Subthreshold Stimulation of the Human Heart

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Abstract

The effects of long duration subthreshold conditioning stimuli on refractory periods in the human heart have been studied in patients undergoing clinical electrophysiological studies. It has been shown that unipolar cathodal stimuli produce inhibition (lengthening of effective refractory period), and unipolar anodal stimuli can produce either summation (shortening of effective refractory period) or inhibition, in both atrial and ventricular myocardium. Long duration conditioning stimuli produce much greater changes in refractory period than those shown in previous studies using short duration stimuli.

Inhibitory effects can be produced 20 - 50 ms after the end of a subthreshold stimulus. Stimuli of shorter duration (20 ms or less) must have a greater amplitude to produce the same degree of inhibition as longer duration stimuli. The mechanism of the effect is uncertain, but may be related to sodium channel activation or inactivation by subthreshold electrical current. The spatial effects of subthreshold stimuli are very limited, inhibitory effects not being demonstrable 1 mm or more away from the site of delivery of the subthreshold pulses.

Attempts to terminate reentrant arrhythmias were made using subthreshold pulses. Despite optimal mapping techniques, it was not possible to terminate any cases of atrioventricular reentrant tachycardia, atrioventricular nodal reentrant tachycardia or ventricular tachycardia using long duration cathodal conditioning stimuli. Higher amplitude pulses occasionally terminated the tachycardia, but only as a result of local capture. Thus it is likely that the spatial limitations of subthreshold stimuli preclude their routine use in the termination of tachycardias. Furthermore, the use of subthreshold stimulation as a mapping tool to identify suitable sites for catheter ablation for ventricular or supraventricular tachycardia seems to be impractical.

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Author's Declaration

Material contained in this thesis has been presented in abstract form at the Fortieth Annual Scientific Sessions of the American College of Cardiology, March 1991 (Connelly *et al.*, 1991a), at the annual meetings of the British Cardiac Society, April 1991 and May 1992 (Connelly *et al.*, 1991b, 1992a), at the Ninth World Symposium on Cardiac Pacing and Electrophysiology, May 1991 (Connelly *et al.*, 1991c), at the Thirteenth Annual Scientific Sessions of the North American Society of Pacing and Electrophysiology (Connelly *et al.*, 1992b), and at the Fourteenth Congress of the European Society of Cardiology (Connelly *et al.*, 1992c). A report of the findings detailed in Chapters 3 and 4 has been provisionally accepted for publication by the *Journal of the American College of Cardiology.*

All the studies described in this thesis were performed by myself in the cardiac catheterisation laboratories of the Royal Brompton National Heart & Lung Hospital. Technical assistance in the operation of the Constant Current Stimulator was provided in the early studies (described in Chapters 3 and 4) by Mr. K. Boone, Mr. M. Spicer, and Mr. D. Pitty. The studies in which monophasic action potentials were recorded (described in Chapter 6) were performed jointly by myself and Dr. J. Morgan, and the studies during catheter ablation procedures (described in Chapter 7) were performed with the assistance of Dr. E. Rowland and Dr. J. Morgan. All data analysis has been performed by myself.

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Chapter 1

Introduction

Subthreshold Electrical Stimulation of Excitable Tissue

The concept of a threshold for excitation is one of the most fundamental principles in cellular electrophysiology. It has long been recognised that action potentials in nerve and muscle cells are 'all-or-nothing" phenomena, and stimuli below a certain threshold will not elicit a propagated response.

Following on from the realisation that a threshold existed for excitation, it was subsequently noticed that electrical stimuli of lower magnitude could have an effect on excitability. The earliest recordings from the motor end-plates of skeletal muscle led to the discovery that the release of neurotransmitter from a single nerve axon does not always depolarise a muscle cell to threshold, but usually results in a transient subthreshold depolarisation, the miniature end-plate potential (Fatt & Katz, 1952), and a large number of these depolarisations must summate in order for the membrane to be depolarised to threshold and an action potential to be elicited.

Subsequently, neurophysiologists discovered that cells in the central nervous system were under a multitude of excitatory and inhibitory influences, and the net sum of these influences determined whether or not the cell's membrane potential would reach the threshold level and result in an action potential. Subthreshold depolarisations became known as excitatory post-synaptic potentials (Coombs, Eccles & Fatt, 1955a), and subthreshold hyperpolarisations were called inhibitory post-synaptic potentials (Coombs, Eccles & Fatt, 1955b). Two or more subthreshold depolarisations might summate by occurring at the same point on a membrane in rapid succession (temporal summation; Curtis & Eccles, 1959) or by activating adjacent points on the same cell membrane (spatial summation); similarly, hyperpolarising potentials might inhibit the response to a depolarising potential by influencing the local membrane potential at an adjacent point and within a few milliseconds of the depolarising potential (spatial and temporal inhibition).

The term "subthreshold" is sometimes used loosely by cardiac electrophysiologists when working with multicellular preparations, intact animals and humans. Strictly speaking the term should mean that the stimulus is too small to result in an action potential in the cells which are stimulated; however it is not always possible to record close enough to the stimulation site to ascertain whether or not a small amount of myocardium has been activated close to the stimulating electrodes. Instead, what is often assessed is whether a *propagated* response is produced, as measured at a recording site some distance from the site of stimulation. For practical purposes this is seldom of importance, unless the experiments involve stimulation close to a site of slow conduction or decremental conduction, in which case a stimulus may result in local capture but a electrogram may not be registered at the recording site. Thus it might be possible to confuse subthreshold stimuli with non-propagated stimuli.

Measurement of Threshold and Refractory Period in Cardiac Muscle

The threshold for myocardial capture by a pacing pulse, although a common measurement in the assessment of patients with permanent pacemakers, is still poorly understood at the cellular level. It has been known for many years that a bipolar stimulus produces different effects at the anode and the cathode, and with unipolar stimulation the threshold at the cathode is usually lower than at the anode. Formerly it was believed that an anodal (hyperpolarising) stimulus could only capture by 'break excitation', i.e. that capture only occurred at the termination of the stimulus (the 'break' or trailing edge) rather than its initiation (the 'make' or leading edge of the stimulus) (Cranefield, Hoffman & Siebens, 1957). The mechanism of anode break excitation might be either because of a 'rebound' in membrane potential to a suprathreshold level at the break of the pulse, or because of adaptation of threshold to a lower level during the pulse (Aidley, 1971). Subsequent studies using long duration constant current pulses in frog (Goto & Brooks, 1969) and canine (Dekker,

1970) ventricular myocardium have shown that both anodal and cathodal pulses can capture at both the make and the break of a long duration pulse. The explanation for anodal capture at the "make" of a stimulus is thought to be due to a "virtual cathode" effect, whereby an electrical dipole is induced in the myocardial cells adjacent to the electrode. When cells close to the electrode are hyperpolarised by anodal current, cells at some distance from it are therefore depolarised, and may reach threshold. Conversely, a cathodal pulse is thought to be able to capture at the "break" by a "virtual anode break" effect. Cathodal make excitation seems consistently to have the lowest threshold, followed by anodal make excitation, with break excitation of both types having higher thresholds (Goto & Brooks, 1969; Dekker, 1970).

The threshold for capture in the intact heart is conventionally measured late in diastole. As a stimulus is brought progressively more premature in the cardiac cycle, the threshold begins to rise. The point at which a rise in threshold is first seen is known as the **relative refractory period**. More premature stimuli encounter a further rise in threshold (although with short duration anodal stimuli there is often a transient lowering of threshold) until a point is reached at which excitation cannot be produced no matter how large the stimulus. This point is known as the **absolute refractory period**. Conventionally, clinical electrophysiologists tend to use stimuli of a fixed amplitude (usually twice the late diastolic threshold), and the point at which this stimulus just fails to capture is known as the **effective refractory period**.

Subthreshold Stimulation of Cardiac Muscle

The effect of subthreshold stimuli on cardiac muscle was first considered by Drury and Love, working in Sir Thomas Lewis' laboratory, in 1926. While studying the effects of veratrine and other drugs on frog ventricular myocardium, they discovered that a conditioning stimulus delivered during the effective refractory period could prevent the response to a subsequent stimulus which would otherwise have captured.

They attributed this effect to concealed conduction induced by the drugs. Subsequent studies using other drugs and in different preparations (Love, 1926; Lewis & Drury, 1926) showed similar results.

The credit for the introduction of the terms "summation" and "inhibition" to cardiac electrophysiology must go to Cranefield and Hoffman (1971). They performed experiments on preparations of canine Purkinje fibres in which conduction block was produced by encasing the central portion of the fibre in a high-potassium buffered agar, and were able to demonstrate that stimuli which could not conduct through this area of block could nevertheless influence excitability in the myocardium beyond it. Depending on the relative timing of the stimuli, two impulses from either side of the preparation could be shown to summate to produce a propagated response in the central region; under different circumstances, stimulation of one end of the preparation could be shown to inhibit the effects of stimulation of the other end. The phenomenon of summation was considered to be analogous to that of spatial summation as described by neurophysiologists; that of inhibition was attributed to concealed conduction into the area of conduction block, thus making that region refractory to the next impulse. It is worth stressing at this point that the *stimuli* used by Cranefield and Hoffman were themselves *suprathreshold*, and the effects observed were all attributed to non-propagation of action potentials rather than to the effects of subthreshold fluctuations in membrane potential.

Tamargo, Moe & Moe (1975) studied the effect of stimuli of two to ten times the late diastolic threshold applied during the relative refractory period in the ventricles of anaesthetised dogs. Bipolar stimuli were used, and delivered after ten or more drive stimuli at a separate site. Recording sites were not necessarily adjacent to stimulation sites. They found three patterns of response to these premature stimuli. In the first pattern, a suprathreshold stimulus delivered during the relative refractory period, which would normally not elicit a propagated response, became effective when one or two identical stimuli were delivered 10 milliseconds earlier. In the

second pattern of response, a stimulus just outside the effective refractory period, which normally gave rise to a propagated response, was inhibited from doing so by a preceding stimulus of equal magnitude. In the third pattern, two stimuli, both suprathreshold and both applied after the end of the effective refractory period, would normally each elicit a propagated response, but when applied together they failed to do so. The first type of response was called summation, the second was termed inhibition, and the third was described as mutual inhibition. Since the stimuli were delivered at different sites on the myocardium, Tamargo *et al.* attributed inhibition to inhomogeneity of refractoriness at different sites, and summation to subthreshold responses interacting at a common path.

In the same laboratory, Jalife and Antzelevitch (1979) studied the effects of brief subthreshold depolarising and hyperpolarising pulses of duration 30 - 50 ms on pacemaker activity in feline sinoatrial node cells and canine Purkinje fibres. Interested in the use of perturbation techniques in the study of biological oscillators, they had previously shown that brief perturbations of either polarity could shorten or prolong the affected cycle, depending on the precise timing of the stimulus. In some experiments, however, they found that critically timed subthreshold pulses of either polarity could abolish pacemaker activity in spontaneously depolarising cells.

Antzelevitch and Moe (1983) used an experimental preparation similar to that of Cranefield & Hoffman (1970), using strips of unbranched Purkinje fibres the central parts of which were rendered inexcitable. They demonstrated the electrotonic effect of an action potential on one side of a gap could either facilitate (electrotonic summation) or inhibit (electrotonic inhibition) capture on the other side of the gap, the response observed being dependent primarily on the relative timing of the events. They considered that electrotonic inhibition might be an explanation of the phenomenon of concealed conduction observed in the atrioventricular node and under certain circumstances in diseased myocardium.

Human Studies

The first studies of subthreshold stimulation in human myocardium were performed by Prystowsky and Zipes (1983). They studied sixteen patients undergoing clinical electrophysiological studies. Basic drive trains (S1) and premature stimuli (S2) were delivered from the proximal or distal bipole of a quadripolar electrode in the atrium (interelectrode distance 5 mm) or ventricle (interelectrode distance 10 mm) and conditioning stimuli (Sc) were delivered at the other bipole on the same catheter; all stimuli were bipolar and the distal electrode of each pair was always the cathode. They found that inhibition could be produced in all patients by conditioning stimuli with an amplitude of less than 10 mA, occurring 40 to 120 ms before S2, and was more likely to occur if the conditioning stimulus was delivered close to the site of delivery of S2. The threshold for capture by S2 increased as the conditioning stimulus amplitude increased. These results were attributed to an electrotonic effect of the conditioning stimulus on the response of the tissue to S2, possibly by modifying the threshold for capture by S2.

Prystowsky and Zipes also observed one example of summation by a conditioning stimulus. In one patient, two subthreshold stimuli, 8 ms and 6 ms respectively before S2, did not result in capture by S2, but when the first conditioning stimulus was positioned 7 ms before S2, capture occurred. The reason for this was not clear, although the authors pointed out that Tamargo *et al.* (1975) had also sometimes observed that two conditioning stimuli were necessary to produce summation.

Further studies from the same department, in the canine heart (Skale *et al.*, 1985) and in humans (Windle *et al.*, 1986), demonstrated that trains of subthreshold conditioning stimuli could inhibit the response to S2 up to 152 ms beyond the effective refractory period, whereas a single 2 ms conditioning stimulus could produce inhibition by only up to 20 ms. Similarly, longer duration conditioning stimuli (up to 100 ms) could produce greater degrees of inhibition than short duration

pulses, and higher amplitudes of conditioning stimuli could also produce further prolongation of the effective refractory period.

The effect of trains of stimuli has also been studied by Swerdlow, Liem & Franz (1987). They compared the effects of single extrastimuli and 100 Hz trains of duration 100 ms in the right ventricle in 29 patients. They found that trains of stimuli prolonged the effective refractory period when the stimulus intensity was low (0.5 mA) but caused a shortening of the effective refractory period at high stimulus intensity (16 mA). Similar results were obtained in dogs by Inoue *et al.* (1989).

Stevenson *et al.* (1987a) studied the effect of noncapturing stimuli on refractoriness in 23 patients, using single short duration conditioning stimuli with amplitudes of twice the late diastolic threshold and 10 mA. The effects of bipolar and unipolar cathodal and anodal conditioning stimuli were studied, but the study protocol was not designed to look for evidence of shortening of the effective refractory period (summation). They found that, when the conditioning stimulus was delivered at the same electrode as the premature beat (S2), the ventricular effective refractory period could be prolonged by 10 to 20 ms in all but one patient using bipolar or unipolar conditioning stimuli, the polarity of the unipolar stimuli apparently being unimportant. However, if the conditioning stimulus was delivered at an adjacent electrode 3 mm away, inhibition was observed in only one patient.

Recently, Saihara *et al.* (1990a,b) have studied the effects of single extrastimuli on refractory periods in the canine heart and in humans. Saihara *et al.* (1990a) studied the effect of a single conditioning stimulus on ventricular effective refractory period in nineteen anaesthetised dogs. Effective refractory period was determined with a premature beat (S2) with an amplitude of twice the late diastolic threshold and 2 ms duration, after eight-beat drive trains (S1S1). S2 was initially set 1 ms shorter than the effective refractory period, and the conditioning stimulus was interpolated 1 to 5 ms before S2. With a conditioning stimulus amplitude of twice the late diastolic

threshold, summation was not observed, but higher amplitudes of conditioning stimuli resulted in shortening of the effective refractory period in up to 90% of studies. Summation was much less likely to occur when the conditioning stimulus was delivered at a distance of 1 to 3 mm from S2, and was never observed when the interelectrode distance was 5 mm.

The same authors (Saihara *et al.*, 1990b) studied the effects of a single conditioning stimulus in thirteen patients undergoing clinical electrophysiological study. Bipolar conditioning stimuli were used, with amplitudes of two to four times the late diastolic threshold. They found that summation (shortening of the effective refractory period by 10 to 30 ms) could be produced if the interval from the conditioning stimulus (Sc) to the premature beat (S2) was 5 ms or less; at longer coupling intervals, inhibition could be demonstrated, the effective refractory period being prolonged by 5 ms in each case.

The results of these studies are summarised in Table 1.1 (overleaf).

Limitations of Previous Studies

A major limitation of all the studies listed in Table 1.1 is the technique used to measure effective refractory period in each case. In all these studies, effective refractory period was assessed by a premature beat delivered after a short drive train (usually eight beats), with pauses of variable duration before commencing the next drive cycle. Recent studies (Franz *et al.*, 1988; Morgan, Cunningham & Rowland, 1990) have shown that, after a change in drive cycle length, it takes from one to three minutes for the effective refractory period to stabilise at a new level. One reason for the apparently haphazard effects of lengthening and shortening of refractory periods seen in these studies may be that the refractory period may have gradually

shortened after successive drive cycles interspersed with short pauses, and lengthened again if a longer gap was left before a subsequent drive cycle (Morady *et al.,* 1990).

Table 1.1 - Previous Studies of Summation and Inhibition

Reference	Species	Stimuli	Prevalence of Inhibition	Increase in ERP	Prevalence of Summation	Decrease in ERP
Prystowsky (1983)	Human	Single, bipolar, 2 ms	16/16	10-20 ms	1/6	10 ms
Skale (1985)	Dog	Trains, bipolar, 1ms, 333 Hz	20/20	152 ms (mean)	*	*
Windle (1986)	Human	Single, bipolar, 2-100 ms	34/34	81 ms with long stimuli	*	*
Swerdlow (1987)	Human	Trains, Bipolar, 1 ms	29/29	47 ± 6 ms	26/29	12 ± 1 ms
Stevenson (1987a)	Human	Single, uni & bipolar, 2-9 ms	22/23	10-20 ms	*	*
Inoue (1989)	Dog	Trains, bipolar, 2 ms	Not stated	25-80 ms	Not stated #	20-28 ms
Saihara (1990a)	Dog	Single, bipolar, 2 ms	**	**	11/12	1 ms
Saihara (1990b)	Human	Single, bipolar, 2 ms	13/13	5 ms	7/13#	10-30 ms

Key: * Summation not investigated. ** Inhibition not investigated

   # Conditioning stimuli of larger amplitude produced summation in these studies

Kadish, Schmaltz & Morady (1991) have recently quantitated the amount of variability that may occur in ventricular refractoriness as a result of variable lengths of drive trains, intertrain pauses, and other factors, and have shown that conventional measurement of ventricular effective refractory period is often associated with variability in the range of 10 to 15 ms, and differences of up to 40 ms between the shortest and longest determinations of ventricular effective refractory period may sometimes occur. With this information, therefore, the significance of the small changes in effective refractory period seen in some of the studies listed in table 1.1 must be viewed sceptically.

Termination of Tachycardias by "Subthreshold" Stimuli

Several authors have reported cases in which a tachycardia could be terminated by a stimulus which did not result in a propagated response. Ruffy, Friday & Southworth (1983) first described this phenomenon in a patient with ventricular tachycardia secondary to coronary artery disease. The tachycardia was reproducibly terminated by a single extrastimulus delivered within the effective refractory period of the right ventricle, provided that the stimulus had an amplitude of at least four times the late diastolic threshold. The authors considered that the mechanism of this effect might be partial depolarisation of a critical part of the reentrant circuit as a result of electrotonic activity from the point of stimulation. A related phenomenon had been described by Wellens, Lie & Durrer (1974), who described a patient whose ventricular tachycardia could be reliably terminated by a single atrial premature beat without apparent ventricular capture. The mechanism of this effect was unclear, but the authors suggested that the tachycardia might be caused by bundle branch reentry, the atrial premature beat resulting in concealed conduction into the Purkinje system and rendering the tissue refractory to the next beat of tachycardia.

Similar cases of termination of ventricular tachycardia by a non-propagated impulse delivered within the ventricular effective refractory period have been described by Garan & Ruskin (1988), Podczeck *et al.* (1988), Ruffy (1990b) and Kuck *et al.* (1991a). In all these cases, detailed endocardial catheter mapping was carried out, and in each case the site at which the non-propagated stimulus was delivered was demonstrated to be within the reentrant circuit of the ventricular tachycardia. The stimulus intensity required to terminate tachycardia was always considerably higher than the late diastolic threshold, and in one of the cases (Ruffy, 1990b) it was demonstrated that the stimulus resulted in local capture, although propagation to the rest of the ventricular myocardium did not occur. In the other three cases, endocardial catheter ablation (by high energy shocks in the first two cases, and by radiofrequency energy in the case of Kuck *et al.* (1991)) was performed successfully at the site of delivery of the non-propagated stimuli; in fact, Kuck *et al.* (1991) identified several points along an area of slow conduction at which ventricular tachycardia could be terminated by a non-propagated stimulus.

Shenasa *et al.* (1988) studied the effects of rapid trains of stimuli, with amplitudes of 10-90% of late diastolic threshold, during ventricular tachycardia in fifteen patients undergoing preoperative catheter mapping or arrhythmia surgery. They showed that ventricular tachycardia could be terminated by trains of subthreshold stimuli in eight of the fifteen patients, and 75% of episodes of ventricular tachycardia could be reproducibly terminated by this method. The most effective cycle lengths for tachycardia termination were 50 and 40 ms, and longer bursts were more effective than shorter bursts. The most important factor in determining successful termination of tachycardia by subthreshold stimulation was proximity to the site of earliest activation during ventricular tachycardia. Unipolar stimulation was neither more nor less effective than bipolar stimulation. No episodes of acceleration of ventricular tachycardia were seen, and electrograms recorded at sites adjacent to the stimulation sites did not show evidence of local capture by the subthreshold pulses.

Other authors have attempted to terminate atrioventricular reentrant tachycardia with subthreshold stimuli. Gang *et al.* (1988) delivered rapid trains of stimuli, with an amplitude of up to 80% of late diastolic threshold, in the coronary sinus close to the site of a left-sided accessory pathway in ten patients, and were able to terminate atrioventricular reentrant tachycardia in seven of the patients. In each case, termination of tachycardia was brought about by one or two instances of atrial capture, the premature beats blocking in the atrioventricular node. Gang *et al.* attributed these results to summation of subthreshold impulses at the atrial insertion of the accessory pathway; however, a more likely explanation (not considered by the authors) is that the threshold for atrial capture from within the coronary sinus is likely to vary during different parts of the cardiac cycle, depending on the proximity of the stimulating electrodes to the atrial aspect of the coronary sinus. Thus there is no guarantee that the threshold in late diastole will be higher than that in early or mid-diastole, and the stimuli used by Gang *et al.* were likely to have been *suprathreshold* in certain patients at certain parts of the cardiac cycle.

By contrast, Rothschild *et al.* (1987) reported a case in which a premature stimulus at a coupling interval shorter than the atrial effective refractory period appeared to reset atrioventricular reentrant tachycardia in a child with incessant long R-P' tachycardia (the permanent form of junctional reentrant tachycardia, as described by Coumel *et al.*, 1967). High amplitude stimuli applied close to the site of the posteroseptal accessory pathway reset the tachycardia without evidence of local atrial or ventricular capture. One possibility is that the stimulus captured the (slowly conducting) accessory pathway, or a small portion of ventricular myocardium close to the ventricular insertion of the pathway.

Recently Hindricks *et al.* (1992) have presented preliminary results of studies in which they delivered long duration subthreshold stimuli close to the site of an accessory pathway in 21 patients during orthodromic atrioventricular reentrant tachycardia. They were able to terminate tachycardia in seventeen patients using long

duration stimuli using this technique. Radiofrequency energy application at the sites where subthreshold stimuli were effective was successful in abolishing accessory pathway conduction in 15 of 17 cases, and in only one case was radiofrequency application successful where subthreshold stimulation had been ineffective. In most cases, subthreshold stimulation terminated atrioventricular reentrant tachycardia by blocking ventriculoatrial conduction, but in one case it was effective by shortening the tachycardia cycle length, which the authors attributed to enhanced conduction (but which might also be produced by local capture). In these studies, the amplitude of the subthreshold pulses was often several milliamperes. and the duration up to five seconds. The pulses were bipolar, the distal pole being positive. A full report of the methodology and results is awaited. A similar study from the same investigators (Shenasa *et al.*, 1992) found that long duration subthreshold stimuli were more effective in terminating ventricular tachycardia than trains of subthreshold stimuli.

Fromer and Shenasa (1992) have used rapid trains of subthreshold stimuli delivered to the low septal right atrium and proximal coronary sinus during atrioventricular nodal reentrant tachycardia, and have been successful in terminating tachycardia in fifteen out of seventeen patients, without evidence of local capture. Trains of three to sixteen stimuli were used, at cycle lengths of 100 ms to 20 ms and pulse width of 2 ms. All the stimuli were bipolar, the distal pole being positive. The threshold at each site was measured in sinus rhythm, and whether the threshold increased or decreased with the onset of tachycardia was not tested. Therefore, although no local capture was seen, it remains possible that in some of these cases the stimuli might have been suprathreshold during atrioventricular nodal reentrant tachycardia, and tachycardia could have been terminated by local capture with subsequent conduction block within the slow pathway of the atrioventricular node.

Mechanisms of Tachycardia Termination by Subthreshold Stimuli

Ruffy (1990a) considered the possible mechanisms by which a non-propagated stimulus might terminate a tachycardia. The first possible mechanism is *electrotonic inhibition*: as a result of the local electrotonic effect of the stimulus, the threshold for excitation of a region of myocardium would be temporarily raised, the next beat of tachycardia to encounter that region would fail to depolarise the myocardium to threshold, and the tachycardia would terminate. Such a mechanism would only be feasible if the subthreshold stimulus were to be delivered very close to a narrow isthmus of conducting tissue, such as the atrioventricular node or His bundle, an accessory pathway, or a narrow region of slow conduction surrounded by scar tissue in patients with ventricular tachycardia. Not only would the position of delivery of the subthreshold pulse be critical, but its timing would also be crucially important, as the duration of the electrotonic effect would likely be short compared to the cycle length of the tachycardia. As all published examples of termination of reentrant tachycardias by non-propagated impulses, except those of Shenasa and colleagues (Shenasa *et al.*, 1988, 1991, 1992; Fromer & Shenasa, 1992; Hindricks *et al.*, 1992), have utilised stimuli which were at least twice the late diastolic threshold in amplitude, there is as yet little convincing evidence that this mechanism of tachycardia termination is possible in practice.

The second possible method is *concealed conduction* (Langendorf, 1948; Langendorf & Pick, 1956). Concealed conduction is manifest when conduction or formation of a subsequent impulse is unexpectedly delayed or stopped. This is due to creation of refractoriness in conduction pathways by penetration of a preceding impulse which 'blocks" within the pathway. The phenomenon is often observed in regions of decremental conduction such as the atrioventricular node, and recent studies in single atrioventricular nodal cells have suggested that the mechanism of this effect involves inhibition of the transient inward calcium current, I_{CaT} (Liu *et al.*, 1993). In the case of termination of ventricular tachycardia by a non-propagated stimulus, it is feasible

that the stimulus might activate the myocardium within an area of slow conduction, but that this impulse might only propagate a short distance along this zone of slow conduction before abating. The tissue would then be refractory to the next reentrant beat of the tachycardia, and if adjacent recording electrodes were not close enough (or the amplifiers not sensitive enough) to detect local activation within the zone of slow conduction, the tachycardia would apparently have been terminated by a non-capturing impulse. El-Sherif, Gough & Restivo (1987) provided strong evidence for this mechanism in their studies on experimental ventricular tachycardia in the canine post-infarction model. In this model, simultaneous recordings from multiple sites in and around the border zone of the infarct are made during tachycardia, and the results stored and analysed on computer. They describe one experiment in which a critically timed stimulus delivered during ventricular tachycardia resulted in local activation with conduction into the ischaemic zone and termination of the tachycardia without propagation of activity to normal myocardium. Similar effects were seen in five other experiments.

The third possibility is that *inhomogeneity of refractoriness* within the components of a reentry circuit could lead to the formation of 'islands" of tissue which are electrically excitable, but surrounded on all sides by tissue which is still refractory or by inexcitable tissue. Thus a critically timed and critically positioned stimulus might reactivate this tissue, but the impulse elicited would be unable to progress 'forward" in the tachycardia circuit, since that tissue would still be refractory, and the depolarisation of this excitable 'island" would render it refractory to the next reentrant beat coming from 'behind". This mechanism is analogous to the situation of concealed conduction described above, but it avoids the necessity for delivery of the non-propagated stimulus within an area of slow conduction, although it necessarily involves a narrow isthmus of excitable tissue with a refractory period longer than that of the myocardium proximal to it in the circuit. This mechanism was considered by

Garan & Ruskin (1988) to explain their findings, and a computer modelled simulation of this effect has been described by Malik & Camm (1990).

Two other possibilities are considered. Jalife & Antzelevitch (1979) have demonstrated that critically timed low amplitude premature stimuli can terminate rhythms due to oscillatory activity in experimental preparations, and Wit & Cranefield (1976) have shown similar effects in triggered activity. The possibility that this mechanism may be feasible clinically cannot be discounted. It seems unlikely to be the mechanism of tachycardia termination in the cases described above, however, as these arrhythmias behaved much more like reentrant tachycardias. Nevertheless, the observations of Wit & Cranefield and Jalife & Antzelevitch should cause some reexamination of accepted concepts and definitions of reentry, as it was previously thought that termination of a tachycardia by premature stimulation was proof of a reentrant mechanism.

Finally, Wedensky phenomena have been described in the human heart. In 1886, Wedensky described experiments on a nerve-muscle preparation, in which subthreshold stimulation of the nerve supply to a muscle, if preceded by a strong stimulus, could elicit a propagated response resulting in contraction of the muscle. The reason for this prolonged lowering of threshold after a strong stimulus is unclear, but similar effects have been observed in cardiac tissue. Castellanos *et al.* (1966) studied the effect of different amplitudes of pacing stimuli in seven patients with complete atrioventricular block. They showed that, in two patients, subthreshold pulses could result in propagated responses if preceded by a stimulus of 15 to 20 times the threshold value. One possible explanation for this might be enhanced excitability as a result of activation of sympathetic nerve terminals and local catecholamine release by the strong pulse (Inoue *et al.*, 1989; Langberg *et al.*, 1991a,b).

