to 2000 mg every 6 to 8 hours. The dosage was selected as far as possible to attain similar serum levels as those obtained during the intravenous study.

Electrophysiological testing on oral therapy was performed after 2 to 4 days when a steady state level had been achieved.

In both intravenous and oral studies, serum levels of both procainamide and N-acetyl procainamide were estimated at the time of arrhythmia induction or completion of the stimulation protocol.

Data are reported as the mean $\pm$ standard deviation. The Student's t test for paired and unpaired data, contingency tables with Fisher's exact test and linear regression analysis were applied as appropriate. A P value of <0.05 was considered significant.

Sensitivity, specificity, predictive value and predictive accuracy were calculated as follows:-

TP = true positive TN = true negative

FP = false positive FN = false negative

$$\text{Sensitivity} = \frac{TP}{TP + N} \qquad \text{Specificity} = \frac{TN}{TN + FP}$$

$$\text{Positive predictive value} = \frac{TP}{TP + FP}$$

$$\text{Negative predictive value} = \frac{TN}{TN + FN}$$

$$\text{Predictive accuracy} = \frac{TP + TN}{\text{All tests}}$$

5.2 RESULTS

In the baseline study sustained ventricular tachycardia (mean cycle length = 246 ± 53 msec.) was induced in 18 patients and ventricular fibrillation in 1 patient. The mode of induction was double extrastimuli in 6 patients and triple extrastimuli in 13 patients (Table 5.1).

Procainamide Levels

The mean intravenous dosage of procainamide administered was 1238 ± 243 ug/ml. The mean serum level of procainamide during the study was 9.6 ± 3.6 ug/ml and of N-acetyl procainamide was <1.5 ug/ml (Table 5.2).

For the oral study the mean dosage per day was 5386 ± 1386 mg producing a mean serum level of procainamide of 9.4 ± 3.6 ug/ml and of N-acetyl procainamide of 9.7 ± 3.2 ug/ml. There was no significant difference in the serum levels of procainamide between the intravenous and oral studies (Table 5.2).

Drug Efficacy

Intravenous procainamide suppressed induction of ventricular arrhythmias in 9 (47%) of the 19 patients

PATIENT NO.	BASELINE			IV PROCAINAMIDE			ORAL PROCAINAMIDE		
	ARRHYTHMIA INDUCED	MODE OF INDUCTION	CYCLE LENGTH (msec)	ARRHYTHMIA INDUCED	MODE OF INDUCTION	CYCLE LENGTH (msec)	ARRHYTHMIA INDUCED	MODE OF INDUCTION	CYCLE LENGTH (msec)
1	SUVT	T	220	SUVT	D	300	SUVT	D	270
2	SUVT	D	240	NONE	-	-	NONE	-	-
3	SUVT	T	270	SUVT	D	330	SUVT	S	420
4	SUVT	T	200	SUVT	D	280	SUVT	T	350
5	SUVT	T	220	NONE	-	-	SUVT	T	380
6	SUVT	T	200	SUVT	T	280	SUVT	T	280
7	SUVT	T	290	NONE	-	-	SUVT	D	490
8	SUVT	D	300	NSVT	D	-	NSVT	D	-
9	SUVT	T	160	NONE	-	-	NONE	-	-
10	SUVT	T	240	NONE	-	-	SUVT	T	260
11	SUVT	T	200	SUVT	T	250	SUVT	T	320
12	SUVT	T	170	NONE	-	-	SUVT	T	310
13	SUVT	D	300	SUVT	S	460	SUVT	S	400
14	SUVT	T	200	NONE	-	-	NONE	-	-
15	SUVT	T	270	NONE	-	-	NONE	-	-
16	SUVT	D	310	NSVT	D	-	NSVT	D	-
17	SUVT	T	330	NONE	-	-	NONE	-	
18	SUVT	D	270	SUVT	T	370	SUVT	T	360
19	VFIB	T	-	SUVT	T	290	SUVT	T	280

TABLE 5.1 Arrhythmia induction in the baseline study and studies with intravenous and oral procainamide.

SUVT = sustained ventricular tachycardia. VFIB = ventricular fibrillation. NSVT = nonsutained ventricular tachycardia

S = single extra stimuli. D = double extrastimuli. T = triple extrastimuli.

	INTRAVENOUS STUDY			ORAL STUDY		
PATIENT NO.	DOSAGE (mg)	DRUG LEVEL (ug/ml) PROC	NAPA	DOSAGE (mg/day)	DRUG LEVEL (ug/ml) PROC	NAPA
1.	1500	16.4	<1.0	4000	9.7	9.7
2.	1500	19.4	1.3	4000	11.1	10.7
3.	1000	12.3	1.9	4000	12.3	9.8
4.	1300	13.2	<1.0	6000	10.0	6.8
5.	1500	8.3	1.4	5000	10.0	11.4
6.	1200	8.1	<1.0	6000	8.9	6.3
7.	1000	11.6	1.6	4000	20.6	7.5
8.	1500	8.7	2.0	6000	9.8	13.4
9.	1000	6.7	1.6	4000	4.4	9.3
10.	1000	6.8	2.0	4000	7.4	10.6
11.	1500	6.1	2.2	8000	9.4	18.8
12.	1500	8.6	1.9	7000	14.0	10.0
13.	1000	7.6	2.3	4000	6.7	11.7
14.	1000	5.8	1.4	4000	7.0	-
15.	1000	8.9	1.7	6000	9.4	7.7
16.	1500	9.4	1.8	6000	6.3	9.7
17.	1500	9.6	<1.0	6000	7.9	4.2
18.	1000	7.7	1.4	6000	5.7	8.8
19.	1000	6.3	<1.0	6000	8.9	7.8

TABLE 5.2 Dosage of intravenous and oral procainamide administered and serum drug levels at time of study

(PROC = Procainamide)

(NAPA = N-acetylprocainamide)

(Table 5.1). In the remaining 10 patients, sustained ventricular tachycardia was induced in 8 patients and nonsustained ventricular tachycardia in 2 patients. There was no difference in the serum procainamide level between responders and nonresponders (9.5 $\pm$ 4.1 v 9.6 $\pm$ 3.3 ug/ml).

On oral procainamide, suppression of induction was obtained in only 5 (26%) of the 19 patients (Table 5.1). The inducible arrhythmias were sustained ventricular tachycardia in 12 patients and nonsustained ventricular tachycardia in 2 patients. Of note, the nonsustained tachycardia was induced in the same 2 patients in both the intravenous and oral studies. There was no difference, either in serum procainamide level or N-acetyl procainamide level between responders and nonresponders (8.0 $\pm$ 2.5 v 10.0 $\pm$ 3.8 ug/ml and 8.0 $\pm$ 2.8 v 9.9 $\pm$ 3.3 ug/ml respectively).

From Table 5.1, it can be seen that all 5 of the successful patients on oral procainamide were identified in the intravenous study. However, in 4 patients in whom intravenous procainamide was effective, subsequent testing on oral therapy demonstrated induction of a sustained arrhythmia. The mean serum level of procainamide in these 4 patients was 8.8 $\pm$ 2.0 ug/ml during intravenous therapy and 13.0 $\pm$ 5.7 ug/ml on oral therapy, confirming that inefficacy on oral therapy was not related to lower serum levels. In patient 12, two trials on oral therapy were performed, the serum level of the first trial being 6.3

ug/ml and the second 14.0 ug/ml. Sustained ventricular tachycardia was inducible in both studies.

On the premise that suppression of induction of tachyarrhythmia on oral therapy is the required end-point, the sensitivity of the intravenous procainamide study is 100%, specificity 71%, positive predictive value 56%, negative predictive value 100% and an overall accuracy of 79%. Of practical clinical importance is the negative predictive value, i.e. there were no cases where the intravenous study predicted failure and the oral study proved successful.

Mode of Induction and Cycle Length of the Tachycardia

In 10 patients a ventricular arrhythmia remained inducible in both procainamide studies. In 8 of these patients the number of premature stimuli required for induction was the same during the intravenous and oral studies. In patient 3(Fig. 5.1), double extrastimuli were required during the intravenous study and single extrastimuli on oral procainamide and in patient 4, double extrastimuli were required compared to triple extrastimuli. In 7 patients, sustained ventricular tachycardia was induced in the baseline and both drug studies. The mean cycle length in the baseline study was 243 $\pm$ 49 msec. which was significantly prolonged by both intravenous and oral procainamide (333 $\pm$ 76 and 347 $\pm$ 59 msec. respectively) ($p<0.001$). There was no statistical difference in the change in cycle length between the intravenous and oral

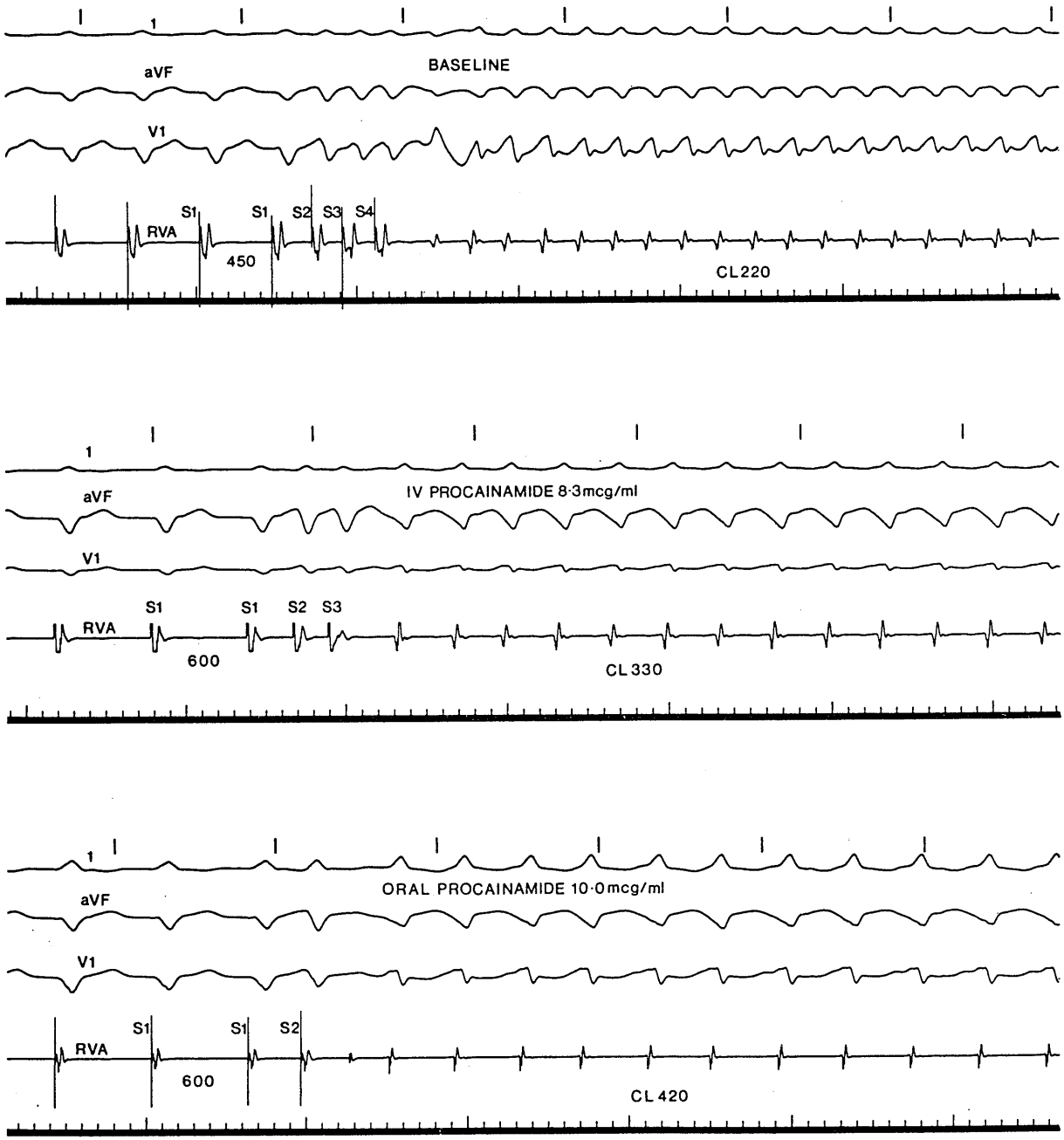

Fig. 5.1 Comparative effects of intravenous and oral procainamide on arrhythmia induction. Upper panel: baseline induction; middle panel: induction on intravenous procainamide; lower panel: induction on oral procainamide.

studies (90 ± 34 v 100 ± 32 msec. respectively). Furthermore, there was no correlation between change in cycle length and serum level of procainamide either in the intravenous study (r = 0.174) or in the oral study (r = 0.219).

Ventricular Refractoriness (Table 5.3).

In the baseline study, the mean ventricular refractory period was 257 ± 21 msec. which increased with intravenous procainamide to 288 ± 32 msec. ($p<0.0001$) and oral procainamide to 286 ± 34 msec. ($p<0.0001$). There was no difference between the mean change in refractory period between intravenous and oral administration (32 ± 22 msec. v 29 ± 27 msec. respectively). In 3 of the 4 patients with discordant results for arrhythmia induction the ventricular effective refratory period was shorter during oral administration than intravenous administration compared to only 3 of 15 patients with concordant responses ($p<0.05$). There was no correlation between the effective refractive period and the serum level of procainamide either in the intravenous study (r = 0.399) or in the oral study (r = 0.364).

5.3 DISCUSSION

Serial electrophysiological drug testing to identify an effective antiarrhythmic therapy is time-consuming and

PATIENT NO.	VENTRICULAR EFFECTIVE REFRACTORY PERIOD (msec)		
	BASELINE	INTRAVENOUS STUDY	ORAL STUDY
1.	260	300	300
2.	260	300	320
3.	270	320	280
4.	260	290	300
5.	260	300	250
6.	260	280	260
7.	310	390	380
8.	270	300	320
9.	250	250	270
10.	260	290	240
11.	270	270	300
12.	240	270	300
13.	260	300	300
14.	260	260	260
15.	240	240	240
16.	260	280	290
17.	200	260	260
18.	240	290	300
19.	250	290	270

TABLE 5.3 Ventricular effective refractory periods during both intravenous and oral procainamide studies

demanding both for patient and physician. Evaluation of oral agents necessitates delay of 2 or more days between studies to permit steady-state levels of the drug to be attained. If complete concordance between intravenous and oral formulations of a certain agent can be demonstrated, such protracted periods of testing may not be required.

Potentially, certain factors mitigate against the predictive value of intravenous administration[217]. Several antiarrhythmic agents including procainamide[218,219], encainide [220] and lorcainide[221] have been shown to have active metabolites which may influence the response to oral therapy. In addition, the vehicle for the intravenous formulation, itself, may possess electrophysiological activity as in the case of amiodarone and Tween 80[222]. Time dependent changes may also occur due to the possibility that the antiarrhythmic effect of an agent is due to "tissue uptake" and that slow accumulation in myocardial muscle obtained by oral therapy does not occur with intravenous administration. A further factor which might explain a discrepancy in effect between intravenous and oral studies is the impact of autonomic and/or haemodynamic changes produced by the rapid administration of the drug by the intravenous route.

Procainamide, a Class IA agent, is frequently employed both intravenously and orally for the treatment of ventricular arrhythmias[223,224,225]. It is commonly administered as the initial agent during serial

electrophysiological drug testing in many laboratories because of its ease of administration.

Effect on Arrhythmia Inducibility

The success rate for procainamide in suppressing the induction of ventricular arrhythmias during electrophysiological testing ranges from 15 - 50% depending on patient population, dosage schedule and stimulation protocol[223,224, 225]. In the present study, the efficacy rate was 47% for the intravenous study and 26% for the oral study. In the study from Marchlinski et al.[216], the efficacy rates were 26% and 39% respectively. Of particular note in the latter study, however, was the observation that the suppression of inducibility in the intravenous study had a 100% correlation with the results in the oral study when similar serum procainamide concentrations were achieved. Furthermore, since the drug efficacy for oral procainamide was higher than that for intravenous procainamide, the study concluded that repeat testing on oral therapy was only indicated if higher serum drug levels could be achieved. These results are at variance with those obtained in the present study in which 4 patients had successful studies on the intravenous agent although, on oral therapy, the tachycardia remained inducible despite higher serum levels of procainamide in every case. Whether the rapid attainment of the serum levels of procainamide with intravenous therapy in

comparison to oral therapy in some way influences the subsequent response is not known. Indeed these 4 patients subsequently underwent 1 to 4 studies on other antiarrhythmic therapy and remained inducible. The study does, however, confirm that failure of suppression of the tachycardia on intravenous therapy is predictive of failure of suppression on oral therapy (negative predictive value 100%).

Effect on Mode of Induction and Tachycardia Cycle Length

In 4 intravenous studies and 4 oral studies, the tachycardia was inducible with at least 1 extrastimulus less than that required for the baseline arrhythmia induction. This observation has been noted previously[216,226] and whether this reflects a proarrhythmic potential in these cases is debatable (see Chapter 11).

Procainamide increased the cycle length of the induced tachycardia by a mean of 90 to 100 msec. which is similar to that reported by Wellens et al.[227] although higher than the 50 to 60 msec. observed by Marchlinski et al.[216] and Kang et al.[226]. There was no significant difference in the mean cycle length between the intravenous and oral studies and no definite relationship between serum drug levels and change in cycle length.

Effect on Ventricular Refractoriness

The change in ventricular effective refractory period

observed in this study was similar to the changes reported in previous studies[216,227]. Although no differences were noted in the change of ventricular refractoriness between intravenous and oral procainamide, the observation that 3 of the 4 patients who were inducible on oral therapy despite noninducibility on intravenous therapy had a shorter refractory period is interesting. Theoretically the shorter refractory period could have permitted penetration of the reentrant circuit by the closer-coupled extrastimuli and this observation might explain the observed discordance. It should be stressed however that measurement of refractory periods is dependent on various factors and comparison may be unreliable especially when the compared measurements have been obtained on different days after re-insertion of the catheter.

Effect of N-acetyl Procainamide

Despite the reported electrophysiological activity of the main metabolite of procainamide, N-acetyl procainamide,[218,219,228] this study did not demonstrate any benefit of oral procainamide over intravenous procainamide. A lack of effect of N-acetyl procainamide on the response to procainamide during acute testing was also observed by Marchlinski et al.[216]. This may reflect the serum levels of N-acetyl procainamide attained during the short period of oral administration prior to testing. In the previous study by Sung et al.[219], the N-acetyl procainamide levels

were significantly higher in the range from 20 - 50 ug/ml, than in the present study.

CONCLUSIONS

The predictive accuracy of the response to intravenous procainamide in predicting the response to oral therapy was 79%. This study does not support the contention that repeat testing of oral therapy is not required if intravenous procainamide suppresses arrhythmia induction. The study does, however, confirm that failure of suppression by intravenous procainamide does predict failure of oral procainamide despite the generation of an active metabolite.

In clinical practice, therefore, confirmation of drug efficacy on oral therapy is required before long-term prescription of procainamide, despite the need for a further invasive procedure. Similar studies should be performed with other antiarrhythmic drugs before accepting the predictive value of an intravenous study with these agents.

CHAPTER 6

SERIAL ELECTROPHYSIOLOGICAL DRUG TESTING IN PATIENTS WITH VENTRICULAR TACHYARRHYTHMIAS RELATED TO CORONARY ARTERY DISEASE

The development of serial electrophysiological drug testing to determine effective long-term therapy in patients with ventricular tachyarrhythmias was discussed in Chapter 1. These initial studies included relatively small study populations and the duration of follow-up was limited[42,43,157]. Subsequent larger studies involved more heterogenuous groups of patients[170,229]. In particular, the impact of underlying heart disease on the response to therapy was not taken into account. Furthermore, in many studies, the stimulation protocol changed during the study period with the introduction of a third extrastimulus[230].

The aim of this study was to determine (1) the effectiveness of serial electrophysiological drug testing in a homogenuous group of patients with ventricular tachyarrhythmias related to coronary artery disease, in whom a uniform stimulation protocol was applied in all cases, and (2) whether a less rigid end-point for drug success provided a satisfactory long-term result.

6.1 PATIENTS AND METHODS

The patient population consisted of 160 consecutive patients referred for electrophysiological testing in whom a ventricular tachyarrhythmia was reproducibly induced during the baseline study. There were 143 men and 17 women with ages ranging from 42 to 84 years (mean = 62 years). All patients had coronary artery disease documented by standard electrocardiography, exercise stress testing, thallium scintigraphy and/or coronary angiography, and 150 of these had sustained a previous myocardial infarction. Global ejection fraction as measured by radionuclide ventriculography or contrast angiography ranged from 8 to 72% (mean = 29%).

The indications for electrophysiological study included sustained ventricular tachycardia in 73 patients, out-of-hospital cardiac arrest in 28 patients, syncope of undetermined origin in 35 patients, symptomatic nonsustained ventricular tachycardia in 22 patients and palpitation in 2 patients.

Prior to electrophysiological testing the patients had undergone 0 to 6 (mean = 2.0) empirical trials of anti-arrhythmic therapy.

The standard electrophysiological stimulation protocol was applied in both the baseline study and subsequent drug studies. In patients with documented sustained ventricular tachycardia or out-of-hospital cardiac arrest,

left ventricular stimulation at 2 sites was performed, if right ventricular stimulation did not induce an arrhythmia. Left ventricular stimulation was performed during the subsequent drug studies only in patients in whom it was required during the initial study.

The standard definitions for sustained ventricular tachycardia, ventricular fibrillation and nonsustained ventricular tachycardia were employed.

Drug success was defined at the completion of the stimulation protocol as:

Complete success - initiation of fewer than 6 repetitive ventricular response.

Partial success - initiation of 6 to 15 repetitive ventricular responses in patients with sustained ventricular tachycardia or ventricular fibrillation. Partial success was not considered possible if the baseline arrhythmia was nonsustained ventricular tachycardia.

Overall success - the sum of complete and partial success.

Patient success was defined as the identification of at least one successful drug regimen in a patient, irrespective of how many trials had been unsuccessful in that patient.

The antiarrhythmic therapy employed in this study included 10 single agents and 7 combinations (Table 6.1).

SINGLE AGENTS

REGIMEN	NO. OF STUDIES	REGIMEN	NO. OF STUDIES
Procainamide	98	Indecainide	10
Quinidine	70	Phenytoin	1
Mexiletine	46	Lignocaine	6
Amiodarone	93	Disopyramide	5
Flecainide	6	Bethanidine	1

COMBINATIONS

REGIMEN	NO. OF STUDIES
Quinidine + Mexiletine	41
Procainamide + Mexiletine	15
Amiodarone + Procainamide	27
Amiodarone + Quinidine	1
Amiodarone + Mexiletine	6
Quinidine + Phenytoin	3
Procainamide + Phenytoin	3

TABLE 6.1 Single and combination drug regimens employed

Selection of regimens was based on the patient's history of exposure to antiarrhythmic drugs. A history of hypersensitivity, allergy or proarrhythmic response to a drug precluded its use in this study. Previous ineffectiveness did not preclude its use unless concomitant serum levels of the drug at the time of arrhythmia recurrence were satisfactory. The drug studies were performed after a steady-state level was obtained. If both parenteral and oral forms of the same regimen were studied, the result during oral therapy was used in the analysis of effectiveness.

If no regimen was identified which prevented initiation, the long-term regimen selected was that which produced the greatest slowing of ventricular tachycardia or made the initiation more difficult. If no regimen had such an effect, amiodarone was selected.

The dosages of the drug regimens employed are tabulated in Table 2.2.

The patients with inducible sustained arrhythmias were entered into the follow-up phase of the study. All symptomatic episodes, compatible with arrhythmia recurrence, were evaluated by ambulatory, transtelephonic or in-hospital telemetric monitoring. In patients whose presenting complaint was syncope and for whom no arrhythmia documentation was available, recurrence of syncope was considered to be an arrhythmic recurrence. At the conclusion of the study the status of each patient was

confirmed by contact with the patient or the patient's physician. Sudden death was defined as an unexpected witnessed death occurring within 1 hour of the onset of symptoms or an unwitnessed death if the patient had been seen in his usual state of health within 12 hours of the event. An arrhythmic event requiring cardiopulmonary resuscitation and defibrillation was considered a sudden death for the purposes of this study. Nonarrhythmic death was death from a cardiovascular event unrelated to an arrhythmia.

Standard statistical techniques were used. For continuous variables, unpaired t test and analysis of variance were used. For discrete variables, contingency tables were constructed using either chi-squared or Fisher's exact tests.

Duration of follow-up was calculated from the date of the electrophysiological study to the date of recurrence of arrhythmia, sudden death or nonarrhythmic death or the most recent follow-up date. For statistical purposes, if anti-arrhythmic therapy was discontinued, the patient was censored as of the date of discontinuation. Patients who had antiarrhythmic therapy identified as successful by electrophysiological testing but whose therapy was changed empirically because of side-effects, were considered censored as of the date of change of therapy. If no successful therapy was identified and the patient was discharged on empirical therapy which was subsequently

changed to another regimen, the patient was not censored unless all antiarrhythmic therapy was discontinued. The Mantel-Cox and Breslow statistics were used to test equality of survival curves using life-table analysis. A p value of <0.05 was considered significant.

6.2 RESULTS

Results of Baseline Study

In the baseline study, sustained ventricular tachycardia was induced in 121 patients, ventricular fibrillation in 16 patients and nonsustained ventricular tachycardia in 23 patients. The arrhythmia was induced by right ventricular stimulation in 156 (97%) patients and in 4 (3%) patients, left ventricular stimulation was required.

6.3 Results of Drug Studies

The 160 patients underwent a total of 432 individual trials of therapy (mean = 2.9 $\pm$ 1.4). The studies were performed until an adequate drug regimen was identified (Fig. 6.1) or drug alternatives were exhausted (Fig. 6.2).

Complete success was achieved in 63 (15%) of the 432 trials and partial success in 28 (6%). The overall success rate was 91 (21%) of the 432 trials (Table 6.2).