Spatial Effects of Suprathreshold and Subthreshold Stimuli

An important factor when considering the possible effects of stimuli which do not result in local capture (i.e. truly subthreshold stimuli) is how much myocardium needs to be activated in the intact heart for an impulse to form and propagate. This is a difficult subject both for theoretical and experimental study. Theoretical models are of necessity more complex that those of nerve cells, as the heart acts as a syncytium with anisotropic conduction properties, and there tends to be a variable amount of connective tissue at the electrode-tissue interface.

Lindemans *et al.* (1975), in a study of the effect of electrode radius on stimulation threshold in the canine heart *in vivo*, found that thresholds for cathodal stimuli were proportional to electrode radius to the power 1.5, and explained these results theoretically assuming that a propagated response was reached if a critical current density was reached at a point where the tissue made contact with the electrode edge. Using an array of individually isolated recording electrodes with interelectrode spacing of 1.5 mm, they were able to obtain an impression of the site of initial depolarisation and to demonstrate spread of excitation across the tissue in contact with the electrode, starting at the site of capture at a point on the electrode edge when the stimulus was equal to threshold. Suprathreshold stimuli resulted in capture from the whole tissue ring in contact with the electrode. Anodal stimuli behaved similarly, although the point of activation for a threshold anodal "make" stimulus was clearly different from the point at which a cathodal stimulus captured. Further studies from the same investigators (Lindemans & Denier van der Gon, 1978) showed that the radius-threshold relationship does not apply for electrode radii of less than 0.2 mm. With such small electrodes the threshold is independent of electrode radius. The authors explained this theoretically by assuming that excitation occurs if the current passing through a "liminal area" (with dimensions of about 0.3 mm) exceeds a critical value.

More recently, Frazier *et al.* (1988a, b) have used a three-dimensional electrode array to study the transmural pattern of extracellular potential changes around a unipolar pacing site on the ventricular epicardium or endocardium in intact dogs. Using suprathreshold stimuli and recording at points spaced 2-5 mm apart, they showed extracellular potential changes in a region extending approximately 5-7 mm across the myocardial fibres and 10-12 mm along the lengths of the fibres. Using stimuli of less than 5 mA in amplitude, most of the volume of tissue containing the recording electrodes was excited after the stimulus by an activation front propagating away from the stimulus site; as the stimulus strength was increased, the amount of tissue activated directly by the stimulus appeared to increase. All these stimuli, however, were suprathreshold, and an attempt to define the minimum volume of myocardium which a stimulus must activate for threshold to be reached could not be made using these techniques (Ideker *et al.*, 1990).

Thus it appears that little is known about the spatial effects of threshold and suprathreshold stimuli, and even less is known about the spread of effects of subthreshold stimulation outwith the region of myocardium in direct contact with the stimulating electrode. Recently, Paya *et al.* (1991, 1992) have studied the spatial effects of trains of subthreshold stimuli on ventricular myocardium in anaesthetised dogs. Initial studies using standard catheter electrodes positioned at the right ventricular apex showed that, although ventricular effective refractory period could be prolonged by up to 50 ms at the site of stimulation, no effect could be seen at adjacent electrodes 3 mm away. Subsequent studies using a plaque of seven electrodes (six arranged hexagonally around a central electrode, the interelectrode distance being 3 mm) attached to the right ventricular free wall at thoracotomy showed that inhibition could be produced at the central electrode by simultaneous trains of subthreshold stimuli delivered to the surrounding electrodes. The same investigators (Chorro *et al.*, 1992) have demonstrated a similar effect in the atria of

anaesthetised dogs, producing inhibition at a central electrode by subthreshold stimuli delivered to an array of electrodes as above, and to a ring electrode 1 mm in width.

Background to the Present Studies

The precise mechanisms of summation and inhibition in the human heart remain unexplained. Some of the studies mentioned above suggest that the responses to subthreshold stimuli may be maximised by increasing the strength and either the duration or frequency of stimulation. However, precisely why summation occurs in one set of circumstances and inhibition in another remains obscure. In addition, the effect of stimulus polarity has never been adequately assessed in previous studies. The purpose of the present study, therefore, was to explore in greater detail the effects of subthreshold conditioning pulses which lasted throughout the repolarisation phase, in order to determine whether this would result in a more profound effect on effective refractory period than short duration pulses. The use of pulse amplitudes lower than the late diastolic threshold should allow the conditioning stimulus to be continued beyond the baseline effective refractory period if inhibition were to be produced, thus maximising the inhibitory effect of a conditioning stimulus. In addition, the present study sought to determine whether the polarity of a conditioning stimulus was important in determining whether it resulted in lengthening or shortening of the refractory period.

The possible use of long duration subthreshold pulses in the attempted termination of reentrant arrhythmias has also been investigated. Cunningham & Kennedy (1985) studied the effect of long duration constant current pulses on atrial flutter in man. Detailed atrial mapping was carried out in 65 patients during spontaneous episodes of atrial flutter and long duration pulses were delivered at sites close to the reentrant circuit, with a mean duration of 250 ms and a mean amplitude of 10 mA (Cunningham, 1988). Termination of atrial flutter was achieved in up to 90% of

cases, and the results appeared to be superior to those obtained with conventional overdrive pacing techniques. Subsequent studies (Kennedy *et al.*, 1986) showed that certain cases of ventricular tachycardia could also be terminated using this technique.

The mechanism of termination of atrial flutter by a long duration constant current pulse remains unclear. Possible mechanisms include repetitive activity during the pulse, sustained depolarisation or hyperpolarisation, hyperpolarisation with break excitation, or an alteration in the threshold to the next spontaneous impulse. One of the purposes of the present study was to extend the work of Cunningham & Kennedy (1985) to other reentrant arrhythmias, to determine the mechanism by which long duration pulses can terminate tachycardias, and to determine whether the technique of application of subthreshold pulses can be developed as an alternative pacing method for termination of tachycardias. In particular, if a tachycardia could be reliably terminated by a subthreshold pulse which did not itself capture the myocardium and produce a propagated response, it might be a potentially safe method of tachycardia termination, since there should be no risk of acceleration of the tachycardia. Furthermore, if the technique were feasible but the results were limited by the spatial resolution of subthreshold pulses, the technique might prove to be a potentially useful method of identifying critical sites in a reentrant circuit (such as an accessory pathway, or a site of slow conduction in ventricular tachycardia) at which catheter ablation might be attempted.

Outline of the Present Studies

Chapter 2 describes the patient population studied and the equipment used, and introduces the methods used for investigating the effects of long duration subthreshold stimuli. Chapters 3 and 4 report the results of bipolar and unipolar conditioning stimuli on refractory periods, and Chapter 5 expands these studies, exploring the temporal and spatial effects of the conditioning stimuli. Chapter 6

describes the use of monophasic action potential recordings in the investigation of the cellular effects of conditioning stimuli, and Chapter 7 deals with the use of long duration pulses in attempts at termination of reentrant tachycardias. Finally, Chapter 8 is a general discussion of the results.

Chapter 2

Patients, Materials and Methods

Patients

All studies were performed on patients undergoing clinical electrophysiological studies in the cardiac catheterisation laboratories of the Brompton and National Heart Hospital, Fulham Road, London SW3, and subsequently the Royal Brompton National Heart and Lung Hospital, Sydney Street, London SW3, between March 1990 and March 1992. Informed consent was obtained for the research study, and the protocol was approved by the Ethics Committee of the National Heart and Chest Hospitals. A copy of the consent form approved for this project is shown in Appendix 1.

In total, 95 studies were performed on 93 patients. The age range of the patients was 12-77 years (mean 44.8, standard deviation 16.1). 60 studies were performed on patients free of antiarrhythmic drugs, and in the other 33 studies the patients were taking either amiodarone (25), amiodarone and sotalol (1), atenolol (1), digoxin (1), flecainide (1) or sotalol (4). All patients were studied in the postabsorptive state under mild sedation with a benzodiazepine. In two patients, long duration pulses were delivered while the patient was under general anaesthesia prior to attempted catheter ablation for ventricular tachycardia or Wolff-Parkinson-White syndrome.

Figure 2.1 shows the diagnoses of the patients studied. The majority of patients (47/93; 50.5%) had supraventricular arrhythmias (Wolff-Parkinson-White syndrome in 31, atrioventricular reentrant tachycardia utilising a concealed accessory pathway in four, atrioventricular nodal reentrant tachycardia in eight, atrial tachycardia in one, paroxysmal sinus tachycardia in two and atrial flutter in one), and of these patients, 42/47 (89%) had no accompanying structural heart disease. 35 patients were being studied because of a history of sustained ventricular tachycardia or ventricular fibrillation; of these, the majority (25/35; 71%) had coronary artery disease, and all of these had had one or more previous myocardial infarctions; the other patients with ventricular arrhythmias had either right ventricular dysplasia (seven patients), non-

Figure 2.1. Diagnoses of Patients Studied
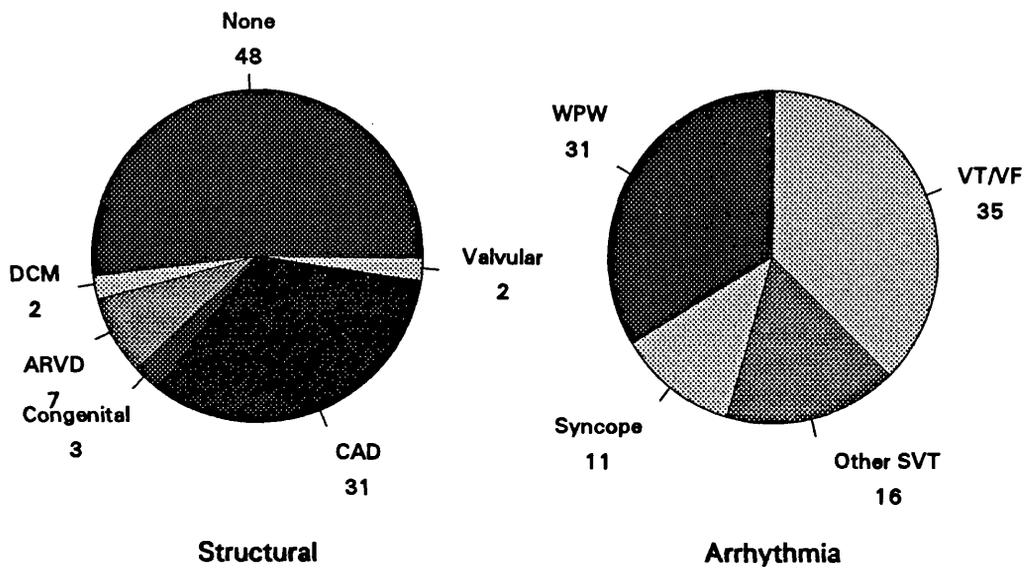
Key: ARVD = arrhythmogenic right ventricular dysplasia; CAD = coronary artery disease; DCM = dilated cardiomyopathy; SVT = supraventricular tachycardia; VT/VF = ventricular tachycardia/ventricular fibrillation; WPW = Wolff-Parkinson-White syndrome.

ischaemic dilated cardiomyopathy (two patients) or right ventricular outflow tract tachycardia (one patient). Eleven patients were studied because of unexplained syncope; five of these had no underlying structural heart disease, two had valvular heart disease and four had coronary artery disease.

Electrophysiological Studies

Under local anaesthesia, two or more multipolar electrode catheters were inserted via one or more veins (usually the right femoral vein and, if necessary, the right subclavian vein) and positioned under fluoroscopic guidance in various parts of the heart. In some studies (when left ventricular mapping or ablation of a left-sided accessory pathway was being performed), a multipolar electrode catheter was also inserted via the right femoral artery, and in these cases the patients were given intravenous heparin in doses of 50-100 units per kilogram body mass. Intracardiac signals were filtered at 30 - 500 Hz and amplified using custom-built amplifiers (Department of Biomedical Engineering, Royal Brompton National Heart & Lung Hospital, London), and recorded on paper, together with three to six surface ECG leads, at speeds of 50 to 100 mm/s using a Siemens-Elema Mingograph recorder. Constant rate atrial or ventricular pacing was carried out using a Biotronik UHS-20 Universal Heart Stimulator (Biotronik GmbH, Berlin, Germany). Catheters used were manufactured by Bard Electrophysiology (Tewkesbury, Massachusetts, USA), with 5, 6 or 7 French diameters, apart from the catheters used for radiofrequency ablation (Mansfield-Webster Polaris, 7 French diameter, Boston Scientific Corporation, Watertown, Massachusetts, USA), the catheters used for monophasic action potential recording (manufactured by EP Technologies, Mountain View, California) and a custom-made catheter used for some of the later studies on spatial effects of subthreshold pulses. Bipolar and quadripolar catheters with 5 or 10 mm

interelectrode spacing   were used except where stipulated otherwise for specific protocols.

The Constant Current Stimulator

Long duration constant current pulses were delivered using a custom-built software-driven constant current stimulator, which had been specified for this study and designed and built by the Department of Biomedical Engineering, National Heart and Chest Hospitals. The design, construction and function of the constant current stimulator are described in more detail in Appendix 2. In brief, the stimulator is designed to produce unipolar or bipolar current pulses of complex shape and duration up to 800 ms. The pulse shape is specified as one or more segments, the maximum number of segments in any one pulse being 255, and the minimum duration of each segment being 100μs, and each segment can consist of either a constant current output, a gap (zero current), or a gradual slope from one current value to another. The maximum output is 51 mA, provided that tissue impedance does not rise above 1 kΩ. The amplitude of each section of the pulse can be varied in steps of 0.02 mA when set to low range (0 to 5.1 mA) or 0.2 mA on high range (0 to 51 mA). The onset of the pulse is synchronised with an amplified intracardiac electrogram or the output of another stimulator (in this case, the Biotronik UHS-20).

The stimulator includes a number of safety features in addition to the standard safety requirements for a device connected directly to the heart. These include defibrillator protection up to 360 Joules, current limiting circuitry and over-current detection, a fuse-linked output, error traps in the software controlling the stimulator, and a patient isolation switch.

The constant current stimulator is programmed and controlled from an IBM PC-AT compatible computer (Dell 200, Dell Computer Corporation, Austin, Texas, USA),

using software written specifically for the evaluation and use of the stimulator. Written in 'C" language, the software is menu-driven and stored on the computer's hard disc. The software communicates with the constant current stimulator via the computer's serial port, transmitting the data on each current pulse in a coded form. The software includes the facility to edit one pulse shape while another pulse is being delivered to the patient , and to start or stop the current output with or without loading new pulse data. There is also a facility for saving pulse shapes on disc.

Figure 2.2 shows a photograph of the constant current stimulator and the computer used to operate it, and figure 2.3 shows the appearance of the menu screen on the computer when the software is running. Figure 2.4 is a diagram of the equipment used for the studies.

Figure 2.2. Constant Current Stimulator and Computer
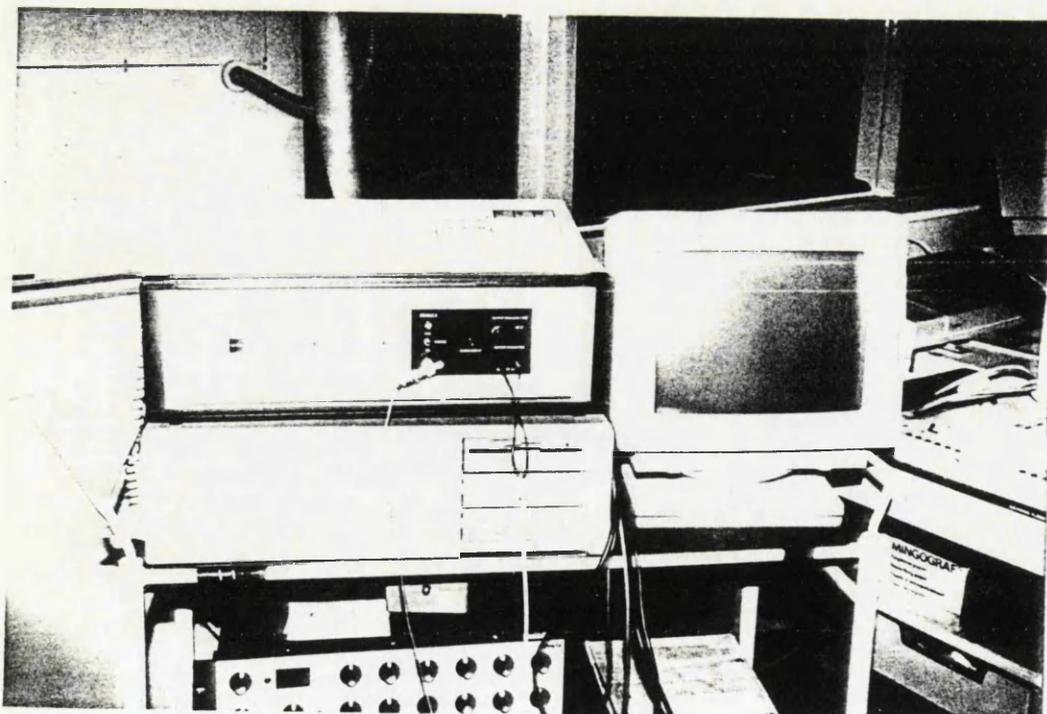
Figure 2.3. Appearance of Menu Screen for Constant Current Stimulator

See Appendix 2 for details

```
                            CCS Editor/Driver                    KB 1989
 dit      ile      pdate      uit        ontrol    elp       ystem
  default.dat
      Range: ▓
      Delay: .1      msec
   Hold-off: .1      msec

 Wave Segment  0 from 0      mA to 0      mA for 260    msec
 Wave Segment  1 from .5     mA to .5     mA for 2      msec




 CCS status: Stopped        Out Switch.: Off              Session Time: 0:1:0
 Delivered 0 uJ/ohm      in  0      pulses of 0 uJ/ohm    from 0     triggers.
 Report from CCS: None
```

Figure 2.4. Equipment Used for Studies
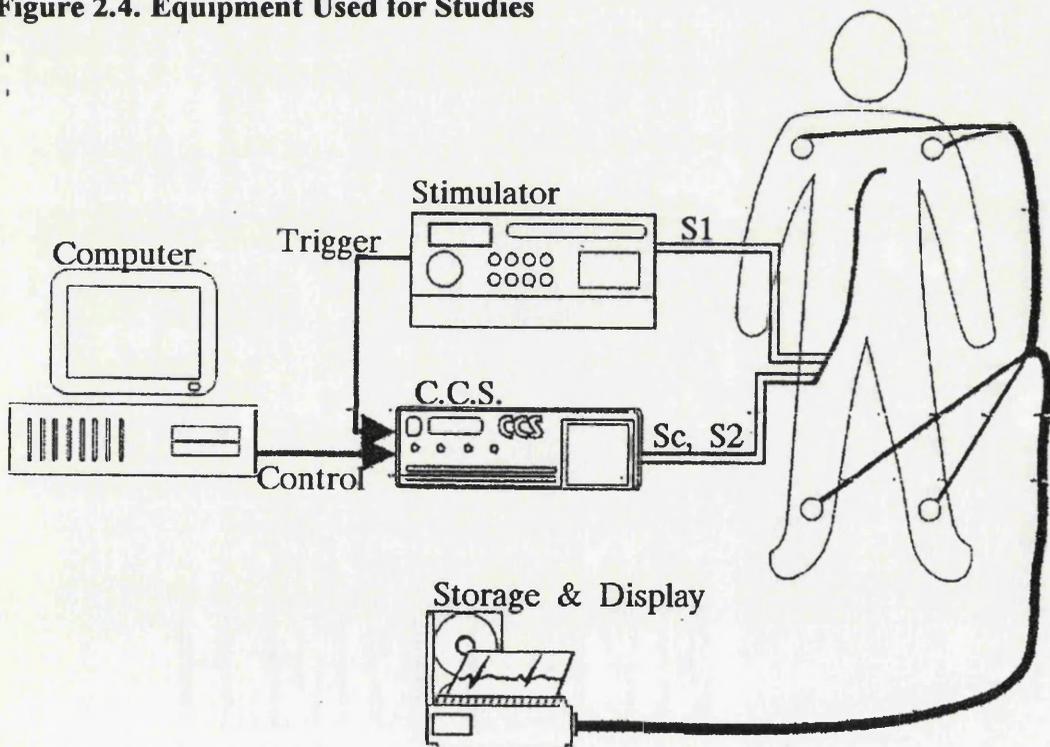
Validation of Output Parameters of Constant Current Stimulator

In order to test the output of the Constant Current Stimulator, various pulse shapes were programmed and discharged through resistances of various sizes, and the measured current displayed on the screen of a storage oscilloscope. Figures 2.5 to 2.7 (overleaf) show sample waveforms from the Constant Current Stimulator, produced by delivering specified pulses through a 470 Ω resistance and measuring the current using a digital storage oscilloscope (Gould DSO 1604; Gould Electronics, Cleveland, Ohio, USA). The data stored in the oscilloscope's memory was imported into a spreadsheet program (Lotus 1-2-3 Release 2.2; Lotus Development Corporation, Boston, Massachusetts, USA) in order to produce an output on paper.

Figure 2.5 shows the typical waveform used in the studies described in Chapters 3 and 4 to study the effects of subthreshold stimuli on the effective refractory period. The stimulus would usually commence synchronous with the last beat of the drive cycle, delivered by the Biotronik stimulator. The output consists of a long duration phase (the conditioning stimulus), the amplitude of which is less than the late diastolic threshold, followed by a short duration (2 ms) segment with an amplitude of twice the late diastolic threshold (the premature beat) In this case the amplitude of the conditioning stimulus is 1 mA, its duration is 100 ms,' and the amplitude of the premature beat (S2) is 3 mA. Figure 2.6 shows a similar pulse shape, but with the interpolation of a 10 ms gap (programmed as a segment of the stimulus with an amplitude of zero) between the conditioning stimulus and the premature beat. Figure 2.7 shows a long duration stimulus, the trailing edge of which does not fall sharply, but slopes down to zero over a period of 40 ms, in order to minimise the likelihood of break excitation by the pulse. If this pulse were to be examined with the oscilloscope gain and time base increased, it would be seen that the "slope" is in fact a series of "steps", each with an amplitude of 0.02 mA (the minimum step size of the Constant Current Stimulator output). Whenever the Constant Current Stimulator is programmed to produce a pulse shape which includes a "sloping" section, it divides
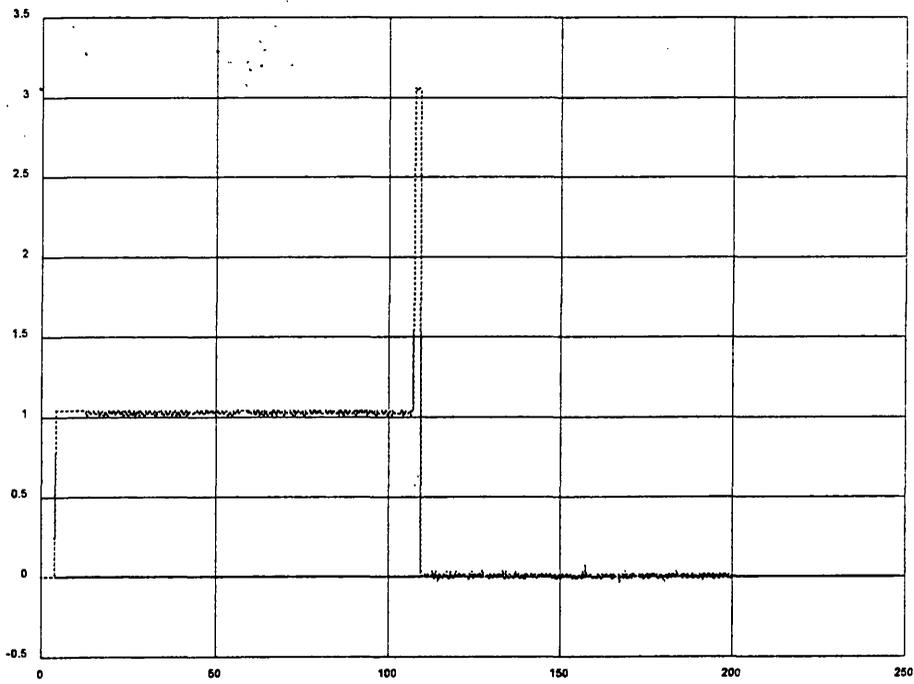
Figure 2.5 (above) and 2.6 (below). Sample outputs from Constant Current Stimulator

See text for details
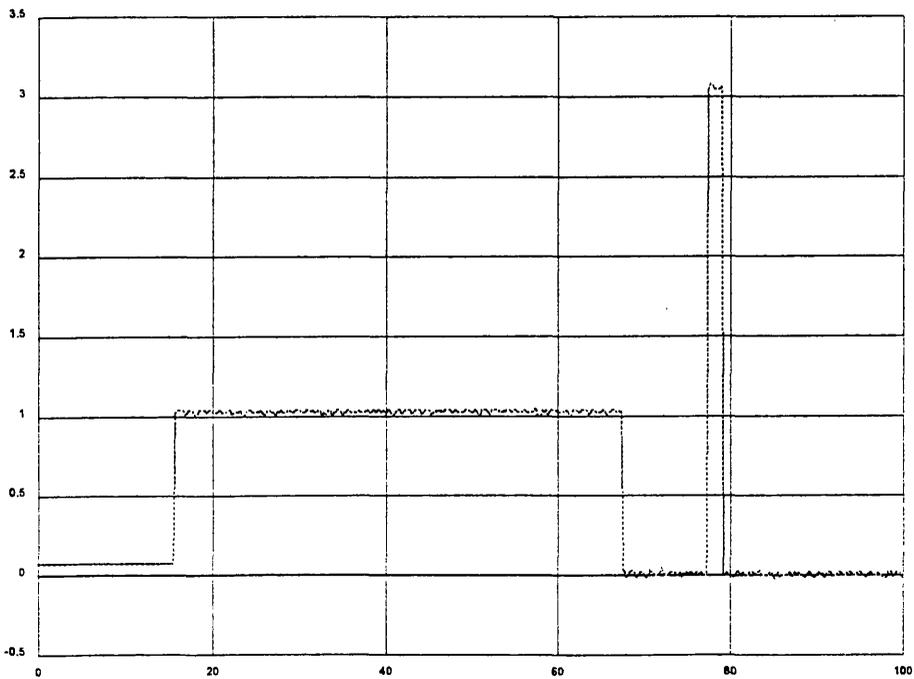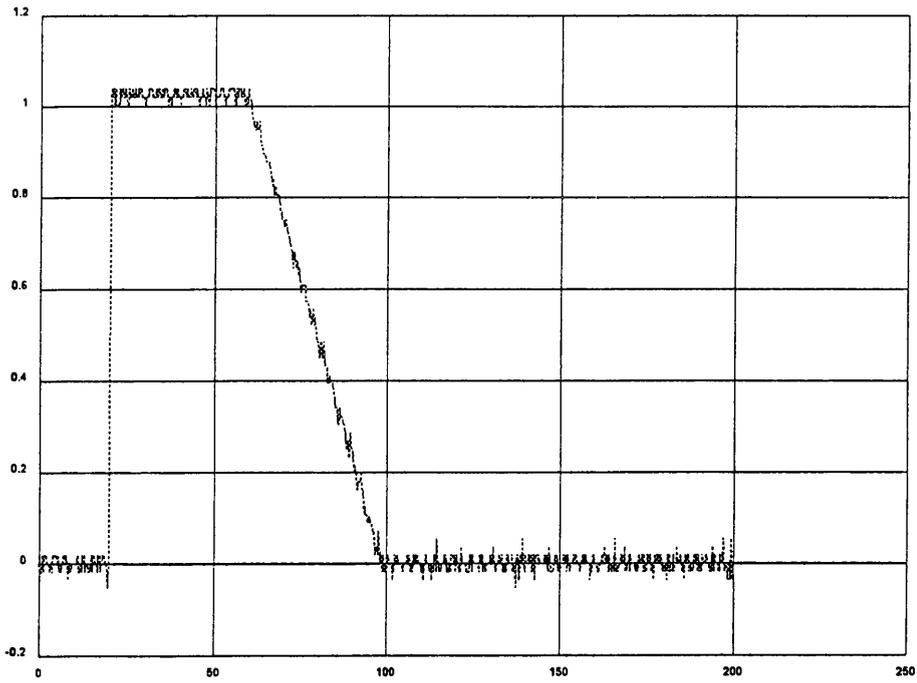
Figure 2.7. Sample output from Constant Current Stimulator

See text for details

that section into "steps" of equal duration and amplitude of 0.02 mA. For example, a "slope" from 0.1 mA to zero over 100 ms will consist of ten "steps" each lasting 10 ms; a slope from 0.2 mA to zero over 100 ms will consist of twenty steps of 5 ms.