Since certain of the regimens were employed in only a relatively small number of cases, only those regimens

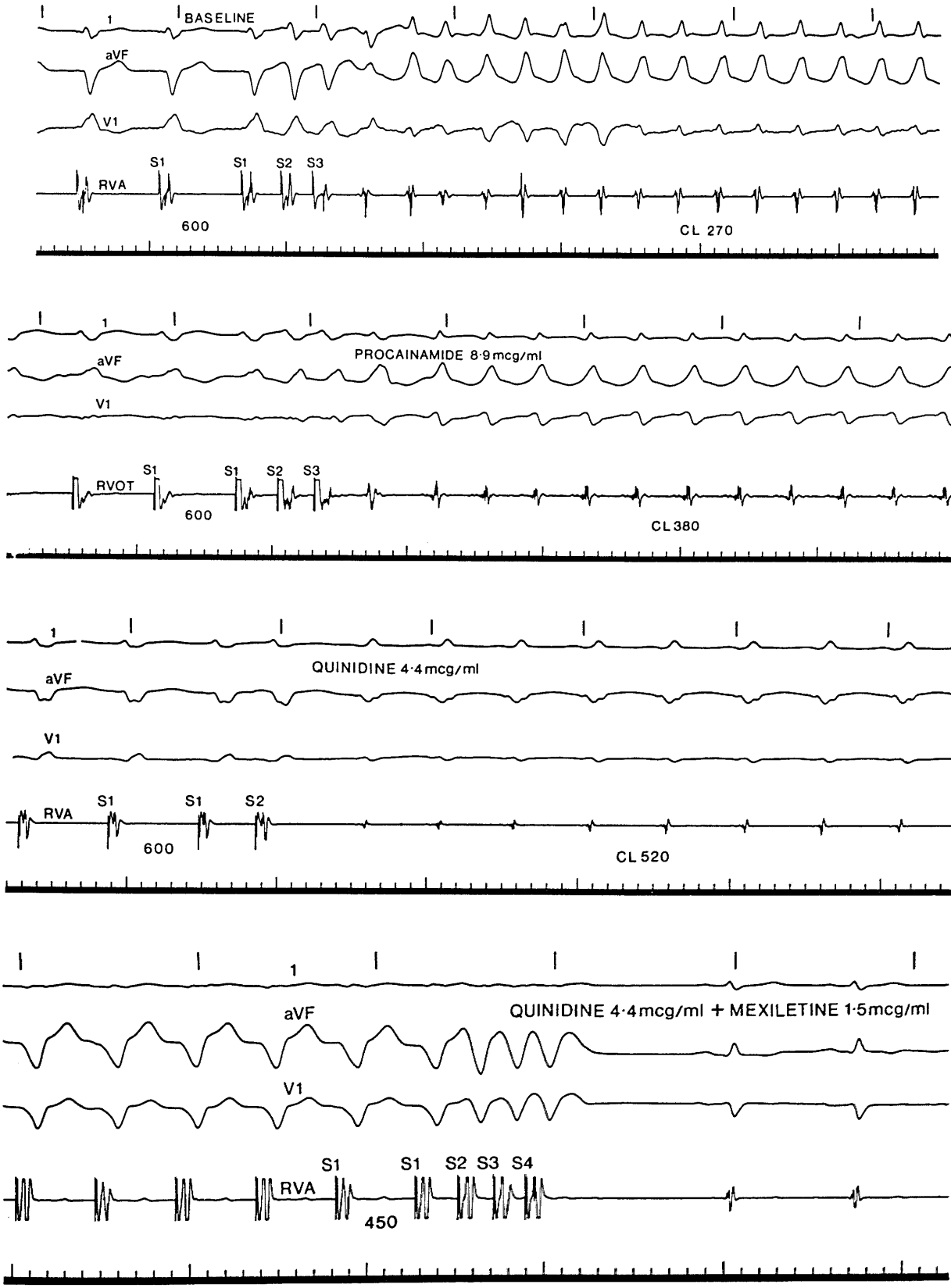

Fig. 6.1 Example of serial electrophysiological drug testing. Suppression of tachycardia induction by the combination of quinidine + mexiletine.

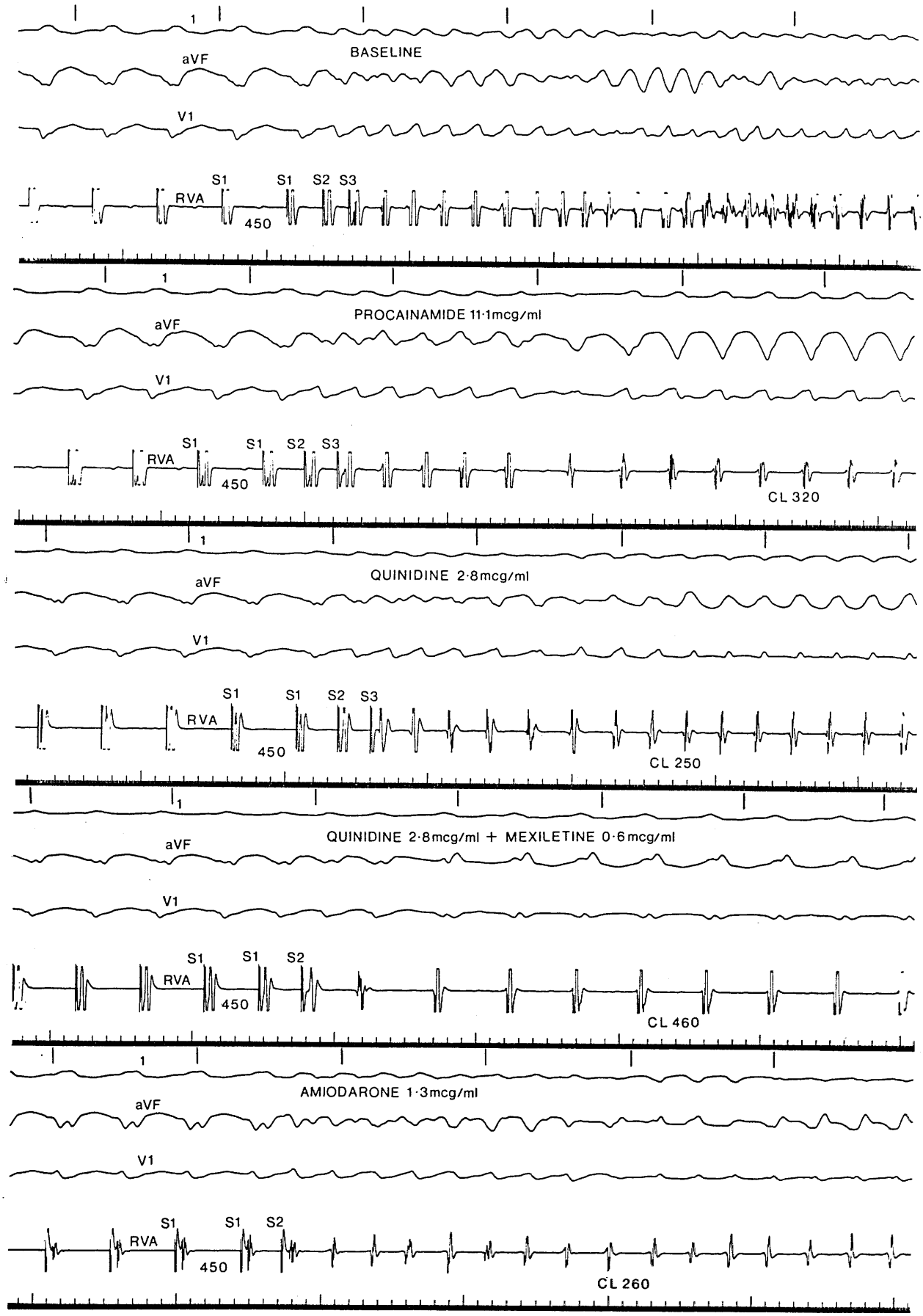

Fig. 6.2 Example of serial electrophysiological drug testing. Continuing inducibility despite multiple drug trials.

TOTAL NO. OF PATIENTS	160
TOTAL NO. OF STUDIES	432
MEAN NO. OF STUDIES PER PATIENT	2.9±1.4
DRUG SUCCESS	
Complete	63 (15%)
Partial	28 (6%)
Overall	91 (21%)
PATIENT SUCCESS	
Complete	47 (29%)
Partial	14 (9%)
Overall	61 (38%)

TABLE 6.2 Response to drug therapy classified as both drug regimen success and patient success (identification of at least one successful regimen for the patient)

employed in at least 15 studies were analysed separately (Table 6.3).

Procainamide and quinidine were the most successful agents with success rates for mexiletine and amiodarone significantly lower ($p<0.01$).

The combination of a Class IA drug with mexiletine was the most successful combination used. The least successful combination was amiodarone plus procainamide.

In contrast to the previous reported studies, the newer agents, amiodarone, mexiletine, flecainide and indecainide were employed and 245 (57%) of the drug regimens tested involved one of these agents either alone or in combination with a standard agent. Of the 63 completely successful trials, 29 (46%) involved the use of one of these newer agents.

Patient success, the end-point of drug testing in clinical practice, occurred more frequently than success of individual regimens. Of the 160 patients evaluated, complete success was achieved in 29% and partial success in an additional 9% of patients. Thus, a successful drug regimen was identified by serial electrophysiological testing in 38% of the study population.

Results of Drug Therapy in Relation to Induced Arrhythmia Type

The overall drug success rate for suppression of induced sustained ventricular tachycardia was significantly

DRUG REGIMEN	NO. OF STUDIES	DRUG SUCCESS		
		COMPLETE	PARTIAL	OVERALL
PROCAINAMIDE	98	16 (16%)	8 (8%)	24 (24%)
QUINIDINE	70	15 (21%)	10 (14%)	25 (35%)
MEXILETINE	46	4 (9%)	1 (2%)	5 (11%)
AMIODARONE	93	11 (12%)	2 (2%)	13 (14%)
QUINIDINE + MEXILETINE	41	5 (12%)	4 (10%)	9 (22%)
PROCAINAMIDE + MEXILETINE	15	3 (20%)	1 (7%)	4 (27%)
AMIODARONE + PROCAINAMIDE	27	3 (11%)	1 (4%)	4 (15%)
OTHER	42	6 (14%)	1 (2%)	7 (16%)
TOTAL	432	63 (15%)	28 (6%)	91 (21%)

TABLE 6.3 Efficacy of individual drug regimens

lower than for either ventricular fibrillation ($p<0.005$) or nonsustained ventricular tachycardia ($p<0.05$). A similar pattern was observed for the patient success rate (Table 6.4).

6.4 Results of Follow-Up

Of the 137 patients with either sustained ventricular tachycardia or ventricular fibrillation, 42 patients were discharged on an antiarrhythmic regimen which was identified as successful during serial electrophysiological testing. The therapy was completely successful in 30 patients and partially successful in 12 patients. In a further 7 patients, a successful regimen was identified but could not be used because of adverse effects. In 87 patients, an antiarrhythmic regimen which suppressed arrhythmia induction was not identified. The discharge therapy in this group included amiodarone alone or in combination in 73 patients. Subsequent follow-up data was available in all but one patient who was lost to follow-up. After discharge, a change in the drug regimen was made in 7 patients (2 patients in the successful group and 5 patients in the nonsuccessful group) because of the development of adverse effects. The duration of follow-up was 16 $\pm$ 9 months (range 2 weeks to 35 months).

In patients on successful regimens there were 4 (10%) arrhythmia recurrences (4 non-fatal) compared with 37 (43%) recurrences (22 non-fatal and 15 fatal) in the patient

	INDUCED VENTRICULAR ARRHYTHMIA		
	SUSTAINED VT	VFIB	NONSUSTAINED VT
DRUG SUCCESS			
No. of drug studies	325	48	59
Complete	32 (10%)	14 (29%)	17 (29%)
Partial	16	12	-
Overall	48 (15%)	26 (54%)**	17 (29%)*
PATIENT SUCCESS			
No. of patients	121	16	23
Complete	26 (22%)	9 (56%)	12 (52%)
Partial	11	3	-
Overall	37 (31%)	12 (75%)**	12 (52%)*

TABLE 6.4 Drug efficacy in relation to the type of induced arrhythmia.

* $p < 0.05$ ** $p < 0.005$

VT = ventricular tachycardia VFIB = ventricular fibrillation

group on regimens which failed to prevent arrhythmia induction. There were 2 non-arrhythmic deaths in the former group and 5 nonarrhythmic deaths in the latter group. Life-table analysis revealed a significant difference in the arrhythmia-free interval between these groups ($p<0.0001$) (Fig. 6.3). Furthermore, there was no significant difference between patients discharged on completely successful regimens (< 6 induced repetitive responses) and those with overall successful regimens ($\leq$ 15 induced repetitive responses) ($p = 0.71$) (Fig. 6.4).

In patients in whom the arrhythmia remained inducible, there was no difference in the arrhythmia-free interval between patients treated with amiodarone alone or in combination and patients on other regimens ($p = 0.51$) (Fig. 6.5).

6.5 DISCUSSION

In Chapter 3, the induction of ventricular arrhythmias by programmed stimulation was discussed. In this present study, the application of these techniques to the evaluation of antiarrhythmic therapy has been addressed, in particular in patients with ventricular arrhythmias related to underlying coronary artery disease. Initial studies[42,43,157] demonstrated that suppression of arrhythmia inducibility by drug therapy identified a good long-term response. These studies, however, involved only

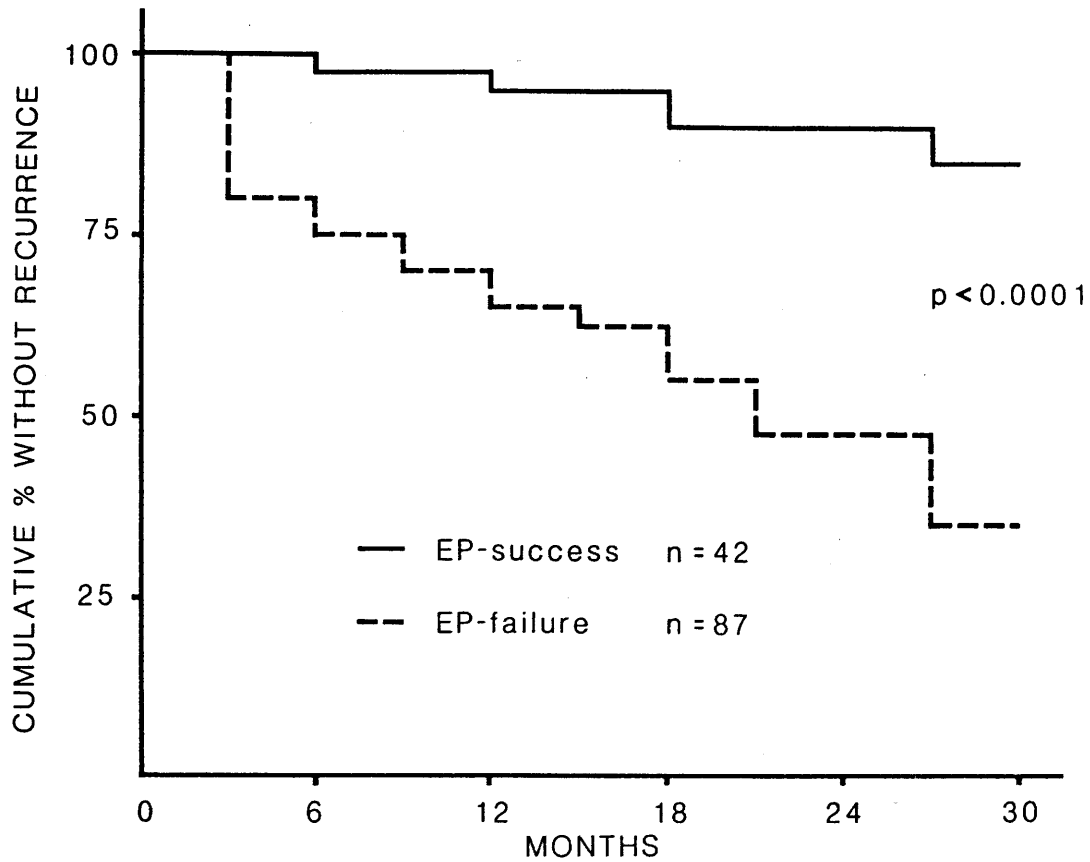

Fig. 6.3 Life-table analysis demonstrating a significant difference in the arrhythmia-free interval in patients discharged on therapy determined as successful by electrophysiological testing and patients whose arrhythmia remained inducible.

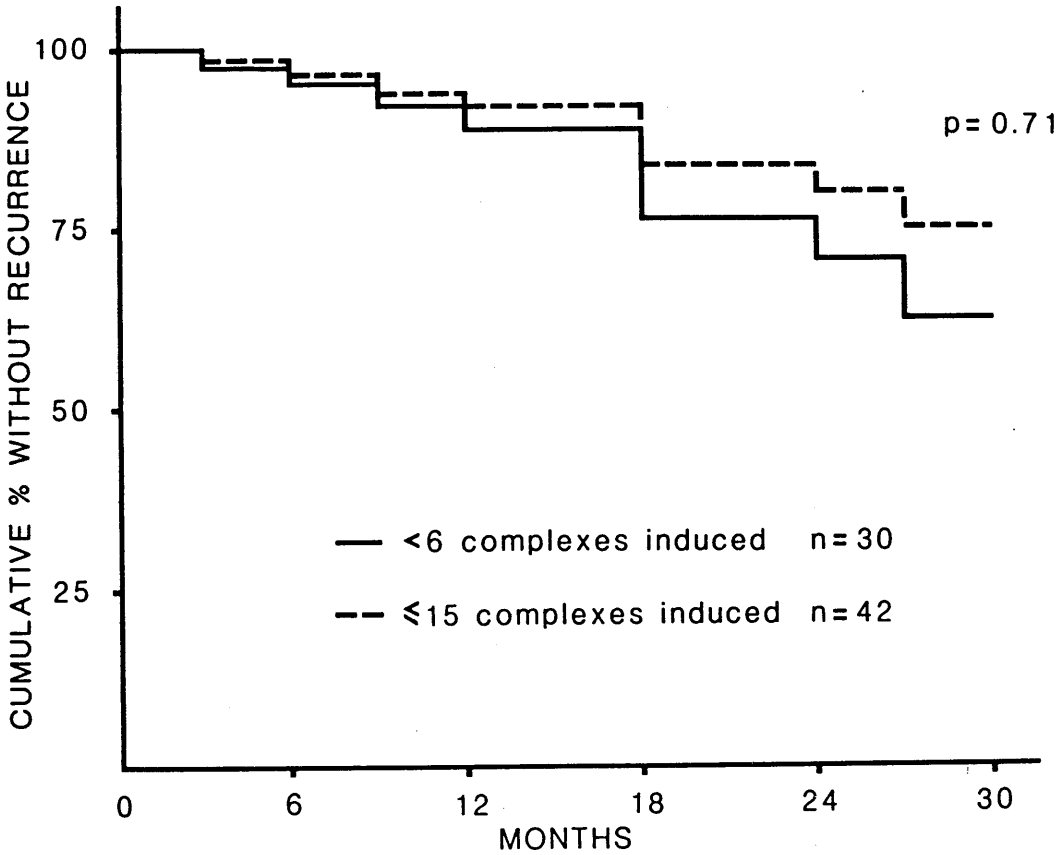

Fig. 6.4 Life-table analysis showing no difference in the arrhythmia-free interval in patients on therapy determined as successful using the two different stimulation end-points.

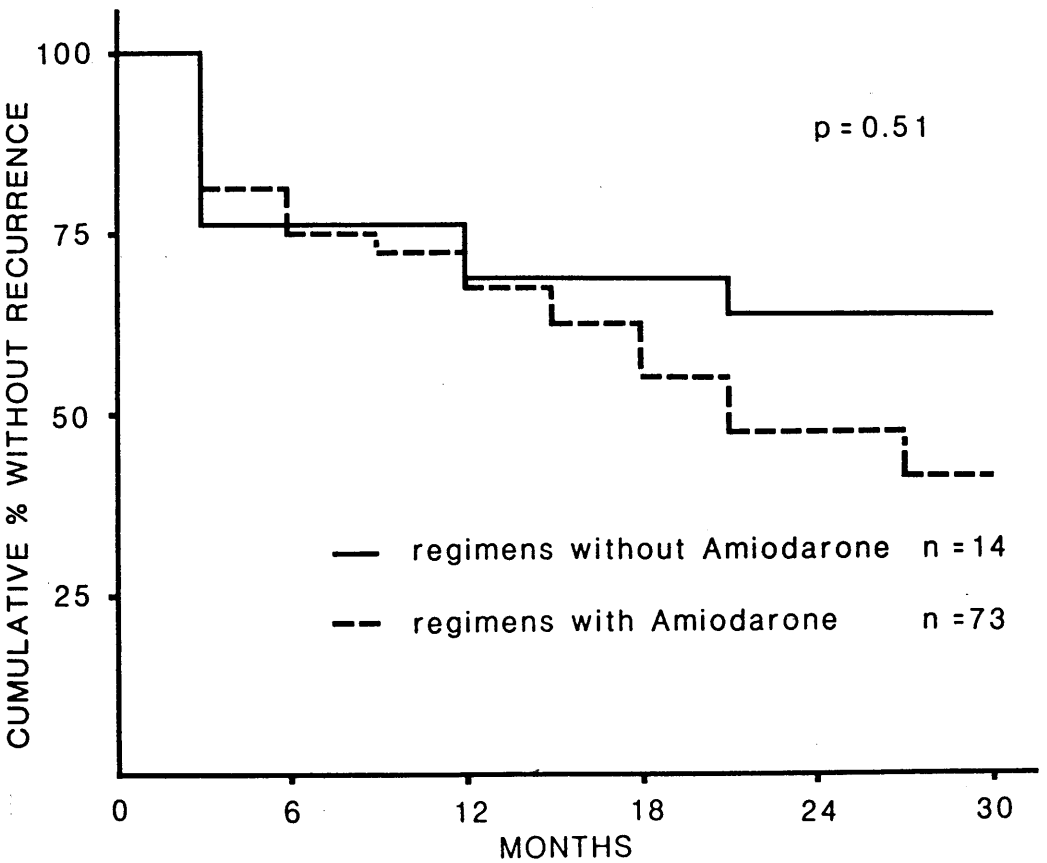

Fig. 6.5 Life-table analysis showing no difference in the arrhythmia-free interval in patients discharged on regimens with or without amiodarone.

small patient populations, employed relatively non-aggressive stimulation protocols and evaluated a limited number of antiarrhythmic agents. Although later studies included larger patient groups, no account was taken of the type of underlying heart disease[170,229]. In two studies, the presence of coronary artery disease has been shown to be a univariate predictor of response to medical therapy [231,232]. It is important therefore in evaluating the results of serial electrophysiological drug testing to define the type of underlying heart disease in the patient population under study. An important consideration in the present study is that all the patients had underlying coronary artery disease. A further confounding factor in these larger studies is that the stimulation protocol changed during the course of the studies. The initial studies involved the use of only double extrastimuli, and efficacy rates of 60-70% were obtained for medical therapy whereas with the use of more aggressive stimulation, including triple extrastimuli, efficacy rates fell to about 30%[230]. In addition to a homogenuous patient population, a uniform unchanging protocol was applied in all cases in this study.

Criteria for Drug Efficacy

Complete suppression of arrhythmia inducibility has been considered the optimum end-point for serial drug testing [42,43,159]. Less rigid end-points, however, have

been suggested as also reflecting a long-term benefit. Breithardt et al.[170] have reported their experience using change in mode of inducibility as a criterion for drug efficacy. Ventricular tachycardia was classified as more difficult to induce if the tachycardia was not inducible employing the baseline mode of induction, but required a basic drive rate of 20 bpm or more above the baseline mode. In 95 patients followed for a mean of 12 $\pm$ 11 months, there was no difference in arrhythmia recurrence between patients discharged on therapy which produced complete suppression of inducibility and therapy which made arrhythmia induction more difficult. Similar results have also been reported in a preliminary study from DiMarco et al.[233]. Alternatively, Swerdlow et al.[234] demonstrated that in patients with inducible sustained arrhythmias, induction of 15 or fewer repetitive responses on drug therapy provided a satisfactory long-term outcome. Adoption of this criterion in the present study increased the number of successful studies by 31%.

Although Morady et al.[235] has advocated confirmation of suppression of arrhythmia induction using left ventricular stimulation, the stimulation protocol in that study was performed at only one right ventricular site and is therefore not necessarily applicable to the present study.

Individual Drug Efficacy

The efficacy rates for individual regimens reported

here are similar to those reported in other studies which have employed similar stimulation protocols and end-points for drug success[224,236-242].

Since each patient cannot, practically, be exposed to every drug regimen a certain hierarchical approach to their prescription is necessary. In practice, standard agents are tested initially before newer drugs are selected. This strategy precludes the direct comparison of individual drug efficacy because failure with one drug regimen may preselect patients who have a low probability of success with any drug (see Chapter 10). In this study, since patients tended to be exposed to procainamide and quinidine initially, the higher efficacy rates of these agents may well reflect the inherent bias toward their choice as first therapy.

In contrast to previous studies, newer antiarrhythmic agents including amiodarone and flecainide were more frequently employed. In particular, these agents were employed in 57% of trials of therapy, with 31% of successful regimens involving newer agents, either alone or in combination.

Relation of Drug Efficacy to Induced Arrhythmia Type

The results from the present study support previous observations on the variable response to drug therapy in relation to induced arrhythmia type[237]. Sustained ventricular tachycardia was significantly more difficult to

suppress than either ventricular fibrillation or nonsustained ventricular tachycardia. Since the type of induced arrhythmia may be an independent predictor of response to therapy, analyses of drug efficacy should address this potential differential response. This aspect is discussed further in Chapter 9.

Long-Term Efficacy

The results of the long-term follow-up confirm that in patients with ventricular tachyarrhythmias related to coronary artery disease serial electrophysiological testing can be used to identify an effective anti-arrhythmic regimen. Furthermore a good long-term response was obtained using the strict end-point of induction of fewer than 6 complexes but also the definition of efficacy of 15 or fewer repetitive responses as suggested by Swerdlow et al.[234]. With this latter end-point drug efficacy was achieved in 38% of the present study population.

Although the predictive value of electrophysiological testing to predict the long-term response of amiodarone has been controversial[243-249] it is of interest to note that in the patients who remained inducible, there was no significant difference in arrhythmia free interval between patients on amiodarone and those on other therapy.

CONCLUSIONS

This study confirms the benefits of an electrophysio-

logical approach to the identification of antiarrhythmic therapy in a homogenuous population of patients with arrhythmias related to coronary artery disease and demonstrates that with the availability of newer agents successful therapy can be identified for 38% of patients. In addition, the more relaxed end-point for drug efficacy of induction of $\leqslant$ 15 repetitive responses equates with a good long-term outcome.