Studies on Summation and Inhibition

As mentioned in Chapter 1, a major limitation of previous studies on the effects of subthreshold stimulation on effective refractory period is that none of these studies took adequate precautions to minimise the variability in effective refractory period which occurs as a result of short drive trains and pauses of varying duration between each train. The present study was therefore designed from the outset to minimise these sources of variability in refractoriness. Continuous single chamber pacing (right atrium or right ventricle) was performed at a constant cycle length (S1S1 = 500 or 600 ms) for at least two minutes prior to the interpolation of any premature beats, and after each premature beat there was no pause before recommencement of pacing at the same drive cycle. The late diastolic threshold was determined, and a premature beat (S2) was introduced at an adjacent site, initially in late diastole, with an amplitude of twice the late diastolic threshold. There was no pause between S2 and the beginning of the next drive cycle (S1), and the drive cycle lasted for at least 20 beats before each subsequent interpolation of S2. The coupling interval (S1S2) was gradually reduced until the point at which S2 just failed to capture, and this was defined as the effective refractory period. Estimation of the effective refractory period was repeated at least four times before proceeding with the study, and was repeated at intervals throughout the study; if S2 always failed to capture when S1S2 was equal to the effective refractory period, and always captured at a coupling interval 10 ms longer, this was considered to be satisfactory for the study. Further definition of the effective refractory period (to an accuracy of less than 10 ms) was not usually attempted, as it soon became apparent that, even under optimal

conditions, the spontaneous variability in effective refractory period made such accuracy impossible and unrealistic. If, however, the effective refractory period could not be defined to within 10 ms, or appeared to vary with time, the study was abandoned at that site and a more stable catheter position was sought.

Continuous background pacing (S1S1) was usually performed in the high right atrium or the right ventricular apex, using a bipolar catheter or the proximal or distal bipole of a quadripolar catheter with 5 mm or 10 mm interelectrode spacing. In the earliest studies, the premature beat (S2) was delivered either from an adjacent catheter or from another bipole on the same catheter as S1. Subthreshold conditioning stimuli (Sc) were delivered at the same site as S2. The reason that Sc and S2 were delivered at a site adjacent to S1 rather than through the same electrode is that Sc and S2 were delivered from a different stimulator (the Constant Current Stimulator) from that used for S1 (the Biotronik UHS-20). In the majority of the studies, conditioning stimuli and premature beats were delivered in a unipolar fashion, the indifferent electrode always being the distal tip of a 5 or 6 French diameter bipolar electrode catheter positioned in the inferior vena cava. The initial amplitude of Sc was usually 10-20% of the late diastolic threshold; depending on the effect of the conditioning stimulus on the effective refractory period, the amplitude, duration and/or polarity of the conditioning stimulus were varied, and the coupling interval (S1S2) was adjusted accordingly.

Inhibition

Figure 2.8 shows schematically the technique used when a conditioning stimulus was found to produce inhibition (lengthening of effective refractory period). Initially, without a conditioning stimulus, the effective refractory period was determined with a premature beat (S2). The coupling interval (S1S2) was then set at 10 ms longer than the effective refractory period, so that S2 consistently captured and produced a

propagated response (Fig. 2.8a). A conditioning stimulus (Sc) was then introduced at the same site as S2, beginning syncronous with S1 and of duration equal to S1S2 (Fig. 2.8b). The conditioning stimulus was increased in amplitude until S2 failed to capture (Fig. 2.8c). The coupling interval and the duration of the conditioning stimulus were then increased by 10 ms, and if S2 still failed to capture they were lengthened still further (fig. 2.8d). If capture occurred at a longer coupling interval, the amplitude of the conditioning stimulus was increased, and the process was repeated until the coupling interval approached the drive cycle length (S1S1) or until the amplitude of the conditioning stimulus approached 100% of the late diastolic threshold. Periodically during these procedures the effective refractory period was checked without a conditioning stimulus, to ensure that it had not changed.

Summation

Figure 2.9 shows schematically the protocol used when a conditioning stimulus was found to produce summation (shortening of the effective refractory period). The coupling interval (S1S2) was initially equal to the effective refractory period (fig. 2.9a), and S2 did not produce a propagated response. A conditioning stimulus (Sc) was then introduced at the same site as S2, beginning synchronous with S1 and of duration equal to S1S2 (fig. 2.9b). The conditioning stimulus was increased in amplitude until S2 captured (fig. 2.9c). The coupling interval and the duration of the conditioning stimulus were then shortened by 10 ms. and if S2 still captured at the shorter coupling interval (fig. 2.9c) they were shortened still further. If S2 failed to capture at a shorter coupling interval, the amplitude of the conditioning stimulus was increased until the amplitude of the conditioning stimulus approached 100% of the late diastolic threshold. As well as checking the effective refractory period (without a conditioning stimulus) periodically during these procedures, the effect of the conditioning stimulus alone (without S2) was also determined from time to time, to ensure that break excitation was not occurring with the conditioning stimulus alone.

Figure 2.8. Inhibition by Conditioning Stimulus
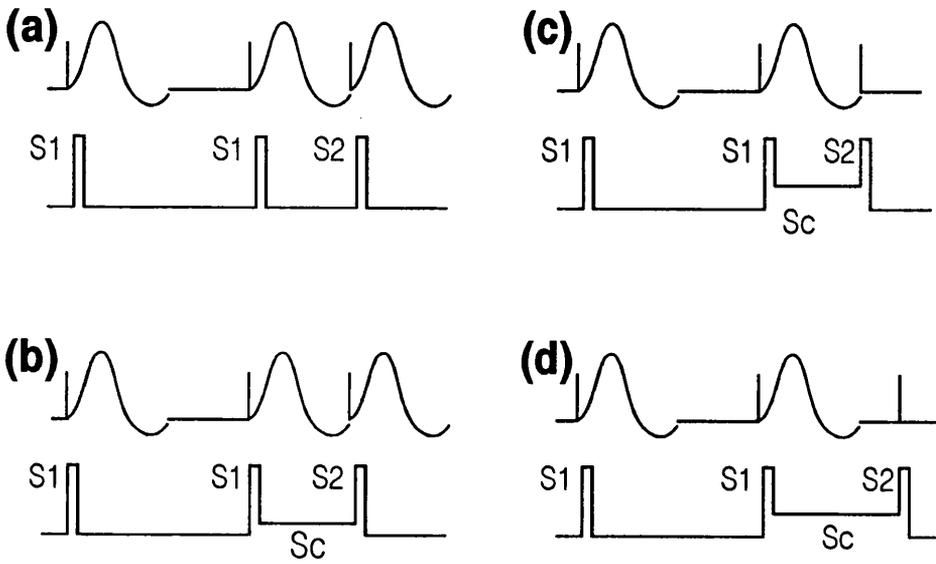
Figure 2.9. Summation by Conditioning Stimulus
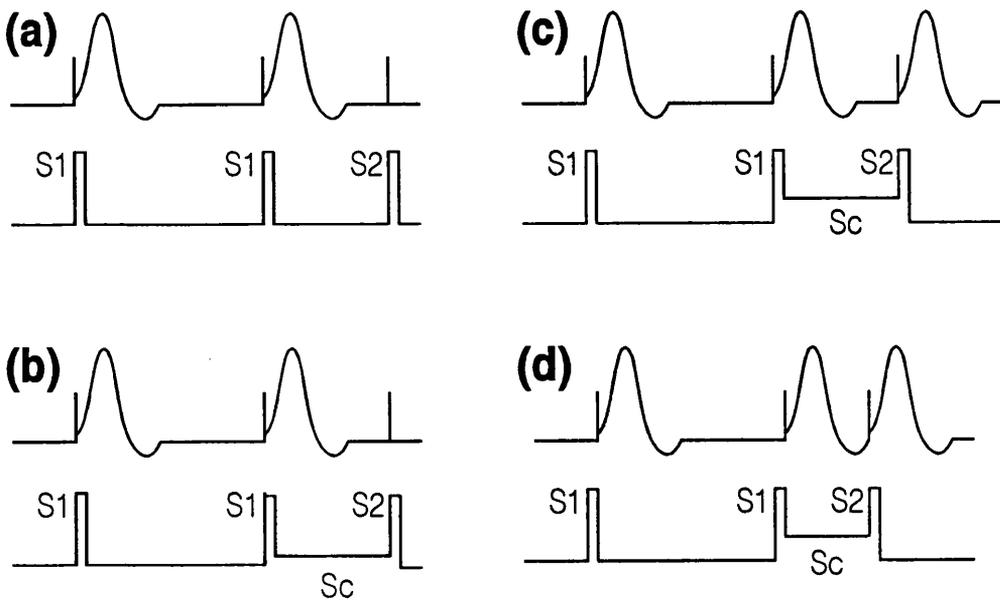
Temporal and Spatial Effects of Subthreshold Stimuli

These studies were undertaken once the results of the above experiments became apparent. Once it was shown that long duration subthreshold stimuli could produce profound effects on refractory periods, it was considered appropriate to determine what pulse durations were required to produce these effects, how long the effects lasted after the end of a pulse, and over what area the effects could be demonstrated. Temporal effects were studied by making use of the Constant Current Stimulator's programmability, which allowed variable delays to be inserted prior to commencement of a programmed pulse, variable gaps between segments of a programmed pulse (e.g. between the conditioning stimulus and S2), and variable pulse shapes. Spatial effects were studied by delivery of long duration pulses at an electrode adjacent to that used for delivery of the premature beat (S2). By using electrode catheters with different interelectrode distances and different electrode sizes the determinants of spatial spread of subthreshold stimuli could be studied, if only in one dimension. The details of each study are described along with the results in Chapter 5.

Monophasic Action Potential Recordings

In 19 studies, long duration constant current stimuli were delivered to the right ventricular endocardium close to the site of recording of a monophasic action potential (MAP). The monophasic action potentials were all recorded using a Franz combination pacing/MAP recording electrode (EP Technologies, Mountain View, California, USA).

Injury to a small area of myocardium will render the myocardial cells inexcitable and partially depolarised. There will therefore be a potential difference between the injured cells and surrounding normal cells. During electrical diastole, an electrode

placed on the injured area will record a negative potential with respect to an electrode overlying nearby healthy myocardium. During electrical systole, the potential is reversed, the injured area becoming positive. Such potentials can be recorded in animal hearts and humans, but until recently required the use of suction electrodes, which could only record for a short length of time and could lead to irreversible damage to the myocardium, because of the large negative pressure that had to be exerted on the catheter tip in order to maintain a stable recording. Recently, Franz (1983) described the use of a contact electrode for the recording of monophasic action potentials, and has shown that the signals recorded can remain stable for periods of three hours or more. The technique has been validated with recordings of transmembrane action potentials at the same sites in the same preparations (Franz *et al.*, 1986). More recently, a new catheter has been introduced which permits unipolar or bipolar pacing at a site close to the monophasic action potential recording site (Franz *et al.*, 1990), and it is this combination catheter which was used in the studies described in Chapter 6.

The electrode design is shown in figure 2.10. The catheter shaft is constructed of Teflon tubing and the electrodes are made from non-depolarising sintered silver-silver chloride. The tip electrode protrudes to form a smooth spherical surface 1 mm in diameter. The reference electrode is 0.5 mm in diameter and located 5 mm proximal to the tip. It is recessed into the shaft of the catheter so that it does not make contact with the endocardium, to avoid an injury potential being created at that point. The combination pacing/MAP catheter also has two pacing electrodes located 2 mm from the tip, oriented perpendicular to the axis of the monophasic action potential recording electrodes. The electrode assembly is spring-mounted in order to improve the contact of the distal electrode with the myocardium.

Monophasic action potentials were amplified using high impedance, DC coupled differential amplifiers (Gould Electronics, Cleveland, Ohio, USA). A high frequency cutoff of 1 kHz was used for filtering, and no low frequency filtering was used.

Signals were accepted for analysis if the monophasic action potential had a sharp upstroke, a typical configuration, a plateau amplitude of at least 15 mV, and a stable diastolic baseline. The recording techniques used have been validated in our laboratory (Morgan, 1991).

Further details of analysis and measurement of the signals obtained by this technique are given in Chapter 6.

Figure 2.10. Electrode Used for Recording Monophasic Action Potentials

(Reproduced by kind permission of Dr. M.R. Franz)

Spring Mechanism

Insulation

Epoxy Resin

Ag/AgCl

Electrode Terminals
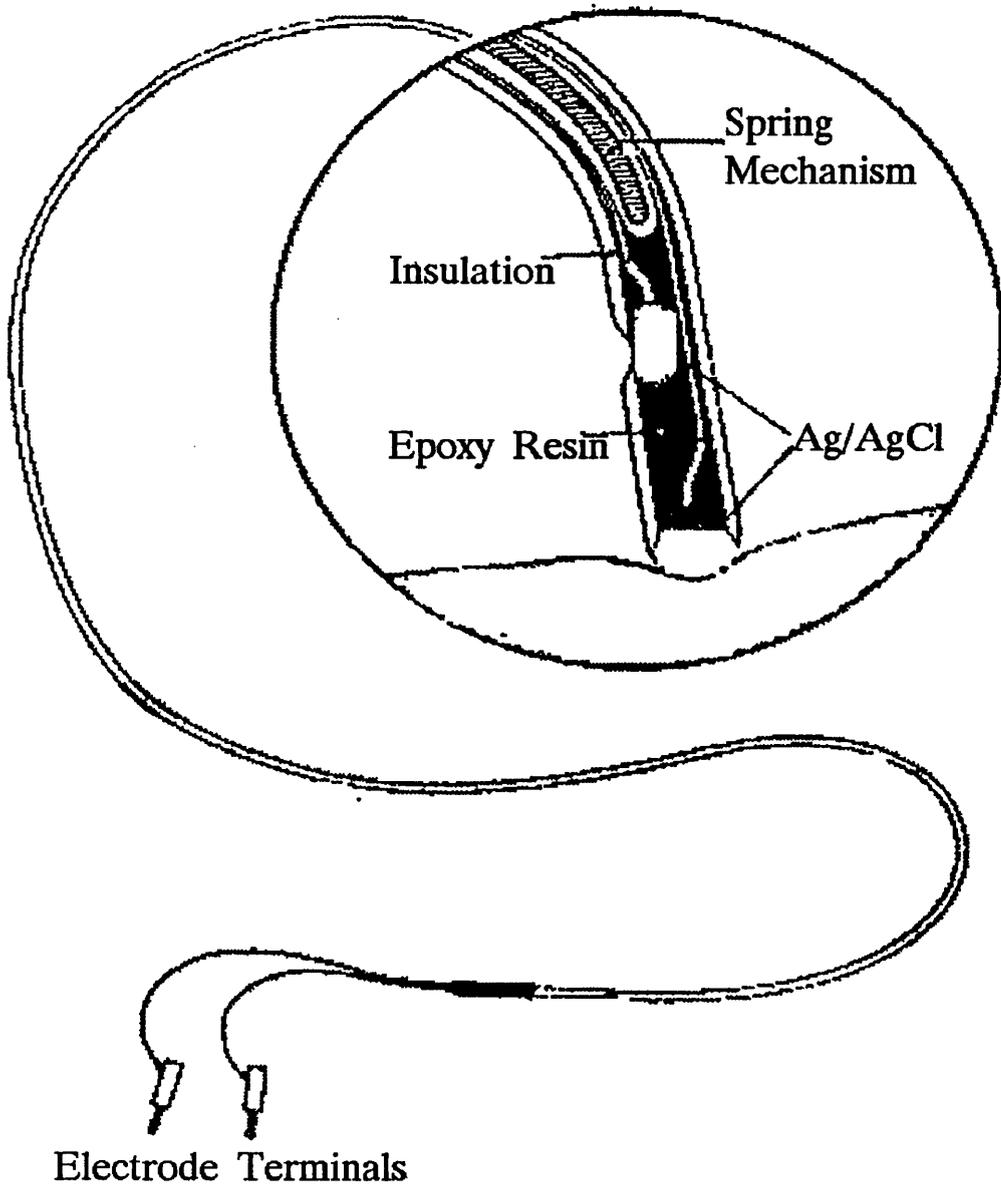
Constant Current Stimuli During Tachycardias

Long duration constant current stimuli were delivered during ventricular tachycardia in one patient, during atrioventricular reentrant tachycardia in ten patients, and during atrioventricular nodal reentrant tachycardia in two patients. In each case, the stimuli were delivered at a site close to a critical point on the reentrant circuit of the tachycardia. Precise details for each case are given in Chapter 7.

The purpose of delivery of long pulses during tachycardia was to attempt to terminate the tachycardia with a stimulus which did not itself result in either a propagated response or local capture. The aim of the technique used was to produce maximal inhibition at a critical site on a reentrant circuit by delivering unipolar cathodal conditioning stimuli with a duration greater than the excitable gap at that point in the tachycardia circuit. The technique involved determining the threshold for atrial or ventricular capture at the site of stimulation, and the effective refractory period as measured by a short duration (2 ms) stimulus with an amplitude of twice the late diastolic threshold. Long duration constant current pulses were then delivered at that site, commencing synchronous with a sensed local electrogram and with a duration 10% to 25% longer than the tachycardia cycle length. The initial amplitude of the long duration pulses was less than the late diastolic threshold in each case; the amplitude was increased stepwise until the tachycardia terminated or reset without capture, or until local capture was seen during the pulse, until a maximum current of 20 mA was reached, or until the patient complained of discomfort during delivery of the pulse. Further details of the current pulses delivered in each case are given in Chapter 7, along with the results of these experiments.

Chapter 3

Studies Using Bipolar Conditioning Stimuli

Patients and Methods

The effects of bipolar conditioning stimuli were studied in eight patients. The first six studies (patients one to six) were performed using bipolar conditioning stimuli in the right atrium, and two subsequent studies (patients 25 and 26) utilised bipolar conditioning stimuli in the right ventricle. The drive cycle length used was 600 ms in all except patient 26, in whom sinus tachycardia necessitated a drive cycle length of 500 ms.

Table 3.1 describes the characteristics of the eight patients. None of the patients was receiving antiarrhythmic drugs at the time of the study. Patient six had had two previous homograft aortic valve replacements and was being studied on account of unexplained syncope; none of the other patients, who were being investigated because of supraventricular arrhythmias, had structural heart disease.

Table 3.1. Bipolar Stimulation - Patients studied

Patient No.	Age (years)	Structural Heart Disease	Diagnosis	Rx	Stim Site
1	30	None	Sinus Tachy	Nil	RA
2	26	None	AVNRT	Nil	RA
3	16	None	WPW	Nil	RA
4	37	None	WPW	Nil	RA
5	19	None	ConcAP	Nil	RA
6	53	AVR	Syncope	Nil	RA
25	52	None	Syncope	Nil	RV
26	20	None	AVNRT	Nil	RV

Key: AVNRT = Atrioventricular nodal reentry tachycardia; AVR = Aortic valve replacement; ConcAP = concealed accessory pathway; RA = right atrium; RV = right ventricle; Rx = treatment at time of study; WPW = Wolff-Parkinson-White Syndrome.

The protocol used was as described in the previous chapter. In each of the first six studies, two quadripolar pacing catheters with interelectrode distances of 10 mm

Figure 3.1. Effect of Bipolar Conditioning Stimuli
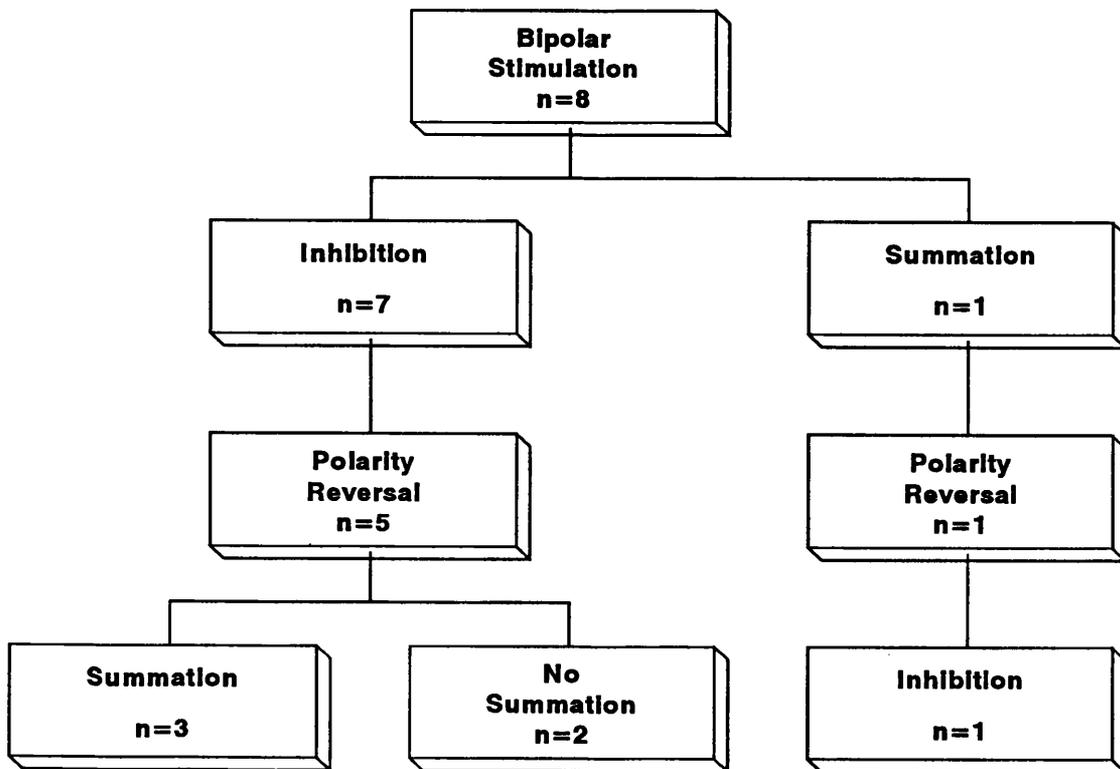
Table 3.2. Bipolar Stimulation - Results

Patient No.	Drive Cycle Length (ms)	LDT (mA)	ERP (ms)	ERP$_{max}$ (ms)	I (%LDT)	ERP$_{min}$ (ms)	I (%LDT)
1	600	1.12	300	420	90	*	
2	600	0.5	310	600	30	*	
3	600	0.72	200	365	80	170	80
4	600	0.46	190	280	40	**	
5	600	0.5	200	550	60	180	60
6	600	1.1	260	540	40	190	80
25	600	0.1	215	550	100	190	100
26	500	0.04	225	450	100	**	

Key: ERP = effective refractory period; ERP$_{max}$ = maximum effective refractory period; ERP$_{min}$ = minimum effective refractory period; I = conditioning stimulus current (as percentage of late diastolic threshold) which produced maximum effect on effective refractory period; LDT = late diastolic threshold; * - summation not sought in these patients (stimulus polarity not reversed); ** - no summation observed in these patients.

were placed adjacent to each other in the high right atrium. Continuous atrial pacing (S1S1) was performed using the distal bipole of catheter 1, and premature beats (S2) and conditioning stimuli (Sc) were delivered to the distal bipole of catheter 2. Local electrograms were recorded using the distal bipole of each catheter. In patients 25 and 26, continuous pacing was performed through a bipolar catheter in the right ventricular apex, and premature beats and conditioning stimuli were delivered to the pacing poles of a Franz (TM) combination pacing and monophasic action potential (MAP) recording catheter (EP Technologies, Mountain View, California, USA), which permitted recording of monophasic action potentials close to the site of delivery of the conditioning stimuli. Details of the recording techniques for monophasic action potentials, and the results obtained with these recordings, are given in Chapter 6.

In each of the eight studies it was first determined whether a conditioning stimulus could prolong the effective refractory period (inhibition), using the technique described in Chapter 2 and Figure 2.8. If no inhibition was produced, it was then determined whether the conditioning stimulus would result in shortening of the effective refractory period (summation), as described in Chapter 2 and Figure 2.9. In all but the first two studies, the polarity of the conditioning stimulus was then reversed and the process repeated.

Results

The results produced by bipolar conditioning stimuli are summarised in Figure 3.1 and Table 3.2.

In patients 1 and 2, inhibition was produced by conditioning stimuli, the effective refractory period being prolonged in patient 1 from 300 ms to 420 ms by a conditioning stimulus with an amplitude of 90% of late diastolic threshold, and in patient 2 from 310 ms to 600 ms with a conditioning stimulus of amplitude 30% of late diastolic threshold.

In patient 3, initially no inhibition was produced, but when the S1S2 interval was reduced it was found that the conditioning stimulus could shorten the effective refractory period. The amount of shortening of the effective refractory period increased as the conditioning stimulus current increased, and with a conditioning stimulus amplitude of 80% of late diastolic threshold the effective refractory period was reduced from 200 ms to 170 ms (summation). The polarity of the conditioning stimulus was then reversed, and it was discovered that the effective refractory period could be prolonged, the amount of prolongation increasing with increasing conditioning stimulus current. With a conditioning stimulus amplitude of 80% of late diastolic threshold, the effective refractory period was prolonged to 365 ms (inhibition). Samples of the electrograms recorded from this patient are shown in Figure 3.2, and the results shown graphically in Figure 3.3.

In the next five patients in whom bipolar conditioning stimuli were delivered, initial testing showed inhibition in all patients. Reversal of the conditioning stimulus polarity resulted in summation in patients 5, 6 and 25, but not in patients 4 and 26 (Figure 3.1). In the eight studies, the effective refractory period was lengthened by a mean of 97%, from 238 ± 44 ms to 469 ± 103 ms (mean $\pm$ SD); in the four patients in whom summation was observed, the effective refractory period was shortened from 219 ± 25 ms to 183 ± 8 ms.

Figure 3.2. Electrograms from Patient 3

(a) S1S2 = 210 ms (ERP + 10 ms); no conditioning stimulus
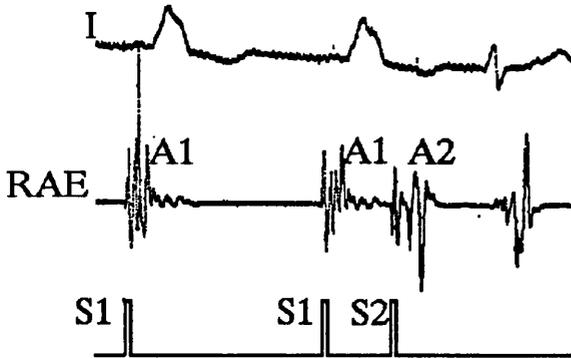
(b) S1S2 = 175 ms; Sc = 80% of late diastolic threshold
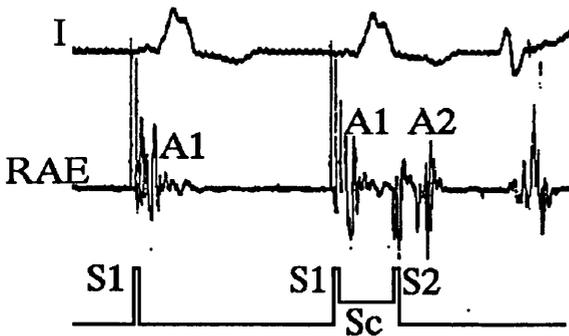
(c) S1S2 = 365 ms; Sc = 80% of late diastolic threshold (opposite polarity from (b))
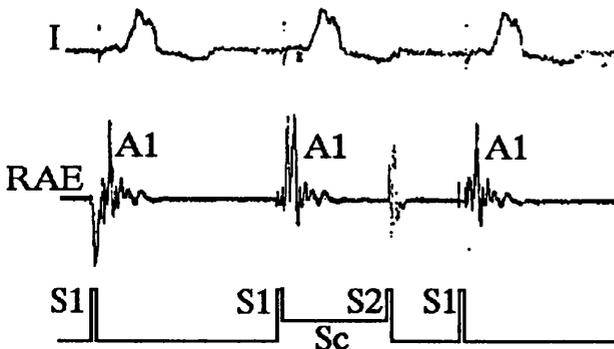
Figure 3.3. Bipolar Conditioning Stimuli: Effect of Changing Polarity: Patient 3
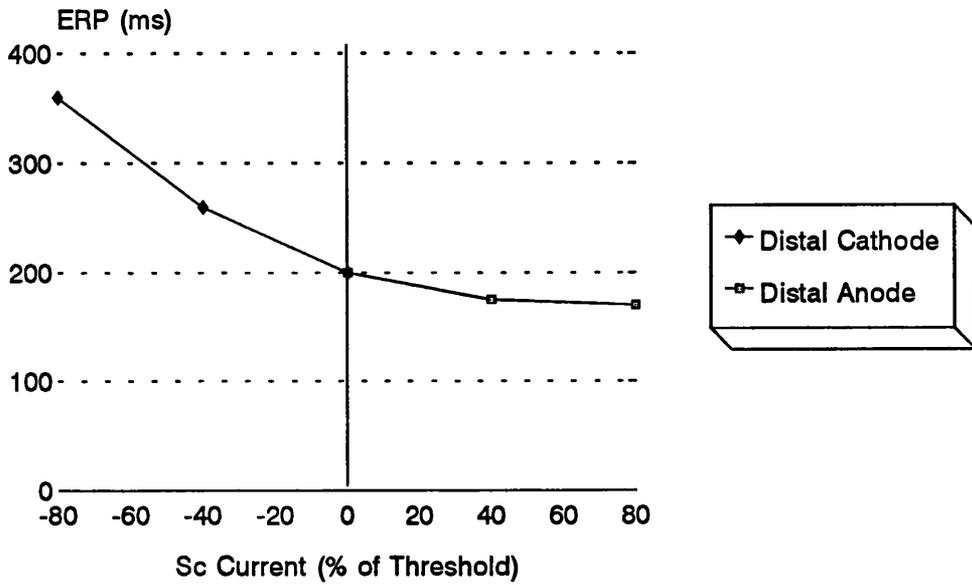
Discussion

These initial studies demonstrated that long duration subthreshold conditioning stimuli give rise to variable but profound effects on atrial and ventricular refractory periods. The changes observed in effective refractory period were of much greater magnitude than those produced in other studies using stimuli of short duration. Furthermore, when inhibition was seen, the degree of lengthening of the effective refractory period tended to increase as the amplitude of the conditioning stimulus increased.