CHAPTER 7

SERIAL ELECTROPHYSIOLOGICAL DRUG TESTING IN PATIENTS WITH VENTRICULAR TACHYARRHYTHMIAS RELATED TO DILATED CARDIOMYOPATHY

In Chapter 6 serial electrophysiological drug testing was evaluated in a study population with arrhythmias related to coronary artery disease. Few studies, however, have investigated the response to drug therapy in patients with arrhythmias related to other types of underlying structural heart disease to determine the validity of this approach.

A recent study from Poll et al.[145] in a small but well defined group of patients with inducible sustained ventricular tachycardia secondary to dilated (idiopathic) cardiomyopathy observed a particularly low response to drug therapy and suggested that alternative therapeutic modalities should be considered earlier for these patients.

The aims of this study, therefore, were to evaluate the success of drug therapy in patients with dilated cardiomyopathy and to determine whether serial electrophysiological drug testing was predictive of the long-term response.

7.1 PATIENTS AND METHODS

The patient population consisted of 38 consecutive patients with dilated cardiomyopathy who were referred for electrophysiological study and in whom a ventricular tachyarrhythmia was reproducibly induced. Patients with angina pectoris or history of previous myocardial infarction were excluded from this study. Further exclusion criteria included investigational evidence of underlying coronary disease viz: electrocardiographic evidence of myocardial infarction, exercise stress testing demonstrating reversible myocardial ischaemia, myocardial perfusion defects on thallium scintigraphy, or segmental dyskinetic regions on radionuclide angiography indicative of myocardial ischaemia or coronary obstructive lesions >50% on selective coronary angiography.

There were 30 men and 8 women with ages ranging from 34 to 76 years (mean = 56 $\pm$ 13 years). The mean ejection fraction as measured by radionuclide ventriculography or contrast left ventriculography ranged from 7 to 55% (mean = 35 $\pm$ 15%).

Indications for electrophysiological study included sustained ventricular tachycardia in 11 patients, out-of-hospital cardiac arrest in 3 patients, syncope in 7 patients, symptomatic nonsustained ventricular tachycardia in 15 patients and palpitation in 2 patients.

Prior to undergoing electrophysiological study, the

patients had failed a mean of 2.2 $\pm$ 1.6 (range 0 to 6) trials of empirical antiarrhythmic therapy because of either ineffectiveness or intolerable side-effects.

The standard electrophysiological stimulation protocol was applied in both the baseline study and subsequent follow-up studies. In this study population left ventricular stimulation was not required.

Standard definitions for sustained ventricular tachycardia, ventricular fibrillation and nonsustained ventricular tachycardia were applied. Similarly the definitions for drug success and patient success including complete, partial and overall success, as employed in the previous Chapter were applied.

In this study, the drug regimens included 10 single agents and 6 combinations (Table 7.1). The dosages of the antiarrhythmic agents are tabulated in Table 2.2. Selection of therapy was based on the patient's previous exposure to antiarrhythmic therapy. Electrophysiological testing was performed after a steady state level was obtained. If both parenteral and oral forms of the same regimen were tested, the result on oral therapy was used for the subsequent analyses. If no regimen was identified which prevented the initiation of the arrhythmia, the regimen selected for long-term therapy was the regimen which produced the greatest slowing of tachycardia or made initiation more difficult. If no such regimen was identified, amiodarone was selected.

SINGLE AGENTS

REGIMEN	NO. OF STUDIES	REGIMEN	NO. OF STUDIES
Procainamide	19	Propranolol	1
Quinidine	9	Disopyramide	2
Mexiletine	9	Tocainide	1
Amiodarone	18	Lignocaine	1
Flecainide	4	Phenytoin	1
Indecainide	2		

COMBINATIONS

REGIMEN	NO. OF STUDIES
Quinidine + Mexiletine	3
Procainamide + Mexiletine	5
Amiodarone + Procainamide	6
Procainamide + Phenytoin	1
Amiodarone + Lignocaine	1
Quinidine + Phenytoin	1

TABLE 7.1 Drug regimens employed

During follow-up all symptomatic events compatible with an arrhythmia recurrence were evaluated as far as possible by ambulatory, transtelephonic or in-hospital telemetric monitoring. In patients whose presenting complaint was syncope and for whom no arrhythmia documentation was available, recurrence of syncope was considered to be an arrhythmic recurrence.

Sudden death and nonarrhythmic death was defined as in Chapter 6.

Standard statistical analyses were performed. For continuous variables, unpaired t test and analysis of variance were used and for discrete variables contingency tables were constructed using either chi-square or Fisher's exact tests. A value of $p<0.05$ was considered significant. In the follow-up, difference in arrhythmia free interval between the two groups was analysed using the Mantel-Cox and Breslow statistics.

7.2 RESULTS

Baseline Study

In the baseline study, sustained ventricular tachycardia was induced in 18 patients, ventricular fibrillation in 7 patients and nonsustained ventricular tachycardia in 13 patients. The mode of induction was single extrastimuli in one patient, double extrastimuli in 15 patients and triple extrastimuli in 22 patients. The

duration of the induced nonsustained ventricular tachycardia ranged from 10 to >100 complexes.

7.3 Results of Drug Evaluation

The 38 patients underwent a total of 84 trials of different antiarrhythmic therapy regimens (mean = 2.3 $\pm$ 1.4 trials per patient).

Complete drug success was obtained in 19 (23%) of 84 trials with partial success in 7 (8%). The overall success rate was therefore 26 of 84 trials (31%) (Table 7.2). A variable response rate in respect of the type of induced arrhythmia was observed with a higher success rate obtained for nonsustained ventricular tachycardia (40%) than for sustained ventricular tachycardia (16%) or ventricular fibrillation (20%) although this did not reach statistical significance (Table 7.3).

Analysis of the response rates for individual regimens was limited by the relatively small numbers of studies employed (Table 7.4). In addition since each patient was not exposed to every regimen a direct comparison cannot be made. Of particular note, however, was the efficacy of the combination of mexiletine plus a Class IA agent (procainamide or quinidine) which was successful in 6 of 8 trials (75%). In this study the newer antiarrhythmic agents, amiodarone, flecainide, indecainide, mexiletine and tocainide were employed either alone or in combination in 49 (58%) of the trials with 15 (31%) of these trials being

TOTAL NO. OF PATIENTS	38
TOTAL NO. OF STUDIES	84
MEAN NO. OF STUDIES PER PATIENT	2.3±1.4
Drug Success	
Complete	19 (23%)
Partial	7 (8%)
Overall	26 (31%)
Partial Success	
Complete	16 (42%)
Partial	4 (11%)
Overall	20 (53%)

TABLE 7.2 Response to drug therapy classified as drug success and patient success

	INDUCED VENTRICULAR ARRHYTHMIA		
	SUSTAINED VT	VFIB	NONSUSTAINED VT
DRUG SUCCESS			
No. of drug studies	44	20	20
Complete	7 (16%)	4 (20%)	8 (40%)
Partial	3	4	-
Overall	10 (23%)	8 (40%)	8 (40%)
PATIENT SUCCESS			
No. of patients	18	7	13
Complete	6 (33%)	4 (57%)	6 (46%)
Partial	3	1	-
Overall	9 (50%)	5 (71%)	6 (46%)

TABLE 7.3 Drug efficacy in relation to type of induced arrhythmia

VT = ventricular tachycardia VFIB = ventricular fibrillation

REGIMEN	NO. OF STUDIES	DRUG SUCCESS		
		COMPLETE	PARTIAL	OVERALL
PROCAINAMIDE	19	6 (32%)	2 (10%)	8 (42%)
QUINIDINE	9	2 (22%)	0 (0%)	2 (22%)
MEXILETINE	9	2 (22%)	1 (11%)	3 (33%)
AMIODARONE	18	2 (11%)	2 (11%)	4 (22%)
MEXILETINE + CLASS IA (PROCAINAMIDE OR QUINIDINE)	8	5 (62%)	1 (13%)	6 (75%)
AMIODARONE + PROCAINAMIDE	6	0 (0%)	0 (0%)	0 (0%)
OTHERS	15	2 (13%)	2 (13%)	4 (26%)

TABLE 7.4 Efficacy of individual drug regimens

successful.

Drug Efficacy Assessed by Patient Success

For the 38 patients in the study at least one drug regimen determined to be completely successful was identified for 16 (42%) of the patients and partially successful for 4 (11%) of the patients. For the study population, therefore, an overall successful drug regimen was obtained for 20 patients (53%) (Table 7.2).

7.4 Results of Follow-Up Study

The follow-up phase of the study included all patients with an inducible sustained arrhythmia. Of the 25 patients, 11 patients were discharged on a drug regimen determined to be successful by electrophysiological testing. The remaining 14 patients were discharged on antiarrhythmic therapy which did not suppress arrhythmia induction. In 3 of these patients, although a successful regimen had been identified, development of side-effects had precluded its use. In the 14 patients, the discharge therapy included amiodarone in 12 of the patients either alone or in combination with other therapy. Over the follow-up period, 3 patients were censored because of change of therapy due to development of toxicity.

The duration of follow-up was 21 $\pm$ 13 ranging from 6 weeks to 48 months.

In patients on drug therapy deemed to be successful

there was no arrhythmic recurrence and no episodes of sudden death. In comparison, in the group on therapy which did not prevent induction of the arrhythmia there were 3 arrhythmia recurrences and 2 sudden deaths (35%). In the latter group there was also one nonarrhythmic death. Life table analysis of recurrence-free interval demonstrated a significant difference between the two groups ($p<0.05$) (Fig. 7.1).

7.5 DISCUSSION

The risk of sudden death in patients with coronary disease is well recognised[29-34]. Recent studies have also demonstrated the high mortality associated with dilated (idiopathic) cardiomyopathy[38,39,250,251]. In particular, this mortality is related to arrhythmic sudden death.

In coronary artery disease, subendocardial scarring, particularly in relation to aneurysm formation provides the substrate for the subsequent development of a reentry tachycardia[10,252]. Pathological studies in dilated cardiomyopathy have demonstrated similar although more diffuse and patchy areas of endocardial scarring[253] and, although less well defined, a similar reentrant mechanism is probably operative in the related ventricular arrhythmias[254].

In patients with life-threatening ventricular arrhythmias, serial electrophysiological testing has been

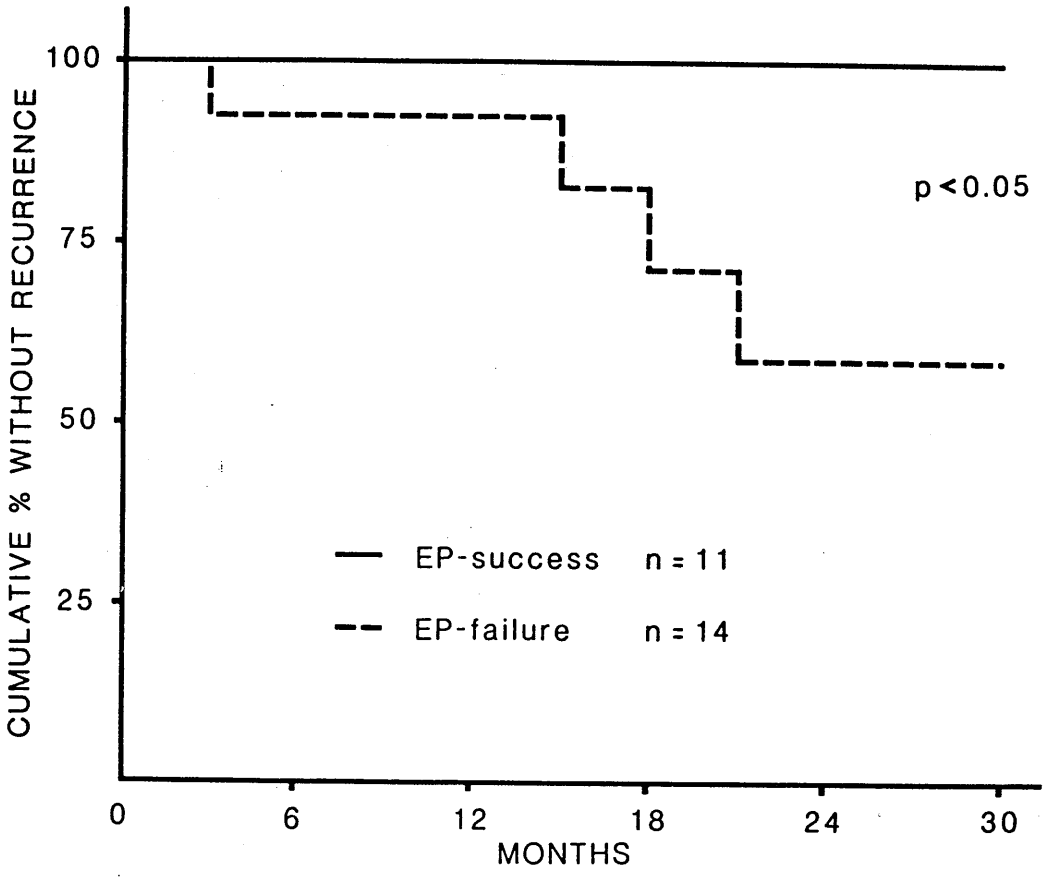

Fig. 7.1 Life-table analysis demonstrating a significant difference in the arrhythmia-free interval in patients on therapy determined as successful and patients whose arrhythmia remained inducible.

employed to determine an effective therapeutic strategy. These studies however have included relatively small numbers of patients in whom the ventricular arrhythmia was not related to coronary artery disease.

Nacarelli et al.[144] evaluated this approach in a heterogenuous group of 83 patients with ventricular tachycardia related to cardiomyopathy, mitral valve prolapse and primary electrical disease. An arrhythmia induction rate of only 46% was observed for patients with cardiomyopathy which was lower than in either patients with mitral valve prolapse or primary electrical disease. Thirty one patients underwent serial electrophysiological drug testing and in 14 (45%) an effective regimen was identified. Unfortunately the types of underlying heart disease in this latter patient group were not documented.

More relevant to the present study, however, is the study from Poll et al.[145] who performed electrophysiological testing in 11 patients with sustained ventricular tachycardia related to dilated cardiomyopathy. No drug regimen provided complete suppression of inducibility although in two patients a regimen producing nonsustained tachycardia only, was identified. During follow-up, arrhythmia recurrence or sudden death occurred in 6 (55%) of the 11 patients. Poll et al.[145] concluded that, with the apparent refractoriness to drug therapy in this patient group, a non-pharmacological therapy should be considered as a primary modality. In contrast in the

present study, in a similar group of patients with inducible sustained ventricular tachycardia, complete suppression was obtained in 5 (30%) of 17 patients and over the follow-up period arrhythmia recurrence or sudden death occurred in 4 (24%) of the group.

Since the methodology applied to the patients in this study was identical to that for patients with ventricular arrhythmias related to coronary artery disease, discussed in the previous Chapter, an analysis on drug and patient success was performed. There was no significant difference in the response to medical therapy between patients with dilated cardiomyopathy and patients with coronary artery disease, whether the results are analysed for the total group or in relation to induced arrhythmia type, using both complete and overall success end-points. This observation, that response to therapy is not related to the aetiology of ventricular dysfunction has also been noted by Chacco et al.[250].

CONCLUSIONS

The results of this study suggest that in patients with ventricular arrhythmias related to dilated cardiomyopathy, serial electrophysiological drug testing can determine an acutely effective drug regimen in a significant number of patients. In addition, such therapy is also effective in the long-term. In patients with dilated cardiomyopathy,

drug therapy should still be considered as the first-line management for ventricular tachyarrhythmias.

CHAPTER 8

THE EFFICACY OF THE COMBINATION OF AMIODARONE PLUS PROCAINAMIDE IN THE TREATMENT OF VENTRICULAR TACHYCARDIA

During serial electrophysiological testing, the efficacy rates for antiarrhythmic agents in patients with ventricular tachycardia are relatively low. The prescription of drug therapy tends also to be limited by the need for high dosages with subsequent development of side-effects. The use of combination regimens increases the available choice of medical therapy and may also permit reduction in the dosages of the individual agents. Furthermore, a combination of agents with dissimilar electrophysiological properties may provide more effective suppression because of their different effects on the components of the tachycardia circuit. Previous studies however have not confirmed these potential benefits[255,256] although a more recent study has been significantly more encouraging[257].

The aim of this study was to evaluate the efficacy of the combination of amiodarone plus procainamide in patients with inducible sustained ventricular tachycardia.

8.1 PATIENTS AND METHODS

The patient population consisted of 35 consecutive patients with inducible sustained ventricular tachycardia who underwent testing with amiodarone alone and the combination of amiodarone plus procainamide. In 24 of these patients, procainamide alone had also been tested.

There were 32 men and 3 women with ages ranging from 44 to 80 years (mean = 62 years). Underlying heart disease was present in all patients, 30 patients having sustained a previous myocardial infarction and 5 patients had dilated cardiomyopathy. Indications for electrophysiological study included sustained ventricular tachycardia in 15 patients, out-of-hospital cardiac arrest in 6 patients, recurrent syncope in 11 patients and symptomatic nonsustained ventricular tachycardia in 3 patients. The ejection fraction ranged from 10 to 52% (mean = 30 $\pm$ 15%).

The standard stimulation protocol for both the baseline study and subsequent drug studies was employed. In 2 patients, left ventricular stimulation was required for tachycardia induction.

Drug efficacy was defined as the induction of <6 repetitive responses after completion of the stimulation protocol.

For analysis of symptoms experienced by the patients during the arrhythmia a symptom score was applied[229]: No symptoms = 0, palpitation = 1, angina, dyspnoea or

dizziness = 2, syncope = 3 and syncope plus the need for cardioversion = 4.

By study design, all patients underwent trials of both amiodarone alone and amiodarone plus procainamide.

Amiodarone was prescribed in a dosage of 1000 mg./day for 7 days followed by 800 mg./day for the subsequent 7 days. Electrophysiological testing was performed 12 to 14 days after the initiation of therapy.

For the studies with combination therapy, in all but one case, procainamide was administered intravenously at a rate of 50 mg./min. to a total dose of 1000 mg. or to the maximum tolerated dose if less than 1000 mg. In one patient a sustained release preparation of procainamide at a dose of 750 mg. six hourly was administered.

In the 24 patients who underwent testing on procainamide alone, 19 patients were tested on intravenous therapy (mean dosage = 1456 $\pm$ 404 mg.) and 5 patients on oral therapy (mean dosage = 5125 $\pm$ 1031 mg/day).

Serum levels of amiodarone and procainamide were obtained at the time of induction of a sustained arrhythmia or at completion of the stimulation protocol.

All patients were discharged on amiodarone 600 mg./day. In 15 patients procainamide was also prescribed. The dosage of amiodarone was reduced to 400 mg. in all patients after four months.

Attempts were made to obtain electrocardiographic documentation of any symptomatic event compatible with

arrhythmia recurrence including syncope. Sudden death, defined as an unexpected witnessed death occurring within 1 hour of the onset of symptoms or an unwitnessed death if the patient had been seen within the previous 12 hours and been free of chest pain, was also considered an arrhythmia recurrence.

Standard statistical analysis was performed. Intergroup differences were analysed using the Student's t test for paired data and the chi squared test for discrete variables. Values are expressed as the mean $\pm$ 1 standard deviation. A p value of <0.05 was considered significant. Breslow and Mantel-Cox analyses were applied to evaluate differences in survival curves for patients discharged on amiodarone alone and the combination of amiodarone plus procainamide (see Chapter 6).

8.2 RESULTS

INDUCTION AND TERMINATION OF ARRHYTHMIA

a) Baseline Study

In the baseline study, all patients had inducible sustained ventricular tachycardia (Table 8.1). The mode of induction was single extrastimuli in 4 patients, double extrastimuli in 13 patients and triple extrastimuli in 18 patients (Table 8.2). The induced tachycardia cycle length ranged from 180 to 400 msec. (mean = 257 $\pm$ 59 msec).

	ELECTROPHYSIOLOGICAL STUDY			
	BASELINE	PROC	AMIO	AMIO + PROC
NO. OF PATIENTS	35	24	35	35
SUVT	35 (100%)	22 (92%)	30 (85%)	29 (83%)
VFIB	0 (0%)	0 (0%)	2 (6%)	0 (0%)
NSVT	0)0%)	2 (8%)	3 (9%)	4 (11%)
NIL	0 (0%)	0 (0%)	0 (0%)	2 (6%)
MEAN CYCLE LENGTH (msec)	257 ± 59	321 ± 54*	301 ± 69*	355 ± 61*

TABLE 8.1 Induction of ventricular tachyarrhythmias

AMIO = Amiodarone
PROC = Procainamide

SUVT = sustained ventricular tachycardia
VFIB = ventricular fibrillation
NSVT = nonsustained ventricular tachycardia

* Significantly different from baseline at $P<0.001$.

	BASELINE	PROC	AMIO	AMIO+PROC
NO. OF PATIENTS	35	24	35	35
NO. OF EXTRASTIMULI				
SINGLE	4	3	8	7
DOUBLE	13	12	13	13
TRIPLE	18	9	14	13

TABLE 8.2 Comparison of mode of arrhythmia induction

Abbreviations as in Table 8.1

	BASELINE	PROC	AMIO	AMIO+PROC
NO. OF PATIENTS	35	24	35	35
PACING	19 (54%)	15 (63%)	23 (66%)	22 (63%)
CARDIOVERSION	16 (46%)	7 (29%)	9 (26%)	5 (14%)*
SPONTANEOUS	0 (0%)	2 (8%)	3 (8%)	6 (17%)
NIL	0 (0%)	0 (0%)	0 (0%)	2 (6%)

TABLE 8.3 Comparison of mode of arrhythmia termination

Abbreviations as in Table 8.1

* Significantly different from baseline at $P<0.01$.

For termination of the tachycardia, pacing modalities were successful in 19 (54%) patients, (overdrive pacing in 18 patients and double extrastimuli in 1 patient), and cardioversion was required in 16 (46%) patients (Table 8.3).

b) Amiodarone Alone

By study design all patients had inducible ventricular tachyarrhythmias on amiodarone alone. These included sustained ventricular tachycardia in 30 patients, ventricular fibrillation in 2 patients and nonsustained ventricular tachycardia in 3 patients (Table 8.1). The mode of induction was single extrastimuli in 8 patients, double extrastimuli in 13 patients and triple extrastimuli in 14 patients (Table 8.2). In 10 patients a sustained ventricular arrhythmia was inducible with at least one less extrastimulus than that required in the baseline study.

On amiodarone, the mean cycle length of sustained tachycardia was significantly longer than baseline at 301 $\pm$ 69 msec. ($P<0.001$). The mean increase in cycle length was 53 $\pm$ 50 msec. with a shortening of the cycle length of the tachycardia observed in only 3 cases.

In contrast to the baseline study, cardioversion was required for termination in only 9 (26%) patients. In 21 patients, overdrive pacing was successful and in 2 patients the tachycardia was terminated by single extrastimuli (Table 8.3).

The mean serum amiodarone level for the group was 1.4 ± 0.7 ug./ml.

c) Amiodarone Plus Procainamide

In 2 patients, the combination regimen completely suppressed induction of tachycardia and in a further 4 patients only nonsustained ventricular tachycardia was induced (Table 8.1). Sustained ventricular tachycardia was induced in 29 patients, with a mean cycle length of 355 ± 61 sec. which was significantly longer than both the baseline tachycardia cycle length and the tachycardia cycle length on amiodarone alone ($P<0.001$ and $P<0.01$ respectively). The mean increase in cycle length relative to baseline was 98 ± 58 msec. An example of the effect of amiodarone and amiodarone plus procainamide on the induced arrhythmia is shown in Fig. 8.1.

Tachycardia was induced by single extrastimuli in 7 patients, double extrastimuli in 13 patients and triple extrastimuli in 13 patients (Table 8.2). Fewer extrastimuli were required for tachycardia induction in 12 patients and an increased number of extrastimuli in 6 patients.

Cardioversion for termination was required in 5 patients which was significantly less than in the baseline study ($P<0.01$) with successful termination by pacing modalities in 22 patients. In 2 patients, the sustained ventricular tachycardia terminated spontaneously during

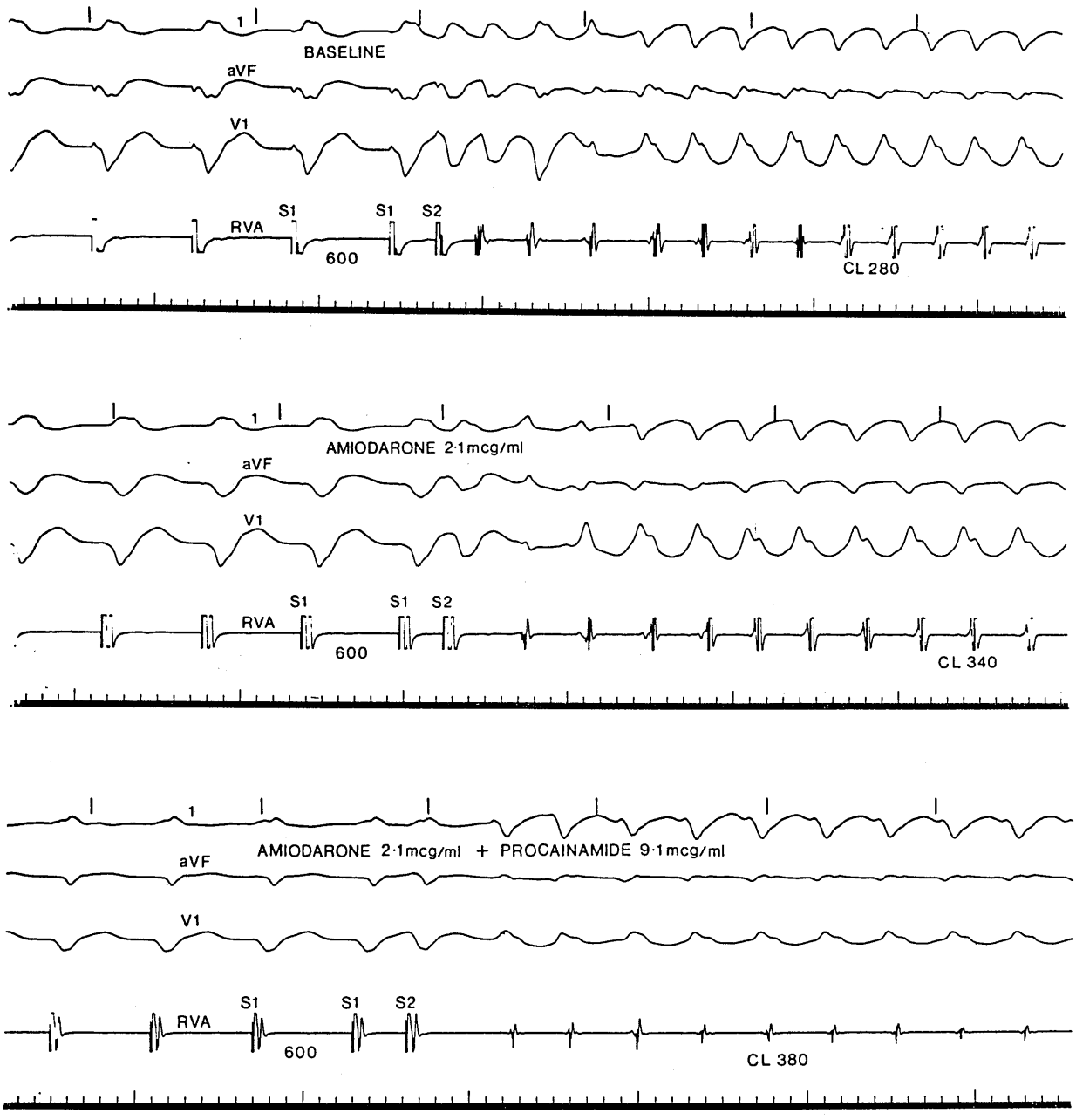

Fig. 8.1 Response to combination therapy. Induction of tachycardia in baseline (upper panel), amiodarone (middle panel) and amiodarone plus procainamide (lower panel). Note slowing of tachycardia with addition of procainamide.

attempts at pacing termination (Table 8.3).

The serum procainamide level in the combination regimen was 7.2 ± 2.1 ug./ml.

d) Procainamide Alone

In 24 patients, procainamide alone was tested. Sustained ventricular tachycardia was induced in 22 patients and nonsustained ventricular tachycardia induced in 2 patients (Table 8.1). Tachycardia was induced by single extrastimuli in 3 patients, double extrastimuli in 12 patients and triple extrastimuli in 9 patients (Table 8.2). The mean cycle length of induced tachycardia was 321 ± 54 msec. which was significantly longer than the mean cycle length of tachycardia induced in the baseline study (262 ± 66 msec. $P<0.001$).

Pacing termination was successful in 15 (68%) patients with sustained tachycardia with cardioversion required for termination in 7 (32%) patients (Table 8.3).

The mean serum procainamide level was 11.2 ± 4.9 ug./ml.

8.3 VENTRICULAR REFRACTORINESS

In 30 patients, the effective refractory period was measured in the baseline study and during testing with amiodarone alone and amiodarone plus procainamide. In 5 patients, there was incomplete data because of induction of

tachycardia by a single extrastimulus, and these patients have therefore been excluded from this analysis. In the baseline study, the mean ventricular effective refractory period was 253 ± 22 msec. which lengthened to 279 ± 16 msec. with amiodarone alone ($p<0.0001$) and to 300 ± 28 msec. with the combination of amiodarone plus procainamide ($p<0.0001$). The mean change in the refractory period was 26 ± 21 msec. and 45 ± 31 msec. respectively ($p<0.001$). The addition of procainamide lengthened the refractory period by a mean of 20 ± 20 msec. In patients who were tested on procainamide alone, the mean change in effective refractory period was 23 ± 20 msec. but there was no correlation between the change produced by procainamide relative to the baseline study and relative to amiodarone ($r = -0.138$).

8.4 SURFACE QT INTERVAL

A potential limitation of the combination of amiodarone plus procainamide is marked prolongation of the surface QT interval with an increased propensity to development of torsade de pointes. The QT_c intervals in response to amiodarone alone and the combination regimen were analysed. The baseline QT_c interval for the group was 445 ± 37 msec. with a significant prolongation with amiodarone alone to 505 ± 49 msec. ($P<0.001$) and further lengthening with the regimen to 529 ± 56 msec. ($P<0.001$). The mean absolute

and percentage increase with amiodarone relative to the baseline value was 56 ± 55 msec. and 14 ± 3% respectively and with amiodarone plus procainamide it was significantly longer at 76 ± 57 msec. and 18 ± 13% respectively ($P<0.05$).

8.5 ARRHYTHMIA SYMPTOMS

The symptoms experienced by the patients during the tachycardia are shown in Table 8.4. In the baseline study 28 (85%) of the patients experienced syncope compared to 14 (42%) of the patients on amiodarone alone and 8 (24%) on the combination regimen. The total symptom scores for the three groups were 108, 75 and 53 respectively and the mean scores were 3.3 ± 0.9, 2.3 ± 1.4 and 1.6 ± 1.4 respectively. Of the five patients on the combination who required cardioversion, three of these patients also required cardioversion in the amiodarone study.

8.6 FOLLOW-UP

At discharge, 20 patients were prescribed amiodarone alone and 15 patients were prescribed amiodarone plus procainamide. The mean dose of procainamide was 3212 ± 1060 mg/day. In one patient, procainamide was discontinued after 21 months' therapy because of the development of drug-induced lupus. The follow-up ranged from 2 weeks to 51 months (mean 18 ± 15 months). Over

SYMPTOM	BASELINE	AMIODARONE	AMIODARONE + PROCAINAMIDE
NONE	0 (0%)	4 (12%)	8 (24%)
PALPITATION	2 (6%)	6 (18%)	10 (30%)
DYSPNOEA	1 (3%)	2 (6%)	2 (6%)
ANGINA	1 (3%)	5 (15%)	3 (9%)
DIZZINESS	1 (3%)	2 (6%)	2 (6%)
SYNCOPE	12 (36%)	5 (15%)	3 (9%)
SYNCOPE REQUIRING CARDIOVERSION	16 (48%)	9 (27%)	5 (15%)
SYMPTOM SCORE			
TOTAL	108	75	53
MEAN	3.3±0.9	2.3±1.4	1.6±1.4

TABLE 8.4 Comparison of symptoms experienced due to induced tachyarrhythmia

this period, in the group discharged on amiodarone, there were 5 (25%) arrhythmia recurrences and 6 (30%) sudden deaths, and in the group discharged on amiodarone plus procainamide there were 3 (20%) arrhythmia recurrences and 2 (13%) sudden deaths. In addition there were two nonsudden deaths in the latter group. Although there was a trend towards fewer sudden deaths in the combination group, there was no statistical significance in overall recurrence, using survival curve analysis (P = 0.45). Of the eight patients who sustained a sudden death, six patients developed syncope during electrophysiological testing on their discharge therapy and two patients experienced angina.

8.7 DISCUSSION

The use of combinations of different antiarrhythmic agents with differing electrophysiological profiles has provided an effective modality for the treatment of supraventricular arrhythmias[258]. Combination therapy for ventricular arrhythmias, however, has been somewhat disappointing. Ross et al.[255] evaluated combinations of quinidine, procainamide or encainide with lignocaine or propranolol and did not find additional effects produced by the combination. In another study, Duffy et al.[256] demonstrated that combinations of the Class I agents procainamide, quinidine and disopyramide did not prevent

induction of ventricular tachycardia if the patients were refractory to large doses of the individual agents. In addition, although the combination regimens lengthened the tachycardia cycle length, the induction of the tachycardia was easier suggesting that the spontaneous development of the arrhythmia might occur more frequently.

Recently Greenspan et al.[257] employed the combination of a Class IA agent, either procainamide or quinidine, with the Class IB agent mexiletine and demonstrated a 35% efficacy rate in patients with inducible ventricular tachyarrhythmias unresponsive to the individual agents alone.

In clinical practice, amiodarone is usually reserved for patients with ventricular tachycardia refractory to other medical therapy because of its potentially serious side-effects and its particularly long half-life which can interfere with further testing of single agents.

The efficacy of the combination of amiodarone with a Class I agent has been reported in two preliminary studies. Marchlinski et al.[259] evaluated the combination of amiodarone plus either procainamide or quinidine in 34 patients. Addition of the Class I agent prevented induction in 3 patients and although the cycle length of induced tachycardia was prolonged, there was no difference in the outcome of patients randomised to either amiodarone or the combination over a 9 month follow-up.

In contrast, Bellocci et al.[260] studied a combination

of amiodarone plus either mexiletine or propafenone. In 14 of 26 patients who were inducible on amiodarone alone, the combination either prevented induction or produced a significantly slower rate.

These two preliminary studies unfortunately did not provide data on change in either mode of induction or termination of the tachycardias.

In the present study, the combination of amiodarone plus procainamide prevented induction in only 2 (6%) of the 35 patients all of whom had been inducible on amiodarone alone, although only nonsustained tachycardia was inducible in another 4 patients. The increase in cycle length of induced tachycardia from 282 $\pm$ 34 msec. to 346 $\pm$ 43 msec. reported by Marchlinski et al was very similar to the increase from 301 $\pm$ 69 msec. to 355 $\pm$ 61 msec. reported here.

The combination regimen produced a reduction in the number of extrastimuli required for tachycardia induction in 12 patients compared to 10 patients on amiodarone alone. Although Duffy et al.[256] suggested that this was a negative feature, reflecting an increased potential for spontaneous development of tachycardia the prognostic implication of change in mode of induction remains debatable (see Chapter 11).

Although there was a trend towards a reduction in the proportion of sudden deaths during follow-up, there was no difference in arrhythmia-free interval which is similar to

the observation of Marchlinski et al.[259].

The relevance of haemodynamic stability of the induced tachycardia to subsequent type of clinical recurrence has been discussed by Buxton and Josephson[261]. In a study of 101 patients discharged on amiodarone, 10 of 12 patients who had a haemodynamically stable tachycardia induced had a stable tachycardia at the time of recurrence. In contrast, only 3 of 17 patients with induction of a haemodynamically unstable tachycardia were stable at the time of tachycardia recurrence.

The increased lengthening of tachycardia cycle length, the decreased need for cardioversion for tachycardia termination and improvement of symptomatic tolerance in patients on the combination regimen in comparison to amiodarone alone, suggests that the combination may provide an added protection from the risk of sudden death.

The dosage of intravenous procainamide was limited to 1000 mg. in this study. Saal et al.[262] have reported the interaction of amiodarone with procainamide demonstrating an increase in procainamide levels possibly due to a decrease in tissue binding. This group recommended a 30% reduction in procainamide when combined with amiodarone. The major reason however for limitation of the dosage of procainamide, was because of the potential additive side-effects especially prolongation of the QT interval. The association of development of torsade de pointes and QT prolongation due to both amiodarone and procainamide is

well recognised (see Chapter 11). The significant increase in QT_c observed in this study underlines the need for careful monitoring of this parameter. The addition of procainamide lengthened the QT_c by a further 23 msec. over amiodarone alone with an overall 83 msec. increase relative to the baseline interval. Recently, polymorphous ventricular tachycardia has been reported in 2 patients on the combination of amiodarone and quinidine[263]. The two patients in this study on the combination who sustained sudden death had QT_c intervals of 520 and 560 msec. In neither case was documentation of the terminal arrhythmia available.

CONCLUSIONS

In patients with sustained ventricular tachycardia who remain inducible on amiodarone alone, the combination of amiodarone plus procainamide is only infrequently effective in suppressing the arrhythmia. By lengthening the cycle length of the tachycardia, however, a more haemodynamically tolerable arrhythmia can be produced, potentially affording the patient greater protection from sudden death. Significant prolongation of the QT interval occurs with this combination and this may limit its application.

CHAPTER 9

DETERMINANTS OF RESPONSE TO MEDICAL THERAPY IN PATIENTS WITH INDUCIBLE VENTRICULAR ARRHYTHMIAS

The individual success rate for antiarrhythmic agents in patients with tachyarrhythmias is relatively low and patients are exposed to multiple drug tests to define an effective treatment. Repeated electrophysiological testing is costly[264] and demanding for both patient and physician[265]. Furthermore, each invasive study carries a small but definite risk of complication[266,267]. The aim of the first section of this analysis was to define variables which predicted the success or failure of medical therapy during electrophysiological testing. Identification of these variables might permit stratification of patients who were unlikely to respond to drug therapy and for whom alternative therapeutic modalities could be considered at an earlier stage.

The studies discussed in Chapters 6 and 7 demonstrated that patients discharged on therapy determined as successful by electrophysiological testing have a significantly better longterm outcome than patients on therapy which does not prevent arrhythmia inducibility. Response to electrophysiological testing might, however, only identify high- and low-risk groups and not in itself

be an independent predictor of subsequent arrhythmia recurrence. In the second section the determinants of arrhythmia recurrence were analysed to evaluate the prognostic power of this technique.

Despite a directed therapy approach, patients with sustained arrhythmias have a significant recurrence rate. The aim of the third section of this analysis was to identify which factors might predict the type of recurrence experienced by the patient, i.e. the development of a haemodynamically tolerated tachycardia or sudden death. Premorbid determination of these factors might provide an additional safety factor for patients discharged on medical therapy.

9.1 PATIENTS AND METHODS

The patient population consisted of 186 patients who underwent electrophysiological studies and in whom a ventricular tachyarrhythmia was induced in the baseline study. Ten major variables were analysed. The demographic variables were age and sex. Underlying heart disease was classified as none, angina (coronary artery disease but no previous infarction), recent myocardial infarction (infarction within the previous six weeks), remote myocardial infarction, cardiomyopathy and valvular heart disease. The diagnostic criteria for classification have been discussed in previous chapters. Congestive

heart failure was defined as the presence of significant effort breathlessness despite current antifailure therapy. Ejection fraction was measured by radionuclide ventriculography or contrast angiography. Number of previous drug studies was the number of failed trials of empirically prescribed antiarrhythmic therapy. Indication for electrophysiological study was classified as sustained ventricular tachycardia, cardiac arrest, syncope of undetermined origin, nonsustained ventricular tachycardia or palpitation. Baseline mode of induction was classified as the number of ventricular extrastimuli required for induction in the baseline study, i.e. single, double or triple. Number of drug studies indicated the number of serial electrophysiological drug studies performed on the patient. Arrhythmia type classified the induced arrhythmia in the baseline study as sustained ventricular tachycardia, ventricular fibrillation or nonsustained ventricular tachycardia.

For the analysis of type of recurrence, additional variables reflecting the induced arrhythmia both in the baseline study and in the study on the antiarrhythmic regimen on which the patient was discharged, were included. These additional variables were: baseline induced arrhythmia cycle length and need for cardioversion and mode of arrhythmia induction, cycle length of arrhythmia, need for cardioversion and symptoms during induced arrhythmia on drug therapy. The latter variable was classified using a

modification of that used by Swerdlow et al.[229] viz 0 - no symptoms, 1 - palpitation, 2 - angina, dyspnoea, lightheadedness, 3 - syncope, 4 - cardiac arrest (i.e. syncope plus need for cardioversion).

The standard electrophysiological protocol was applied to both baseline and subsequent drug studies.

The uniform definitions were employed as in previous studies. Since the results from Chapters 6 and 7 demonstrated that for sustained arrhythmias induction of $\leqslant$15 repetitive responses denoted a good long-term benefit, this definition was employed for drug success for patients with inducible sustained ventricular tachycardia and ventricular fibrillation. For induced nonsustained ventricular tachycardia drug success was defined as the induction of <6 repetitive responses. Drug failure was therefore defined as the inability to identify a drug therapy which satisfied the definitions for drug success. Patients with drug success were considered "responders" and those with drug failure "nonresponders".

Clinical follow-up was performed as previously discussed in Chapters 6 and 7.

9.2 STATISTICAL ANALYSIS

Continuous data are presented as mean $\pm$ 1 S.D. The analysed variables were screened by standard univariate statistical methods using chi-square test with Yates'

correction factor or Fisher's exact test for dichotomous variables and the Student's t test for unpaired data for continuous variables.

Stepwise logistic regression was employed for the analyses of response to serial drug testing and type of recurrence (Biomedical Computer Programs P-series, University of California (BMDP)). Stepwise logistic regression identifies and collects variables that most usefully measure the characteristics of the dependent variable. The single best variable is selected and added to the model and the remaining variables repeated. At each subsequent step of the stepping process, variables are added to or removed to maximise separation. The stepping process is based on the maximum likelihood ratio. The process continues until the remaining variables no longer make significant contributions to the separation of the two groups.

For the analysis of the follow-up data, survival analysis using covariates (BMDP) was employed. This analysis is based upon the Cox proportional hazards regression model which presumes that the recurrence rates may be modelled as log-linear functions of the defined covariates which are variables which may influence the time-to-response. A set of regression coefficients is estimated which relates the effect of each covariable to the survival function.

RESULTS

9.3 SERIAL DRUG TESTING

The general characteristics of the patient population are shown in Table 9.1. The 186 patients had previously failed 0-6 (mean = 2.1 ± 1.6) trials of therapy. Coronary artery disease was present in 154 patients of whom 145 had previously sustained a myocardial infarction. Dilated cardiomyopathy was present in 21 patients, valvular disease in 6 patients and in 5 patients no underlying structural heart disease was identified. The ejection fraction for the group ranged from 8 - 72% but was generally low with a mean of 31 ± 16%. Congestive heart failure was present in 54 patients. Indication for study included sustained ventricular tachycardia in 79 patients, cardiac arrest in 32 patients, syncope in 42 patients, symptomatic nonsustained ventricular tachycardia in 29 patients and palpitation in 4 patients. In the baseline study, sustained ventricular was induced in 126 patients, ventricular fibrillation in 24 patients and nonsustained ventricular tachycardia in 36 patients. The mode of induction was single ventricular extrastimuli in 15 patients, double extrastimuli in 70 patients and triple extrastimuli in 101 patients.

The 186 patients underwent a total of 523 trials of drug therapy. The number of trials per patient ranged

NO. OF PATIENTS	186
MALE:FEMALE	154/32
AGE (YR.)	61±10
UNDERLYING HEART DISEASE	
NONE	5
ANGINA	9
RECENT-MI	12
REMOTE-MI	133
CARDIOMYOPATHY	21
VALVULAR HEART DISEASE	6
NO. WITH CARDIAC FAILURE	54
EJECTION FRACTION (%)	31±16
NO. OF PREVIOUS DRUG STUDIES	2.1±1.6
INDICATION FOR ELECTROPHYSIOLOGICAL STUDY	
SUSTAINED VENTRICULAR TACHYCARDIA	79
CARDIAC ARREST	32
SYNCOPE OF UNDETERMINED ORIGIN	42
NONSUSTAINED VENTRICULAR TACHYCARDIA	29
PALPITATION	4
BASELINE MODE OF TACHYCARDIA INDUCTION	
SINGLE EXTRASTIMULI	15
DOUBLE EXTRASTIMULI	70
TRIPLE EXTRASTIMULI	101
TYPE OF INDUCED ARRHYTHMIA	
SUSTAINED VENTRICULAR TACHYCARDIA	126
VENTRICULAR FIBRILLATION	24
NONSUSTAINED VENTRICULAR TACHYCARDIA	36
NO. OF DRUG STUDIES PERFORMED	2.8±1.4

TABLE 9.1 Characteristics of patient population

from 1 - 6 (mean = 2.8 $\pm$ 1.4). A successful drug regimen was identified for 87 (47%) of the patients.

Statistical Analysis

The characteristics of responders and nonresponders are compared in Table 9.2. Four variables were identified as being significantly associated with the success or failure of medical therapy: ejection fraction, type of induced arrhythmia, mode of stimulation and underlying heart disease. Since, however, no individual variable was sufficiently powerful to predict the response to therapy, these variables were entered into the stepwise logistic regression analysis. This identified three independent variables. The most powerful variable predictive of response to medical therapy was ejection fraction ($P<0.001$). The second variable identified was type of induced arrhythmia ($P = 0.002$) and the third variable was mode of stimulation ($P = 0.043$). Patients with a low ejection fraction were less likely to respond to medical therapy. If ejection fraction was dichotomised at a value of 30%, the sensitivity of this variable was 69% and the specificity 61% with an overall predictive accuracy of 70%.

Induction by single ventricular extrastimuli also reflected a poor response to medical therapy. Although the specificity and positive predictive value of this variable were 99% and 93%, this mode of stimulation was

	RESPONDERS	NONRESPONDERS	P VALUE
NO. OF PATIENTS	87	99	
MALE:FEMALE	69/18	85/14	0.3818
AGE (YRS.)	61±11	61±9	0.9242
UNDERLYING HEART DISEASE			0.0062
NONE	4	1	
ANGINA	7	2	
RECENT-MI	3	9	
REMOTE-MI	55	77	
CARDIOMYOPATHY	14	7	
VALVULAR HEART DISEASE	3	3	
EJECTION FRACTION (%)	37±17	26±14	<0.0001
NO. WITH CARDIAC FAILURE	20	34	0.0896
NO. OF PREVIOUS DRUG STUDIES	1.8±1.5	2.2±1.6	0.6299
INDICATION FOR ELECTROPHYSIOLOGICAL STUDY			0.0734
SUSTAINED VENTRICULAR TACHYCARDIA	28	51	
CARDIAC ARREST	17	15	
SYNCOPE OF UNDETERMINED ORIGIN	26	16	
NONSUSTAINED VENTRICULAR TACHYCARDIA	13	16	
PALPITATION	3	1	
MODE OF INDUCTION			0.0012
SINGLE EXTRASTIMULI	1	14	
DOUBLE EXTRASTIMULI	30	40	
TRIPLE EXTRASTIMULI	56	45	
TYPE OF INDUCED ARRHYTHMIA			<0.0001
SUSTAINED VENTRICULAR TACHYCARDIA	44	82	
VENTRICULAR FIBRILLATION	20	4	
NONSUSTAINED VENTRICULAR TACHYCARDIA	23	13	
NO. OF STUDIES PERFORMED	2.6±1.2	3.0±1.5	0.2136

TABLE 9.2 Characteristics of responders and nonresponders during serial electrophysiological testing.

observed in only 15 patients and the sensitivity was therefore only 14%.

The differing response to therapy in relation to the type of induced arrhythmia has already been observed in Chapters 6 and 7. A successful therapy was identified for 44 (35%) of the 126 patients with sustained ventricular tachycardia which was significantly lower than for patients with ventricular fibrillation (20 (83%) of 24 patients) or for patients with nonsustained ventricular tachycardia (23 (64%) of 36 patients).

Effect of Induced Arrhythmia Type

To determine the impact of induced arrhythmia type on the previous analysis, logistic regression was applied to the groups subdivided on the basis of induced arrhythmia. The results are shown in Table 9.3.

Patients with induced sustained ventricular tachycardia accounted for 68% of the total study population and the results of the regression analysis for this subset were the same as for the whole group. For patients with ventricular fibrillation, only ejection fraction was identified as an independent variable of response to therapy. In contrast to these results, the independent variables identified for patients with nonsustained ventricular tachycardia were: number of previous drug studies and presence of myocardial infarction. In this population, responders had a fewer number of previous

STEP	VARIABLE	P VALUE
SUSTAINED VENTRICULAR TACHYCARDIA		
1.	EJECTION FRACTION	0.004
2.	MODE OF STIMULATION	0.053
VENTRICULAR FIBRILLATION		
1.	EJECTION FRACTION	0.029
NONSUSTAINED VENTRICULAR TACHYCARDIA		
1.	NO. OF PREVIOUS DRUG STUDIES	0.006
2.	PRESENCE OF MYOCARDIAL INFARCTION	0.026

TABLE 9.3 Stepwise logistic regression analysis in relation to type of induced arrhythmia

trials of therapy (1.6 $\pm$ 1.9) compared to nonresponders (2.2 $\pm$ 1.6). Nine of the 23 responders (39%) had previously sustained a myocardial infarction in contrast to 10 of the 13 nonresponders (77%).

9.4 FOLLOW-UP STUDY

The patients with inducible sustained ventricular tachyarrhythmia were followed up for a mean of 22 $\pm$ 15 months, ranging from 2 days to 46 months (extended from previous studies). Over this period there were 41 patients with arrhythmia recurrence, 21 patients with sudden death and 11 patients with nonsudden death.

Statistical Analysis

Univariable predictors of recurrence of arrhythmia or sudden death were: discharge on a drug regimen determined to be ineffective ($P<0.0001$), lower ejection fraction ($P = 0.001$), and greater number of failed trials of empirical therapy ($P = 0.0179$).

Regression analysis identified that the only independent predictor of recurrence was ineffective discharge therapy ($P<0.001$).

During follow-up, in 54 patients discharged on an effective therapy, there were 9 (17%) arrhythmia recurrences and 1 (2%) sudden death compared to 32 (33%) arrhythmia recurrences and 20 (21%) sudden deaths in 96

patients on therapy determined to be ineffective by serial electrophysiological drug testing.

Patients who experienced arrhythmia recurrence or sudden death had previously failed more trials of empirical therapy (2.4 $\pm$ 1.6) than patients who remained free of arrhythmia (1.7 $\pm$ 1.3). In the regression analysis this variable only just failed to reach significance ($P = 0.055$).

9.5 TYPE OF RECURRENCE

To analyse the variables predictive of the type of recurrence, only those patients with inducible sustained ventricular tachycardia in the baseline study and who experienced either recurrence of tachycardia or sudden death were analysed. Patients with inducible ventricular fibrillation were excluded since the cycle length of the baseline induced arrhythmia could not be classified in the analysis. In addition, nine patients were excluded because of noninducibility on the drug regimen on which they were discharged. This prevented analysis of the variables of arrhythmia induction in the drug study. Interestingly, all nine of these patients subsequently experienced recurrence of arrhythmia and did not have sudden death ($P<0.01$). The patient population therefore consisted of 49 patients, 30 patients with recurrence of arrhythmia and 19 patients with sudden death. The

characteristics of the two groups are shown in Table 9.4 and the characteristics of the induced arrhythmias both in the baseline and in the discharge drug study are shown in Table 9.5.

Statistical Analysis

Univariate analysis of the characteristics of the patient groups identified two significant variables which were associated with recurrence of arrhythmia or sudden death. Patients with cardiac failure experienced sudden death more frequently than arrhythmia recurrence ($P = 0.0021$). A significant difference in indication for study was also noted ($P = 0.0245$). Patients experiencing recurrence of arrhythmia were more often referred for study with a history of sustained ventricular tachycardia ($P<0.01$) and less often with nonsustained ventricular tachycardia ($P<0.01$) than patients with sudden death.

No characteristic of the baseline induced arrhythmia was significantly different between the two groups. In contrast, in the discharge drug study, the tachycardia cycle length, need for cardioversion and symptoms experienced during the arrhythmia were all significantly different between patients with arrhythmia recurrence and sudden death ($P = 0.0109$, $P = 0.0079$ and $P = 0.0003$ respectively).