The design of the study was such that every precaution was taken to ensure that spontaneous variability in the effective refractory period was minimised, as discussed in the Introduction and Methods (Chapters 1 and 2). Thus there was no intertrain pause after each premature beat, as a pause between drive trains is known to contribute to variability in effective refractory period (Morady *et al.*, 1990; Kadish *et al.*, 1991). One result of this aspect of the methodology was that, if a premature beat (S2) was inhibited from capturing, the next beat of the drive cycle (S1) would arrive 'on time', 500 or 600 ms after the previous beat (as shown in figure 3.2). This means that it was not possible to determine whether, in certain studies, the effective refractory period at the site of delivery of the conditioning stimuli and premature beats might be prolonged beyond the drive cycle length. In practical terms this is probably unimportant, as in many of these studies the effective refractory period had already been prolonged by more than 100% of its baseline duration. It was not always possible to determine precisely whether a premature beat at a coupling interval close to the drive cycle length was being inhibited or not, and often it was not thought appropriate to increase the coupling interval to within 50 ms of the drive cycle length. For example, in patients 5 and 25 (Table 3.2), premature beats at 550 ms could be inhibited by subthreshold stimuli, and no attempt was made to determine whether premature beats at 560-590 ms would capture, as a beat (S1) would always arrive at 600 ms.

The most interesting result of the studies on bipolar subthreshold conditioning stimuli is that, in four of the six cases in which it was studied, reversal of the polarity of the conditioning stimulus resulted in reversal of the effect on effective refractory period. Possible reasons for the results observed include:

1) Random variation in effective refractory period

2) Non-specific perturbation of effective refractory period induced by subthreshold stimulation

3) Artifacts induced by polarisation at one or other of the stimulating electrodes

4) Specific effect(s) on cellular excitability induced by subthreshold current.

With only a small number of studies it is not possible to prove conclusively that the changes observed were anything more than random variability in effective refractory periods or a non-specific effect of subthreshold stimulation on atrial and ventricular effective refractory periods. A more likely explanation, however, is that, during bipolar stimulation, separate (and perhaps opposing) effects are occurring at each pole. If so, the dominant effect seen at any particular time might depend on which pole (proximal or distal, anode or cathode) were making better contact with the myocardium at that time. This hypothesis again remains unproven, as it was not always recorded which electrode (proximal or distal) was the anode and which was the cathode in each study, nor was any attempt made to determine whether one electrode was making better contact with the myocardium than the other (for example, by measuring the unipolar electrogram recorded at each electrode of the bipole, using the same amplifier on open band width and at the same gain setting, or by measuring the threshold for unipolar pacing at each of the two poles). Furthermore, the question of electrode polarisation and the possible artifacts induced by this have not yet been dealt with. Nevertheless it seems interesting to postulate at

this stage that two opposing effects are being produced, on at least some occasions, during bipolar subthreshold stimulation. Which effect is occurring at which pole would best be determined by studying separately the effects of cathodal and anodal pulses. It was therefore decided to conduct further experiments using unipolar subthreshold stimulation.

Chapter 4

Studies Using Unipolar Conditioning Stimuli

Patients and Methods

The effects of unipolar conditioning stimuli were studied in 24 patients (patients 7 to 24 and 27 to 32). Stimulation was performed in the right atrium in the first sixteen patients (patients 7 to 22) and in the right ventricle in eight patients (patients 23, 24 and 27 to 32).

The characteristics of the 24 patients studied are listed in Table 4.1. Eight patients were being studied because of a history of sustained ventricular tachycardia or ventricular fibrillation, twelve had Wolff-Parkinson-White syndrome, three had other supraventricular arrhythmias and one had unexplained syncope. Twelve had structurally normal hearts, seven had coronary artery disease with previous myocardial infarction, one had mild aortic regurgitation and one had right ventricular dysplasia. Three patients had congenital heart disease: patient 8 had Ebstein's anomaly and a previous tricuspid valve replacement, patient 13 had atrioventricular and ventriculoatrial discordance and prosthetic valves in the pulmonary and left atrioventricular positions, and patient 14 had an atrial septal defect. At the time of the study, fifteen patients were receiving no antiarrhythmic drugs, seven were being treated with amiodarone, one with sotalol and one with digoxin.

The protocol used was as described in Chapter 2. Right atrial (in the first sixteen patients) or ventricular (in the last eight) bipolar pacing was performed at a constant cycle length of 500 or 600 ms, and premature beats were interpolated either at an adjacent pole on the same catheter or on the distal pole of a catheter positioned close by. The premature beats were unipolar, the indifferent electrode being positioned in the inferior vena cava at least 50 mm below the diaphragm. Local bipolar electrograms were recorded close to the sites of stimulation. As with the studies described in Chapter 3, inhibition was sought first, by prolonging the S1S2 coupling interval beyond the effective refractory period, and if no inhibition could be produced the coupling interval was shortened in order to determine whether summation could

Table 4.1. Unipolar Stimulation - Patients Studied

Patient No.	Age(yrs)	Structural Heart Disease	Diagnosis	Rx	Stim Site
7	59	CAD	V T	Amio	RA
8	48	Ebstein's	AFl	Amio	RA
9	17	None	WPW	Amio	RA
10	27	None	WPW	Nil	RA
11	22	None	WPW	Nil	RA
12	52	CAD	VF	Nil	RA
13	40	Corr TGA	WPW	Nil	RA
14	34	ASD	Atrial Tachy	Nil	RA
15	29	None	WPW	Amio	RA
16	48	CAD	VT	Amio	RA
17	37	None	WPW	Nil	RA
18	56	CAD	VT	Nil	RA
19	37	ARVD	VT	Nil	RA
20	55	AR	Syncope	Nil	RA
21	63	CAD	VT	Amio	RA
22	62	CAD	VF	Nil	RA
23	20	None	WPW	Nil	RV
24	16	None	WPW	Nil	RV
27	56	CAD	VT	Sot	RV
28	36	None	WPW	Nil	RV
29	62	None	AVNRT	Dig	RV
30	31	None	WPW	Nil	RV
31	57	None	WPW	Amio	RV
32	14	None	WPW	Nil	RV

Key: AFl = atrial flutter; Amio = amiodarone; AR = aortic regurgitation; ARVD = arryhthmogenic right ventricular dysplasia; ASD = atrial septal defect; AVNRT = atrioventricular nodal reentrant tachycardia; CAD = coronary artery disease; Corr TGA = congenitally corrected transposition of the great arteries; Dig = digoxin; RA = right atrium; RV = right ventricle; Rx = treatment; Sot = sotalol; VF = ventricular fibrillation;   VT = ventricular tachycardia; WPW = Wolff-Parkinson-White Syndrome.

be produced. The polarity of the conditioning stimulus was initially negative in all studies, and was subsequently changed to positive in all patients except patient 21, in whom time constraints prohibited the investigation of effects of anodal conditioning pulses.

Statistical analysis of the changes observed in effective refractory period was performed using two-way analysis of variance (ANOVA). Comparison between atrial and ventricular effective refractory periods was performed using two-tailed Student's t-tests, and comparison between the effects of anodal stimulation on atrium and ventricle was performed using Fisher's exact test.

Results

Cathodal Conditioning Stimuli

Table 4.2 summarises the results obtained with unipolar cathodal conditioning stimuli, and figures 4.1 and 4.2 show these results graphically.

Inhibition was produced in all patients by cathodal conditioning stimuli. In patients 7 to 22, baseline mean ($\pm$ standard deviation) atrial effective refractory period was 236.2 $\pm$ 40.8 ms (figure 4.1). A conditioning stimulus with an amplitude of 20% of late diastolic threshold prolonged the effective refractory period to 271.2 $\pm$ 49.9 ms. When the conditioning stimulus amplitude was increased to 50% of late diastolic threshold the effective refractory period was prolonged to 370.0 $\pm$ 115.5 ms. The maximum atrial effective refractory period was 475.0 $\pm$ 94.0 ms, with a mean conditioning stimulus amplitude of 55% of late diastolic threshold. Analysis of variance showed that the changes in effective refractory period were highly significant ($p < 0.01$).

Table 4.2. Unipolar Stimulation - Results of Subthreshold Cathodal Pulses

Patient No.	LDT (mA)	ERP (ms)	ERP $_{20}$ (ms)	ERP $_{50}$ (ms)	ERP $_{max}$ (ms)	I $_{max}$ (%LDT)
7	0.32	310	360	520	520	40
8	0.98	230	270	350	350	50
9	0.62	200	260	350	440	60
10	0.44	220	250	280	530	60
11	0.18	230	240	280	460	80
12	0.30	210	240	320	540	60
13	0.84	280	310	400	400	40
14	0.52	200	220	240	550	80
15	0.30	210	240	260	550	70
16	0.50	320	370	500	500	40
17	0.70	230	260	280	550	70
18	0.40	250	350	550	550	50
19	1.50	180	210	210	210	20
20	0.40	220	240	550	550	40
21	0.40	290	300	310	380	70
22	0.30	200	220	520	520	50
23	0.20	200	210	230	525	80
24	0.50	200	280	340	550	60
27	0.20	270	290	320	450	60
28	0.30	230	240	250	450	90
29	0.40	260	280	310	370	90
30	0.60	280	290	320	320	50
31	0.20	240	260	340	550	60
32	0.60	280	290	340	550	60

Key: ERP = effective refractory period; ERP $_{20}$ = effective refractory period after conditioning stimulus of 20% of late diastolic threshold; ERP $_{50}$ = effective refractory period after conditioning stimulus of 50% of late diastolic threshold; ERP $_{max}$ = maximum ERP; I $_{max}$ = conditioning stimulus current (as percentage of late diastolic threshold) required to produce maximal prolongation in effective refractory period; LDT = late diastolic threshold.

Figure 4.1. Effect of Unipolar Cathodal Conditioning Stimuli on Atrial Effective Refractory Period

Mean ± SD
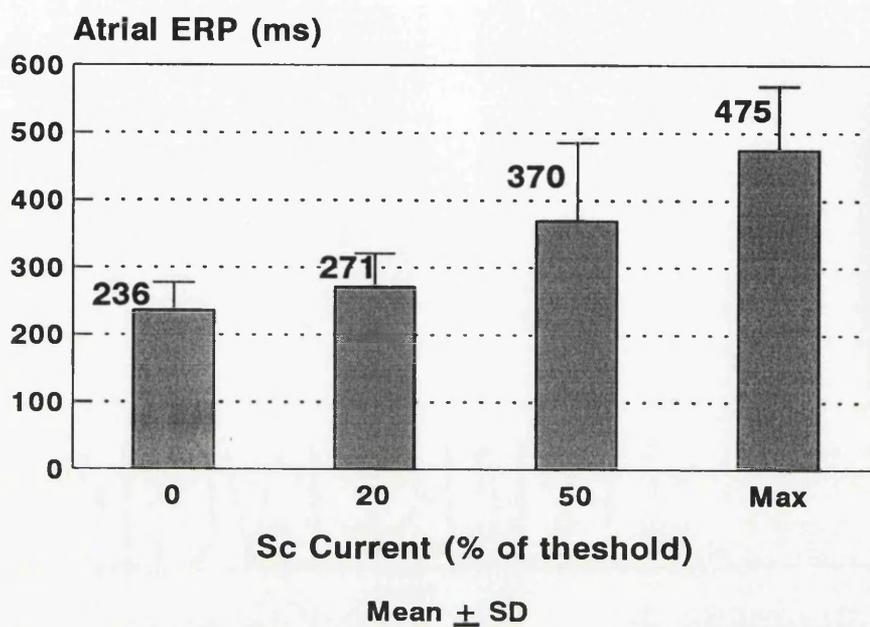
Figure 4.2. Effect of Unipolar Cathodal Conditioning Stimuli on Ventricular Effective Refractory Period

Mean ± SD
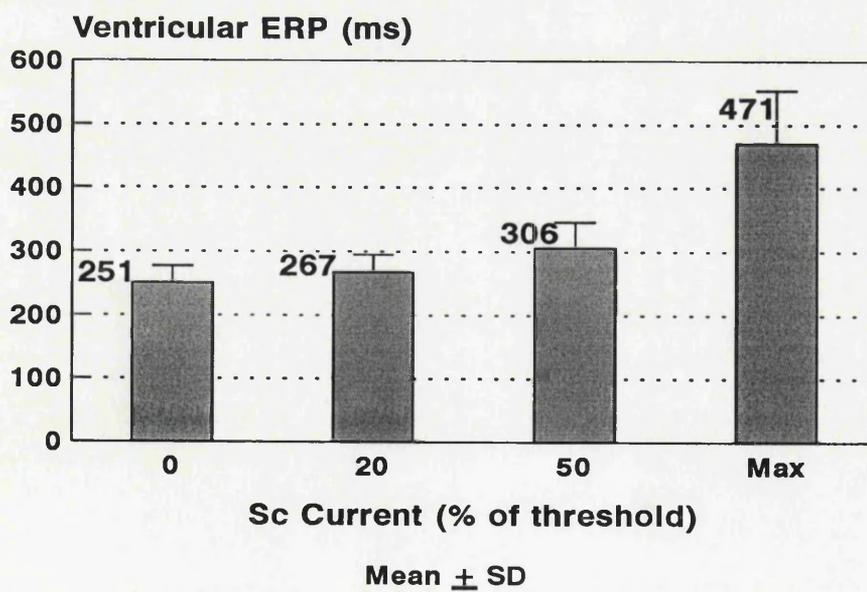
Similar results were produced with ventricular stimulation (figure 4.2). Baseline effective refractory period was 251.2 ± 25.7 ms. Conditioning stimulus currents of 20% and 50% of late diastolic threshold prolonged the effective refractory period to 267.5 ± 27.3 ms and 306.2 ± 40.0 ms respectively. The maximum effective refractory period was 470.6 ± 83.3 ms, with a mean conditioning stimulus current of 61.1% of late diastolic threshold. Once again, the changes in effective refractory period induced by subthreshold cathodal current were shown to be highly significant ($p < 0.01$).

There was no significant difference between the results obtained with atrial stimulation (patients 7 to 22) and those obtained with ventricular stimulation (patients 23, 24 and 27 to 32).

Anodal Conditioning Stimuli

Anodal stimulation was performed in 23 of the 24 patients, and the results are summarised in Table 4.3 and Figure 4.3.

In eleven patients the conditioning stimulus produced a shortening of the effective refractory period (summation) from 230 ± 37 ms to 165 ± 34 ms. Conversely, in eight patients, the effective refractory period was lengthened by anodal current (inhibition), from 233 ± 33 to 385 ± 107 ms. In each of these cases, the magnitude of the effect (summation of inhibition) increased as the conditioning stimulus current was increased. The incidence of summation and of inhibition in the atrium (patients 7 to 22) were similar to those observed in the ventricle (patients 23, 24 and 27 to 32; no significant difference using Fisher's exact test).

In patient 13, anode break excitation occurred at values shorter than the effective refractory period, and it was not possible to demonstrate summation as a consequence of this. In patients 7 and 8, anodal current had no significant effect upon the effective refractory period. In patient 24, low intensities of anodal current (up to 60% of late diastolic threshold) produced shortening of the effective refractory

Table 4.3. Unipolar Stimulation - Results of Subthreshold Anodal Pulses

Patient No.	LDT (mA)	ERP (ms)	Resp-onse	ERP $_{min}$ (ms)	I (% LDT)	ERP $_{max}$ (ms)	I (% LDT)
7	1.4	240	Nil				
8	0.92	220	Nil				
9	0.62	230	In	-	-	430	50
10	0.98	220	In	-	-	480	60
11	0.62	200	S	150	90	-	-
12	1.5	220	S	160	60	-	-
13	2.26	280	ABE				
14	1.98	200	S	140	50	-	-
15	0.,70	220	In	-	-	550	40
16	2.20	280	In	-	-	310	20
17	0.80	220	S	120	80	-	-
18	0.80	230	S	130	80	-	-
19	1.50	170	S	130	50	-	-
20	1.90	180	S	140	90	-	-
22	2.00	200	In	-	-	370	70
23	0.50	250	S	185	40	-	-
24	1.00	250	S & In	200	60	500	100
27	0.60	270	S	210	70	-	-
28	0.70	220	In	-	-	250	80
29	1.20	290	In	-	-	480	30
30	0.50	280	S	220	80	-	-
31	0.50	260	In	-	-	380	100
32	1.00	290	S	200	100	-	-

Key: ABE = anode break excitation; ERP = effective refractory period; ERP$_{max}$ = maximum effective refractory period; ERP $_{min}$ = minimum effective refractory period; I = conditioning stimulus current (as percentage of late diastolic threshold) required to produce maximum change in effective refractory period; In = inhibition; LDT = late diastolic threshold; S = summation. Anodal stimulation not performed in patient 21.

Figure 4.3. Effect of Unipolar Anodal Conditioning Stimuli on Atrial and Ventricular Effective Refractory Periods
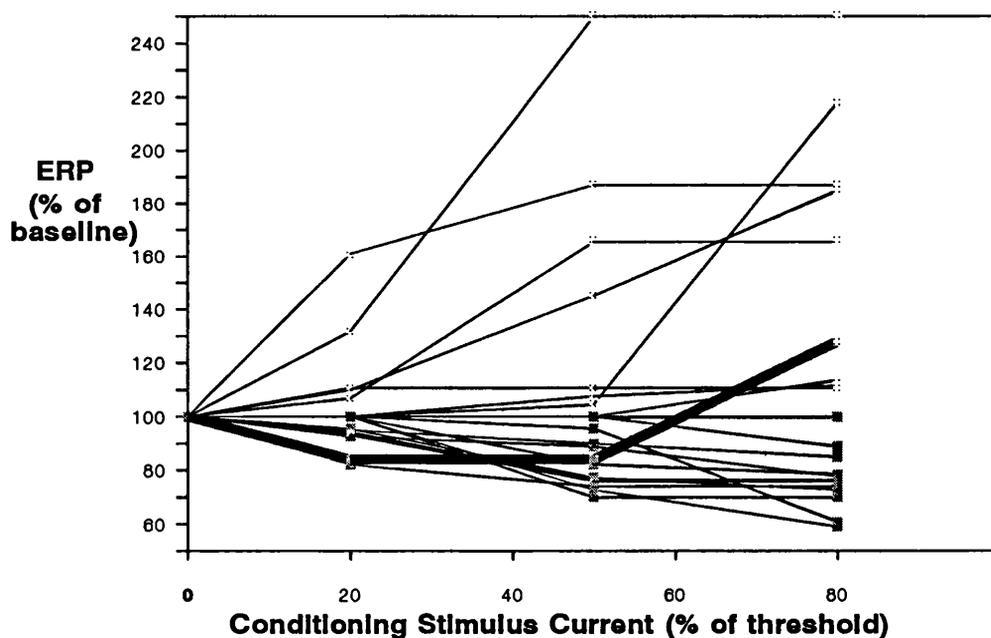
Each line represents a single patient. The effective refractory periods are displayed as percentage change from baseline. In eleven patients, effective refractory period was shortened by anodal conditioning stimuli (Summation), and in eight patients effective refractory period was lengthened (Inhibition). In one patient (thick line - patient 24 - see figure 4.6) summation was observed at conditioning stimulus amplitudes of 20% and 50% of late diastolic threshold, and inhibition was observed at a conditioning stimulus amplitude of 80% of late diastolic threshold. No effect was seen in two patients. See text for further details.

period, but as the conditioning stimulus current was increased beyond this level the opposite effect was produced, the effective refractory period being lengthened to a maximum of 500 ms.

Figures 4.4 to 4.6 show graphically the results of unipolar cathodal and anodal stimulation in three patients. In patient 12 (figure 4.4), cathodal current produced inhibition and anodal current produced summation; in patient 10 (figure 4.5), inhibition was produced by conditioning stimuli of both positive and negative polarity. In patient 24 (figure 4.6), as described above, cathodal current produced inhibition, low amplitude anodal current (up to 60% of late diastolic threshold) produced summation, and higher amplitudes of anodal current (80 to 100% of late diastolic threshold) produced inhibition.

Comparison of Unipolar and Bipolar Stimuli

In four patients, both unipolar (cathodal and anodal) and bipolar (with polarity reversal) stimuli were studied. Figure 4.7 shows an example of the effects observed. In this case, as in one other case, inhibition was produced by all types of stimuli; in the other two examples, summation was produced by unipolar anodal stimuli and by bipolar stimuli with the distal pole as the anode. In each case, the effects of unipolar stimulation mirrored the effects of bipolar stimulation, and summation was only produced when the distal pole was the anode.

Figure 4.4. Effects of Unipolar Cathodal and Anodal Stimulation in Patient 12
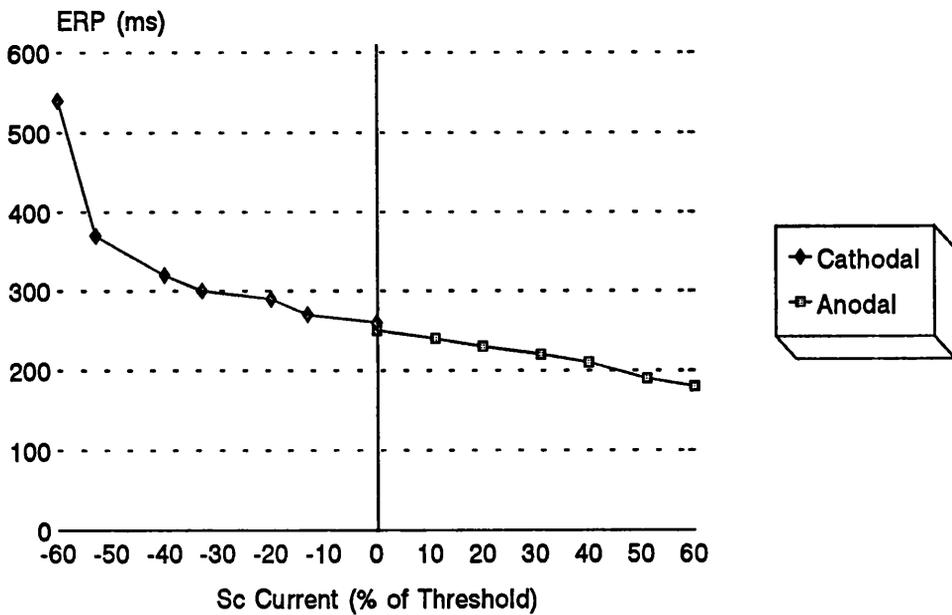
Figure 4.5. Effects of Unipolar Cathodal and Anodal Stimulation in Patient 10
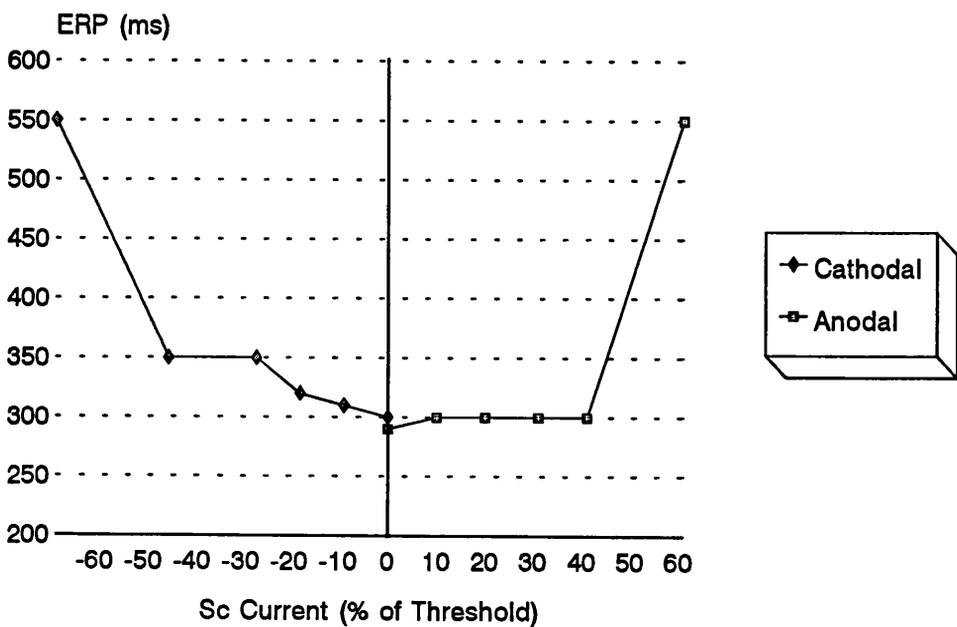
Figure 4.6. Effects of Unipolar Cathodal and Anodal Stimulation in Patient 24
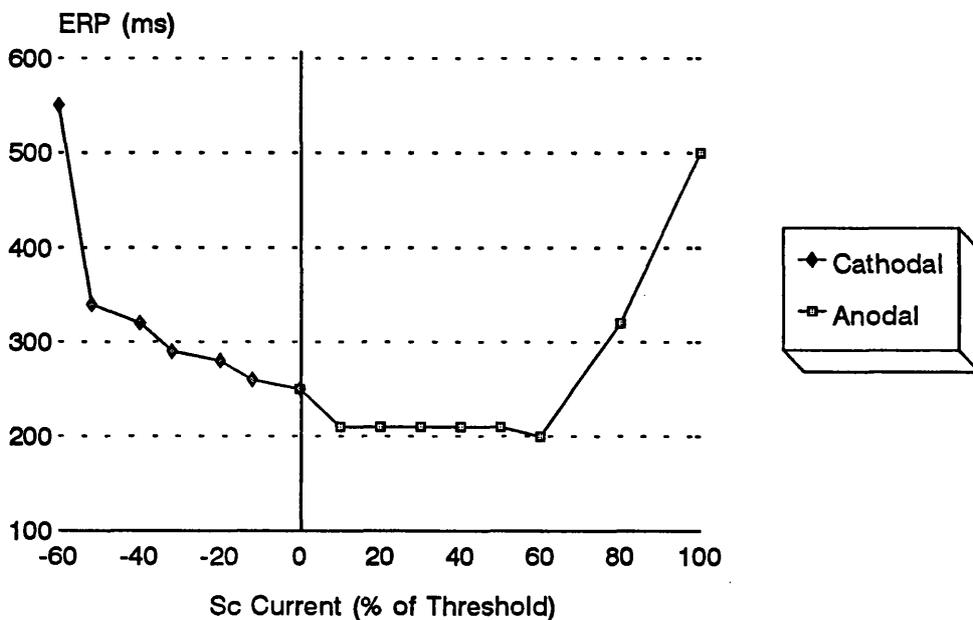
Figure 4.7. Effects of Unipolar (Cathodal and Anodal) and Bipolar Stimulation in Patient 57
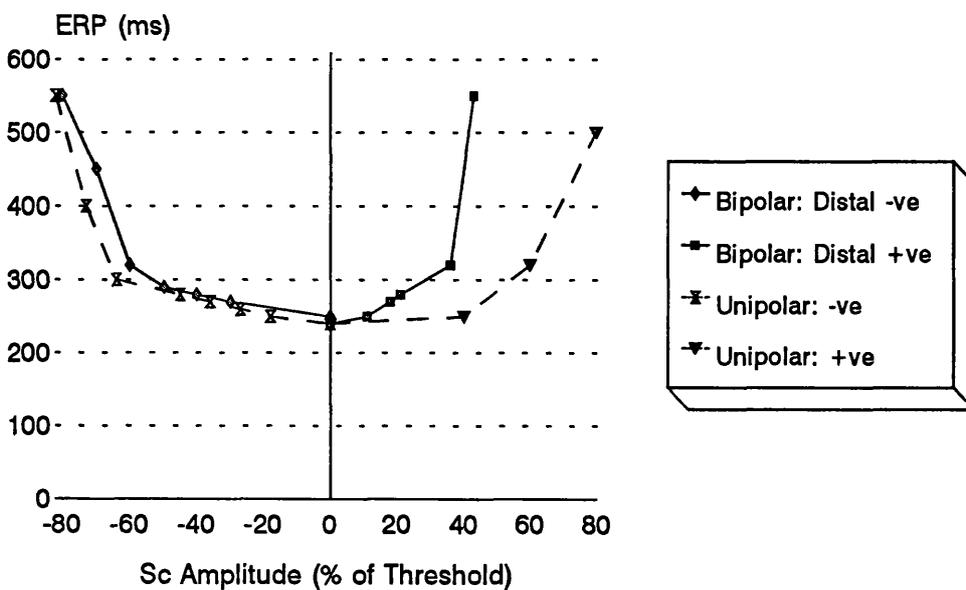
Discussion

Cathodal Conditioning Stimuli

In all patients studied, subthreshold cathodal conditioning stimuli always produced an increase in the effective refractory period (inhibition). Moreover, the magnitude of the effect on the effective refractory period tended to increase as the amplitude of the conditioning stimulus increased in each case. At no time was summation (shortening of effective refractory period) observed with cathodal conditioning stimuli. The changes in effective refractory period were highly significant.

Possible explanations for this effect include:

1) Lengthening of the action potential duration at the site of delivery of the conditioning stimuli, by an effect on potassium or calcium conductance.

2) Increase in threshold induced by cathodal current, perhaps by partial depolarisation of the membrane inducing inactivation of sodium channels.

3) Polarisation of the stimulating electrode.

4) A consequence of the fact that, at the end of a conditioning stimulus, the amplitude of the leading edge of the premature beat is reduced, and may be subthreshold.

Mechanisms (1) and (2) are of particular interest, but the question of the mechanism of the inhibitory effect of long duration subthreshold stimuli cannot be answered by the results of the studies described above. However, consideration of the possible mechanisms does lead to suggestions for further experiments, especially when considered in conjunction with the results of anodal stimulation.