Stepwise logistic regression was performed on all variables which were marginally significant. Two

	ARRHYTHMIA RECURRENCE	SUDDEN DEATH	P VALUE
NO. OF PATIENTS	30	19	
MALE:FEMALE	27/3	15/4	0.1071
AGE (YRS.)	59±8	61±7	0.3356
UNDERLYING HEART DISEASE			
ANGINA	-	1	
RECENT-MI	2	2	
REMOTE-MI	26	13	
CARDIOMYOPATHY	1	3	
VALVULAR HEART DISEASE	1	-	
EJECTION FRACTION (%)	25±13	21±14	0.3338
NO. WITH CARDIAC FAILURE	6	11	0.0021
NO. OF PREVIOUS DRUG STUDIES	2.1±1.8	2.6±1.3	0.1668
INDICATION FOR ELECTROPHYSIOLOGICAL STUDY			
SUSTAINED VENTRICULAR TACHYCARDIA	24	19	
CARDIAC ARREST	4	2	
SYNCOPE OF UNDETERMINED ORIGIN	1	3	
NONSUSTAINED VENTRICULAR TACHYCARDIA	1	5	
NO. OF STUDIES PERFORMED	3.0±1.4	2.7±1.6	0.6498

TABLE 9.4 Characteristics of patients with either recurrence of arrhythmia or sudden death

BASELINE	ARRHYTHMIA RECURRENCE	SUDDEN DEATH	P VALUE
MODE OF INDUCTION			0.0742
SINGLE	6	-	
DOUBLE	13	10	
TRIPLE	11	9	
CYCLE LENGTH OF TACHYCARDIA (msec.)	292±71	275±43	0.1256
NEED FOR CARDIOVERSION	11	7	0.9904
DISCHARGE DRUG STUDY			
MODE OF INDUCTION			0.1081
SINGLE	9	1	
DOUBLE	14	11	
TRIPLE	7	7	
CYCLE LENGTH OF TACHYCARDIA (msec.)	389±90	326±62	0.0109
NEED FOR CARDIOVERSION	3	7	0.0079
SYMPTOMS DURING ARRHYTHMIA	0.097±0.97	2.4±1.0	0.0003

TABLE 9.5 Characteristics of induced arrhythmia both in baseline and discharge drug study

independent variables were identified: severity of symptoms during induced tachycardia in the discharge drug study ($P<0.001$) and the presence of cardiac failure ($P = 0.049$). Of 12 patients who experienced significant symptoms (i.e. angina, dyspnoea or lightheadedness or more severe) and had cardiac failure, 9 (75%) had sudden death. Conversely, of 21 patients who were essentially asymptomatic or experienced only palpitation during the induced arrhythmia in the discharge drug study and did not have cardiac failure, only 1 (5%) had sudden death.

Since the classification of symptoms was somewhat subjective and empirical, the regression analysis was repeated without this variable. In this second analysis, the independent predictive variables were: presence of cardiac failure ($P = 0.003$) and cycle length of the tachycardia in the discharge study ($P = 0.023$). If tachycardia cycle length is dichotomised at 350 msec. the predictive accuracy for sudden death in patients with cardiac failure and a tachycardia cycle length of <350 msec. was 73% (sensitivity = 73%, specificity = 75%). For recurrence of arrhythmia, in patients without cardiac failure and a tachycardia cycle length of >350 msec., the predictive accuracy was 62% (sensitivity = 62%, specificity = 63%).

9.6 DISCUSSION

In Chapters 7 and 8, the favourable long-term outcome of patients prescribed antiarrhythmic therapy based on the response to serial electrophysiological testing was demonstrated. With the currently available antiarrhythmic agents, however, multiple testing is generally required. In addition, a significant proportion of patients remain refractory to medical therapy. It would obviously be of major advantage if those patients who were unlikely to respond to medical therapy could be identified before exposure to the stress and potential morbidity of repeated invasive procedures.

Serial Electrophysiological Drug Testing

Swiryn et al.[268] analysed seven factors predicting the response to drug therapy in 41 patients with sustained ventricular arrhythmias. Using a logistic regression technique the only significant independent factor identified was the number of antiarrhythmic agents received by the patient prior to study. There are several limitations in this study apart from the relative small size of the patient population. Drug response was defined, unusually, as induction of less than two minutes of sustained arrhythmia and only three Class I agents, procainamide, quinidine and disopyramide were tested. A further difference in the study from other reported series

is that the stimulation protocol did not include triple ventricular extrastimuli.

In a study of 51 patients with sustained ventricular tachycardia, Gold et al.[269] evaluated the response to intravenous procainamide and quinidine and found no predictive clinical or electrophysiological variable.

Logistic regression was employed by Swerdlow et al.[231] in a much larger study of 142 patients. Twenty five clinical and haemodynamic variables were analysed but no single variable was a satisfactory predictor of drug response. Multivariate analysis identified three variables (extent of coronary artery disease, female sex and fewer number of arrhythmia episodes) which could be constructed into a predictor function. This multivariate function had a sensitivity and specificity of 70%, a positive predictive value of 52% and a negative predictive value of 81%. The authors further refined this function by establishing high, intermediate and low probabilities for success of medical therapy. When applied to a prospective group of 25 patients, it accurately identified those patients for whom an effective regimen could not be determined. In this study, a more strict definition of induction of less than six repetitive responses was used, investigational drugs were employed and the stimulation protocol employed included routinely triple ventricular extrastimuli. Spielman et al.[232] in a group of 84

patients identified, by univariate analysis, four variables; age less than 45 years, ejection fraction greater than 50%, hypokinesia as the only contraction abnormality, and the absence of organic heart disease, which were associated with medical success. Four variables also predicted medical failure including induction of ventricular tachycardia with a single ventricular extrastimulus, an HV interval greater than 60 msec., the presence of a left ventricular aneurysm and Q waves on a baseline electrocardiogram. As in the previous study, no single variable was accurately predictive and this group also constructed a predictor function by stepwise discriminant analysis. The most accurate application of the predictor function was in patients for whom successful medical therapy could not be identified. This study employed the same drug success end-point as the study from Swerdlow et al.[231] but fewer investigational agents were used and triple extrastimuli were employed only in a few patients.

Despite the methodological differences in the present study, including a less rigorous end-point for drug success and the greater use of newer agents, in particular amiodarone, some agreement in the independent variables are apparant. The major independent variable in the present study, ejection fraction, was also identified by Spielman et al.[232]. Swerdlow et al.[231] considered that the impact of left ventricular function might have been a

statistically significant factor in their study if complete catheterisation data had been available. It is interesting to note that prognostic studies in post myocardial infarction have demonstrated the high risk of the association between ventricular arrhythmias and left ventricular dysfunction[33,34,35]. The present study suggests that such a patient group has a low probability for the identification of successful therapy.

Induction by a single extrastimulus, as identified by Spielman et al.[232], was also a significant variable in the present study. A similar correlation between induction with single extrastimuli and poor response to medical therapy was reported by Amann and colleagues[270].

Effect of Type of Induced Arrhythmia

Previous studies in this thesis have shown that the efficacy rates for antiarrhythmic therapy are different depending on the type of arrhythmia induced in the baseline study. Inducible sustained ventricular tachycardia is more difficult to suppress than either ventricular fibrillation or nonsustained ventricular tachycardia. Schoenfeld et al.[271], in a study of 261 patients, using linear regression analysis demonstrated that the major independent determinants of the ability to suppress arrhythmia induction were the number of trials of empirical therapy prior to electrophysiological testing, similar to the result of Swiryn et al.[268] and the type of induced

arrhythmia. Drug efficacy rates were 52% for sustained ventricular tachycardia, 73% for nonsustained ventricular tachycardia and 75% for ventricular fibrillation (P = 0.016). These results are similar to those obtained in the present study. To further elucidate this aspect, the regression analysis was applied to the individual types of induced arrhythmia.

Ejection fraction as the major independent variable applied to both sustained ventricular tachycardia and ventricular fibrillation. In contrast, for nonsustained ventricular tachycardia the independent variables were number of previous trials of empirical therapy and the presence of myocardial infarction. The spectrum of underlying heart disease in patients with nonsustained ventricular tachycardia was more varied than in patients with sustained ventricular tachycardia, and both Spielman et al.[232] and Swerdlow et al.[231] have observed a poorer response to medical therapy in relation to previous myocardial infarction.

Follow-Up

In the majority of studies evaluating the utility of electrophysiological testing in determining the effectiveness of long-term therapy, the only variable analysed was arrhythmia inducibility. Little attention has been directed towards other potential factors related to long-term outcome and their interrelation with response

to programmed stimulation. This has recently been discussed by Friedman and Yusuf.[272].

Gomes et al.[273] evaluated patients with high-grade ectopy and found that both arrhythmia inducibility and an ejection fraction <40% predicted a poor long-term prognosis.

Swerdlow and coworkers[229] analysed the determinants of total cardiac death and sudden death in 166 patients with ventricular tachycardia or fibrillation. Higher New York Heart Association function class and lack of response to therapy at electrophysiological study were identified as independent predictors of outcome ($P = 0.0006$ and $P = 0.0341$ respectively). In this study both medical and surgical therapies were included in the analysis. An important difference in the present study was that the dependent variable was arrhythmia recurrence in addition to sudden death and this may explain the predictive value of the number of previous failed trials of therapy identified in the analysis, since this factor presumably identified a group with drug-refractory tachycardia. Of major importance, however, is the observation that the major independent prognostic factor for recurrence of arrhythmia or sudden death was whether the drug regimen on which the patient was discharged was effective or ineffective as determined by electrophysiological testing. This finding validates the use of electrophysiological testing in the management of ventricular tachyarrhythmias in this patient

population.

Type of Recurrence

Occurrence of a ventricular tachyarrhythmia during follow-up can manifest itself as either sustained ventricular tachycardia sufficiently tolerated by the patient that he can be admitted to hospital for treatment or as sudden death, which by definition includes the development of cardiac arrest requiring cardiopulmonary resuscitation.

Hamer et al.[274] evaluated the factors which predicted syncope in patients with inducible ventricular tachycardia. The major independent determinants of syncope were: history of syncope in the patient prior to study and the rate of induced ventricular tachycardia. In the supine position, a tachycardia rate of less than 200 bpm was generally well tolerated whereas with rates exceeding 230 bpm syncope invariably ensued. Development of syncope however was not related to resting ejection fraction. Although this group also investigated the effect of antiarrhythmic therapy on haemodynamic response, no follow-up data was provided.

In the present analysis the subsequent type of recurrence was also not dependent on resting ejection fraction but the major independent predictive variable was the presence of cardiac failure. Although this variable may be more subjective than the measurement of ejection

fraction it probably better reflects the overall haemodynamic status of the patient and the ability to respond to haemodynamic insults.

The other independent variable reflected the arrhythmia induced in the discharge drug study. Using a symptom code, patients who experienced severe symptoms during the tachycardia were more likely to sustain sudden death during the follow-up period. This observation suggests that the haemodynamic impact of the arrhythmia induced in the laboratory is similar to that produced by the spontaneously occurring arrhythmia. If the symptom code is not employed, cycle length of the induced arrhythmia adopts independent significance similar to the study from Hamer et al.[274].

These findings are important if patients are discharged on therapy on which a sustained arrhythmia continues to be inducible. Although noninducibility of a sustained arrhythmia is considered the optimum end-point, some laboratories also consider change in mode of induction as a satisfactory criterion. Furthermore with amiodarone, because of a lower recurrence rate, patients tend to be discharged on this therapy despite continuing inducibility. The presence of cardiac failure and a poorly tolerated induced tachyarrhythmia suggests that such patients are more likely to have sudden death if recurrence occurs, and alternative therapeutic modalities should be considered. For patients without heart failure and with a slow

tachycardia which is well tolerated, sudden death is less likely and trial of therapy may therefore be justified.

CONCLUSIONS

In patients with ventricular tachyarrhythmias undergoing serial electrophysiological drug testing, patients with more severe impairment of left ventricular function are less likely to respond to medical therapy. In addition, the type of induced arrhythmia is an important predictor of drug success. Sustained ventricular tachycardia is more difficult to control than either ventricular fibrillation or nonsustained ventricular tachycardia.

Importantly, this study also confirms the predictive value of determining drug efficacy by serial electrophysiological testing. In this study this variable was the only independent determinant of arrhythmia recurrence or sudden death.

In patients who subsequently develop recurrence, the type of recurrence is dependent upon overall cardiac status and the characteristic of the induced arrhythmia in the discharge drug study.

CHAPTER 10

FAILURE OF PROCAINAMIDE DURING ELECTROPHYSIOLOGICAL TESTING: RESPONSE TO OTHER ANTIARRHYTHMIC THERAPY

In Chapter 9, the demographic, clinical, haemodynamic and electrophysiological factors influencing the response to medical therapy were analysed, and the profile of patients unlikely to respond were discussed.

An alternative approach in an attempt to limit the number of drug evaluation studies to which a patient may be subjected is based on the premise that the response to one antiarrhythmic agent can predict the response to other agents[268]. Waxman et al.[225] reported that in patients in whom a sustained arrhythmia remained inducible on procainamide therapy, only 7% of subsequent trials of medical therapy were effective.

The aims of this study were to determine whether the failure of procainamide during electrophysiological testing predicted failure of subsequent therapy with the availability of newer agents including amiodarone and the use of combination regimens, and whether the results were influenced by the type of arrhythmia under study.

10.1 PATIENTS AND METHODS

The study group consisted of 81 consecutive patients with a ventricular tachyarrhythmia induced during the baseline electrophysiological study and in whom the arrhythmia remained inducible on a maximally tolerated dose of procainamide. In no case was the induction of the arrhythmia related to acute myocardial ischaemia or metabolic or electrolyte imbalances. There were 73 men and 8 women ranging in age from 42 to 84 years. All patients had underlying coronary artery disease and 75 had sustained a previous myocardial infarction. The ejection fraction obtained from either radionuclide ventriculography or contrast left ventriculography ranged from 9 to 72% (mean 33 $\pm$ 17%). Indications for study included sustained ventricular tachycardia in 33 patients, cardiac arrest in 20 patients, syncope in 21 patients and symptomatic non-sustained tachycardia in 7 patients.

Prior to electrophysiological study, the patients had undergone 0 to 6 (mean 1.8 $\pm$ 1.4) empirical trials of drug therapy.

The ventricular tachyarrhythmias induced in the baseline study were sustained monomorphic ventricular tachycardia in 59 patients, ventricular fibrillation in 8 patients and nonsustained ventricular tachycardia in 14 patients.

The demographic and clinical characteristics of the study population in relation to the type of induced arrhythmia are shown in Table 10.1.

The standard electrophysiological protocol was applied to both baseline and subsequent drug studies. All initiations of arrhythmia were repeated at least once. In patients with nonsustained ventricular tachycardia, more than 10 episodes were required before inclusion in this study.

The uniform definitions for sustained ventricular tachycardia, ventricular fibrillation and nonsustained ventricular tachycardia were employed. For the purpose of this study, noninducibility was defined as the induction of fewer than 6 repetitive ventricular responses at the completion of the stimulation protocol.

By study design, only patients in whom a ventricular tachyarrhythmia remained inducible after procainamide administration were included. Procainamide was administered intravenously or orally to the maximally tolerated dose, defined as the development of symptoms of toxicity, an increase of more than 25% in QRS duration, lengthening of the QT interval to greater than 500 ms on the surface electrocardiogram, or hypotension that could not be supported by saline infusion. The intravenous procainamide dosage was 1000 to 2000 mg. infused at a rate of 50 mg./min. followed by a maintenance infusion of 4 to 8 mg./min. Oral procainamide was administered as a

	INDUCED VENTRICULAR TACHYARRHYTHMIA		
	SUSTAINED VT	VFIB	NONSUSTAINED V
NO. OF PATIENTS	59	8	14
AGE (YEARS)	61±10	65±7	63±8
SEX (M/F)	55/4	8/0	10/4
PREVIOUS INFARCTION	57	7	11
EJECTION FRACTION (%)	28±16	38±16	31±14
PREVIOUS DRUG TRIALS	1.9±1.5	1.6±1.2	1.2±1.4

TABLE 10.1 Characteristics of study population

VT = ventricular tachycardia
VFIB = ventricular fibrillation

	INDUCED VENTRICULAR TACHYARRHYTHMIA		
INDICATION FOR STUDY	SUSTAINED VT	VFIB	NONSUSTAINED VT
SUSTAINED VT	32	1	-
CARDIAC ARREST	13	3	4
SYNCOPE	9	4	8
NONSUSTAINED VT	5	-	2

TABLE 10.2 Type of induced arrhythmia in relation to indication for study

Abbreviations as in TABLE 10.1

sustained release preparation in doses of 750 to 2000 mg. every 6 hours.

In the additional drug studies, the following drugs were employed: quinidine, mexiletine, amiodarone, lignocaine, disopyramide, bethanidine, phenytoin, flecainide, and indecainide. The dosages of these drugs are tabulated in Table 2.2.

Statistical analysis was performed using the unpaired t test and analysis of variance for continuous variables and RXC contingency tables for discrete variables. A value of $p<0.05$ was considered significant.

10.2 RESULTS

Clinical Characteristics

The patients were grouped for analysis on the type of ventricular arrhythmia initiated in the baseline study (Table 10.1). There was no statistical difference in age or global cardiac function as assessed by ejection fraction among the three groups. Patients with nonsustained ventricular tachycardia had undergone significantly fewer trials of therapy, prior to electrophysiological study, than patients with sustained ventricular tachycardia ($p<0.05$) but not patients with ventricular fibrillation.

In patients with induced nonsustained ventricular tachycardia the duration of the longest episode ranged from 14 to 161 complexes (4 to 29 seconds). The mean duration

of the longest episode was 46 complexes. In 3 of the 14 patients, the duration of the longest episode was less than 20 complexes. The cycle length of the longest episode ranged from 160 to 250 ms (mean = 196 ms). The type of induced ventricular arrhythmia in relation to the indication for study is shown in Table 10.2.

In all patients, the type of induced arrhythmia during procainamide administration was the same as that induced during the baseline study. The mean serum procainamide level at the time of study was 12.1 $\pm$ 4.4 ug./ml. for the total group and was not statistically different within each subgroup: 12.1 $\pm$ 4.1 ug./ml. for patients with sustained ventricular tachycardia, 12.0 $\pm$ 6.2 ug./ml. for patients with ventricular fibrillation, and 12.2 $\pm$ 5.9 ug./ml. for patients with nonsustained ventricular tachycardia.

Overall Results of Subsequent Drug Therapy

The total group of 81 patients underwent 216 additional drug studies, ranging from 1 to 5 studies per patients (mean 2.6 $\pm$ 1.2). Twenty six (12%) of these studies were successful which represents the identification of at least one effective drug regimen in 22 (27%) of the 81 patients.

There was no significant difference in the drug success rate in relation to indication for study among patients with cardiac arrest (9 of 20 studies), syncope (6 of 21 studies) and nonsustained ventricular tachycardia (2 of 7

studies). The drug success rate however for patients with sustained ventricular tachycardia (5 of 33 studies) was significantly lower than for patients with cardiac arrest ($p<0.05$).

Results of Drug Therapy in Relation to Induced Arrhythmia Type

The subsequent success of drug therapy was related to the type of arrhythmia induced in the baseline study (Table 10.3).

Twelve (7%) of 163 drug studies were successful in patients with sustained ventricular tachycardia, 6 (24%) of 25 studies in patients with ventricular fibrillation, and 8 (29%) of studies in patients with nonsustained ventricular tachycardia. The number of drug trials which suppressed sustained ventricular tachycardia was significantly less than that which suppressed either ventricular fibrillation or nonsustained ventricular tachycardia ($p<0.01$) and ($p<0.005$), respectively. There was no statistical difference between the number of drug trials which suppressed ventricular fibrillation and nonsustained ventricular tachycardia.

For individual patients a subsequent effective drug regimen was found in 11 (19%) of 59 patients with sustained ventricular tachycardia, 4 (50%) of 8 patients with ventricular fibrillation and 7 (50%) of 14 patients with

	SUSTAINED VT	VFIB	NONSUSTAINED VT
NO. OF PATIENTS	59	8	14
NO. OF STUDIES	163	25	28
MEAN NO. OF STUDIES PER PATIENT	2.8±1.3	3.1±1.2	2.0±1.1
NO. OF DRUG SUCCESS	12 (7%)	6 (24%)	8 (29%)
NO. OF PATIENTS WITH AT LEAST ONE DRUG SUCCESS	11 (19%)	4 (50%)	7 (50%)

	DRUG SUCCESS	PATIENT SUCCESS
Sustained VT vs VFIB	$p<0.01$	$p<0.05$
Sustained VT vs Nonsustained VT	$p<0.005$	$p<0.025$
VFIB vs Nonsustained VT	N.S.	N.S.

TABLE 10.3 Relationship of induced ventricular tachyarrhythmia to subsequent drug response

Abbreviations as in TABLE 10.1

nonsustained ventricular tachycardia. As with drug success, a statistical difference was apparent in the identification of at least one effective drug regimen between patients with either ventricular fibrillation or nonsustained ventricular tachycardia and patients with sustained ventricular tachycardia ($p<0.05$) and ($p<0.025$), respectively (Figs. 10.1 and 10.2).

There was no significant difference between the mean serum procainamide level in patients responding to another drug regimen compared with those who responded to no other regimen (11.9 ± 4.0 versus 12.0 ± 4.9 ug./ml.).

Overall Success of Individual Drug Regimens

In the total study group, drug success was obtained using quinidine, mexiletine and amiodarone, both individually and in combination. In addition, flecainide was effective in one patient with sustained ventricular tachycardia. Because of the small number of trials involving certain regimens, only those employed in 15 or more studies were analysed separately.

Quinidine was successful in a total of 4 (9%) of 47 studies, mexiletine in 2 (6%) of 33 studies, amiodarone in 9 (17%) of 54 studies, the combination of quinidine plus mexiletine in 6 (19%) of 32 studies, the combination of procainamide plus mexiletine in 3 (20%) of 15 studies and the combination of amiodarone plus procainamide in 1 (6%)

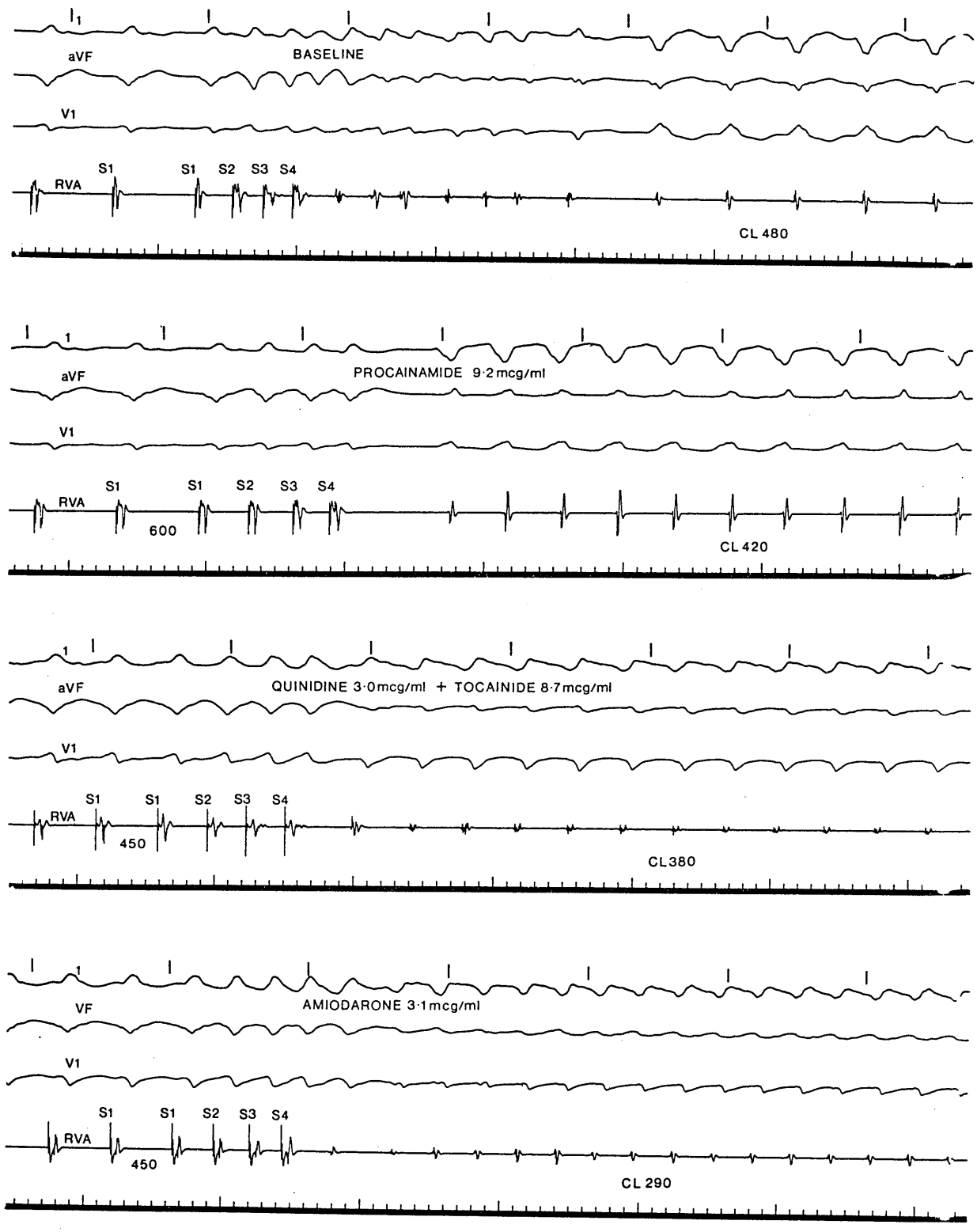

Fig. 10.1 Failure of procainamide in a patient with inducible sustained ventricular tachycardia. Continuing inducibility on other antiarrhythmic therapy.

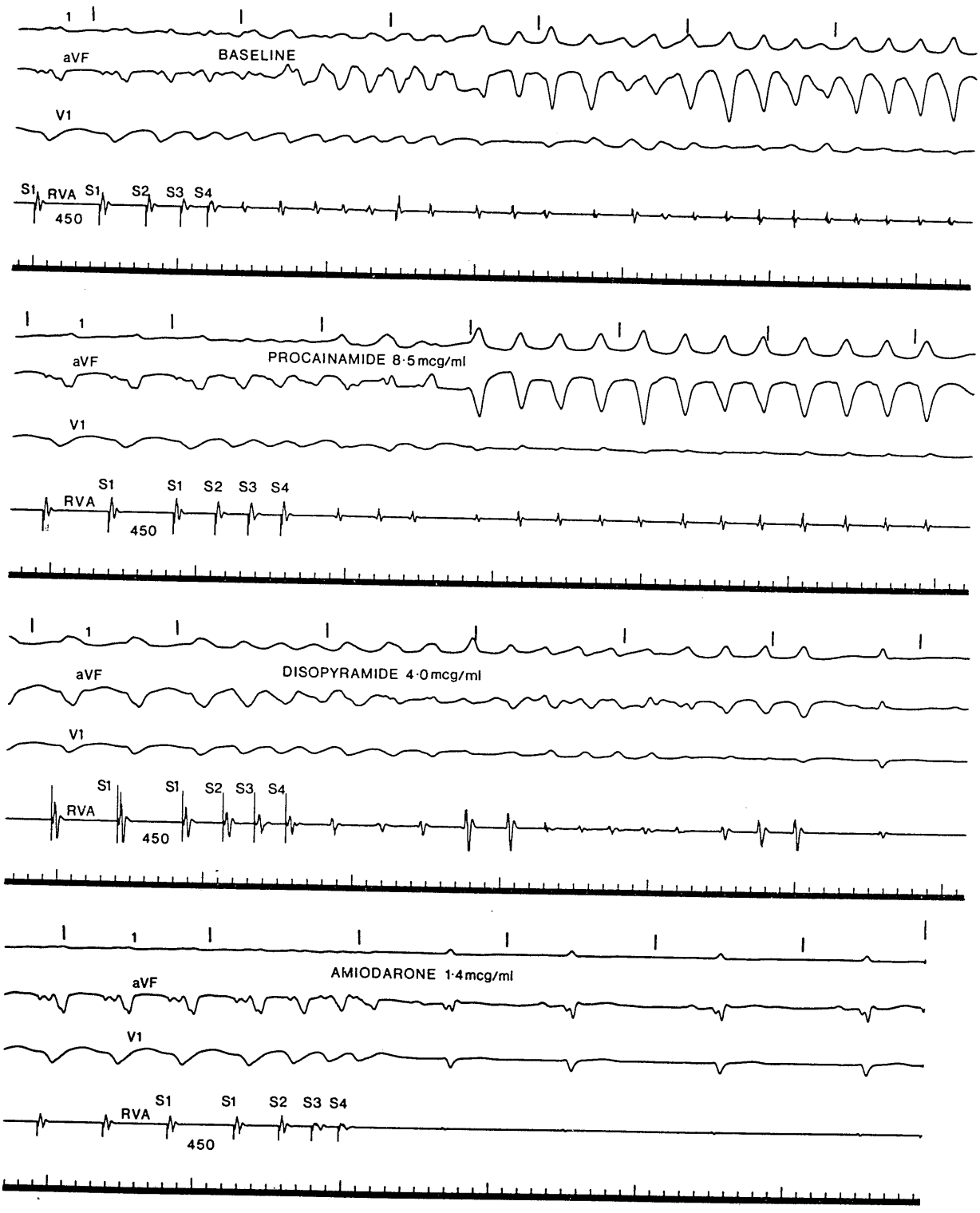

Fig. 10.2 Failure of procainamide in a patient with induced nonsustained ventricular tachycardia. Subsequent suppression of inducibility by amiodarone.

of 17 studies.

Success of Individual Drug Regimens in Relation to Induced Arrhythmia Type

Certain trends were apparent in relation to the effectiveness of a particular drug regimen and the type of induced arrhythmia (Table 10.4).

In sustained ventricular tachycardia, quinidine was ineffective in all 34 subsequent trials and effective in only 1 of 7 trials in ventricular fibrillation. In contrast, in nonsustained ventricular tachycardia, quinidine effectively suppressed the arrhythmia in 3 (50%) of 6 trials ($p<0.025$). A similar differential pattern was observed with mexiletine which was ineffective in suppressing sustained ventricular tachycardia in all 19 trials and ventricular fibrillation in all 4 trials but was successful in 2 (20%) of 10 studies in nonsustained ventricular tachycardia ($p<0.005$).

Amiodarone was evaluated in 44 patients with sustained ventricular tachycardia, 5 patients with ventricular fibrillation and 5 patients with nonsustained ventricular tachycardia and effectiveness was obtained in 7 (16%), 0 (0%) and 12 (40%) studies respectively.

Despite the infrequent success of quinidine and mexiletine individually in suppressing sustained arrhythmias, the combination of quinidine plus mexiletine was successful in 4 (17%) of 24 trials in patients with

	INDUCED VENTRICULAR TACHYARRHYTHMIA		
	SUSTAINED VT	VFIB	NONSUSTAINED V
QUINIDINE	0/34 (0%)	1/7 (14%)	3/6 (50%)
MEXILETINE	0/19 (0%)	0/4 (0%)	2/10 (20%)
AMIODARONE	7/44 (16%)	0/5 (0%)	2/5 (40%)
QUINIDINE+MEXILETINE	4/24 (17%)	2/5 (40%)	0/3 (0%)
PROCAINAMIDE+MEXILETINE	0/11 (0%)	2/2 (100%)	1/2 (50%)
AMIODARONE+PROCAINAMIDE	1/14 (7%)	0/2 (0%)	0/1 (0%)

TABLE 10.4 Subsequent drug regimen response
Abbreviations as in TABLE 10.1

DRUG	RESPONDERS	NONRESPONDERS
QUINIDINE	2.4±0.8	3.1±1.3 (NS)
MEXILETINE	1.6±0.6	1.1±0.6 (NS)
AMIODARONE	1.6±0.6	1.6±0.7 (NS)

TABLE 10.5 Serum drug levels (ug/ml) during subsequent drug trials

(NS=not significantly different compared with responders)

sustained ventricular tachycardia and in 2 (40%) of 5 trials in patients with ventricular fibrillation. The combination was used in only 3 studies in patients with nonsustained ventricular tachycardia and proved unsuccessful in all 3 cases.

The combination of procainamide plus mexiletine was unsuccessful in the 11 studies in patients with sustained ventricular tachycardia but was effective in 2 of 2 studies in patients with ventricular fibrillation and in 1 of 2 studies in patients with nonsustained ventricular tachycardia.

The combination of amiodarone plus procainamide had a low success rate in suppressing sustained ventricular tachycardia, being effective in only 1 (7%) of 14 trials. Similarly, it was ineffective in 2 trials in patients with ventricular fibrillation and a single trial in a patient with nonsustained ventricular tachycardia.

There were no significant differences in the mean serum level of quinidine, mexiletine and amiodarone between patients who did and who did not respond to these regiments (Table 10.5).

10.3 DISCUSSION

Despite the advantages of using electrophysiological testing to define a successful antiarrhythmic therapy for

patients with ventricular tachyarrhythmia, a major limitation of this approach is the requirement for patients to undergo repeated invasive investigation.

One potential strategy to reduce the exposure of patients to an empirically selected battery of antiarrhythmic drugs is to determine the predictive value of the response to one drug for the selection of subsequent regimens. Swiryn et al.[268], in patients with sustained ventricular tachycardia, identified a concordant response between procainamide and quinidine in 83% of patients ($p<0.025$); in contrast, only 71% responded to disopyramide a correlation which was not statistically significant. These results suggested that for the class IA agents, procainamide and quinidine, the response to one agent could be used to predict the effect of the other although this did not apply to disopyramide which also possesses class IA activity. Similar results have been reported by Wyse et al.[275] although in the study from Oseran et al.[276] no significant predictive value for procainamide and quinidine was observed.

The use of procainamide to predict response to other drugs was analysed further by Waxman et al.[226]. This study demonstrated that in patients with sustained arrhythmias which remained inducible on procainamide, only 10 (7%) of 145 additional drug regimens were successful. This group suggested that, on the basis of these results, patients should be considered early for alternative

therapeutic modalities. In a much smaller study of 34 patients, however, 9 patients (30%) who had failed procainamide subsequently had an effective regimen identified[277]. These studies however did not evaluate the newer antiarrhythmic agents including amiodarone, flecainide and mexiletine.

In contrast Wynn et al.[278], using investigational agents, observed that if procainamide did not prevent induction of ventricular tachycardia, this was a poor predictor of the effectiveness of other standard and investigational antiarrhythmic drugs. Furthermore, this poor correlation also applied to flecainide when this agent was examined for its predictive value. Comparison of this latter study with other studies including the present study is difficult however because of the methodology employed. This group used only one drive train (500 msec.) and the end-point for the stimulation protocol was tachycardia of more than 10 beats. In addition, all the agents tested were administered intravenously. These differences are manifested by the high success rate obtained for procainamide at 52%.

The results from the present study, for patients with sustained ventricular tachycardia, is similar to those reported by Waxman et al.[225].

Influence of Arrhythmia Type on Drug Response

None of the studies have addressed the relation between

concordance of drug response and the type of arrhythmia. In the study by Swiryn et al.[268], all patients had inducible sustained ventricular tachycardia and in the study by Waxman et al.[225], although 10 of the 126 patients had ventricular fibrillation, these patients were not analysed separately. The impact of the induced arrhythmia type on response to drug therapy has been discussed in Chapter 9. Irrespective of whether variation in response is an expression of differing electrophysiological mechanisms or reflects the clinical and demographic profile of the groups with these arrhythmias, definition of arrhythmia type may have an important bearing on evaluation of predictability of drug response.

Despite failure of procainamide therapy, successful arrhythmia suppression was obtained in 24% of drug trials in patients with ventricular fibrillation and in 29% of drug trials in patients with nonsustained ventricular tachycardia. In contrast, in patients with sustained ventricular tachycardia, only 7% of subsequent drug studies were effective. This response is identical to that reported by Waxman et al.[225] despite the use of the newer antiarrhythmic agents in this present study.

With respect to patient management, however, it is more important to determine the predictive value for identification of a successful drug regimen for each individual patient. In the groups with ventricular fibrillation and nonsustained ventricular tachycardia an

effective therapy was obtained for 50% of the patients. Although the drug success rate was low in sustained ventricular tachycardia, at least one successful regimen was still identified in 19% of these patients, which suggests that failure of procainamide should not preclude evaluation of further medical therapy.

Concordance of Drug Responses

The concordant relationship between failure of procainamide and subsequent failure of quinidine reported in other studies of sustained ventricular tachyarrhythmias is fully supported by the results from this study but importantly this does not hold true for nonsustained ventricular tachycardia. The same pattern of dependence on arrhythmia type was also observed with mexiletine which has a different Class I cellular electrophysiological action than quinidine[279].

In contrast to single agents, certain drug combinations were successful in suppressing sustained arrhythmias. Although Ross et al.[255] demonstrated that inefficacy of several class I agents individually, predicted their inefficacy in combination, DiMarco et al.[280] found that the combination of quinidine plus mexiletine was effective in 7 of 35 patients who did not respond to quinidine alone. Although the numbers are relatively small both in DiMarco's study and in the present study, failure of one component of the combination of quinidine plus mexiletine does not

appear to predict the failure of the combination.

If, as suggested, drug concordance depends, at least in part, on similarities in the mechanism of drug action, the inability to predict the response to amiodarone is not surprising. Amiodarone possessed Class III activity (275) with prolongation of the action potential. In the present study, the success rate of amiodarone for complete suppression of sustained arrhythmias was 16% which is similar to that reported in previous studies[281,282].

Choice of Procainamide

In the reported studies, procainamide has been the agent against which other agents have been evaluated. Procainamide is a standard Class IA agent with the benefits over quinidine that intravenous administration is more predictable and it tends to have less myocardial depressant effect than disopyramide. The importance of dosage of procainamide for arrhythmia has been reported by Greenspan et al[224]. In this study it was demonstrated that high doses were required before inefficacy of procainamide could be assumed. This aspect was further emphasised by Waxman et al.[225]. In this present study, the mean drug levels of 12 ug./ml. obtained suggest that adequate dosages were administered.

In patients with sustained ventricular tachycardia, the low subsequent drug success rate was only 7% despite the use of new agents. To evaluate whether this was specific

for failure of procainamide or whether failure of any drug substratified those patients who were unlikely to respond to any therapy, a separate analysis was performed on 41 patients with inducible sustained ventricular tachycardia which remained inducible on the first therapy (not procainamide) which was administered. In 70 subsequent trials of therapy only 4 (6%) of the trials were successful. This observation suggests that the poor response to subsequent medical therapy is not unique to procainamide. This is an extremely important finding since it has implications with respect to the evaluation of antiarrhythmic therapy using electrophysiological testing. Unless therapy is evaluated in a randomised order comparison of efficacy may be compromised.

CONCLUSIONS

This study has demonstrated that in patients with ventricular arrhythmias in whom the arrhythmia remains inducible on procainamide therapy, the response to subsequent medical therapy is influenced by the type of arrhythmia. With sustained arrhythmias, failure of procainamide suggests that success with either quinidine or mexiletine alone is unlikely although the combination of these agents may be effective. In patients with nonsustained ventricular tachycardia, all individual agents should be evaluated because of the high likelihood of response.

CHAPTER 11

DRUG-RELATED WORSENING OF ARRHYTHMIAS DURING ELECTROPHYSIOLOGICAL TESTING

For many years, isolated reports have attested to the potential of antiarrhythmic agents to worsen existing or produce new, more malignant arrhythmias. This adverse feature has been variously termed aggravation or provocation of arrhythmias or proarrhythmia. Only recently, with improvements in methods for detection and quantification of arrhythmias and the widespread application of such techniques, has the extent of this facet of drug action become apparent. The utility of serial electrophysiological drug testing to identify long-term effective antiarrhythmic therapy has been discussed previously. It has been suggested that this approach may also provide a means of determining the proarrhythmic potential of such therapy and thus prevent the needless exposure of patients to possible sudden death due directly to the treatment prescribed to prevent it.

The aims of this study were to determine the incidence of drug-related worsening of arrhythmias (proarrhythmia) during electrophsyiological testing and its relation to the individual antiarrhythmic drug regimens employed.

11.1 PATIENTS AND METHODS

The patient population consisted of 314 consecutive patients referred for electrophysiological study in whom a ventricular tachyarrhythmia was induced in the baseline study.

There were 270 men and 44 women, with ages ranging from 15 to 84 years (mean = 60 years). Underlying heart disease included 245 patients with coronary artery disease, of whom 229 had sustained a previous myocardial infarction, 37 patients with cardiomyopathy and 7 patients with valvular heart disease. In 25 patients, no structural heart disease was identified and these patients were considered to have primary electrical disease.

The indications for electrophysiological study included sustained ventricular tachycardia in 142 patients, out-of-hospital cardiac arrest in 44 patients, syncope in 58 patients, symptomatic nonsustained ventricular tachycardia in 62 patients and palpitation in 8 patients.

The standard stimulation protocol as previously detailed was applied in both the baseline study and subsequent drug studies.

The standard definitions for sustained ventricular tachycardia, ventricular fibrillation and nonsustained ventricular tachycardia were employed.

There is no standardised definition for drug-related

worsening of arrhythmias during electrophysiological testing although several criteria have been suggested. In this study it was defined in four ways: 1) initiation of a sustained tachyarrhythmia in a patient in whom only nonsustained tachycardia was induced in the baseline state; 2) conversion on drug therapy, of sustained ventricular tachycardia which was terminated by extrastimulation or burst pacing during the baseline study, to a sustained ventricular tachyarrhythmia requiring cardioversion; 3) induction of sustained ventricular tachycardia or ventricular fibrillation by an induction mode during drug study that was deemed less aggressive than that required for induction of the sustained arrhythmia in the baseline study; (For the purposes of this study, the aggressiveness of mode of induction was considered to be: single extrastimuli < double extrastimuli < triple extrastimuli) 4) development of spontaneous sustained ventricular tachycardia on drug therapy, which required programmed stimulation for initiation in the baseline study, and whose time course was consistent with exposure to the therapy.

The antiarrhythmic drug regimens employed, included 15 single agents and 8 combinations (Table 11.1). The dosages of these regimens are tabulated in Table 2.2.

Standard statistical analyses were performed. For discrete variables, contingency tables were constructed

SINGLE AGENTS

REGIMEN	NO. OF STUDIES	REGIMEN	NO. OF STUDIES
Procainamide	208	Flecainide	27
Quinidine	100	Indecainide	16
Disopyramide	9	Bepridil	4
Mexiletine	74	Pirmenol	5
Amiodarone	159	Phenytoin	2
Bethanidine	3	Lignocaine	8
Tocainide	2	Sotalol	3
B-adrenoceptor blockers	4		

COMBINATIONS

REGIMEN	NO. OF STUDIES
Quinidine + Mexiletine	63
Procainamide + Mexiletine	27
Amiodarone + Procainamide	47
Quinidine + Tocainide	11
Quinidine + Phenytoin	4
Quinidine + Lignocaine	2
Quinidine + Atenolol	1
Procainamide + Phenytoin	4
Procainamide + Tocainide	3
Disopyramide + Mexiletine	1
Mexiletine + Propranolol	1
Phenytoin + Propranolol	1
Amiodarone + Lignocaine	1
Amiodarone + Quinidine	2
Amiodarone + Tocainide	2
Amiodarone + Mexiletine	7

TABLE 11.1 Drug regimens employed

using chi square or Fisher's exact test and for continuous variables the unpaired t test and analysis of variance were employed. A p value of <0.05 was considered significant.

11.2 RESULTS

Results of Baseline Study

In the baseline study, programmed ventricular stimulation induced sustained ventricular tachycardia in 220 patients, ventricular fibrillation in 40 patients and nonsustained ventricular tachycardia in 54 patients.

Overall Incidence of Proarrhythmic Responses

The study population of 314 patients underwent a total of 801 separate drug studies. Overall a proarrhythmic response was observed in 189 (24%) of these studies. At least one event occurred in 123 (39%) of the patients (Table 11.2) (Fig. 11.1).

The different forms of proarrhythmic responses will be considered individually.

11.3 Conversion of Nonsustained Ventricular Tachycardia to a Sustained Tachyarrhythmia (Fig. 11.2)

The 54 patients with inducible nonsustained ventricular tachycardia underwent 114 separate trials of therapy. Conversion to a sustained arrhythmia on drug therapy

	TYPES OF PROARRHYTHMIC RESPONSE				
	1	2	3	4	ALL
NO. OF STUDIES	114	578	687	801	801
NO. WITH PROARRHYTHMIA	20(18%)	39(7%)	135(20%)	4(0.5%)	189(24%)
NO. OF PATIENTS	54	220	260	314	314
NO. WITH PROARRHYTHMIA	15(28%)	29(13%)	84(34%)	4(1.3%)	122(39%)

TABLE 11.2 Incidence of proarrhythmic responses

1 = Conversion of nonsustained tachycardia to a sustained arrhythmia.
2 = Conversion of stable sustained tachycardia to a sustained arrhythmia requiring cardioversion.
3 = Reduction in aggressiveness of induction mode.
4 = Spontaneous development of sustained tachycardia.

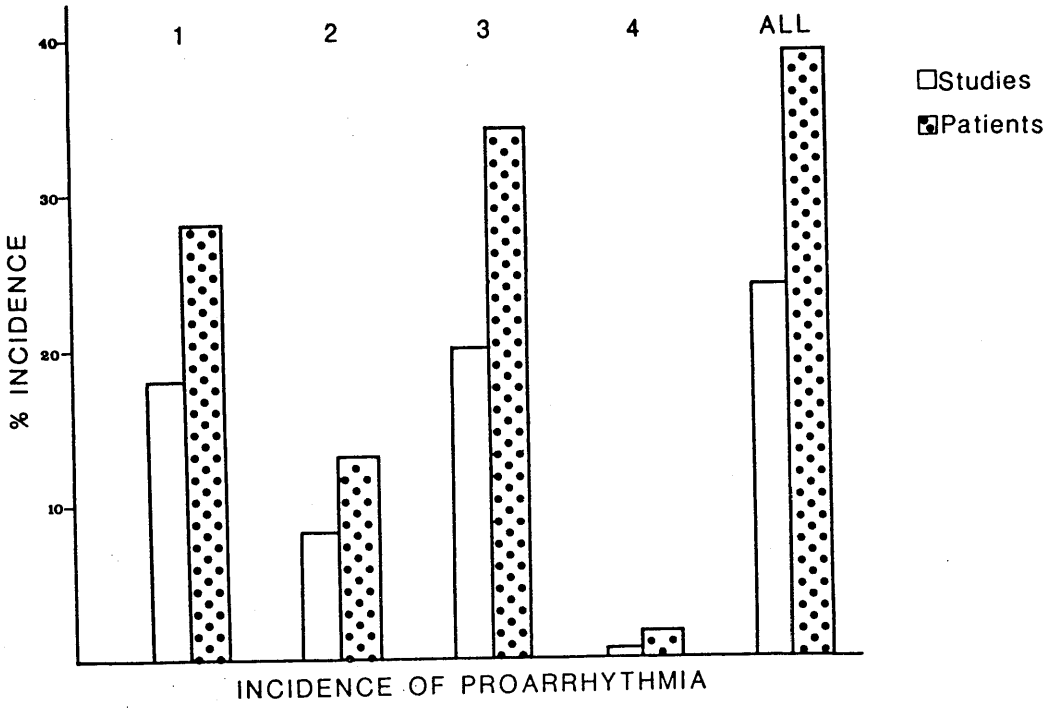

Fig. 11.1 Incidence of types of proarrhythmic responses observed during electrophysiological testing.

Abbreviations as in Table 11.2

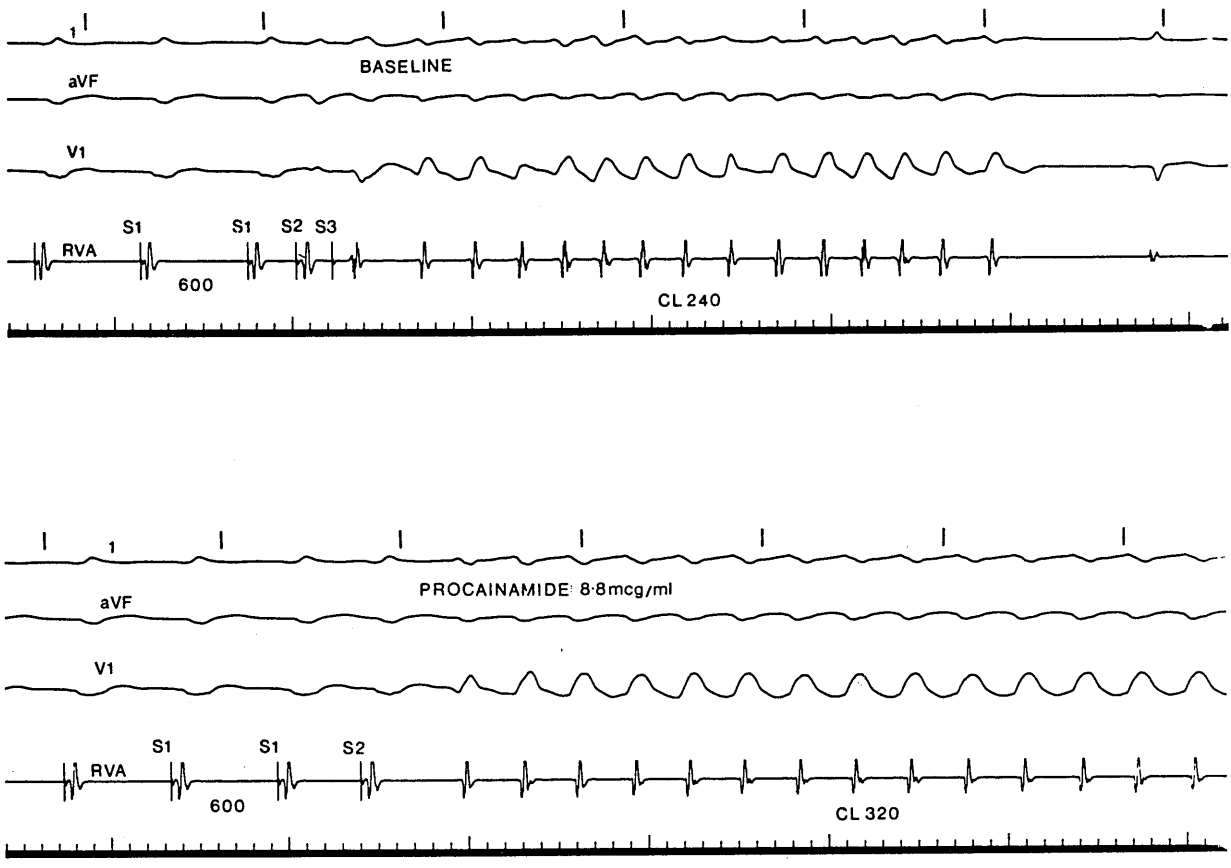

Fig. 11.2 Conversion of a nonsustained tachycardia in the baseline study to a sustained tachycardia on procainamide.

occurred in 20 (18%) of these trials. The arrhythmia was sustained ventricular tachycardia in 18 studies and ventricular fibrillation in 2 studies. Of the 18 episodes of sustained ventricular tachycardia, the cycle length of the tachycardia was increased in 12 episodes relative to the longest cycle length of the baseline nonsustained tachycardia (mean change in cycle length = 65 msec.) and decreased in 6 episodes (mean change in cycle length = 95 msec.). The number of extrastimuli required to induce the sustained arrhythmia was unchanged in 11 trials and induction required fewer extrastimuli in 9 trials.

This form of drug-related worsening of arrhythmia occurred at least once in 15 (28%) of 54 patients (Table 11.2).

11.4 Conversion of Haemodynamically Stable Ventricular Tachycardia to a Sustained Arrhythmia Requiring Cardioversion (Fig. 11.3)

Sustained ventricular tachycardia was induced in the baseline study in 220 patients who subsequently underwent a total of 578 individual drug studies. A proarrhyhmic response of this type was observed in 39 (7%) of these studies, with 29 (13%) of the patients experiencing at least one event (Table 11.2).