The question of electrode polarisation can perhaps only be resolved completely by studies with charge balanced pulses (i.e. unipolar stimuli which reverse in polarity at

one or more points, so that the total charge delivered at the electrode tip is zero). The stimulator used in these studies was not capable of delivering charge balanced pulses. Polarisation artifact is considered further below.

One possible criticism of the above experiments is that, because the conditioning stimulus and premature beat were delivered at the same electrode and there was no gap between the two, the effective amplitude of the premature beat might be considered to be reduced (Figure 4.8), i.e. the leading edge of the premature beat would be less than twice the late diastolic threshold.

Figure 4.8. Leading and Trailing Edges of Premature Beat

Leading Edge of
S2 = (2xLDT)-Sc

Trailing Edge of
S2 = 2xLDT

LDT

Sc

S1   S1   S2
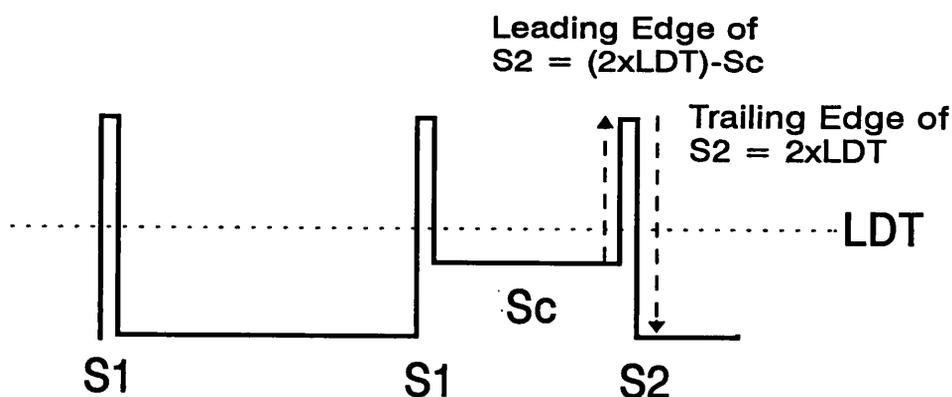
It is by no means certain whether the amplitude of the leading edge or the trailing edge of a unipolar cathodal pulse is more important in determining the threshold for myocardial capture; however, in several studies the effective refractory period was prolonged to beyond the point at which the late diastolic threshold was measured (usually at 500 ms when a 600 ms drive cycle length was used) by a conditioning stimulus amplitude of considerably less than 100% of threshold. In these cases, the

leading edge of the premature beat in late diastole would be greater than the late diastolic threshold, and yet capture did not occur. It seems unlikely, therefore, that the results are explicable entirely on the basis of a reduced leading edge of the premature beat. Further studies were performed in which the amplitude of the premature beat was increased beyond twice the late diastolic threshold, and the results are described in the next chapter.

Lengthening of the action potential duration by a subthreshold cathodal stimulus might possibly occur if the subthreshold current were to inhibit activation of the delayed potassium current (I_K) which is primarily responsible for repolarisation. Evidence for or against this effect might be sought by attempting to record monophasic action potentials at a site very close to the site of delivery of the subthreshold stimuli. If the action potential were to be prolonged at that site, or significant alteration in the shape of the terminal portion of the action potential to be produced, under the action of subthreshold cathodal conditioning stimuli, this might be taken as evidence that the subthreshold current was affecting the membrane currents responsible for repolarisation. Whether this effect might be due to a slowing of the activation kinetics of the I_K channels or inactivation of the channels would remain to be determined; the former seems more likely, as I_K is a time-dependent channel with a linear (i.e. ohmic) voltage-current relationship at an "infinite" time after a step change in voltage. As the potassium equilibrium potential is somewhat negative (i.e. hyperpolarised) to the resting membrane potential, it is likely that a cathodal (depolarising) pulse would tend to activate rather than inactivate I_K. Hence, if a subthreshold cathodal pulse was causing inhibition by an action on I_K, it would be likely to be a slowing of the activation kinetics of that channel. Other possible mechanisms by which the action potential might be prolonged in the immediate vicinity of the stimulating electrode during a long duration pulse might include local changes in extracellular potassium (thus affecting the equilibrium potential for I_K) or inhibition of calcium entry into cardiac muscle cells. Determination of transient

changes such as these in a very small area of myocardium are outwith the scope of studies on the intact human heart.

The effect of subthreshold current on sodium channel activation is worthy of consideration. Sodium currents in cardiac muscle behave similar to those in nerve, in that they undergo activation and inactivation by ionic gating mechanisms (termed m and h). (These can be thought of as "gates" in the membrane channel, which open and close in response to changes in membrane potential. As the membrane potential is changed from resting towards threshold, the m gates tend to open quickly and the h gates tend to close slowly.) An action potential commences when the channel is activated (value of conductance m increases) and the membrane is depolarised to threshold, with a regenerative (positive feedback) increase in conductance in the sodium channel. At the same time, however, the channel is slowly being deactivated by a decrease in conductance h, which has a slower time course than variable m, and thus the sodium conductance is inactivated within a few milliseconds. Were depolarisation to take place slowly enough, the sodium channels may be inactivated by a decrease in conductance h before the regenerative increase in conductance m could take place, i.e. a subthreshold depolarising current would inhibit activation. Were a sustained depolarising pulse to "clamp" the membrane potential of the myocardial cells around a value at which the sodium current continued to be inactivated (e.g. -60 mV), activation of sodium channels would be inhibited for as long as the subthreshold current was being passed.

The situation is made considerably more complex, however, by the fact that the heart is a three-dimensional structure. Myocardial cells are electrically linked by gap junctions between cells, and tend to function as a syncytium, although the spread of excitability is anisotropic. Although much is known about the electrical behaviour of individual cells studied *in vitro*, relatively little is known about cell-to-cell interactions in the myocardial syncytium, and in particular about how many cells, or what area of membrane, needs to be depolarised to what level within what period of time for a

propagated action potential to be initiated. It seems self-evident that, if a small area of membrane is partially depolarised but does not reach threshold, current flow from surrounding (electrically connected) cells will tend to neutralise that effect and return the membrane potential towards the resting level. However, little is known about what is required for a stimulus to reach or exceed threshold, and even less is known about the spatial and temporal effects of a subthreshold stimulus.

The above explanation of the possible effects of a subthreshold cathodal pulse on inactivation of sodium channels is perhaps feasible. It remains conceivable that, even if a conditioning stimulus were to "clamp" the membrane potential at a level at which the sodium current was inactivated, a stimulus of sufficient amplitude might still lead to a propagated action potential, either by activating the slow inward current in those cells which were partially depolarised, or by activating myocardial cells outwith the region of membrane affected by the subthreshold pulse. Since we do not know the extent of the spatial or temporal effects of subthreshold current, it remains to be determined whether recording of monophasic action potentials close to the site of delivery of subthreshold pulses will be informative, whether a larger amplitude of premature beat (S2) will capture by one of these methods, and whether the time course of the inhibitory effect of subthreshold cathodal pulses can be studied by termination of the conditioning stimulus at various intervals before the premature beat.

Anodal Conditioning Stimuli

The effects produced by anodal conditioning stimuli are more difficult to explain, as any explanation must take account of the observation that summation and inhibition are produced with almost equal frequency by anodal stimulation. Ideally the explanation should take account of the observation in patient 24, in whom low amplitude anodal stimuli produced summation and higher amplitude (but still subthreshold) stimuli produced inhibition, although this was only observed in one patient.

The fact that different effects were seen in different patients makes the results of anodal stimulation difficult to explain in terms of artifact such as electrode polarisation or diminution of the leading edge of the stimulus, and it seems more likely that the effects observed represent genuine changes in membrane excitability induced by the subthreshold stimuli. Let us consider first the possible effects on sodium conductance. An anodal stimulus applied during the plateau phase and the repolarisation phase of the action potential would be expected to accelerate the repolarisation process, and perhaps lead to hyperpolarisation. Kavanagh *et al.* (1990) have recently shown that a subthreshold anodal pulse of 10 to 20 ms in duration produced a fall in threshold (at 10 ms beyond the effective refractory period) and a reduction in the absolute refractory period in the canine ventricle. Further studies in rabbit ventricular cells in vitro suggested that the mechanism of this effect was accelerated repolarisation with consequent increase in availability of sodium channels, resulting in a faster upstroke of the subsequent action potential. These conclusions are in accordance with the work of Weidmann (1951), who showed that anodal pulses applied during the repolarisation phase of the action potential could accelerate its repolarisation.

As the range of membrane potentials within which the sodium current can be activated is very narrow, it is conceivable that, under certain circumstances, an anodal current could hyperpolarise the cell membrane beyond the sodium current's excitable region, leading to a reduction in excitability. Thus anodal conditioning stimuli might produce summation or inhibition, depending on the membrane potential to which the myocardial cells are hyperpolarised. The results seen in patient 24, where a low intensity anodal current produced summation and a higher amplitude of anodal current resulted in inhibition, are compatible with this explanation.

Chapter 5

Temporal and Spatial Effects of Subthreshold Pulses

Introduction

In the studies described in the preceding two chapters, it has been shown that long duration subthreshold conditioning stimuli can produce profound changes in effective refractory period in the human atrium and ventricle. Using unipolar stimuli, it has been shown that cathodal pulses always produce inhibition, whereas anodal pulses can have variable effects, producing inhibition in some patients and summation in others.

The purpose of the studies described in this chapter was to investigate the characteristics of subthreshold cathodal conditioning stimuli which produce inhibition, and to attempt to determine the importance of the pulse duration, the effect of a gap between the conditioning stimulus and the premature beat, and the effect of changes in amplitude of the premature beat. In addition, as a prelude to attempting to terminate arrhythmias with subthreshold pulses, the spatial effects of subthreshold conditioning stimuli were studied.

All the studies described in this chapter involved delivery of unipolar cathodal conditioning stimuli, and in each patient it was first demonstrated that the effective refractory period could be prolonged by subthreshold cathodal current using the protocol described in the previous chapter.

Patients and Methods

Protocol 1 - Effect of Decreasing the Length of the Conditioning Stimulus

In six patients, after it was shown that inhibition could be produced by a long duration subthreshold cathodal conditioning stimulus using the protocol described before, a gap was left between the last beat of the drive cycle (S1) and the beginning of the conditioning stimulus (figure 5.1). The initial coupling interval (S1S2) and

Figure 5.1. Protocol 1: Effect of Decreasing Length of Conditioning Stimulus
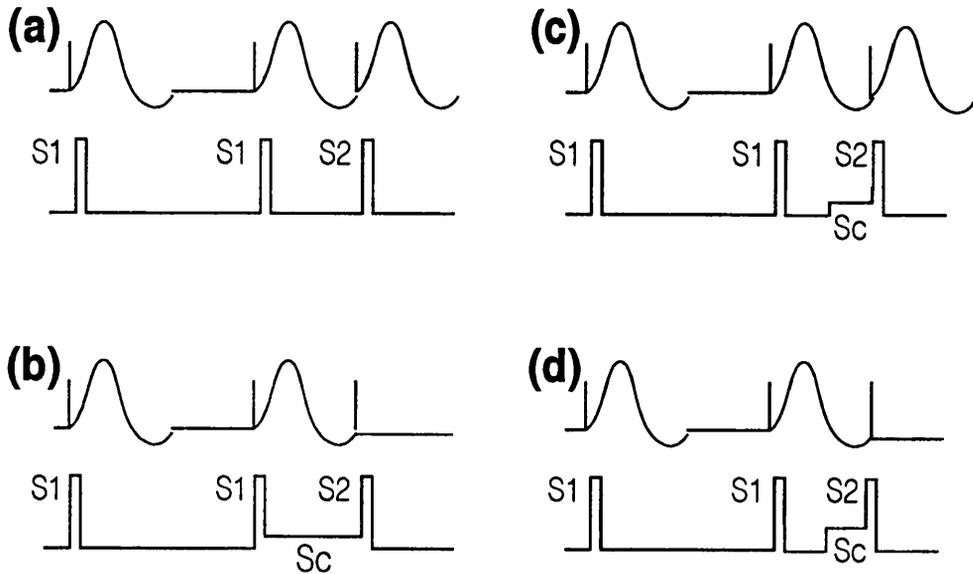
Initially, the S1S2 interval was slightly longer than the effective refractory period, and S2 captured (a). A subthreshold cathodal conditioning stimulus (Sc) was then interpolated as in previous studies, and capture by S2 was inhibited (b). The duration of Sc was shortened (c) until S2 captured again, at which point the amplitude of Sc was increased (d) in order to determine the current required for inhibition at this Sc duration.

amplitude of the conditioning stimulus were such that inhibition could always be produced if the duration of the conditioning stimulus were equal to the coupling interval; in most cases the coupling interval was 10-20 ms longer that the effective refractory period, but in some studies the coupling interval was lengthened further. The initial amplitude of the conditioning stimulus was the minimum required to produce inhibition. A gap of 50 ms was then introduced between the last driven beat (S1) and the conditioning stimulus (the coupling interval S1S2 being kept constant). If inhibition still occurred, the gap was increased (i.e. the conditioning stimulus duration reduced), initially in steps of 50 ms, and subsequently in smaller steps. If capture occurred at a particular pulse duration, the duration was held constant and the amplitude of the conditioning stimulus increased until inhibition was produced again, and the process was repeated until the amplitude of the conditioning stimulus required to produce inhibition approached the late diastolic threshold.

Protocol 2 - Effect of Gap Between Conditioning Stimulus and Premature Beat

In six patients, with the coupling interval set at 10 to 20 ms longer than the effective refractory period and the conditioning stimulus amplitude set at the minimum required to produce inhibition, the conditioning stimulus duration was shortened by 2 ms, leaving a 2 ms gap between the end of the conditioning stimulus and the premature beat. If inhibition still occurred, the gap was widened to 5 ms, then in further steps of 5 ms, the coupling interval being kept constant throughout (figure 5.2). If capture occurred, the conditioning stimulus amplitude was increased until inhibition occurred. The process was repeated until the amplitude of the conditioning stimulus required to produce inhibition approached the late diastolic threshold. In some studies, conditioning stimuli with amplitudes greater than the late diastolic threshold were then introduced, and it was determined whether inhibition could be produced over a larger gap by pulses of larger amplitude.

Figure 5.2. Protocol 2: Effect of Gap between Conditioning Stimulus and Premature Beat
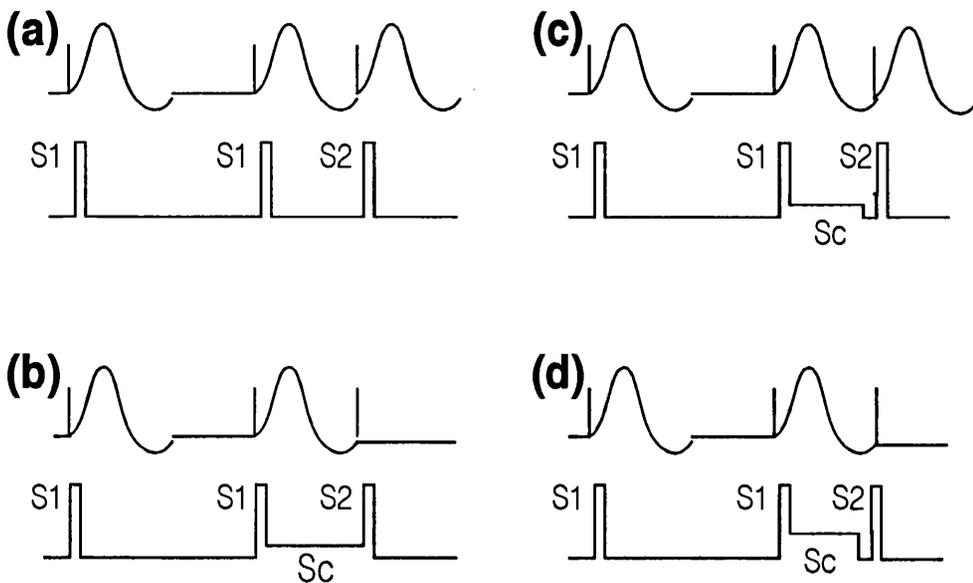
Initially, the S1S2 interval was slightly longer than the effective refractory period, and S2 captured (a). A subthreshold cathodal conditioning stimulus (Sc) was then interpolated as in previous studies, and capture by S2 was inhibited (b). A gap was then introduced between the end of the conditioning stimulus and the premature beat (c), and if inhibition persisted across the gap the duration of the gap was increased. If S2 captured, the amplitude of the conditioning stimulus was increased (d) until inhibition was produced again, or until the amplitude of Sc approached the late diastolic threshold.

Protocol 3 - Effect of Increasing the Amplitude of the Premature Beat

In four patients, the coupling interval was kept constant (usually at 10 to 20 ms longer than the effective refractory period) and the minimum conditioning stimulus current required to produce inhibition (with a pulse duration equal to the coupling interval) was determined. The amplitude of the premature beat was then increased stepwise, and at each stage the conditioning stimulus current required to inhibit the larger premature beat was determined (figure 5.3). The process was repeated until the amplitude of the conditioning stimulus approached the late diastolic threshold.

Protocol 4 - Study of Spatial Effects of Subthreshold Pulses

In 12 patients, the spatial effects of subthreshold pulses were studied by delivering the long duration conditioning stimulus at a point adjacent to the position at which premature beats were delivered. This was accomplished by delivering the drive stimuli (S1) and premature beats (S2) at one pole of a multipolar catheter and delivering the conditioning stimuli at an adjacent pole on the same catheter. Prior to commencing this study, it was first shown that inhibition could be produced at each of the two poles by long duration subthreshold cathodal conditioning stimuli, i.e. the studies described in chapter 3 were performed twice on each patient (once for each pole) before an attempt to demonstrate a spatial inhibitory effect was made. The catheter types used for this study included a quadripolar catheter with a Josephson curve and 5 mm interelectrode spacing (Bard Electrophysiology, Tewkesbury, Massachusetts, USA), a decapolar catheter with 1 mm interelectrode spacing (Bard Electrophysiology), a catheter designed for low energy ablation, with a large (4 mm) contoured distal tip and 2 mm interelectrode spacing (National Heart Hospital Ablation Catheter; Bard Electrophysiology), and a custom made catheter manufactured by the passage of three fine insulated copper wires down the length of a 6F multipurpose angiography catheter (Cordis, Miami, Florida, USA), with the bare

Figure 5.3. Effect of Increasing Amplitude of Premature Beat
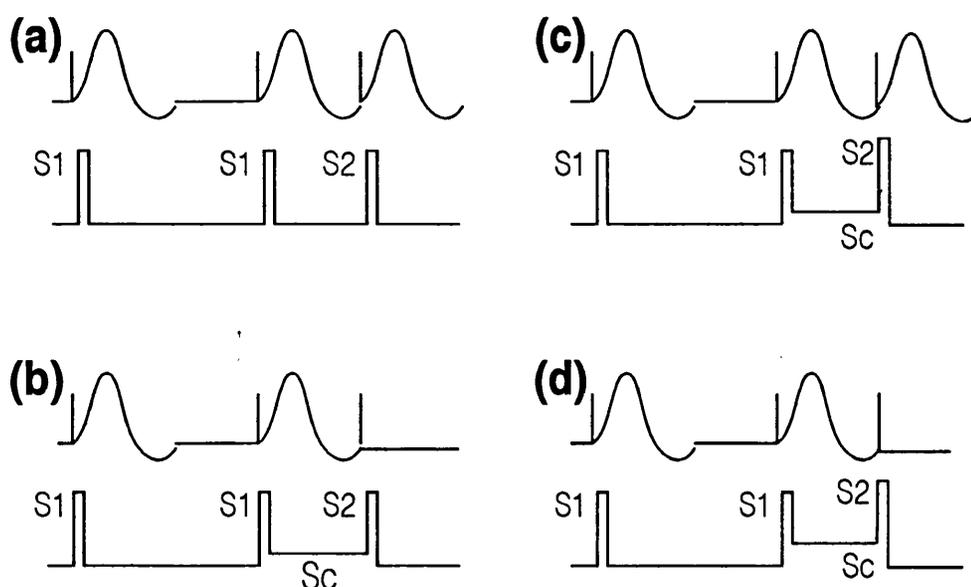
Initially, the S1S2 interval was slightly longer than the effective refractory period, and S2 captured (a). A subthreshold cathodal conditioning stimulus (Sc) was then interpolated as in previous studies, and capture by S2 was inhibited (b). The amplitude of S2 was then increased (c) until it captured again, and the amplitude of Sc was increased in order to inhibit the larger amplitude S2. The process was repeated until the amplitude of Sc approached the late diastolic threshold.

ends of the wires just protruding at the catheter tip and cemented into position with epoxy resin (fig. 5.4), the interelectrode distance being 0.4 mm.

In all cases the catheter was positioned at the apex of the right ventricle, and in the studies using commercially-available catheters the long duration subthreshold conditioning stimuli were delivered at the distal pole (pole 1), and the adjacent pole proximal to it (pole 2) was used for pacing (S1) and premature beats (S2). The two poles of a bipolar pacing catheter positioned in the inferior vena cava functioned as the indifferent electrodes (anodes) for poles one and two of the intracardiac catheter. Late diastolic threshold was determined at each pole, and the amplitude of the pacing stimuli and premature beats was set at twice the late diastolic threshold on pole 2. The duration of the conditioning stimulus was 10-50 ms longer than the S1S2 coupling interval. The initial amplitude of the conditioning stimulus was set at 10-20% of late diastolic threshold on pole 1, and increased stepwise. If no inhibition was produced with conditioning stimuli with amplitudes below the late diastolic threshold, the stimulus amplitude was increased progressively until inhibition occurred, or until capture occurred at the end of the conditioning stimulus (cathode break excitation) or during the stimulus, or until the output reached 20 mA or the patient experienced discomfort.

In some studies, if capture occurred at the end of the conditioning stimulus, the shape and duration of the stimulus were changed so that a sloping termination of the conditioning stimulus was produced, in order to try to prevent capture by the trailing edge of the conditioning stimulus. In these situations and other studies in which high amplitude long duration stimuli were used, a careful note was made of the threshold for capture during or after the long pulse, and any variability in threshold for these parameters.

Figure 5.4. Catheter Used for Study of Spatial Effects of Conditioning Stimuli
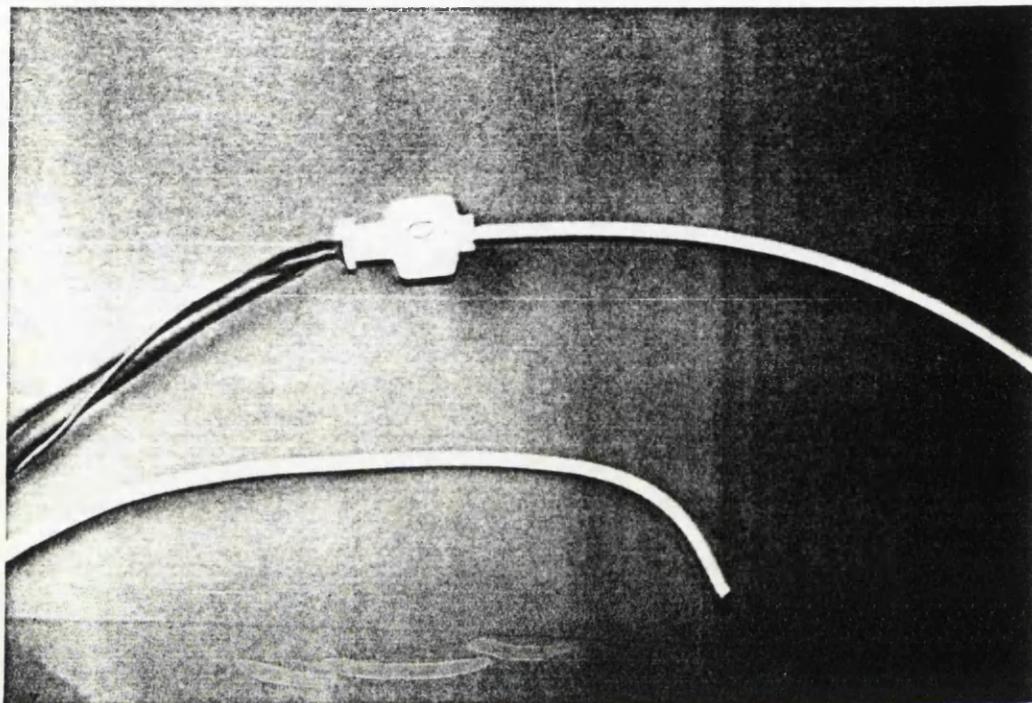
Results

Protocol 1 - Effect of Decreasing the Length of the Conditioning Stimulus

Figure 5.5 shows the effect of variations in conditioning stimulus duration on the threshold for inhibition in six patients, and table 5.1 presents the same information in tabular form. In all these studies the coupling interval was kept constant at 10-20 ms longer than the effective refractory period. In all six patients, inhibition could be produced with conditioning stimulus durations of 20 ms or less. The stimulus amplitude required to produce inhibition with a 20 ms stimulus was 2.3 ± 1.8 times the amplitude required with a stimulus present throughout diastole ($p = 0.116$). Inhibition could be produced with a conditioning stimulus duration of 10 ms in 5 of the six patients, and with a conditioning stimulus duration of 5 ms in one.

Figure 5.6 presents the same data as in figure 5.5, but with the total charge delivered (current x duration) plotted for each conditioning stimulus duration. The mean charge delivered at maximum stimulus duration (i.e. when the conditioning stimulus duration is equal to the coupling interval) was 12.6 ± 5.1 microcoulombs; with a conditioning stimulus duration of 20 ms, the charge required was 2.1 ± 1.5 microcoulombs ($p = 0.004$). Thus, although long duration conditioning stimuli produce inhibition with much less current, the total charge required to produce inhibition is much greater with long duration stimuli.

Figure 5.5. Effect of Conditioning Stimulus Duration on Current Required for Inhibition

Sc Current required for inhibition (% of threshold)

Duration of Sc (ms)

Legend:
- ─ 81 (TC)
- + 82 (CJ)
- * 84 (IB)
- ×- 86 (PB)
- ◆ 87 (AW)
- ▲- 89 (CB)
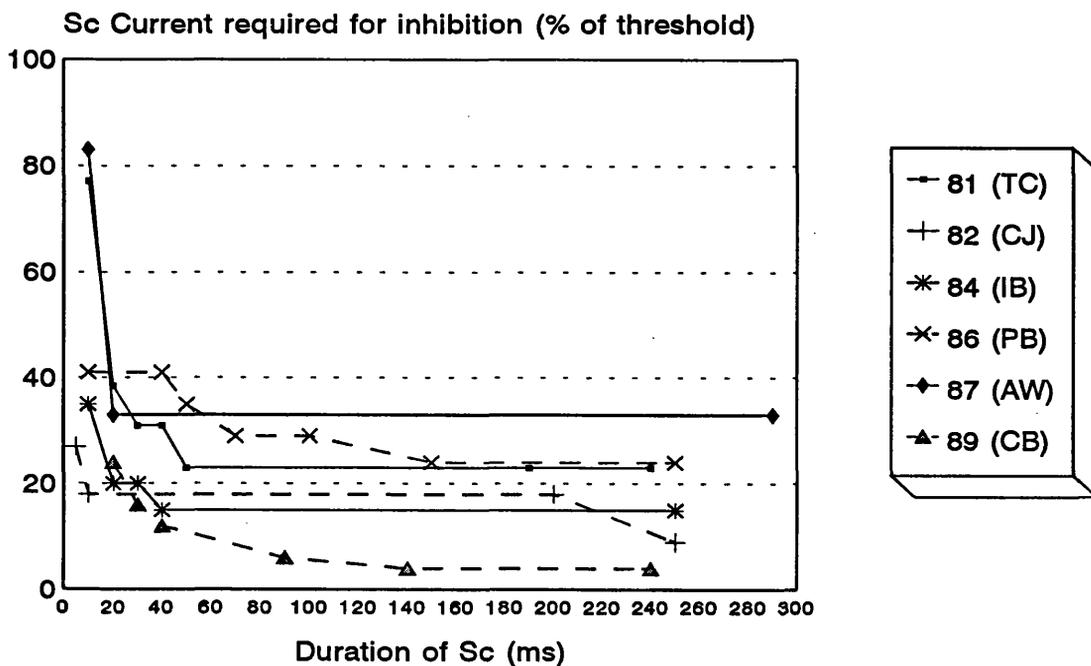
Figure 5.6. Effect of Conditioning Stimulus Duration on Charge Required for Inhibition

Sc Charge required for inhibition (microcoulombs)

Duration of Sc (ms)

Legend:
- ─ 81 (TC)
- + 82 (CJ)
- * 84 (IB)
- ×- 86 (PB)
- ◆ 87 (AW)
- ▲- 89 (CB)
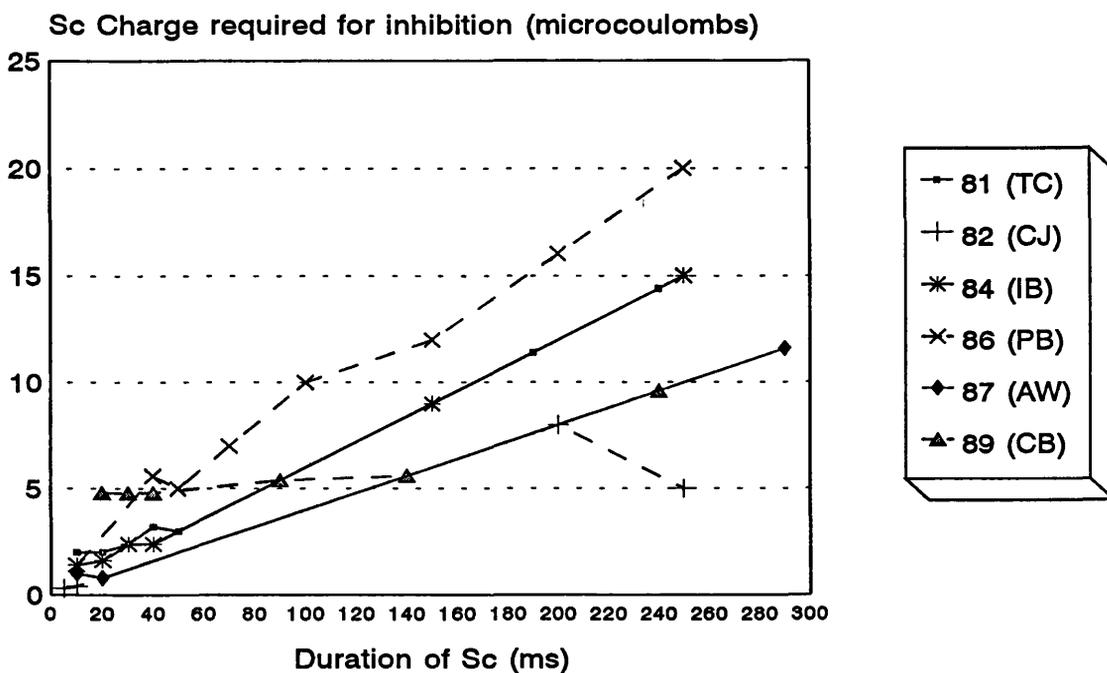
Table 5.1. Effect of Conditioning Stimulus Duration

Patient	82	83	85	89	90	92	Mean$\pm$SD
Age	19	33	43	30	28	58	
Str H Dis	Nil	Nil	Nil	DCM	ARVD	CAD	
Diagnosis	Sinus T	Syncope	Syncope	VT	VT	VT	
Rx	Nil	Nil	Nil	Sot	Amio	Amio	
Stim Site	RV	RV	RV	RV	RV	RV	
LDT (mA)	0.26	0.22	0.40	0.34	0.12	1.10	
S1S2 (ms)	240	250	250	250	290	240	
I_{min} (mA)	0.06	0.02	0.06	0.08	0.04	0.04	0.05$\pm$0.02
I_{20} (mA)	0.1	0.04	0.08	0.14	0.04	0.24	0.11$\pm$0.07
Q_{max}(μC)	14.4	5	15	20	11.6	9.6	12.6$\pm$5.1*
Q_{20} (μC)	2	0.8	1.6	2.8	0.8	4.8	2.1$\pm$1.5*

Key: Amio = amiodarone; ARVD = arrhythmogenic right ventricular dysplasia; CAD = coronary artery disease; DCM = dilated cardiomyopathy; I_{min} = minimum current required to produce inhibition (when conditioning stimulus duration = S1S2 interval); I_{20} = current required to produce inhibition when conditioning stimulus duration = 20 ms; LDT = late diastolic threshold; Q_{max} = maximum total charge delivered (= Imin x S1S2); Q_{20} = charge delivered with 20 ms pulse (= I_{20} x 20 ms); RV = right ventricle; Rx = treatment being received at time of study; S1S2 = coupling interval at which all measurements made; Sinus T = sinus tachycardia; Sot = sotalol; Stim Site = stimulus site; Str H Dis = structural heart disease; VT = ventricular tachycardia; *p<0.01

Protocol 2 - Effect of Gap Between Conditioning Stimulus and Premature Beat

Figure 5.7 shows the effect of a gap of varying duration between the end of the conditioning stimulus and the onset of the premature beat. The results in six patients are presented. In all six patients, inhibition could be produced by subthreshold stimuli with a gap of 5 to 15 ms after the end of the stimulus. In two of the six patients, inhibition could be produced across gaps of 50 ms or more.

Figure 5.8 shows the result of a similar study in one patient, but the amplitude of the conditioning stimulus was increased above the late diastolic threshold when inhibition could not be produced across a gap of more than 35 ms with a conditioning stimulus of subthreshold amplitude. It can be seen that conditioning stimuli of higher amplitude can produce inhibition across larger gaps. In this case, inhibition was produced 100 ms after the end of the conditioning stimulus. No capture was seen during or at the end of the conditioning stimuli in this study.

The results are presented in tabular form in Table 5.2.

Protocol 3 - Effect of Increasing the Amplitude of the Premature Beat

Figure 5.9 shows the result of increasing the amplitude of the premature beat (S2) in patient 47. Initially, the amplitude of S2 is 0.8 mA, twice the late diastolic threshold, the S1S2 coupling interval is 10 ms longer than the effective refractory period, and the conditioning stimulus duration is equal to the coupling interval. The premature beat is inhibited by a conditioning stimulus with an amplitude of 20% of late diastolic threshold. As the amplitude of the premature beat is increased, the amplitude of the conditioning stimulus required to produce inhibition also increases (the duration of the conditioning stimulus and the coupling interval being kept constant). The line in figure 5.9 shows the conditioning stimulus amplitude which would be required if excitation depended solely on the amplitude of the leading edge of the premature beat, i.e. if an increment of x mA in S2 amplitude were to be inhibited by an

Figure 5.7. Effect of Gap Between Conditioning Stimulus and Premature Beat

Sc Current required for inhibition (% of threshold)

Duration of Gap (ms)

Legend:
- 48 (JD)
- 51 (MB)
- 58 (JG)
- 60 (RH)
- 81 (TC)
- 84 (IB)
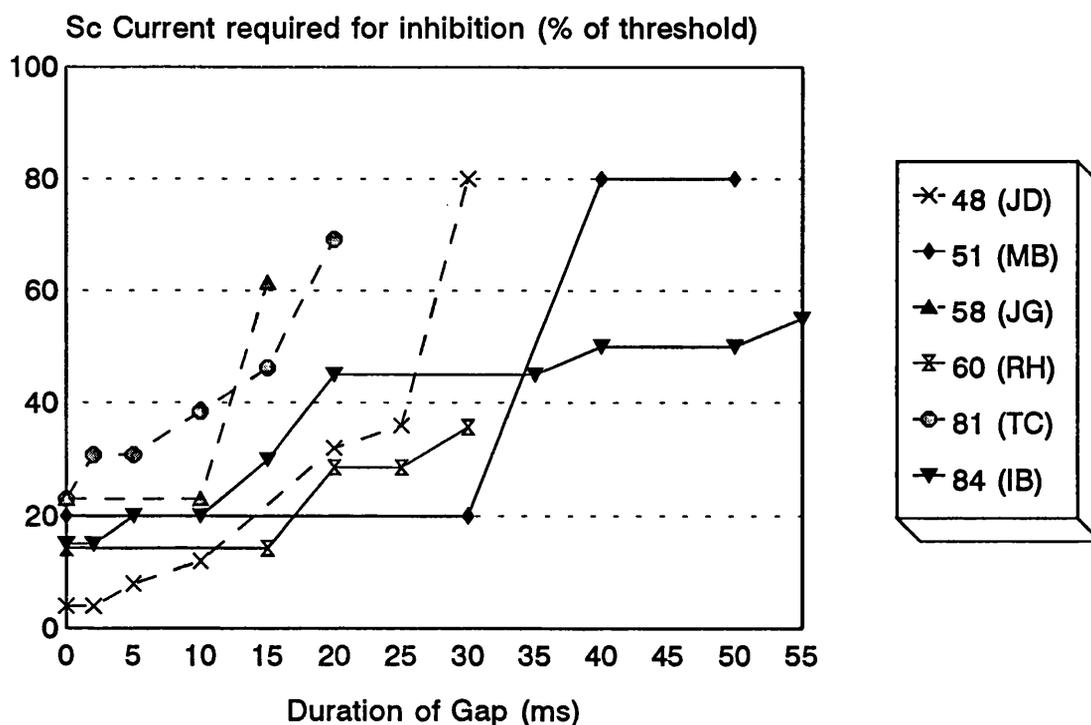
Figure 5.8. Effect of Gap Between Conditioning Stimulus and Premature Beat - Subthreshold and Suprathreshold Values of Conditioning Stimulus (Patient 58)

% of threshold   Microcoulombs

Duration of Gap (ms)

Legend:
- Current
- Charge
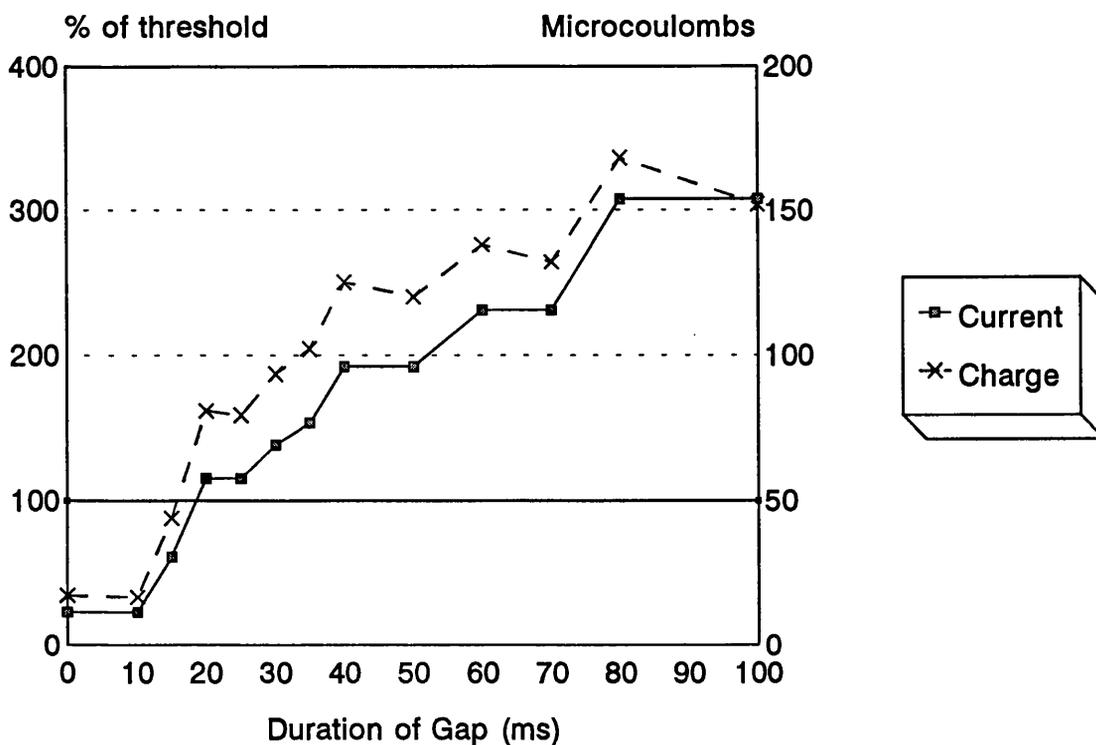
Table 5.2 Effect of Gap Between Conditioning Stimulus and Premature Beat

Patient	Age	Str H Dis	Diagnosis	Rx	Stim Site	LDT (mA)	S1S2 (ms)	I $_{min}$ (mA)	Max gap (ms)
41	44	Nil	WPW	Nil	RV	0.30	260	0.06	20
42	41	ARVD	VT	Nil	RV	0.08	260	0.02	15
43	52	ARVD	VT	Nil	RV	0.30	260	0.06	25
47	51	CAD	VF	Nil	RV	0.40	260	0.08	20
48	53	CAD	VT	Sot	RA	0.50	260	0.02	30
51	43	CAD	WPW	Nil	RV	0.10	290	0.02	50
58	74	Nil	Syncope	Nil	RV	0.26	290	0.06	15
60	66	CAD	VT	Amio	RA	0.28	290	0.04	30
82	19	Nil	S Tachy	Nil	RV	0.26	240	0.06	20
85	43	Nil	Syncope	Nil	RV	0.40	250	0.06	55

Key: Amio = amiodarone; ARVD = arrhythmogenic right ventricular dysplasia; CAD = coronary artery disease; I $_{min}$ = minimum conditioning stimulus current required to produce inhibition; LDT = late diastolic threshold; Max gap = maximum gap over which inhibition could be produced by subthreshold conditioning stimulus; RA = right atrium; RV = right ventricle; Rx = treatment being received at time of study; Sot = Sotalol; S tachy = sinus tachycardia; Stim site = stimulation site; Str H Dis = structural heart disease; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome.

Figure 5.9. Effect of Increasing Amplitude of Premature Beat
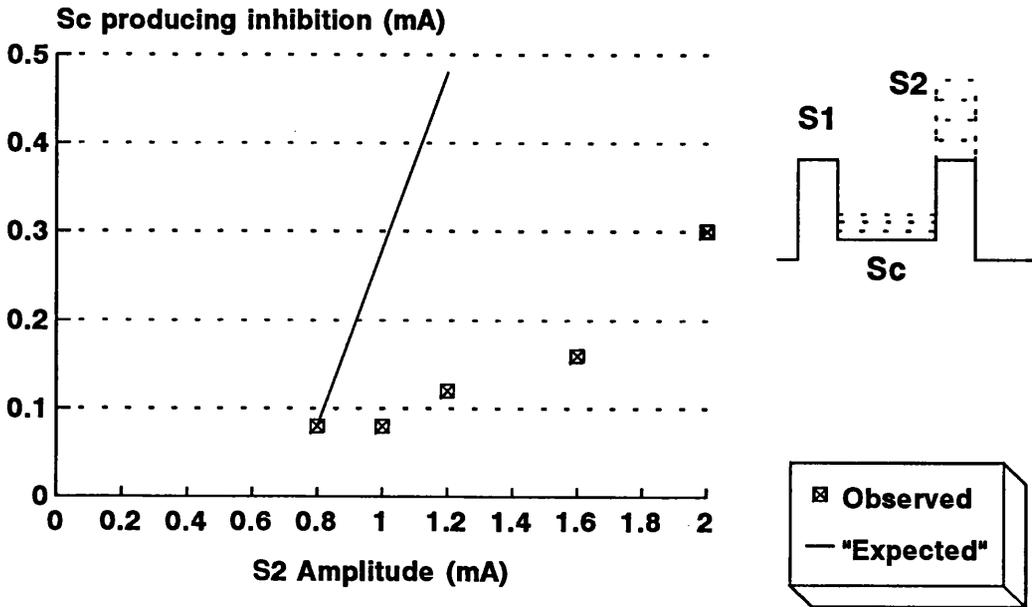
Late diastolic threshold = 0.4 mA

The points are the actual values obtained. The solid line represents the conditioning stimulus amplitude which would be required if excitation depended solely on the amplitude of the leading edge of the premature beat, i.e. if an increment of x mA in the amplitude of the premature beat (S2) were to be inhibited by an increment of x mA in the amplitude of the conditioning stimulus (Sc).

increment of x mA in conditioning stimulus amplitude. In fact, the increment in conditioning stimulus amplitude required to produce inhibition with each successive increase in the amplitude of the premature beat is very much less than predicted, i.e. a small increase in the amplitude of the conditioning stimulus will inhibit capture by a premature beat which has been augmented by a much larger amount. In this case, a premature beat with an amplitude of 2 mA (five times the late diastolic threshold) could be inhibited by a conditioning stimulus which was still subthreshold in amplitude (0.3 mA = 75% of late diastolic threshold), i.e. the premature beat did not capture even although its leading edge was 4.25 times the late diastolic threshold.

Similar results were found in three other patients (table 5.3). In the four patients, premature beats of 4.75 to 5.77 times the late diastolic threshold could be inhibited by subthreshold conditioning stimuli, the amplitude of the conditioning stimulus in each case being 40% to 75% of the late diastolic threshold. The amplitude of the leading edge of the maximum amplitude premature beat which was shown to be inhibited in each case was 4.7 ± 0.5 times the late diastolic threshold (range 4.25 to 5.31 times the late diastolic threshold).

Table 5.3 Effect of Increase in Amplitude of Premature Beat

Patient	40	47	82	83
Age	57	51	19	33
Str H Dis	DCM	CAD	Nil	Nil
Diagnosis	VF	VF	S Tachy	Syncope
Rx	Amio	Nil	Nil	Nil
Stim Site	RV	RV	RV	RV
LDT (mA)	0.80	0.40	0.26	0.22
S1S2 (ms)	340	260	240	250
Max S2 (mA/ %LDT)	3.8/ 475%	2.0/ 500%	1.5/ 577%	1.2/ 545%
Sc (mA/ %LDT)	0.32/ 40%	0.3/ 75%	0.12/ 46%	0.12/ 54.5%
Max S2-Sc (%LDT)	435%	425%	531%	491%

Key: Amio = amiodarone; CAD = coronary artery disease; DCM = dilated cardiomyopathy; LDT = late diastolic threshold; Max S2 = premature beat of maximum amplitude (in mA and as percentage of late diastolic threshold) ; Max S2 - Sc = height of leading edge of premature beat of maximum amplitude (as percentage of late diastolic threshold); RV = right ventricle; Sc = conditioning stimulus amplitude required for inhibition of premature beat of maximum amplitude (in mA and as percentage of late diastolic threshold); S Tachy = sinus tachycardia; Stim Site = stimulation site; Str H Dis = structural heart disease; VF = ventricular fibrillation; VT = ventricular tachycardia.

Protocol 4 - Study of Spatial Effects of Subthreshold Pulses

Attempts were made to produce inhibition at a site remote from the point of stimulation in twelve patients. Details of the patients, the stimulation sites, and the catheters used are listed in table 5.4 .

Using commercially available pacing catheters, it was not possible to demonstrate any spatial effect of subthreshold conditioning stimuli. Even with conditioning stimulus amplitudes as high as five times the late diastolic threshold, no inhibition could be demonstrated at a point 1 mm away. The use of a catheter with a larger tip (National Heart Hospital Ablation Electrode, Bard Electrophysiology) also did not permit the demonstration of an inhibitory effect at a point 2 mm away (Table 5.5).

For these reasons a specially designed catheter was constructed. This consisted of a standard multipurpose angiography catheter (Cordis, Miami, Florida) with a 6 French diameter through which were passed three strips of insulated wire, the bare ends protruding at the end of the catheter (figure 5.4). The tip and the hub of the catheter were then sealed with epoxy resin, and the interelectrode distance at the tip was 0.4 mm.

Using this catheter it was possible to demonstrate inhibition of capture at one pole by a subthreshold conditioning stimulus delivered at an adjacent pole, in three of six patients studied in this way. The current required to produce inhibition at the adjacent site was 25-60% of the late diastolic threshold when the coupling interval was 10 ms longer than the effective refractory period. Subsequent increases in both conditioning stimulus current and duration (so that the conditioning stimulus was always longer than the S1S2 coupling interval) resulted in prolongation of the effective refractory period to 460 ms in patient 90 (figure 5.10) and 500 ms in patients 92 and 95, with conditioning stimulus amplitudes below the late diastolic threshold.

Table 5.4 Spatial Effects - Patients Studied

Patient	Age	Str H Dis	Diagnosis	Rx	Stim Site	Catheter	Electrode Separation
49	76	CAD	VT	Amio	RV	Jos	5 mm
52	44	Nil	Syncope	Nil	RV	Dec	1 mm
53	58	Nil	VT	Nil	RV	Dec	1 mm
58	74	CAD	Syncope	Nil	RV	Jos	5 mm
62	43	Nil	WPW	Nil	RV	Dec	1 mm
65	48	CAD	VT	Amio	RV	NHH	2 mm
69	64	CAD	VT	Amio	RV	NHH	2 mm
78	29	Nil	WPW	Nil	RV	Dec	1 mm
87	67	CAD	VT	Amio, Sot	RV	Cordis	0.4 mm
89	30	DCM	VT	Sot	RV	Cordis	0.4 mm
90	28	ARVD	VT	Amio	RV	Cordis	0.4 mm
91	44	CAD	VF	Amio	RV	Cordis	0.4 mm
92	58	CAD	VT	Amio	RV	Cordis	0.4 mm
95	17	Nil	Syncope	Nil	RV	Cordis	0.4 mm

Key: Amio = amiodarone; ARVD = arrhythmogenic right ventricular dysplasia; CAD = coronary artery disease; Cordis = specially constructed catheter (see text and figure 5.4); DCM = dilated cardiomyopathy; Dec = decapolar catheter; Jos = Josephson type quadripolar catheter; NHH = National Heart Hospital ablation catheter; RV = right ventricle; Sot = Sotalol; Str H Dis = structural heart disease; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome.

Figure 5.10. Spatial Effect of Subthreshold Stimuli - Patient 90
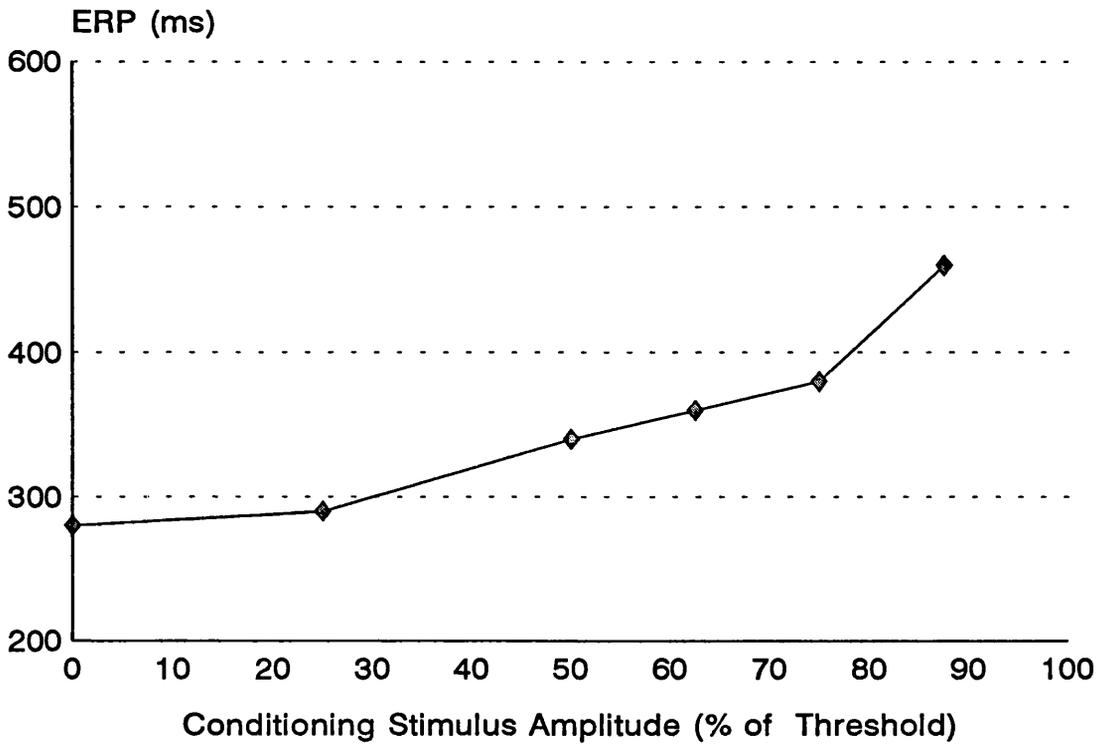
Table 5.5 Spatial Effects - Results

	Proximal Pole			Distal Pole				
Patient	LDT (mA)	ERP (ms)	S1S2 (ms)	LDT (mA)	ERP (ms)	Duration of Sc (ms)	Inhib at Prox Pole?	Threshold for Inhib
49	0.3	300	310	0.3	300	360	No	-
52	0.18	260	270	0.20	270	400	No	-
53	0.24	240	250	0.20	240	400	No	-
58	0.32	280	290	0.30	270	300	No	-
62	0.56	240	250	0.42	250	300	No	-
65	0.52			0.44			No	-
69	1.4						No	-
78	0.16	220	230	0.14	220	300	No	-
87	0.18	290	300	0.20	270	400	No	-
89	0.34	240	250	0.30	240	300	No	-
90	0.12	280	290	0.16	280	350	Yes	0.04 (25%)
91	0.3	300	310	0.32	300	350	No	-
92	1.1	260	270	1.0	260	350	Yes	0.6 (60%)
95	0.16	240	250	0.20	240	300	Yes	0.10 (50%)

Key: ERP = effective refractory period; Inhib = inhibition; LDT = late diastolic threshold; Prox = proximal; S1S2 = coupling interval; Sc = conditioning stimulus. Threshold for inhibition expressed in mA and as a percentage of late diastolic threshold at site of delivery of conditioning stimulus.

Discussion

The spread of subthreshold current in space and time along a passive membrane has been considered in detail by Hodgkin & Rushton (1948), in a mathematical model of a crustacean nerve fibre. The equations which they derived predicted the passive cable properties of a nerve fibre in response to the onset and cessation of a constant current pulse delivered intracellularly. The situation in the human heart is considerably more complex, since (a) spread of excitation in three dimensions has to be considered, (b) cardiac muscle is anisotropic, conductivity varying according to the orientation of the myocardial cells (Roberts et al., 1979; Roberts & Scher, 1982; Rush et al., 1963), (c) stimuli are being delivered extracellularly, and the resistance and capacitance of endocardium and connective tissue elements would have to be considered, and (d) the number and complexity of currents responsible for the cardiac membrane potential and action potential far exceeds that of the squid giant axon.

Effect of Conditioning Stimulus Duration

Some of the points raised in the Discussion section of Chapter 4 are answered by the results presented in this chapter. Considering first the effect of the duration of the conditioning stimulus, it is evident from figure 5.5 that, in most cases, the current required to produce inhibition does not begin to increase until the stimulus duration is shortened to 100 ms or less, and in all cases it was possible to produce inhibition with a conditioning stimulus duration of 20 ms or less. It seems likely, therefore. that the inhibitory effect is occurring during the later part of systole, and is unlikely to be occurring as a result of an effect on a process taking part in early or mid-systole. These results are compatible with the theory that inhibition occurs as a result of a depolarisation of the membrane potential and inactivation of the sodium channels just prior to the end of the refractory period.

One caveat which ought to be considered in the interpretation of the results arises as a result of the electrical limitations of the Constant Current Stimulator. As the

minimum current "step" which the stimulator can deliver is 0.02 mA, small changes in excitability are difficult to assess when the threshold is considerably less than 1 mA. For example, in the studies described under Protocol 1 of this chapter (table 5.1 and figure 5.5), the late diastolic threshold in one patient (patient 87) was 0.12 mA. inhibition did not occur with a conditioning stimulus amplitude of 0.02 mA (18% of late diastolic threshold), but was demonstrable when the conditioning stimulus amplitude was raised to 0.04 mA (36% of late diastolic threshold). The fact that no further rise in conditioning stimulus current required for inhibition was seen until the conditioning stimulus duration was shortened to less than 20 ms conceals the fact that the actual current requirements may have been slowly rising (from just over 18% to just under 36%, i.e. by almost 18% of late diastolic threshold) over that range of conditioning stimulus durations.

Effect of Gap Between Conditioning Stimulus and Premature Beat

By contrast, the fact that an inhibitory effect can be demonstrated 15-55 ms after the end of the conditioning stimulus demonstrates that the inhibitory effect being produced has a finite duration. Furthermore, the demonstration of inhibitory effects up to 100 ms beyond the end of a conditioning stimulus of higher (suprathreshold) amplitude in patient 58 (figure 5.8) is at first difficult to reconcile with the previous observations. The results in figure 5.7 and figure 5.8 show that, as the gap between conditioning stimulus and premature beat is lengthened, the amplitude of the conditioning stimulus has to be increased to produce the same inhibitory effect. There is obviously considerable interpatient variability in this respect, due at least partly to the imprecision of the method as described above (all the patients in this group had late diastolic thresholds of 0.5 mA or less), so it is impossible to determine with any accuracy whether the increase in current with increasing gap duration rises linearly, exponentially, or otherwise, and if exponentially whether there is a measurable 'time constant" of decay in the inhibitory effect after the end of the conditioning stimulus. In this group of patients, the gap duration corresponding to a doubling of the

conditioning stimulus amplitude required for inhibition varied from 5 to 35 ms (figure 5.7).

Effect of Increase in Conditioning Stimulus Amplitude

The studies in which a gap was left between conditioning stimulus and premature beat demonstrated that a premature beat with a leading edge equal to twice the late diastolic threshold could be inhibited by subthreshold stimulation, i.e. inhibition is not merely an artifact of the methodology of the studies. This is demonstrated more strongly by the fact that premature beats of considerably greater amplitude could be inhibited by conditioning stimuli of subthreshold amplitude, as shown in figure 5.9 and table 5.3. Although the number of patients was small, the results showed consistently that subthreshold stimuli could inhibit premature beats of 4-5 times the late diastolic threshold, the amplitude of the leading edge of the premature beat being greater than four times the late diastolic threshold (i.e. greater than twice the threshold at the effective refractory period, since effective refractory period is measured with a stimulus of twice the late diastolic threshold) in each case.

Spatial Effects

A stimulus which just reaches 'threshold" for propagation is thought to do so by activation a critical amount of myocardium. A stimulus of larger amplitude is likely to activate a larger mass of myocardial cells simultaneously, exerting its effects beyond the liminal area excited by a threshold stimulus. As the results above show that subthreshold conditioning stimuli can inhibit capture by premature beats the amplitude of which is considerably greater than threshold, it might seem that the subthreshold stimuli would be likely to be exerting an effect over an area of myocardium greater than the liminal area required for threshold to be reached (perhaps considerably greater). The studies in which attempts were made to demonstrate inhibition at an electrode remote from the site of delivery of the conditioning stimulus showed the limitations of the effects of subthreshold

stimulation. Although effects could be shown in three out of six cases when the interelectrode distance was 0.4 mm, no effect could be shown when the interelectrode distance was 1 mm or greater. This obviously has considerable implications for the potential applicability of the technique of subthreshold stimulation in the termination of tachycardias, as it seems that the effective refractory period can only be prolonged within 1 mm of the site of delivery of the conditioning stimulus, in which case the mapping techniques employed would have to be extremely precise in order to permit any realistic attempt at tachycardia termination. Conversely, if a reentrant tachycardia could be terminated by a subthreshold stimulus without local capture, the site of subthreshold stimulation must be very close to a critical point on the reentrant circuit. The technique might therefore be feasible as a mapping tool for identification of such critical sites, at which catheter ablation might be attempted.