Sustained ventricular tachycardia was induced in 37 studies and ventricular fibrillation in 2 studies. On drug therapy, the cycle length of the tachycardia was

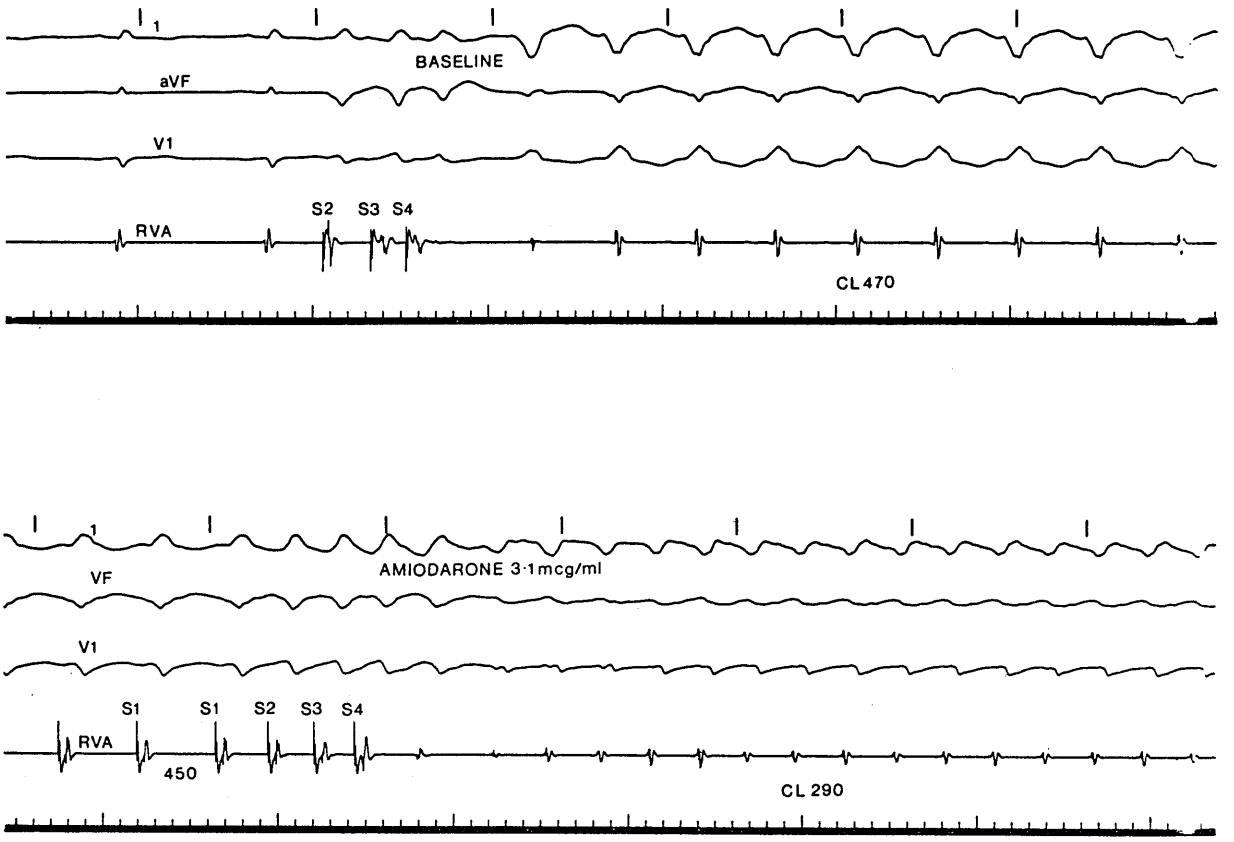

Fig. 11.3 Conversion of a slow stable tachycardia in the baseline study to a faster tachycardia which required cardioversion for termination.

shorter in 7 studies (mean change in cycle length = 78 msec.), unchanged in 3 studies, and longer in 27 studies (mean change in cycle length = 61 msec.). Cardioversion was required in these latter 30 studies despite the same or slower rate because of increased refractoriness to pacing termination with subsequent acceleration of the tachycardia in 13 studies and more profound symptomatic deterioration associated with the tachycardia in 17 studies.

11.5 Induction of a Sustained Arrhythmia by a Less Aggressive Stimulation Mode (Fig. 11.4)

Since the end-point for the stimulation protocol is the reproducible initiation of a sustained arrhythmia, this form of proarrhythmia was analysed only in patients with inducible sustained ventricular tachycardia or ventricular fibrillation.

The 260 patients with a sustained arrhythmia underwent 687 drug studies of which 135 (20%) manifested a proarrhythmic response. The incidence for sustained ventricular tachycardia was 23% (131 of 578 studies) and for ventricular fibrillation was 5% (5 of 109 studies).

Change in stimulation mode of one less extrastimulus occurred in 118 (17%) studies and two extrastimuli in 17 (3%) studies.

Of the 260 patients, reduction in aggressiveness of induction mode was observed at least once in 84 (34%) of the patients. In patients with sustained ventricular

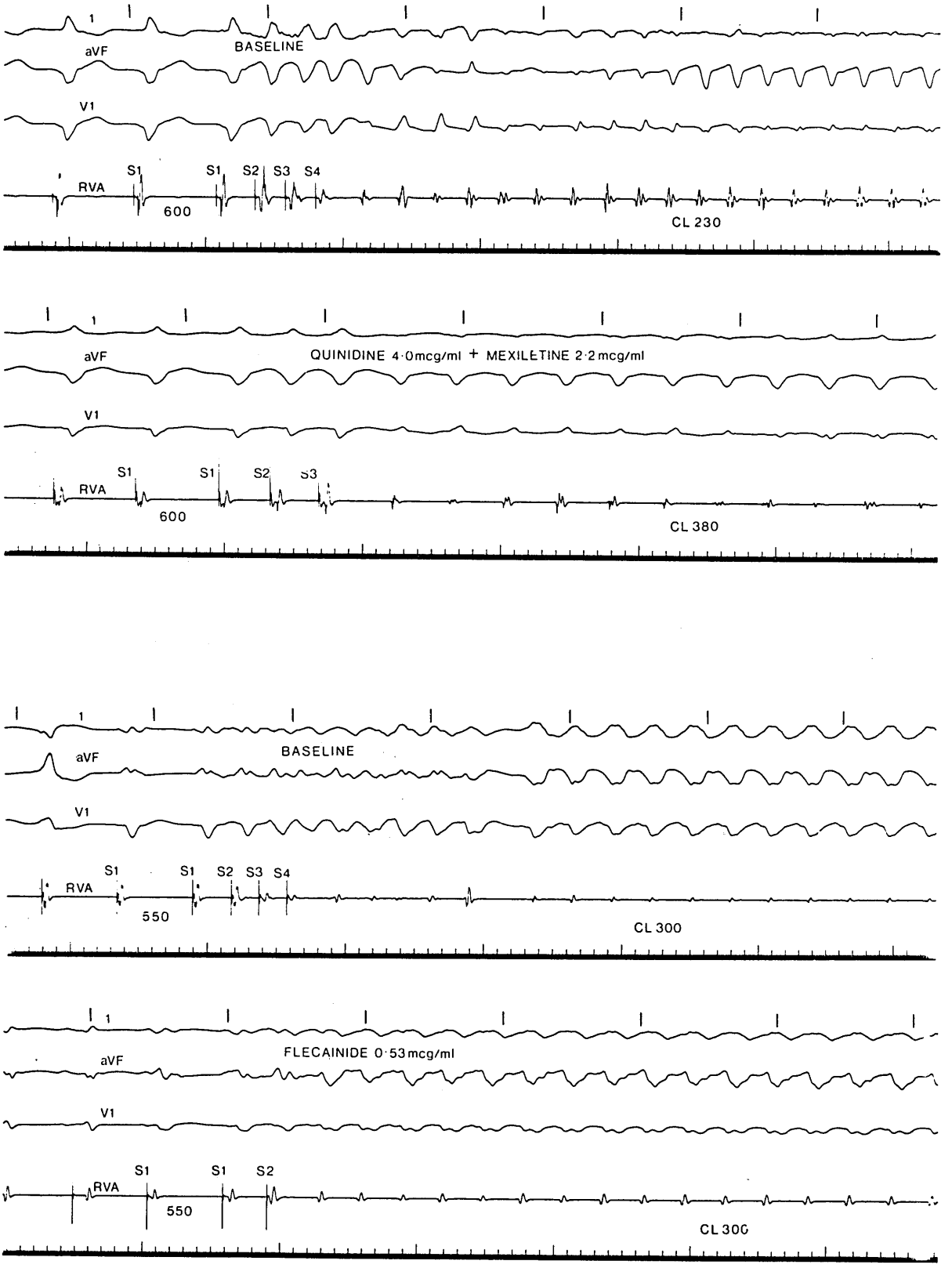

Fig. 11.4 Reduction in aggressiveness of mode of induction by one extrastimulus in upper illustration and by two extrastimuli in lower illustration.

tachycardia the incidence was 36% (80 of 220 patients) and in patients with ventricular fibrillation it was 10% (4 of 40 patients).

11.6 Spontaneous Development of Sustained Tachycardia

The spontaneous development of sustained ventricular tachycardia during the administration of antiarrhythmic therapy occurred in 4 (0.5%) of the 801 studies (Table 11.2). The temporal relationship between onset of the tachycardia and administration of the drug was such that it was considered that the development could be directly attributed to the agent. In addition, in two of these studies, the tachycardia initiated was incessant and refractory to termination (Fig. 11.5).

11.7 Multiple Proarrhythmic Responses

In patients who underwent two or more drug studies, 48 (21%) experienced a proarrhythmic response in more than one study.

The combination of conversion of a haemodynamically stable sustained tachycardia to a sustained arrhythmia requiring cardioversion and reduction in the aggressiveness of the induction mode occurred in the same drug study in 10 (2%) of 578 studies with 9 (4%) of the 220 patients experiencing at least one study with this combination of proarrhythmic responses.

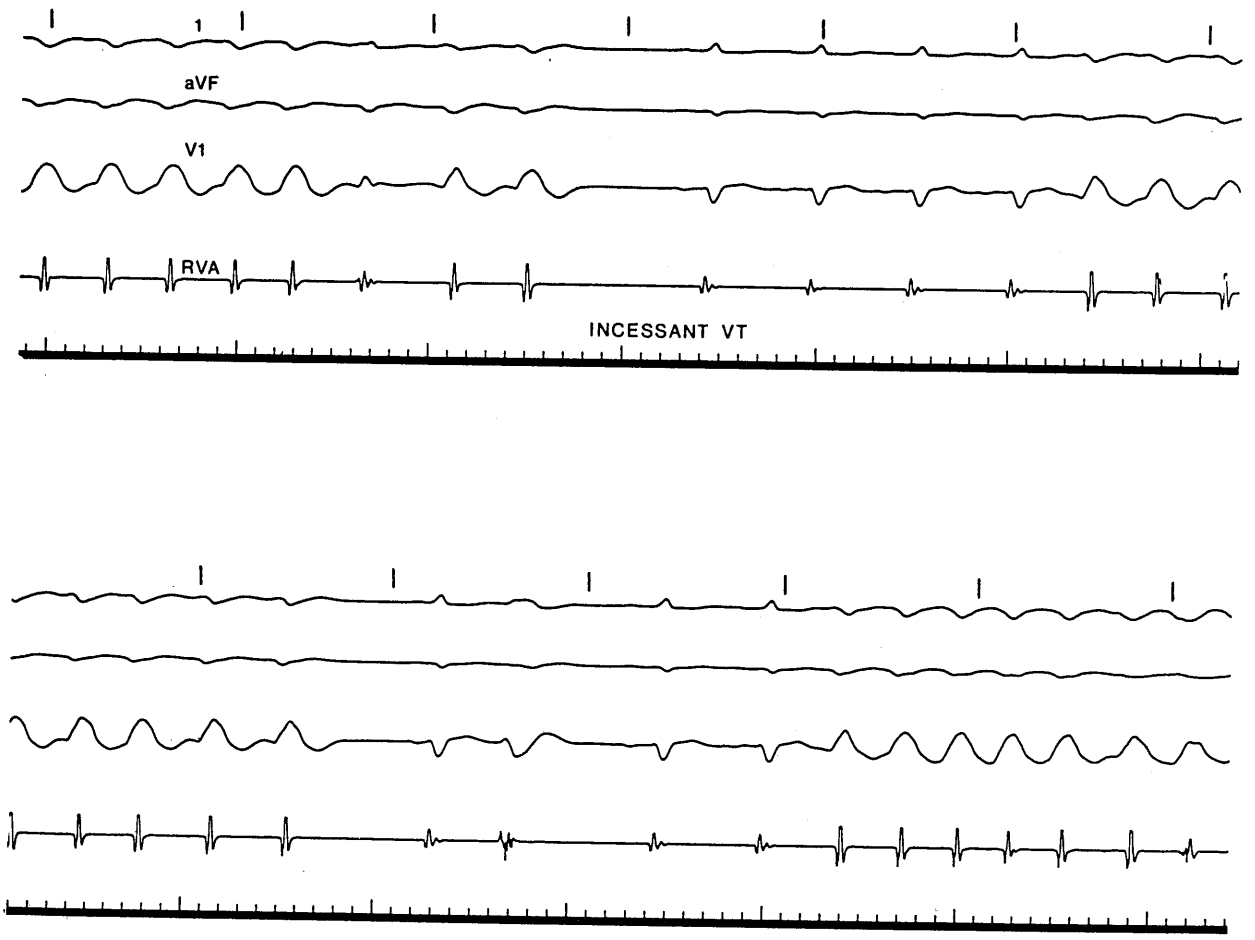

Fig. 11.5 Spontaneous development of an incessant ventricular tachycardia by flecainide.

11.8 Incidence of Proarrhythmic Responses in Relation to Individual Drug Regimens

For individual drug regimens, only those employed in more than 15 studies have been analysed separately (Table 11.3) (Fig. 11.6).

For single agents, the overall incidence was 23% ranging from 15 to 37% and for combination regimens, the incidence was 29%, ranging from 22 to 30%. There was no significant difference in the incidence of worsening of arrhythmias, between single and combination regimens.

Quinidine had the lowest incidence of proarrhythmia at 15% which was significantly lower than amiodarone ($p<0.01$), flecainide ($p<0.05$), indecainide ($p<0.05$), the combination of quinidine plus mexiletine ($p<0.05$) and the combination of amiodarone plus procainamide ($p<0.05$). Procainamide also produced significantly fewer proarrhythmic responses than amiodarone ($p<0.01$).

The highest incidence of proarrhythmic response was observed with the Class IC agents, flecainide and indecainide, at 33 and 37% respectively, although this was not statistically significant in respect of other single regimens except quinidine.

With combination regimens, there was no regimen which manifested significantly more proarrhythmia than other combination regimens.

In 40 patients, a proarrhythmic event was observed in a single drug regimen which was subsequently employed in a

REGIMEN	NO. OF STUDIES	NO. WITH PROARRHYTHMIA
SINGLE AGENTS		
PROCAINAMIDE	208	39 (19%)
QUINIDINE	100	15 (15%)
MEXILETINE	74	14 (19%)
AMIODARONE	159	48 (30%)
FLECAINIDE	27	9 (33%)
INDECAINIDE	16	6 (37%)
OTHERS	40	10 (25%)
COMBINATION		
QUINIDINE + MEXILETINE	63	19 (30%)
PROCAINAMIDE + MEXILETINE	27	6 (22%)
AMIODARONE + PROCAINAMIDE	47	14 (30%)
OTHERS	40	13 (33%)

TABLE 11.3 Incidence of proarrhythmia for individual regimens

DRUG	STUDIES WITHOUT PROARRHYTHMIA	STUDIES WITH PROARRHYTHMIA	
PROCAINAMIDE	10.1±4.0	10.9±4.3	N.S.
QUINIDINE	2.9±1.0	3.8±1.4	P<0.01
MEXILETINE	1.2±0.5	1.3±0.9	N.S.
AMIODARONE	1.5±0.6	1.6±0.9	N.S.
FLECAINIDE	0.6±0.3	0.7±0.3	N.S.
INDECAINIDE	0.5±0.2	0.3±0.1	N.S.

TABLE 11.4 Drug levels (ug/ml) in studies with and without proarrhythmia

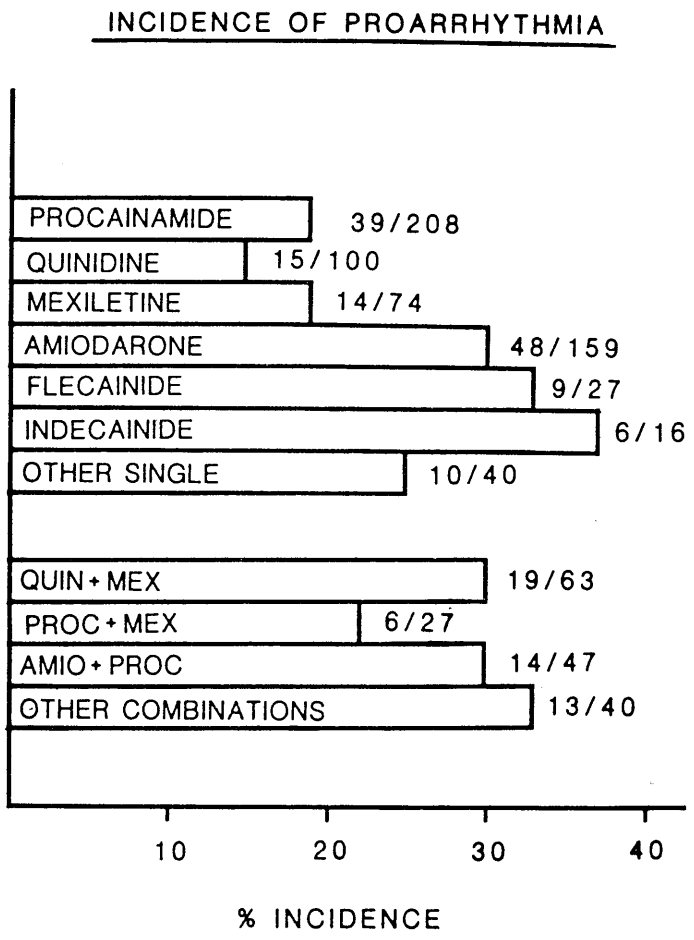

Fig. 11.6 Incidence of proarrhythmia in relation to individual regimens.

combination regimen. In 18 (45%) of patients a further proarrhythmic event occurred in the combination in contrast to 22 (55%) of patients in whom the combination did not manifest a proarrhythmic event. In this latter group, both individual components produced proarrhythmia in 3 patients.

For the single agents, serum drug levels were obtained (Table 11.4). There was no significant difference between the serum drug levels in studies with proarrhythmic responses and those without proarrhythmia except for quinidine where the level was significantly higher (3.8 $\pm$ 1.4 v 2.9 $\pm$ 1.1 ug/ml respectively $p<0.01$) although still within the therapeutic range of 2 - 5 ug/ml for the laboratory.

11.9 Incidence of the Types of Proarrhythmic Response in Relation to Individual Drug Regimens

The incidence of the different types of proarrhythmic responses in relation to individual drug regimens is tabulated in Table 11.5. Only those regimens employed in 15 or more studies were analysed separately.

For conversion of nonsustained ventricular tachycardia to a sustained arrhythmia there was no significant difference in the incidence for procainamide, quinidine or mexiletine. Interestingly, the highest incidence occurred with indecainide and flecainide although the number of trials was too small to reach statistical significance.

DRUG REGIMEN	TYPE OF PROARRHYTHMIC RESPONSE		
	1	2	3
Procainamide	8/46 (17%)*	4/130 (3%)++	30/162 (19%)
Quinidine	1/15 (7%)*	3/67 (4%)+	12/85 (14%)°
Mexiletine	3/20 (15%)*	2/44 (5%)	10/54 (19%)
Amiodarone	4/14 (29%)	11/132 (8%)	33/145 (23%)
Flecainide	2/3 (67%)	4/22 (18%)	4/24 (17%)
Indecainide	1/1 (100%)	2/15 (13%)	2/15 (13%)
Quinidine + Mexiletine	1/4 (25%)	4/50 (8%)	16/59 (27%)
Procainamide + Mexiletine	0/2 (0%)	2/18 (11%)	4/25 (16%)
Amiodarone + Procainamide	0/3 (0%)	1/38 (3%)++	13/44 (30%)
Others	0/6 (0%)	4/62 (6%)	17/74 (23%)

TABLE 11.5 Incidence of type of proarrhythmic response in relation to individual drug regimens

Abbreviations for type of proarrhythmic response same as in Table 11.2.

* Significantly different from Flecainide at $P<0.05$

++ Significantly different from Flecainide at $P<0.01$

\+ Significantly different from Flecainide at $P<0.05$

° Significantly different from Amiodarone + Procainamide at $P<0.05$

The incidence of drug conversion of a stable tachycardia to a tachycardia requiring cardioversion ranged from 3 to 18% with a statistically higher incidence for flecainide than for procainamide $p<0.01$, quinidine $p<0.05$ and the combination of amiodarone plus procainamide $p<0.01$.

Reduction in the aggressiveness of the mode of induction ranged from 13 to 30% with quinidine producing significantly fewer events than the combination of amiodarone plus procainamide $p<0.05$.

Development of spontaneous sustained ventricular tachycardia was observed in only 4 studies involving amiodarone, indecainide, pirmenol and the combination of disopyramide plus mexiletine. Incessant tachycardia was observed in the latter two studies.

For procainamide, quinidine, mexiletine and amiodarone, the incidence was significantly higher for the reduction in aggressiveness of the induction mode as compared to conversion of stable ventricular tachycardia to a sustained arrhythmia requiring cardioversion ($p<0.001$), ($p<0.05$), ($p<0.05$) and ($p<0.01$), respectively. In addition, a significant difference between the incidence for conversion of nonsustained tachycardia to a sustained arrhythmia and conversion of stable tachycardia to a sustained arrhythmia requiring cardioversion was observed for procainamide ($p<0.001$) and amiodarone ($p<0.05$).

11.10 Baseline Characteristics of Patients with Proarrhythmic Responses

The baseline characteristics of patients who did not experience a proarrhythmic event and those who did are shown in Table 11.6. There were no significant differences between these two groups in relation to age, sex or type of underlying heart disease. Patients who experienced a proarrhythmic event had a lower global ejection fraction ($p<0.05$) and a longer baseline QT interval ($p<0.05$) than patients who did not experience proarrhythmia although the latter was still within normal limits.

11.11 Electrocardiographic Intervals and Proarrhythmic Responses

For the 801 drug studies, the electrocardiographic intervals; QRS duration, QTc (QT interval corrected for heart rate) and JTc (JT interval corrected for heart rate) were analysed. There were no significant differences between these intervals or changes from baseline (expressed either as the absolute difference or percentage change) between drug studies without a proarrhythmic response and drug studies manifesting proarrhythmia (Table 11.7). When these values were analysed in relation to the type of proarrhythmic response, the only significant difference was in studies with conversion of nonsustained to sustained arrhythmia where the JTc was shorter in comparison to other

	PROARRHYTHMIA		
	ABSENT	PRESENT	
TOTAL NO.	192	122	
MALES	161	109	N.S.
FEMALES	31	13	
AGE	60±12	60±10	N.S.
HEART DISEASE			
CAD	141	104	N.S.
CARDIOMYOPATHY	28	9	N.S.
VALVULAR	4	3	N.S.
PRIMARY ELECTRICAL	19	6	N.S.
EJECTION FRACTION (%)	33±15	27±15	P<0.01
QT INTERVAL (msec.)	394±42	409±43	P<0.05
QRS DURATION (msec.)	117±18	117±37	N.S.
HV INTERVAL (msec.)	58±11	59±11	N.S.

TABLE 11.6 Clinical characteristics of patients who experienced a proarrhythmic event and those who did not.

PROARRHYTHMIC RESPONSE	ABSOLUTE CHANGE			PERCENT CHANGE		
	QRS(msec)	QTc(msec)	JTc(msec)	QRS	QTc	JTc
TYPE 1	16±21	28±52	-0.3±43*	15±18	6±12	0.7±12
TYPE 2	18±20	48±57	29±60	16±16	5±39	10±23
TYPE 3	15±22	47±84	31±54	13±18	10±22	10±20
ALL	16±24	47±53	28±55	13±18	11±13	9±20
NONE	14±20	45±59	28±54	12±17	10±30	11±26

TABLE 11.7 Electrocardiographic intervals and types of proarrhythmic response.

*P <0.001

Abbreviations for type of proarrhythmia response same as in Table 11.2

studies (Table 11.7).

11.12 Predictive Value of Reduction in Aggressiveness of Mode of Induction

To determine the predictive value of this type of proarrhythmia response, the results of long-term follow up of patients discharged on antiarrhythmic regimens on which a sustained arrhythmia remained inducible, were analysed. Arrhythmia recurrence in 73 patients discharged on a regimen which did not manifest proarrhythmia was compared to arrhythmia recurrence in 40 patients who were discharged on a regimen on which a sustained arrhythmia was induced by at least one less extrastimulus relative to the baseline study. Over a mean follow-up of 17 $\pm$ 14 months, there were 35 (48%) arrhythmia recurrences/sudden death in the former group compared to 22 (55%) arrhythmia recurrences/sudden death in the latter group. Life table analysis demonstrated that there was no significant difference between these two groups (P = 0.35) (Fig. 11.7). Interestingly, five patients were discharged on a regimen on which the mode of induction was reduced by 2 extrastimuli. Over the follow-up period 4 (80%) of these 5 patients experienced recurrence of arrhythmia.