The reason why subthreshold conditioning stimuli were shown to exert spatial effects in only three of the six studies with the custom-built catheter is uncertain, but may be related to the precise geometry of the electrode-endocardium contact in the individual patients. It is thought that capture occurs at an edge of the electrode. If the best tissue contact (and presumably the site of capture of a suprathreshold stimulus) for the two wires occurred at adjacent edges, the two sites would be separated by only the thickness of the insulation between them (0.4 mm). If, however, the best contact sites were to be separated by the additional thickness of the wires themselves, the effective interelectrode distance would be greater, and the likelihood of a spatial effect correspondingly less.

Chapter 6

Studies Using Monophasic Action Potential Recordings

Introduction

The possible effects of subthreshold stimuli on ionic channels in myocardial cells have not yet been explored. Techniques available for studying cellular events in the intact human heart are limited, but one powerful new technique is the use of monophasic action potential recordings. This procedure allows the clinical electrophysiologist to study the effect of interventions (e.g. drug infusions, pacing techniques) on the duration and morphology of the action potential of the cells underlying the electrode tip, and to make inferences about the cellular events responsible for any changes observed.

As mentioned in Chapter 4, the possible mechanisms of the effects of long duration subthreshold stimuli on refractory periods include effects on the availability of sodium channels (by partially depolarising or hyperpolarising the cell membrane) or on the potassium currents (either the delayed inward current (I_K) or the voltage-dependent inward-rectifying current (I_{K1}) responsible for repolarisation. If a subthreshold anodal or cathodal stimulus affected the latter, it might be expected to produce predictable and reproducible changes in the action potential morphology at the point of stimulation. Studies were therefore performed to record monophasic action potentials as close as possible to the point of delivery of long duration conditioning stimuli.

Methods

The methods and equipment used for recording monophasic action potentials are described in Chapter 2. Nineteen patients were studied using the Franz combination pacing/monophasic action potential recording electrode (Table 6.1). In all studies, the catheter was placed in the right ventricle (apex or outflow tract) and unipolar ventricular pacing at a constant cycle length (S1S1) of 600 ms was performed using

Table 6.1. Monophasic Action Potential Recordings - Patients Studied

Patient No.	Age (yrs)	Structural Heart Disease	Diagnosis	Rx	Unipolar/ Bipolar	Catheter Used
23	20	None	WPW	None	Unipolar	Franz
25	52	None	Syncope	None	Bipolar	Franz
26	25	None	AVNRT	None	Bipolar	Franz
36	56	CAD	Syncope	None	Unipolar	Franz
38*	55	CAD	Syncope	None	Unipolar	Franz
39	50	CAD	VF	None	Unipolar	Franz
40	57	DCM	VF	Amio	Unipolar	Franz
42*	41	ARVD	VT	None	Unipolar	Franz
43*	52	ARVD	VT	Amio	Unipolar	Franz
45*	60	CAD	VF	None	Unipolar	Franz
46*	54	CAD	Syncope	None	Unipolar	Franz
65	48	CAD	VT	Amio	Unipolar	Franz + NHH
68*	47	None	WPW	None	Unipolar	Franz + NHH
69*	64	CAD	VT	Amio	Unipolar	Franz + NHH
70*	55	CAD	VF	None	Unipolar	Franz + NHH
71*	57	CAD	VT	Amio	Unipolar	Franz
73*	29	None	WPW	Amio	Unipolar	Franz
76*	52	CAD	VT	Amio	Unipolar	Franz
77*	49	CAD	VT	Amio	Unipolar	Franz

Key: Amio = amiodarone; AVNRT = atrioventricular nodal reentrant tachycardia; ARVD = arrhythmogenic right ventricular dysplasia; CAD = coronary artery disease; DCM = dilated cardiomyopathy; Franz = Franz combination pacing/MAP recording catheter; NHH = National Heart Hospital ablation catheter; Rx = treatment at time of study; VF = ventricular fibrillation; VT = ventricular tachycardia; WPW = Wolff-Parkinson-White syndrome. * = patients in whom analysable traces were obtained.

one of the two pacing poles of the combination catheter as the cathode and one pole of a bipolar catheter in the inferior vena cava as the indifferent. In all but four studies, long duration conditioning stimuli were delivered at the other pacing pole of the combination catheter. The conditioning stimuli were unipolar, the indifferent electrode being the other pole of the bipolar catheter in the inferior vena cava. The duration of the conditioning stimuli was 500 ms in each case. The onset of the conditioning stimulus was synchronous with the paced beat (S1), and at least 20 pacing cycles separated each conditioning stimulus. The pacing train was not interrupted by a pause before or after each conditioning stimulus. The effects of anodal and cathodal conditioning stimuli were studied in each patient. In four patients, a large tipped electrode (National Heart Hospital Ablation Electrode, Bard Electrophysiology), positioned as close as possible to the Franz combination catheter without actually touching it, was used to deliver the conditioning stimuli.

The amplitude of the conditioning stimuli was initially 20% of late diastolic threshold, and was increased to 50%, then 100% of late diastolic threshold. If no effect was seen on action potential duration or shape with subthreshold conditioning stimuli, the amplitude was increased to 200% of late diastolic threshold. The polarity of the stimulus was then reversed, late diastolic threshold measured with stimuli of the opposite polarity, and the process repeated.

Measurement of Monophasic Action Potentials

Monophasic action potentials were recorded on paper at a speed of 100 mm/s, using a Siemens-Elema Mingograph inkjet recorder. Figure 6.1 (a) shows the measurements made on each monophasic action potential recording. Recordings were only accepted for analysis if they had a sharp upstroke, a plateau, a smooth return to baseline, the characteristic configuration as shown, and an amplitude of at least 15 mV. If the recording was of lower amplitude, or if the shape suggested poor contact or demonstrated beat-to-beat variability, the catheter was repositioned and an

Figure 6.1 (a). Measurements Made on Monophasic Action Potential Recordings
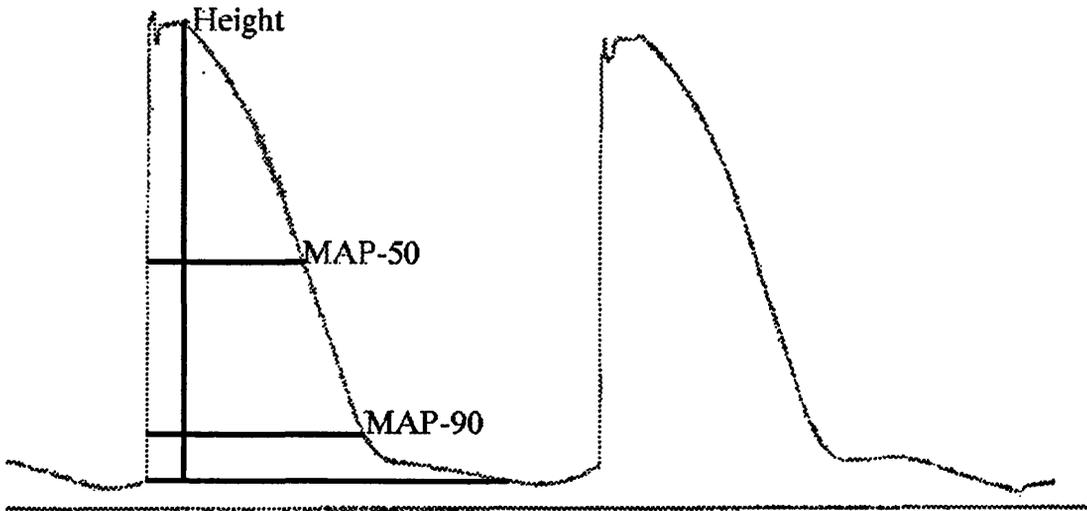
Figure 6.1 (b). Artifact Produced by Long Duration Stimulus on Monophasic Action Potential Recordings
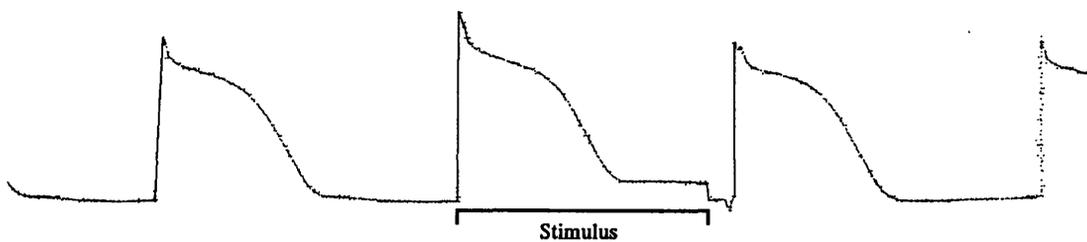
alternative site was sought. If suitable recordings and a stable position could not be achieved, the procedure was abandoned.

The height (in millimetres) from baseline to the plateau of the monophasic action potential was measured, and the voltage calculated with reference to a 1 mV calibration pulse. As the precise point at which the monophasic action potential signal returns to the baseline is usually difficult to measure, the time taken for repolarisation to be 90% complete was measured. The time to 50% repolarisation was also measured, and the ratio between these figures was calculated for each monophasic action potential, in order to quantify changes in the shape of the monophasic action potential induced by cathodal or anodal conditioning stimuli.

The delivery of long duration constant current unipolar stimuli inevitably produced an artifact which affected the measurement of the monophasic action potentials, as shown in figure 6.1 (b). The shift in baseline produced by the stimulus artifact had a duration equal to the conditioning stimulus duration, an amplitude proportional to the stimulus amplitude, and a direction (upwards of downwards) dependent on the polarity of the conditioning stimulus. The magnitude of this stimulus artifact had to be taken into account when measuring the height and repolarisation times of each monophasic action potential, and in some cases the DC offset on the amplifier had to be adjusted to ensure that the monophasic action potential recording would not be moved out of the range of movement of the inkjet of the Mingograph recorder when the conditioning stimulus was delivered.

Care was taken to ensure that the monophasic action potential signal did not deteriorate with time over the course of each study. Often there was a slight fall in the amplitude of the monophasic action potential signal with time, and if this constituted less than 10% of the total amplitude this was considered acceptable. In these cases, when monophasic action potential heights were calculated as a percentage of baseline (figure 6.2), the height of the monophasic action potential

Figure 6.2. Effect of Conditioning Stimulus on Monophasic Action Potential Amplitude.

Height (mm)   Height (% of baseline)

Cathodal   Anodal

Control 50% 100% 200% 50% 100% 200%

Amplitude (% of late diastolic threshold)
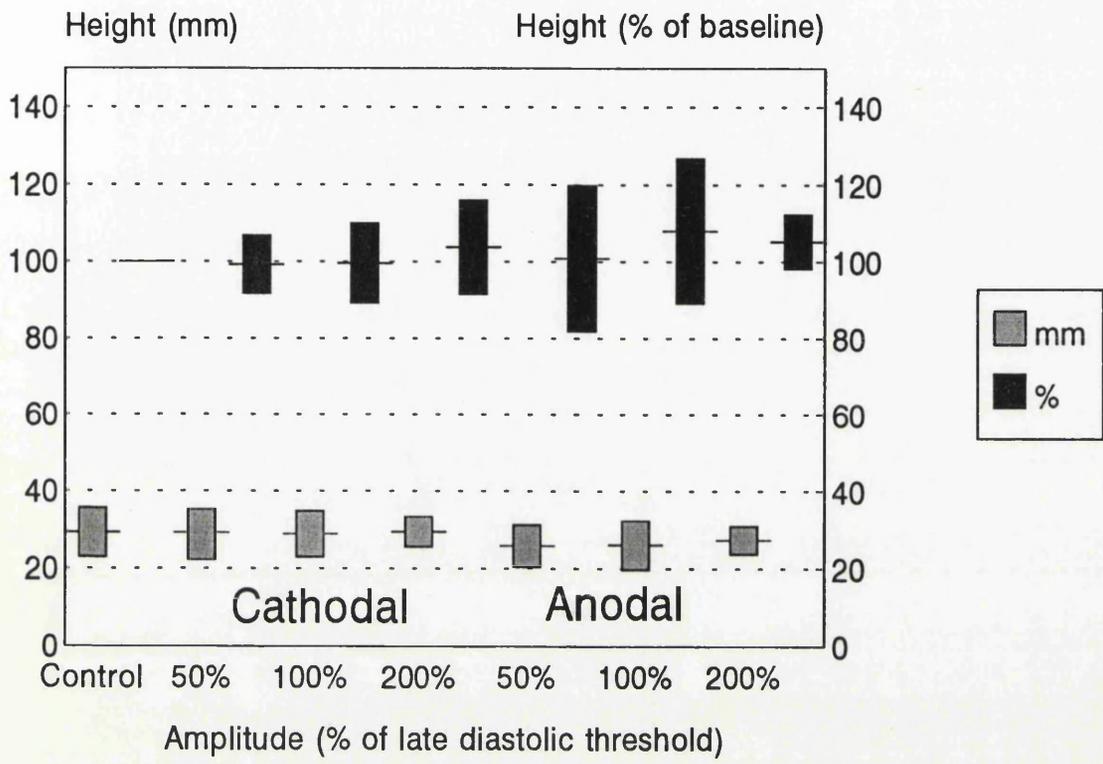
recorded synchronous with delivery of a conditioning stimulus was compared with that recorded at the previous paced beat, in order to eliminate a systematic error as a result of a gradual diminution in monophasic action potential height.

Results

Monophasic Action Potential Height

Figure 6.2 shows the effects of subthreshold and suprathreshold stimuli on the height of the plateau of the monophasic action potentials in twelve patients. The results are plotted both as absolute height in millimetres (as listed in Table 6.2) and as a percentage of the height of the baseline monophasic action potential height. As can be seen, there is no evidence from these results that either cathodal or anodal conditioning stimuli with amplitudes of up to twice the late diastolic threshold have any influence on the amplitude of the monophasic action potential plateau.

Time to 50% and 90% Repolarisation

The results of these measurements are presented in Table 6.2 and Figures 6.3 and 6.4. As above, the results are plotted both as absolute times, and normalised with respect to the control measurements. The time to 50% repolarisation was 207 ± 22 ms (mean $\pm$ standard deviation) and the time to 90% repolarisation was 260 ± 49 ms. There was no evidence from these studies that cathodal or anodal conditioning stimuli had any consistent effect on these parameters, or on the ratio between them (Figure 6.5), either when absolute measurements were made or when percentage changes from baseline values were calculated.

As shown in Table 6.1, six of the twelve patients in whom satisfactory traces were obtained were receiving amiodarone at the time of the study. However, when the two groups (amiodarone *versus* no therapy) were analysed separately there was no evidence that an effect was occurring in one group of patients but not the other.

Table 6.2. Effect of Conditioning Stimuli on Monophasic Action Potential Parameters

Cathodal	0	50% LDT	100% LDT	200% LDT
Height (mm)	29.3 ± 6.3	29.2 ± 7.0	28.9 ± 5.9	29.5 ± 3.9
MAP $_{50}$ (ms)	207 ± 22	209 ± 21	210 ± 26	212 ± 34
MAP $_{90}$ (ms)	260 ± 49	263 ± 48	279 ± 46	269 ± 46
MAP $_{50/90}$	$78 \pm 6\%$	$78 \pm 6\%$	$78 \pm 5\%$	$79 + 4\%$
Anodal				
Height (mm)	29.3 ± 6.3	25.9 ± 5.4	26.1 ± 6.3	27.4 ± 3.6
MAP $_{50}$ (ms)	207 ± 22	207 ± 21	208 ± 18	203 ± 18
MAP $_{90}$ (ms)	260 ± 49	264 ± 28	274 ± 23	274 ± 13
MAP $_{50/90}$	$78 \pm 6\%$	$79 + 4\%$	$76 + 4\%$	$74 \pm 6\%$

Key: 50% LDT, 100% LDT, 200% LDT = Conditioning stimulus amplitudes (as percentage of late diastolic threshold); MAP $_{50}$ = Time to 50% repolarisation; MAP $_{90}$ = time to 90% repolarisation; MAP $_{50/90}$ = ratio of times to 50% and 90% repolarisation, expressed as a percentage. All figures are given as mean $\pm$ standard deviation.

Figure 6.3. Effect of Conditioning Stimulus on Time to 50% Repolarisation of Monophasic Action Potential.
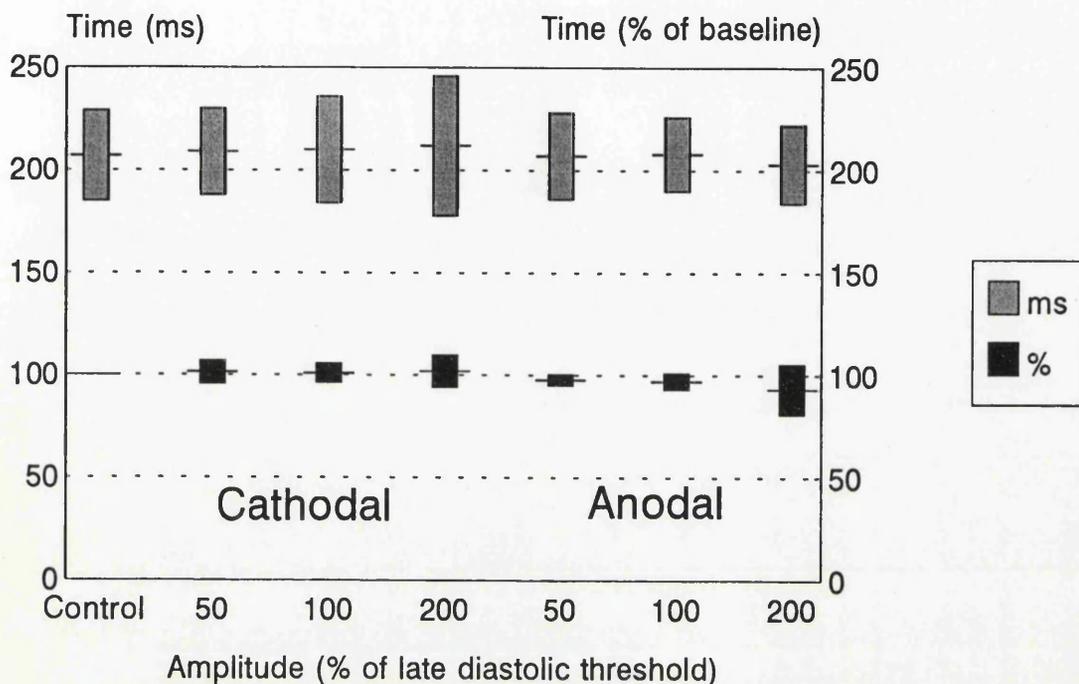
Figure 6.4. Effect of Conditioning Stimulus on Time to 90% Repolarisation of Monophasic Action Potential.
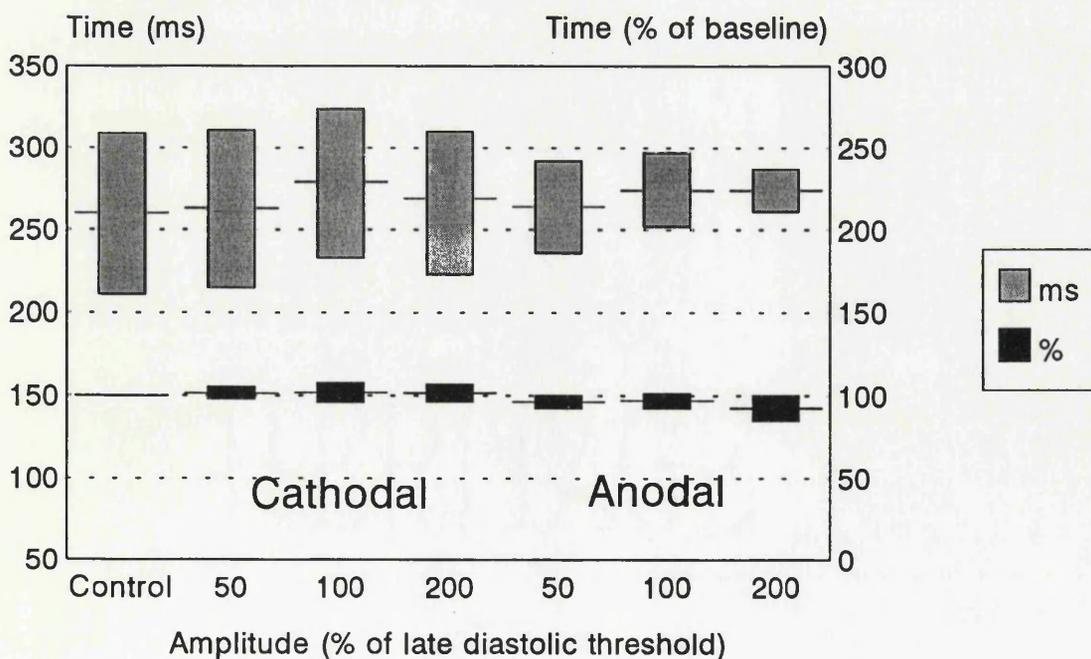
Figure 6.5. Effect of Conditioning Stimulus on Ratio of 50% to 90% Repolarisation Times of Monophasic Action Potential.
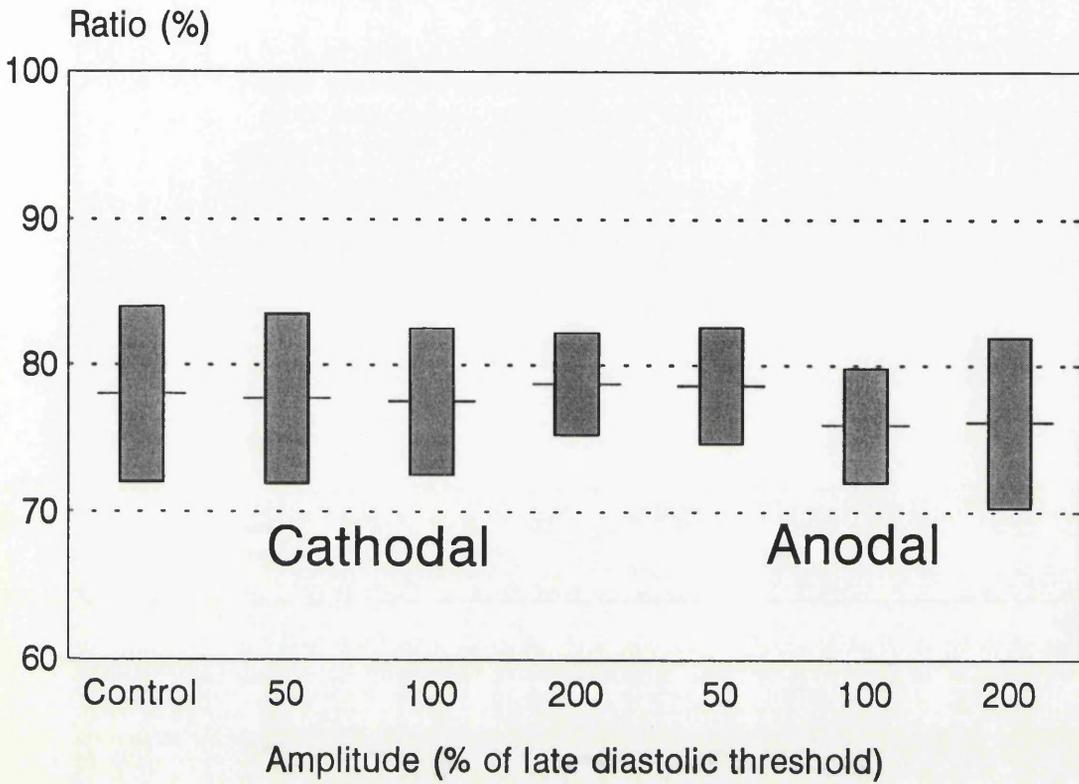
There was a tendency for the monophasic action potential duration (time to 90% repolarisation) to be longer in patients receiving amiodarone (287 $\pm$ 37 ms *versus* 249 $\pm$ 38 ms; p = 0.116), but no significant differences in monophasic action potential characteristics between the two groups.

Discussion

It is obvious from the results presented above that the large changes in refractory periods induced by subthreshold stimuli are not accompanied by large changes in duration of the monophasic action potential recorded as close as possible to the point of delivery of those stimuli. Although the results cannot exclude a small effect on monophasic action potential morphology over a small area, there does not seem to be any consistent measurable effect on any of the repolarisation parameters assessed in this study.

The monophasic action potential is useful for measuring changes in the action potential duration and shape in response to interventions such as changes in heart rate, interpolation of premature beats, and infusions of antiarrhythmic drugs which affect repolarisation (Franz *et al.*, 1988, 1990; Morgan *et al.*, 1990). It is not useful for measuring changes in sodium channel activity, partly because it records from a large number of cells which may be activated asynchronously, but mainly because the response of the inkjet recorder is too slow for reliable measurements of upstroke velocity of the cardiac action potential to be made.

Possible explanations for the lack of any consistent effect of anodal and cathodal conditioning stimuli on monophasic action potential configuration include the following:

1) The effects observed on effective refractory period with conditioning stimuli are mediated solely or principally by effects on sodium channel activation.

2) The point at which the conditioning stimuli were delivered, although within a few millimetres of the monophasic action potential recording site, was nevertheless too far away for a subthreshold effect to be observed.

3) Different effects were occurring in different patients, and the individual changes were obscured by averaging the results.

4) In each patient, a combination of effects was being induced simultaneously (e.g. effects on potassium channels, calcium channels, and external potassium concentration), the net effect of which was to produce little or no change in the shape and duration of the monophasic action potential.

5) The patients studies included too many patients with ventricular disease, or concurrent Class III antiarrhythmic drug treatment, for the results to be meaningful.

Explanation (1) has already been considered in some detail in Chapter 4, in which an explanation for the inhibitory effects of cathodal current and both inhibitory and facilitatory effects of anodal current was put forward in terms of sodium channel activation and inactivation. The above results could be construed as indirect evidence for the sodium-channel hypothesis, although the evidence is "negative" and unconvincing.

Explanation (2) is worthy of serious consideration, especially as the experiments on the spatial effects of subthreshold stimuli (presented in Chapter 5) have shown that no effect can be seen at a point 1 mm or more from the site of delivery of the conditioning stimulus, even if that stimulus exceeds the late diastolic threshold. The electric field produced by stimulation at an electrode depends on the radius of the electrode and the distance from the electrode axis:

$$E \propto (a/r)^2$$

where E is the electric field, a is the radius of the electrode, and r is the distance from the electrode axis. For a 6 French diameter electrode, the electric field strengths at 1, 2 and 3 mm from the catheter tip have been shown to be 25%, 11% and 6% respectively of that produced at the catheter tip.

In all but the last four patients, the conditioning stimulus was delivered at one of the pacing poles on the Franz monophasic action potential/pacing catheter, at a point 2 mm proximal to the site of recording of the monophasic action potential. In the last four patients, a larger tipped catheter was used (National Heart Hospital ablation catheter), but it is unlikely that this was any closer than 2 mm to the point of recording of the monophasic action potential. It is likely that the currently available monophasic action potential recording catheters do not permit stimulation close enough to the point of recording of the monophasic action potential for the effects of subthreshold stimuli to be assessed fully.

Explanation (3), that "different effects were occurring in different patients", might be more accurately stated as "no effect was occurring in the majority of patients, and a small effect in some was not apparent after averaging the results". When the results of each individual patient were examined, some apparent effects on monophasic action potential shape were seen (figure 6.6). These results have not been overstressed because of the difficulty in ensuring accurate measurement, especially as the conditioning stimulus induces a prolonged and large stimulus artifact in the monophasic action potential recording. It may be, however, that the stimuli delivered to the large-tipped National Heart Hospital ablation catheter could have an effect on monophasic action potential morphology, if the catheter were positioned close enough to the monophasic action potential recording site.

Explanation (4), that a combination of effects occurring at the electrode tip resulted in little or no overall change in the morphology or duration of the monophasic action potential, seems unlikely, but cannot be excluded by the above results in the intact

human heart. It may be that studies in cellular preparations, or on computer simulations of the cardiac action potential, will be able to resolve these issues.

Explanation (5), that coexisting ventricular disease or antiarrhythmic drug treatment interfered with the analysis, is unlikely to explain the results. While it is true that eight of the twelve patients in whom measurements were made had coronary artery disease and two had arrhythmogenic right ventricular dysplasia, the recording and stimulating electrodes did not seem to be in close proximity to areas of diseased myocardium. Thresholds for pacing were normal, monophasic action potential morphologies were normal, and in patients in whom ventricular tachycardia was induced the catheters were not at a critical point on the reentrant circuit of the tachycardia. Similarly, in the six patients who were being treated with amiodarone, there was no evidence of afterdepolarisations or other morphological abnormalities of the monophasic action potential, and the thresholds for pacing were similar to those obtained in the other cases. Furthermore, effects of summation and inhibition have been observed in patients with structural heart disease and patients receiving antiarrhythmic drug therapy (Chapter 4, Tables 4.1 to 4.3), and the frequency and extent of these effects was not different from those observed in patients with structurally normal hearts on no therapy.