11.13 DISCUSSION

Over the last 25 years there has been a considerable

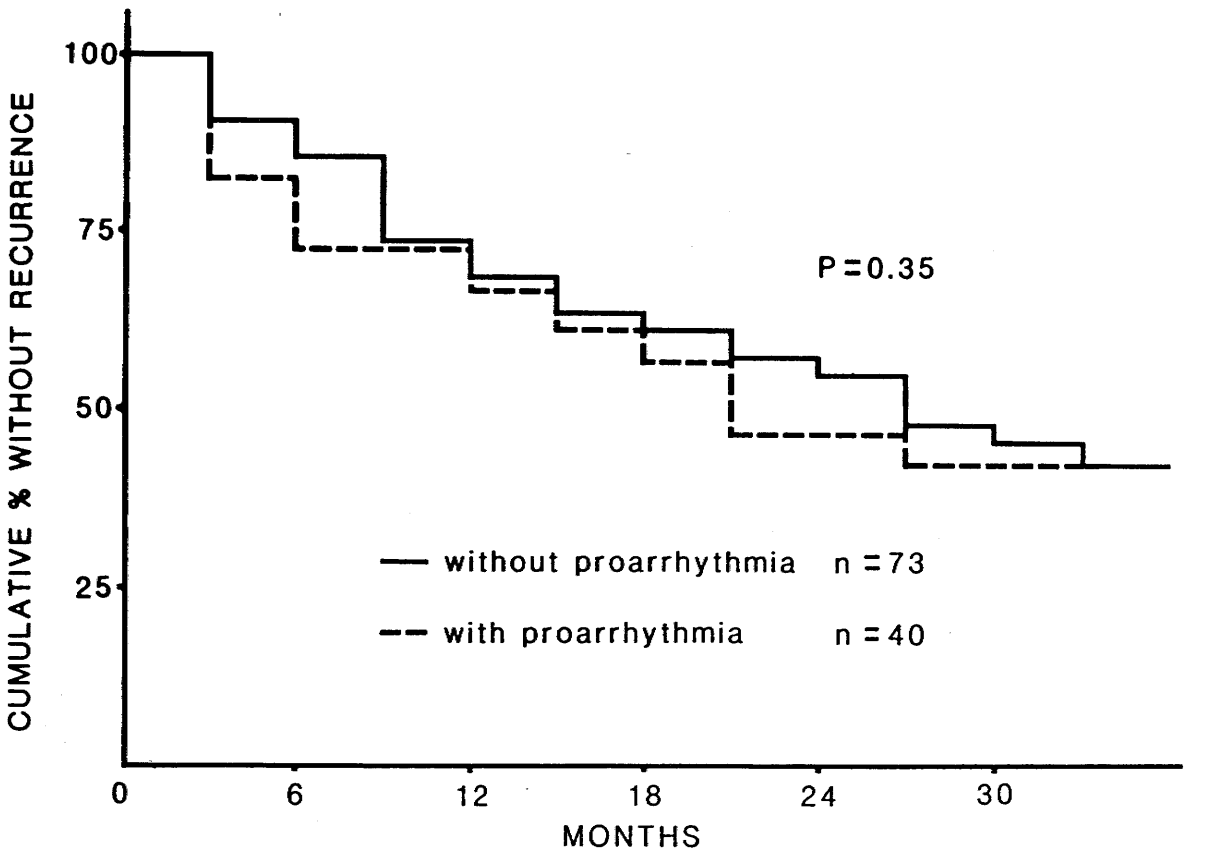

Fig. 11.7 Life-table analysis of patients discharged on regimens with proarrhythmia (reduction in mode of aggression of induction) and without proarrhythmia, showing no significant difference in arrhythmia-free interval.

increase in the prescription of antiarrhythmic therapy. This has been due to several factors including the availability of a wider range of agents, technical advances in the detection of arrhythmias and the recognition of the malignant potential of ventricular arrhythmias in relation to sudden death[29-35].

Although the concept of proarrhythmia as a component of the side-effect profile of antiarrhythmic drugs is not new, the extent and importance of this type of adverse reaction has not been recognised until recently[283,284].

In the early 1960s, Selzer and Wray demonstrated that syncope occurring in patients treated with quinidine for atrial fibrillation was due to the development of a rapid polymorphous ventricular tachycardia[285]. The tachycardia, torsade de pointes, was associated with QT prolongation and although frequently occurring in patients on concomitant digoxin therapy, was also observed in patients treated with quinidine alone[286]. In addition, despite the presence of hypokalaemia or toxic levels of the drug in many cases, this adverse feature could also occur unpredictably with no identifiable risk factor. Since that report, the association of QT interval prolongation and development of ventricular tachyarrhythmias has been reported with many antiarrhythmic agents, especially those belonging to Class I[287-293].

The development of such a characteristic type of new tachyarrhythmia, however, is relatively easy to identify.

Much more difficult to recognise is the drug-related worsening or aggravation of pre-existing arrhythmias. This proarrhythmic component requires the accurate documentation of the frequency of the arrhythmia prior to the initiation of therapy which poses practical difficulties because of the recognised spontaneous variability and unpredictability of arrhythmias [89,90]. Recently, Morganroth and Horowitz have proposed a classification for proarrhythmia to take into account the variability of ventricular ectopy[294].

The problem is further compounded by ethical considerations preventing re-challenge of the patient who has already experienced a potentially lethal adverse arrhythmic response to a certain agent in order to conclusively implicate the drug.

Mechanisms Underlying Proarrhythmia

Various mechanisms may be postulated in the development of proarrhythmia related to antiarrhythmic agents. These mechanisms may relate directly to the primary electrophysiological action of the agent or be a secondary response to other effects in the pharmacological profile.

The most common mechanism underlying chronic recurrent arrhythmias is reentry, and for the development and maintenance of such arrhythmias, a delicate interplay between conduction and refractoriness in the reentrant circuit is required. The same electrophysiological

effects of slowing of conduction and prolongation of refractoriness which can terminate an arrhythmia, may also provide sufficient perturbation of the circuit to initiate and/or sustain a tachycardia either in the same circuit or in a different, previously concealed circuit. Furthermore, in the presence of myocardial disease, with inhomogeneity in the electrophysiological properties of different regions, the effects of antiarrhythmic drugs may be quite variable with suppression and potentiation of different potential circuits.

In addition to these direct mechanisms, indirect or secondary effects on the autonomic nervous system, ventricular function or myocardial perfusion may promote electrical instability or changes in the electrophysiological milieu sufficient to favour arrhythmia development.

Determination of Drug-Related Proarrhythmia

The empirical prescription of antiarrhythmic therapy or a "wait and see" policy places the patient in a precarious position where not only the first manifestation of ineffectiveness of drug therapy may be sudden death, but also the first manifestation of drug-related worsening of arrhythmias[295,296]. Although a minority of proarrhythmic events are related to drug toxicity and/or prolongation of the QT interval on the surface electrocardiogram, these parameters have insufficient discriminatory power to

identify the majority of patients at risk.

Because of the lethal potential of this adverse feature, a directed approach to prospectively identify proarrhythmic responses has been suggested.

In patients with high levels of ambient ventricular ectopy, Holter monitoring techniques have been employed to evaluate antiarrhythmic therapy. The most comprehensive study using Holter monitoring to determine proarrhythmia has been reported by Velebit et al.[297] (recently updated by Podrid[298]). This group employs an aggressive combined Holter monitoring and exercise testing approach to determine baseline arrhythmia frequency followed by two phases of drug evaluation involving acute high dose administration and a short-term maintenance study. The definitions for proarrhythmia were 1) a 4-fold increase in ventricular ectopic frequency; 2) a 10-fold increase in the frequency of repetitive ventricular ectopy, and 3) the occurrence of a sustained tachyarrhythmia not documented during control studies. Worsening of arrhythmia was observed in 80 (11%) of 772 drug trials (123 of 1114 drug trials in the updated series) with the incidence for individual agents ranging from 6 to 16%. At least one proarrhythmic effect was noted in 34% of the patients undergoing testing.

The alternative strategy to define the proarrhythmic potential of antiarrhythmic agents which has been considered, is the response to electrophysiological

testing. The predictive value of this approach was suggested in a retrospective study from Ruskin et al.[299]. In 6 patients, on antiarrhythmic therapy (quinidine in 5 patients and disopyramide in 1 patient) at the time of out-of-hospital cardiac arrest, electrophysiological testing failed to induce a sustained arrhythmia in the drug-free state. With repeat testing on the antiarrhythmic agent, ventricular tachycardia was induced in 4 of these patients. One other patient developed high-grade atrioventricular block followed by ventricular fibrillation on a subsequent exercise test and the remaining non-inducible patient was noted to have been significantly hypokalaemic at the time of the cardiac arrest.

The applicability of electrophysiological testing has been evaluated in three prospective studies[300,301,302]. Unfortunately, as with most studies, interstudy comparison is hampered by differences in patient selection, stimulation protocol and end-points employed. Comparison is made more difficult by the lack of uniformity and standardisation of the criteria used to define a proarrhythmic response induced by programmed stimulation. It is therefore more apposite to consider the individual proarrhythmic criteria.

Conversion of Nonsustained Ventricular Tachycardia to a Sustained Arrhythmia

The most accepted criterion in published studies for proarrhythmia is conversion of nonsustained ventricular tachycardia to a sustained arrhythmia. Rinkenberger et al.[300] reported an incidence of 13% for this response in contrast to the 2% and 9% incidences observed by Torres et al.[301] and Poser et al[302]. In the present study 15% of drug trials manifested this form of proarrhythmia with 28% of patients experiencing at least one event. This higher incidence is presumably related to the differences in end-points for the stimulation protocol. The former studies employed nonsustained tachycardia as an end-point whereas the end-point in the present study was sustained arrhythmia. Despite this more aggressive approach, induction of a sustained arrhythmia was obtained using the same or fewer extrastimuli in all cases.

The cycle length of the sustained arrhythmia in the cases reported by Rinkenberger et al.[300] and in approximately two thirds of the present studies was longer than the cycle length of the nonsustained tachycardia. It was suggested that this reflected an increase in the activation time of the returning tachycardia wavefront permitting distal tissue in the reentrant circuit, time to recover from refractoriness, producing maintenance of the arrhythmia. Conversely, reduction in the cycle length as observed in the majority of the cases of Torres et al.[301] was attributed to an acceleration of the tachycardia wavefront or possibly the creation of a different reentrant

pathway.

Interestingly, Buxton et al.[303] have demonstrated a biphasic response to antiarrhythmic agents in some cases. At moderate dose levels, sustained arrhythmia may be induced whereas with higher levels, suppression of induction may be obtained.

Although this criterion has not been prospectively validated, the results from electrophysiological testing in drug evaluation studies, have demonstrated the predictive accuracy of the type of arrhythmia induced in relation to the subsequent spontaneous development of tachycardia. Conversely, Di Marco[233] has demonstrated that, in patients with inducible sustained ventricular tachycardia, induction of a nonsustained tachycardia denotes a satisfactory end-point for drug therapy, and therefore the reverse hypothesis may also be valid.

Conversion of Haemodynamically Stable Ventricular Tachycardia to a Sustained Arrhythmia Requiring Cardioversion

Less uniformity is seen in definitions of worsening of sustained ventricular tachycardia. Poser et al.[302] have defined this purely in relation to a shortening of the cycle length of the induced tachycardia and observed this response in 2 of 216 drug studies. In contrast, Torres et al.[301] required haemodynamic deterioration in addition to shortening of cycle length. In their study, an incidence of 2% (11 of 478 studies) was reported. The definition

employed in the present study was more inclusive with haemodynamic deterioration being the primary requirement, which in addition to the difference in methodology, is reflected in the higher incidence of 7% (using the Torres et al.[301] definition the comparative incidence was 1%). Although the use of this broader definition may reflect a combination of adverse effects on both electrophysiological and haemodynamic parameters, the clinical importance is suggested by two studies evaluating amiodarone which demonstrated that the stability of induced tachycardia correlated with the stability of the spontaneously occurring arrhythmia[247,261]. In patients with stable induced arrhythmias, arrhythmia recurrence was not associated with syncope or loss of consciousness in contrast to the high incidence of sudden death in patients with inducible arrhythmias which were haemodynamically unstable. These observations are supported by the results presented in Chapter 9 of this thesis.

In addition to the symptomatic response, cardioversion was required in the present study because of increased refractoriness to pacing termination with subsequent acceleration of the tachycardia. Increased difficulty in termination fulfils one of the definitions proposed by Morganroth and Horowitz[294] and may reflect drug induced refractoriness of intervening tissue "protecting" the reentrant circuit.

Reduction in the Aggressiveness of the Mode of Induction

Reduction in the aggressiveness of the mode of induction as evaluated by a reduction in the number of extrastimuli required, is potentially the least conclusive. The rationale is based on the hypothesis that, in patients with ambient ectopy, the frequency of single ventricular ectopic beats is greater than couplets and triplets and therefore reduction in the number of programmed extrastimuli required for tachycardia induction suggests an increased likelihood of the tachycardia occurring spontaneously. This criterion is dependent on the reproducibility of arrhythmia induction. In a study from McPherson et al[202], induction of ventricular tachycardia at a second baseline study required fewer extrastimuli in 15% of studies. To take into account this potential variability, Poser and co-workers[302] subdivided this criterion into definite aggravation of arrhythmias (requirement for one extrastimulus compared to three extrastimuli in the baseline study) and possible aggravation (requirment for one less extrastimulus) and observed and incidence of 4% and 2% respectively. The incidence of definite aggravation in the present study is almost identical at 3% although the incidence of 17% for reduction by one extrastimulus is higher.

The results of the follow-up study demonstrating no significant difference in arrhythmia recurrence rate with the patient groups stratified on the basis of presence or

absence of this type of proarrhythmic response does not confirm the predictability of this criterion. Whether this reflects that the criterion itself is not valid, or that, because of the variability of the mode of induction, the specificity of the response is very low, cannot be answered in this study. The observation, however, that in the 5 cases with reduction by 2 extrastimuli, arrhythmia recurrence occurred in 4 cases may suggest that this stricter criterion could be of predictive value. No other studies have addressed this aspect. The converse observation that, the requirement for a more aggressive induction mode on drug therapy relative to the baseline study denotes a good long-term response to that therapy has been reported by Borggrefe et al[170].

Spontaneous Development of Tachycardia

The spontaneous development of ventricular tachycardia coincident with the administration of antiarrhythmic therapy is not a response specifically attributable to electrophysiological testing, and is generally revealed by noninvasive techniques. It occurred in only 4 of the 801 drug trials in this study. Buxton and Josephson have emphasised the incessant nature of the tachycardia and suggested that an antiarrhythmic agent which slows the conduction wavefront with little change in refractoriness may increase the induction "zone" of the arrhythmia[261].

Multiple Proarrhythmic Responses

More than one type of proarrhythmic response occurred in the same drug study in only 5% of cases although a 21% incidence was reported by Torres et al.[301]. These results tend to confirm that different forms of proarrhythmia are distinct and separate entities.

Incidence of Proarrhythmic Responses Related to Individual Drug Regimens

The incidence of proarrhythmic responses in relation to individual drug regimens has recently been reviewed[294,298]. In Table 11.8, the proarrhythmic responses in the two studies specifically employing electrophysiological techniques, including the results from the present study, have been summarised. Worsening of arrhythmia was observed with every agent although the incidence varies widely, reflecting the previously discussed difficulties in inter-study comparison. In the two previous studies, no drug had a statistically higher incidence of proarrhythmic responses. In comparison this study demonstrated that certain agents, such as quinidine, manifested less proarrhythmia than other single and combination regimens. In both the present study and that from Poser et al.[302], there was a trend towards the Class IC agents having the highest incidence of proarrhythmia, a feature which has been observed previously[261].

In all three studies, drug levels were within the

	Torres et al[29]	Poser et al[19]	Present Study
CLASS 1			
PROCAINAMIDE	8/101 (8%)	4/19 (21%)	39/208 (19%)
QUINIDINE	5/49 (10%)	5/25 (20%)	15/100 (15%)
DISOPYRAMIDE	-	1/21 (5%)	-
LIGNOCAINE	13/81 (16%)	-	-
MEXILETINE	-	8/40 (20%)	14/74 (19%)
TOCAINIDE	-	1/21 (5%)	-
FLECAINIDE	5/32 (15%)	-	9/27 (33%)
LORCAINIDE	9/99 (9%)	4/17 (8%)	-
INDECAINIDE	-	-	6/16 (37%)
ENCAINIDE	-	5/14 (36%)	-
APRINDINE	-	5/26 (19%)	-
CIBENZOLINE	7/34 (21%)	-	-
CLASS 2			
BETA BLOCKERS	-	2/33 (6%)	-
CLASS 3			
AMIODARONE	-	-	48/159 (30%)
BETHANIDINE	4/18 (22%)	-	-
CLASS 4			
VERAPAMIL	9/45 (18%)	-	-

TABLE 11.8 Comparison of incidence of proarrhythmia for individual antiarrhythmic drugs

Results are shown as number of tests with proarrhythmia compared to the total number of tests employing that agent

accepted "therapeutic range" consistent with the fact that these proarrhythmic responses were not related to toxic levels of the agents.

The previous studies have not specifically addressed the worsening of arrhythmias in relation to combination therapy. It is of interest that the incidence for combination regimens was not significantly different from that of single agents. Furthermore, the results suggest that the development of proarrhythmia related to an individual agent does not preclude the use of that drug in combination.

Unpredictability of Proarrhythmic Responses

Of major concern is the observation that these proarrhythmic responses were unpredictable, confirming the findings from previous studies including the Holter monitor study of Velebit et al.[297]. Although patients with more severe left ventricular dysfunction tended to experience more proarrhythmic responses, there were no identifiable premorbid characteristics in the patient population to predict the development of this potentially lethal feature.

Therapeutic Implications

Translation of the results from this and previous studies to clinical practice is somewhat difficult because of the several limitations in interpretation of these observations. The weight of current evidence suggests

that the responses to programmed stimulation which definitely denote a potential proarrhythmic event are; conversion of a nonsustained arrhythmia to a sustained arrhythmia and conversion of haemodynamically stable tachycardia to a faster haemodynamically unstable arrhythmia. These two criteria appear to be accepted by most laboratories and in our present clinical practice, development of either response to drug therapy precludes the use of that therapy in the long-term. The overall incidence of proarrhythmia adopting these strict criteria only, was in the present study 5%. Reduction in the aggressiveness of the mode of induction by at least one extrastimulus is not of clinical value. Employment of the other criteria and their practical utility has not yet been determined.

CONCLUSIONS

Drug-related worsening of arrhythmias is a potentially lethal adverse feature of all antiarrhythmic therapy and there are no predictive clinical parameters which enable the physician to anticipate the development of such a response.

This study demonstrates that the different responses to electrophysiological testing which have been suggested as reflecting potential proarrhythmia, occur in a significant proportion of patients. Certain of these responses are

undoubtedly predictive although the therapeutic implication of others is more debatable.

Although further study is required to fully define the place of electrophysiological testing, the identification of the potential for worsening of arrhythmias may constitute a further indication for the use of this approach in the overall management of patients with ventricular arrhythmias.

CHAPTER 12

GENERAL DISCUSSION

Ventricular tachyarrhythmias are a major cause of cardiovascular morbidity and sudden death. This malignant potential presents the physician with a complex and difficult management problem. Since the first manifestation of ineffectiveness of antiarrhythmic therapy may be sudden death, empirical prescription is inappropriate. Alternative treatment strategies have therefore been advocated and the studies in this thesis have evaluated the use of serial electrophysiological testing as a means of identifying effective long-term therapy.

In addition to the conclusions drawn from these studies, the limitations inherent in this type of approach have been discussed. Several, as yet, unresolved problems constrain the wider application of programmed stimulation.

The sensitivity and specificity of the stimulation protocol employed has been dealt with in Chapter 3. Unfortunately, because of the parallel development of the technique of programmed electrical stimulation in different laboratories, there is a lack of uniformity in the methodology which presents major difficulties in formulating a standardised approach and, therefore, the interpretation of

the results of such studies. With the introduction of more aggressive stimulation protocols, the advantages of an increased sensitivity are compromised by a loss in the specificity of the response. There is an increasing consensus of opinion that the aggressiveness of a stimulation protocol should be modified in relation to the specific patient group being studied. For patients with documented sustained ventricular tachycardia or previous out-of-hospital cardiac arrest, the protocol employed should aim to maximise the sensitivity of the technique. In contrast, patients in whom ventricular tachyarrhythmias have not been documented, for example, patients with syncope of undetermined origin, a less aggressive protocol biased towards a higher specificity would be considered more appropriate.

The specificity of programmed stimulation has adopted greater importance with the increasing use of this technique for risk stratification in patients with complex ectopy [273,304], nonsustained ventricular tachycardia[305], dilated cardiomyopathy[306,307], and in particular in patients after myocardial infarction[149-155]. The results from these studies have been, in general, conflicting. Although, a negative response to programmed stimulation has been associated with a low risk of subsequent sudden death, the specificity of arrhythmia induction has been too low to be of predictive value. What therefore constitutes a specific response? Most investigators would accept that

induction of a sustained monomorphic tachycardia reflects the presence of a stable arrhythmogenic substrate. Differences in rate and/or configuration between the induced and spontaneously occurring tachycardia can be explained on the basis of different exit points from the same reentrant circuit or perturbation of the electrophysiological milieu by dynamic changes in the haemodynamic state or autonomic balance. The relation between induced nonsustained polymorphic ventricular tachycardia or ventricular fibrillation and clinical arrhythmias, is however, more controversial. An increased awareness of their potential nonspecificity has led to attempts to define criteria to differentiate between nonclinical and clinical arrhythmias. Morady and coworkers[308], suggested that the coupling intervals of the extrastimuli that induced nonclinical arrhythmias were significantly shorter than the comparative coupling intervalS that induced clinical arrhythmias. An improvement in specificity could therefore be achieved by applying a lower limit to the coupling intervals employed, without compromising the sensitivity of the stimulation protocol. This observation, however, could not be confirmed by Stevenson et al.[309], who were unable to identify any parameter to distinguish between these arrhythmias. Mahmud et al[310] reported that, even with non-aggressive induction of ventricular fibrillation using single or double extrastimuli, this response was not

necessarily specific. Similarly, reproducibility of arrhythmia induction does not appear to be of value in assessing the specificity of a response to programmed ventricular stimulation[311]. Elucidation of this problem would be a major advance in the applicability of electrophysiological testing, both as a means of determining a therapeutic modality and for risk stratification.

The predictive value of serial electrophysiological drug testing in patients with ventricular tachyarrhythmias related to both coronary artery disease and dilated cardiomyopathy has been confirmed in Chapters 6 and 7. It is important to stress that these observations are valid only in relation to the patient populations studied, the definitions of arrhythmias, stimulation protocol and criteria for drug efficacy employed in this thesis. Furthermore, the inherent biases of nonrandomised studies have to be accepted. The logistic regression analysis performed in Chapter 9, suggests that the response to programmed stimulation on drug therapy is an independent determinant of arrhythmia recurrence and not merely a means of separating patients who have a good long-term prognosis from those who do not. It must be recognised, however, that despite the inclusion of several potentially prognostic factors, other unrecognised or unexamined variables not included in the analysis might have considerable impact on the long-term outcome.

Unfortunately, strict comparative analysis using randomised placebo-controlled studies to determine the benefits of this approach are considered by many investigators to be impractical and unethical. With the availability of the automatic implantable cardioverter/defibrillator, however, the possibility of a placebo group in future studies could be more easily justified.

A further confounding factor which may influence the interpretation of long-term studies, is the intercurrent treatment of the underlying heart disease. The impact of prescription of antianginal therapy in patients with coronary artery disease or antifailure therapy in patients with dilated cardiomyopathy on arrhythmia recurrence is speculative. In this context it is interesting to note the results from two recent studies which suggested that the development of myocardial ischaemia during programmed stimulation might be important for arrhythmia induction [312,313].

Despite the validity of the induction of 15 or less repetitive responses as a criterion for drug success, as demonstrated in this thesis, a significant number of patients considered to be on ineffective therapy did not experience an arrhythmia recurrence. The possibility that the criteria for drug success currently employed are too strict, and, as a consequence, patients are being denied potentially effective long-term therapy has to be considered. This is of particular importance with the

relatively low efficacy of the currently available antiarrhythmic agents when evaluated using programmed stimulation. The initial studies on serial testing reported a 70-80% recurrence rate with continuing arrhythmia inducibility on Class I agents[42,43,157]. With amiodarone, however, the reported recurrence rates have been significantly lower[241-249]. Whether similar low recurrence rates will be found for the newer Class Ic agents has yet to be conclusively demonstrated. Continuing inducibility may therefore not denote failure of therapy[179,195]. The observations in Chapter 9, that the potential for subsequent sudden death is determined, in part, by the haemodynamic impact of the induced arrhythmia in the discharge drug study, would suggest that this approach should only be adopted if, on the antiarrhythmic therapy selected, the induced arrhythmia was relatively slow and haemodynamically tolerated.

In contrast to the use of electrophysiological testing to determine effective long-term therapy, the place of programmed stimulation to reveal the potential for worsening of arrhythmias by antiarrhythmic therapy is less well defined. In Chapter 11, the incidence and predictive value of different responses to programmed stimulation which might reflect the spontaneous manifestation of this type of adverse effect have been discussed. As with other reported studies, evaluation in the present study has been to some extent retrospective because of ethical

considerations and constraints. This imposes significant limitations on the interpretation of the clinical implications of such responses. Confirmation of the validity of this application by future prospective studies would be extremely valuable, since potentially, this aspect might adopt a primary indication for programmed stimulation.

The studies in this thesis did not address the important question of the comparative effectiveness of electrophysiological testing versus Holter monitoring in the management of patients with ventricular tachyarrhythmias. Although uncontrolled trials have suggested that both techniques have predictive value in certain study populations, this aspect is only now being submitted to a randomised study. Unfortunately the same problems of nonuniformity of methodology, definitions of arrhythmia, and criteria for drug efficacy which have been discussed with respect to electrophysiological testing also apply to the techniques of ambulatory monitoring[314]. The dichotomy between the presence of ventricular ectopy and the spontaneous development of a sustained tachyarrhythmia has been previously discussed in Chapter 1. Recently Gradman et al.[315] have suggested that certain forms of complex ectopy could be correlated with arrhythmia inducibility. The concordance between these invasive and noninvasive techniques in determining drug effectiveness, however is low[316,317]. In general, drug success has been

more easily obtained using Holter monitoring than programmed stimulation[314]. Comparative long-term efficacy to date has only been addressed in two studies. Kim et al.[318], in a nonrandomised study reported that both techniques were complementary in predicting the long-term success of therapy. In this study, patients for whom an effective therapy could not be identified by serial electrophysiological testing were discharged on therapy that produced a marked reduction in ventricular ectopy. Over the follow-up period there was no significant difference between this group and patients discharged on therapy, considered to be effective by electrophysiological testing. More recently Skale and coworkers[319] demonstrated that in survivors of cardiac arrest, suppression of inducible ventricular tachycardia predicted a favourable outcome, whereas suppression of spontaneous tachycardia and repetitive beats during continuous electrocardiographic monitoring was often associated with recurrence of cardiac arrest. Whether electrophysiological testing or Holter monitoring is the better technique, is currently being addressed in the multicentre ESVEM Trial (Electrophysiology Study versus Electrocardiographic Monitoring). The results of this trial hopefully, should clarify this unresolved question.

Electrophysiological testing has developed rapidly as a therapeutic strategy. As the technique evolves, it must be continually subjected to critical evaluation. The studies

in this thesis have attempted to clarify certain issues and provide a platform for future research to further define the application of this approach to the management of patients with ventricular arrhythmias.

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