Conclusions

Studies using monophasic action potential recordings have not been useful in elucidating the mechanism of the effects of summation and inhibition observed with long duration subthreshold conditioning stimuli. The main reason for this is likely to be the finite distance between the monophasic action potential recording site and the site of delivery of conditioning stimuli. Although the negative results in this chapter may be taken as indirect evidence that the effects of summation and inhibition are mediated by sodium channel activation and inactivation, they do not rule out an effect on potassium channels or other factors. Possibly a catheter which allows recording of

the monophasic action potential within one millimetre of the point of stimulation might be useful in resolving these problems.

Chapter 7

Attempts at Tachycardia Termination

Introduction

The various methods by which a non-propagated stimulus might conceivably terminate a tachycardia have been discussed in Chapter 1. Briefly, they include electrotonic inhibition, concealed conduction, conduction block related to inhomogeneity of refractoriness, Wedensky effects, and termination of oscillatory or triggered rhythms by low amplitude stimuli. Of these, only the first and last represent genuine subthreshold effects, the other effects being produced by local capture without propagation (or, in the case of the Wedensky phenomenon, by unknown mechanisms which may involve activation of sympathetic nerve fibres by stimuli of large amplitude). Termination of oscillatory and triggered rhythms by subthreshold stimuli has been shown *in vitro*, but the relevance of these findings to clinical arrhythmias is uncertain.

It follows that, if clinically occurring reentrant arrhythmias can be terminated by stimuli which are genuinely subthreshold (i.e. which do not result in local activation), the mechanism most likely to explain this effect would be electrotonic inhibition, i.e. a transient localised prolongation of the effective refractory period at a critical point in a reentrant circuit, such that the excitable gap was eliminated and the next beat of tachycardia could not propagate beyond that point.

The studies presented in this chapter were therefore designed to attempt to produce maximal prolongation of the effective refractory period at a critical point in a reentrant circuit. Many of the studies were performed during catheter ablation procedures, as more precise mapping is performed during these procedures than during routine electrophysiological studies. As it has already been shown that long duration cathodal pulses reliably produce maximal prolongation of the effective refractory period, this method of stimulation was used during tachycardias in order to attempt termination.

Methods

Protocol 1 - Electrophysiological Studies in Patients with Accessory Pathways

These studies were performed during electrophysiological assessment of patients with the Wolff-Parkinson-White syndrome or concealed accessory pathways. All the patients studied had a single accessory pathway in the left free wall position, and had inducible orthodromic atrioventricular reentrant tachycardia utilising the accessory pathway in the retrograde limb of the circuit. Mapping of the retrograde atrial activation sequence was performed with a Josephson quadripolar electrode catheter (Bard Electrophysiology; 5 mm interelectrode spacing) in the coronary sinus, and in each case the pathway was 'bracketed" by recording proximal and distal to the point of earliest retrograde atrial activation. A bipolar catheter was then positioned in the inferior vena cava, and one of the poles of this catheter functioned as the indifferent electrode for unipolar recording from the four poles of the coronary sinus catheter. The pole at which the shortest ventriculoatrial delay was recorded was used for delivery of stimuli during tachycardia. The late diastolic threshold for atrial capture during tachycardia was determined with a 2 ms unipolar cathodal pulse, and whenever possible the effective refractory period at that point during tachycardia was measured, so that the duration of the excitable gap could be determined. Long duration subthreshold unipolar pulses were then delivered at that point, the electrode in the coronary sinus functioning as the cathode and the other pole of the bipolar catheter in the inferior vena cava functioning as the anode. The duration of the stimuli was 10 to 45% longer than the cycle length of the tachycardia, and the stimuli began synchronous with the local sensed ventricular electrogram. The initial amplitude of the stimuli was 20% of the late diastolic threshold, and local electrograms were recorded continuously from the other three unipoles in the coronary sinus to detect local capture during delivery of the subthreshold pulses. If the pulse had no effect on the tachycardia cycle length or failed to terminate the tachycardia, the amplitude of the pulse was increased stepwise until 100% of late diastolic threshold. If there was

still no effect, the amplitude was increased further to a maximum of 20 mA, or until the tachycardia terminated, or until the patient was aware of discomfort during delivery of the stimulus.

Protocol 2 - Catheter Ablation of Accessory Pathways

Similar studies were performed during attempts at radiofrequency catheter ablation of overt or concealed accessory pathways. The aim of these studies was to determine whether atrioventricular reentrant tachycardia could be terminated by a subthreshold stimulus without local capture, and if so whether this technique could be developed as a mapping technique to assist in the accurate localisation of accessory pathways. In each case the ablation catheter used was a Mansfield-Webster Polaris catheter with a 4 mm distal tip (Boston Scientific Corporation, Watertown, Massachusetts). For left-sided pathways (left free wall and left posteroseptal) a multipolar catheter (decapolar or hexapolar) with 1 mm interelectrode spacing was positioned in the coronary sinus to record the sequence of retrograde atrial activation during orthodromic atrioventricular reentrant tachycardia. The ablation catheter was then manoeuvred to the endocardial aspect of the mitral ring (either retrogradely via the aorta or from the right side via a patent foramen ovale) for more precise mapping of the accessory pathway. For right-sided accessory pathways the ablation catheter was manoeuvred around the tricuspid valve in order to identify the site of the accessory pathway. Once a suitable site was found, the late diastolic threshold and effective refractory period were determined during tachycardia as above, and long duration subthreshold cathodal stimuli delivered as above. If subthreshold stimuli did not terminate tachycardia or alter the cycle length, suprathreshold stimuli were used as described above. In each case, unipolar cathodal stimuli were delivered to the distal pole of the ablation catheter, an indifferent electrode in the inferior vena cava functioning as the anode.

The initial protocol for the use of subthreshold stimulation during catheter ablation procedures was altered for pragmatic reasons. Initially it was planned to attempt to terminate atrioventricular reentrant tachycardia using subthreshold stimulation at a site which was thought on conventional mapping criteria to be ideal for catheter ablation; if the subthreshold stimulus did not terminate tachycardia, another catheter position would be sought and the process repeated. Only if subthreshold stimulation did not terminate the tachycardia at any position would catheter ablation be performed at the site which was considered to be ideal on the basis of conventional mapping criteria. In practice, once a suitable site is found for catheter ablation, to move the catheter to a different site would carry the risk that the ideal site might never be found again and the procedure might fail. Furthermore, catheter positions are not always stable enough to allow repeated attempts at tachycardia termination at a particular site, and termination of the tachycardia itself carries the risk that the catheter may move at the moment the tachycardia is terminated. For these reasons, attempts were not made to deliver subthreshold stimuli at several sites in each patient. If a position was thought to be ideal for ablation, radiofrequency energy was delivered at that site irrespective of whether the long duration stimuli influenced the cycle length of the tachycardia.

Protocol 3 - Catheter Ablation for Atrioventricular Nodal Reentrant Tachycardia

A similar technique was used during attempts to map and ablate the slow pathway of atrioventricular nodal reentrant tachycardia. The region between the bundle of His and the ostium of the coronary sinus was mapped with a Polaris ablation catheter in order to record putative slow pathway potentials, and once a suitable position was found, long duration subthreshold and suprathreshold cathodal pulses were delivered as described above.

Protocol 4 - Catheter Ablation for Ventricular Tachycardia

Studies were performed during an attempt at low energy catheter ablation in one patient with ventricular tachycardia. The catheter used for mapping and ablation in this case was the National Heart Hospital low energy ablation catheter (Bard Electrophysiology, Tewkesbury, Massachusetts). Once a suitable position was found at a critical point on the reentrant circuit, late diastolic threshold and effective refractory period were measured during tachycardia, and long duration cathodal pulses were applied at that site, with a duration 16% greater than the tachycardia cycle length and an initial amplitude of 20% of late diastolic threshold. The amplitude of the pulse was increased to suprathreshold levels following the protocol described above.

Results

Protocol 1

Attempts were made to terminate atrioventricular reentrant tachycardia in four patients using long duration pulses delivered in the coronary sinus. Table 7.1 summarises the characteristics of the patients and their tachycardias. Each of the four patients had a single accessory pathway in the left free wall position, and inducible orthodromic atrioventricular reentrant tachycardia utilising that pathway retrogradely. Two of the patients had overt pre-excitation (Wolff-Parkinson-White syndrome) and two had concealed accessory pathways. None of the patients had received any antiarrhythmic medication for at least five half-lives prior to the electrophysiological study, none had received amiodarone, no drugs were given during the study, and none of the patients had any structural heart disease.

None of the four tachycardias was terminated by stimuli with an amplitude less than the late diastolic threshold. In patient 61, tachycardia was reset by a long duration pulse with an amplitude of 83% of late diastolic threshold and terminated by a pulse

Table 7.1 Long Pulse Delivery in Coronary Sinus

Patient	Age	Diag-nosis	TCL (ms)	LDT (mA)	ERP (ms)	Ex. Gap (ms)	Stim (ms)	Reset Thr (mA)	Term Thr (mA)
55	27	WPW	340	2	180	160	400	3	3
61	18	Conc	275	2.4	150	125	400	2	2.6
79	39	WPW	315	2.3	160	155	400	3	4
81	22	Conc	260	5	150	110	300	6	10

Key: Conc = concealed accessory pathway; ERP = effective refractory period; Ex. Gap = duration of excitable gap (TCL - ERP); LDT = late diastolic threshold; Reset Thr = threshold for tachycardia reset by long duration stimulus; Stim = duration of long pulse; Term Thr = threshold for tachycardia termination by long duration stimulus; TCL = tachycardia cycle length; WPW = Wolff-Parkinson-White syndrome.

with an amplitude of 108% of late diastolic threshold; on each occasion the mechanism of reset or termination was atrial capture at the end of a 400 ms pulse, the tachycardia cycle length being 275 ms. Similar results were found in patient 80 (see below). Tachycardia termination occurred in all patients with suprathreshold long duration pulses, and on each occasion the mechanism of termination of the tachycardia was atrial capture during or at the end of the long duration suprathreshold pulse.

Figure 7.1 shows an example of termination of atrioventricular reentrant tachycardia by a long duration stimulus in patient 55. The tachycardia cycle length was 340 ms and the late diastolic threshold was 2 mA. A stimulus with amplitude of 8 mA and duration of 400 ms was delivered to the coronary sinus electrode at which the shortest atrioventricular delay had been recorded, and tachycardia was terminated. Inspection of the high right atrial electrograms at the point of termination shows that the cycle length of the last beat of tachycardia was shortened by 20 ms, and subsequent block in the atrioventricular node terminated the tachycardia. The electrograms recorded from the adjacent coronary sinus electrodes could not be seen, but it is likely that atrial capture occurred during the long duration pulse, resetting the tachycardia.

Figure 7.2 shows an example of tachycardia reset by a "subthreshold" stimulus and termination by a suprathreshold stimulus, in patient 81. In this case the tachycardia cycle length was 260 ms and the late diastolic threshold was 5 mA. A 300 ms stimulus delivered to the distal pole of the coronary sinus catheter resulted in reset of the tachycardia (figure 7.2a) when the stimulus amplitude was 4 mA (80% of late diastolic threshold). The high right atrial electrogram recorded during delivery of the stimulus occurs at the expected interval (260 ms) after the preceding beat, but the next beat is brought forward by 20 ms. This is consistent with left atrial capture at the end of the pulse (which occurs 20 ms before the next left atrial electrogram is due),

Figure 7.1. Effect of Suprathreshold Long Duration Pulse During Atrioventricular Reentrant Tachycardia in Patient 55.
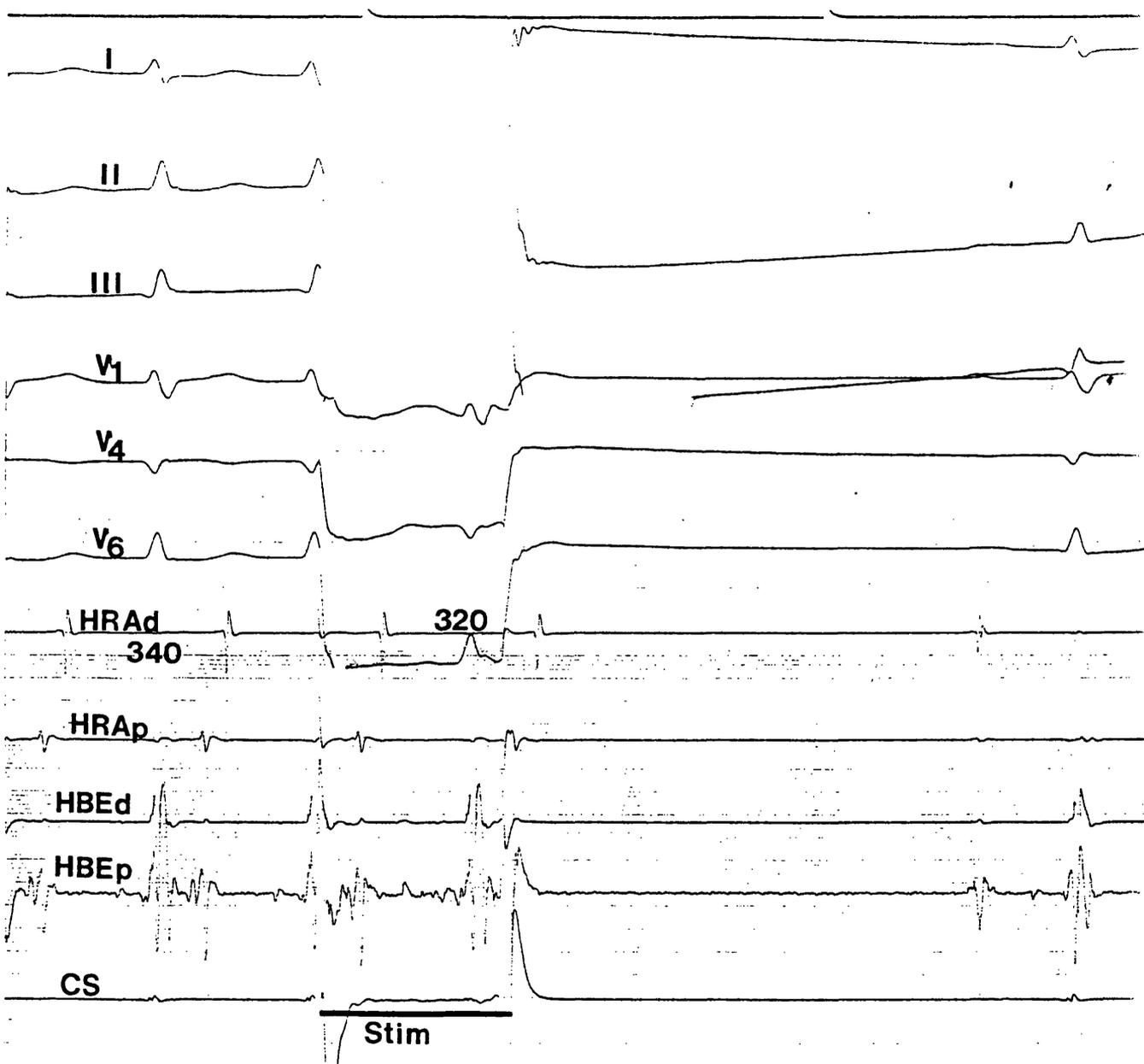
Figure 7.2 (a) Effect of Subthreshold Long Duration Pulses During Atrioventricular Reentrant Tachycardia in Patient 81.
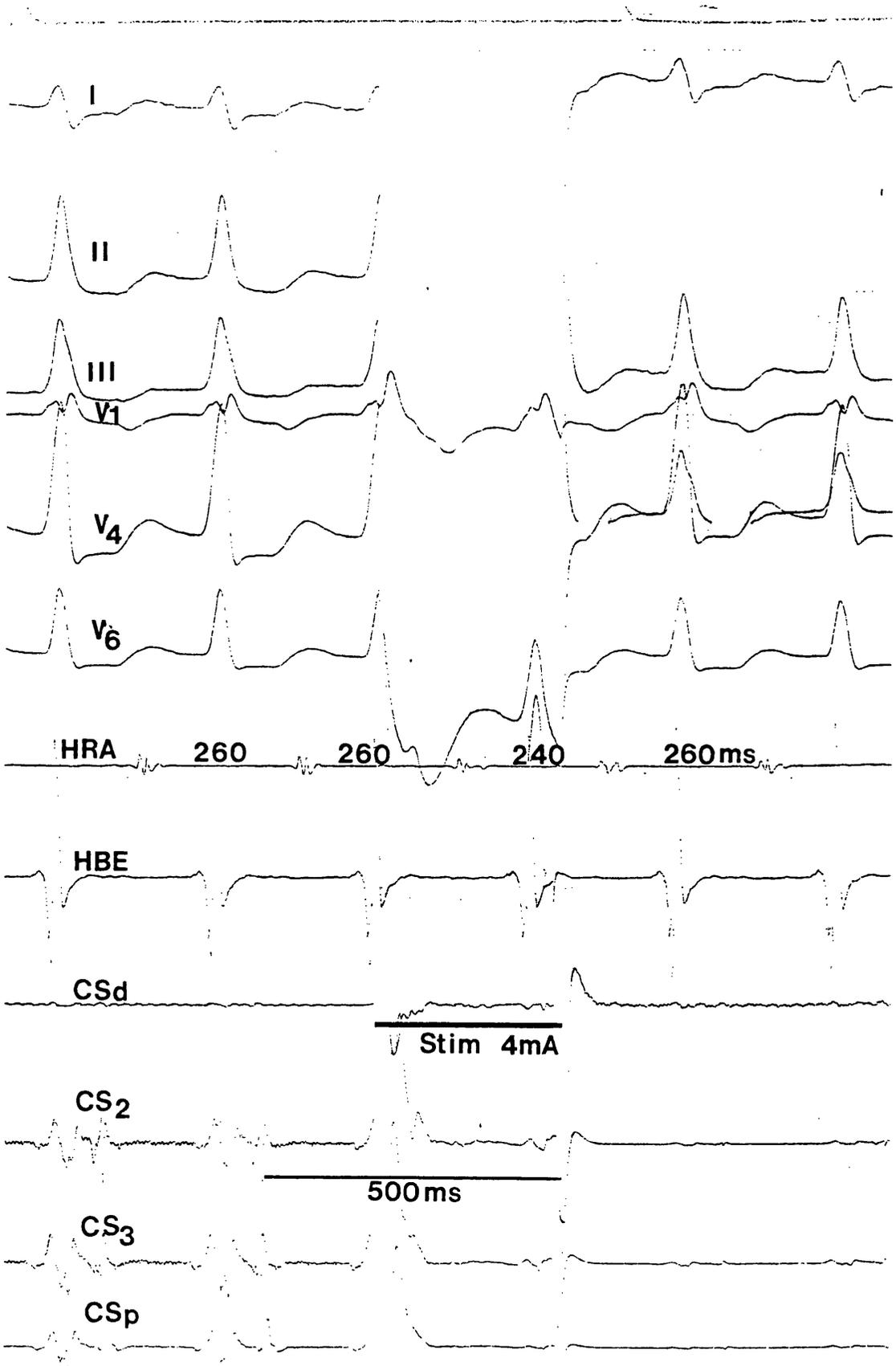
Figure 7.2 (b) Effect of Suprathreshold Long Duration Pulses During Atrioventricular Reentrant Tachycardia in Patient 81.
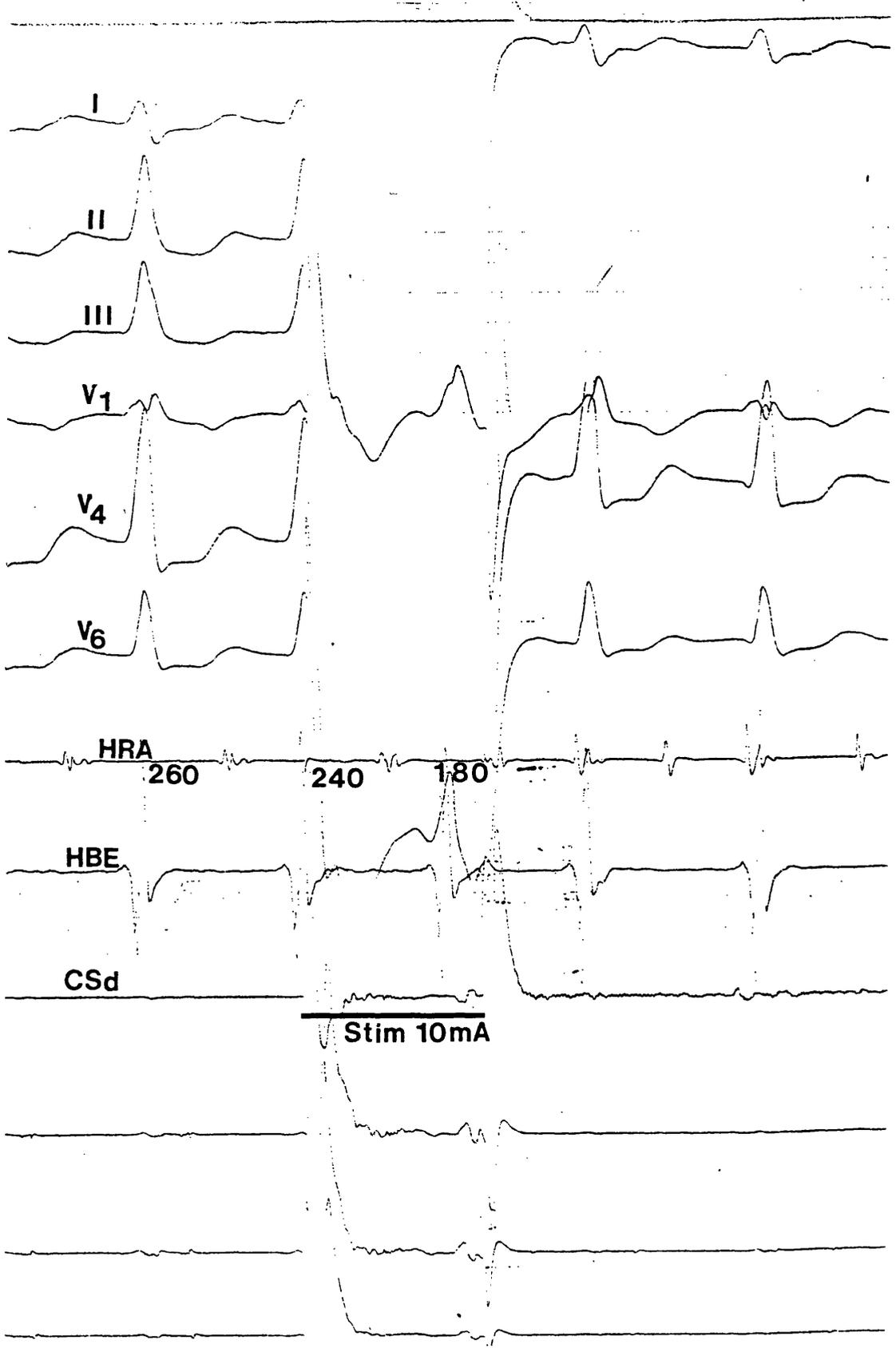
although this hypothesis could not be proven as the local electrograms recorded on the other coronary sinus unipoles were obscured by the delivery of the long pulse. When the stimulus amplitude was increased to 10 mA (figure 7.2b), the high right atrial electrogram recorded during the pulse was brought forward by 20 ms, suggesting left atrial capture at the onset of the pulse. A brief episode of atrial flutter was initiated, which terminated spontaneously after three seconds, restoring sinus rhythm.

Protocol 2

In six patients undergoing catheter ablation of accessory pathways, attempts were made to terminate atrioventricular reentrant tachycardia by delivery of long duration subthreshold stimuli at the ablation site. Table 7.2 summarises the characteristics of the patients and the locations of their accessory pathways.

Figure 7.3 shows the electrograms recorded at the site of subthreshold pulse delivery and subsequent ablation in patient 66. The recordings during atrioventricular reentrant tachycardia (figure 7.3a) show that the ventricular and atrial signals on the ablation electrode are virtually continuous, with a putative accessory pathway potential between them. Delivery of subthreshold stimuli, and suprathreshold stimuli up to a maximum of 5 mA, had no effect on the tachycardia cycle length. Higher amplitude stimuli were not used as the patient was aware of discomfort during the 5 mA stimuli. Delivery of radiofrequency energy (30 Watts) at that site resulted in block of accessory pathway conduction after one second. In order to prevent excessive catheter movement, ventricular pacing at a cycle length of 300 ms was commenced as soon as the tachycardia terminated (figure 7.3b). The radiofrequency pulse was continued for 30 seconds, after which conduction in the accessory pathway did not return. A further pulse of 30 Watts for 30 seconds was delivered at the same

Table 7.2. Long Pulse Delivery at Accessory Pathway Ablation Sites

Patient	Age	Diagnosis	Site of AP	AP Potential	AV interval (ms)	TCL (ms)	Ablation Success?
64	14	WPW	RAS	Y	40	310	No
66	32	Conc	LFW	Y	30*	270	Yes
72	30	WPW	LFW	Y	25	450	Yes
88	50	WPW	LFW	N	20*	320	Yes
93	42	WPW	RPS	Y	60	280	Yes
94	56	WPW	LFW	Y	30	280	Yes

Key: AP = accessory pathway; AP Potential = presence of putative accessory pathway potential at site of ablation; AV interval = atrioventricular interval (or ventriculoatrial interval) recorded at site of ablation; Conc = concealed accessory pathway; LFW = left free wall; RAS = right anteroseptal; RPS = right posteroseptal; TCL = tachycardia cycle length; WPW = Wolff-Parkinson-White syndrome.

* These figures represent the ventriculoatrial intervals at the ablation sites during tachycardia.

Figure 7.3 (a). Electrograms Recorded at Site of Subthreshold Stimulation and Catheter Ablation in Patient 66.
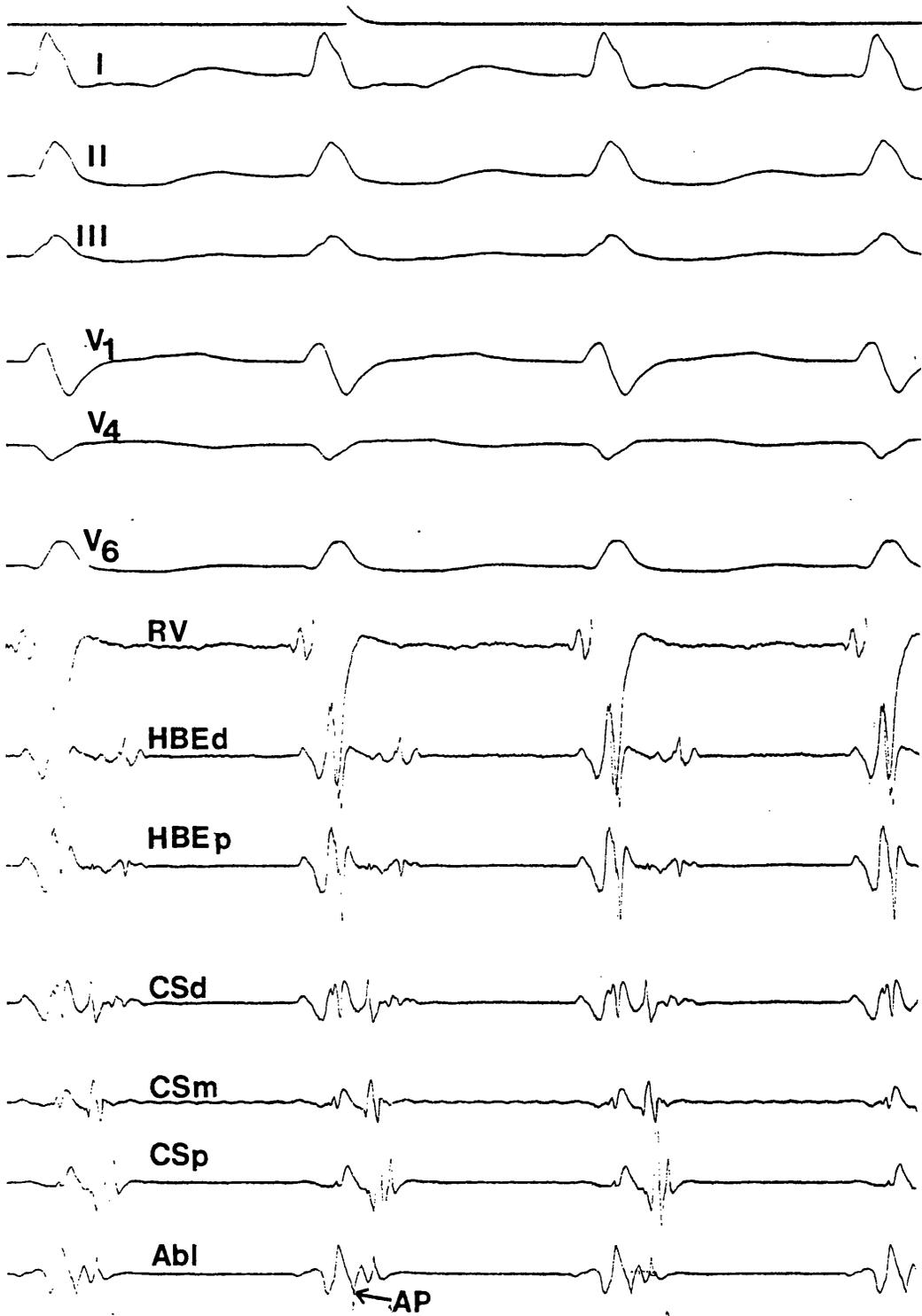
Figure 7.3 (b). Effect of Radiofrequency Energy (30 W) During Tachycardia at Same Site in Patient 66.
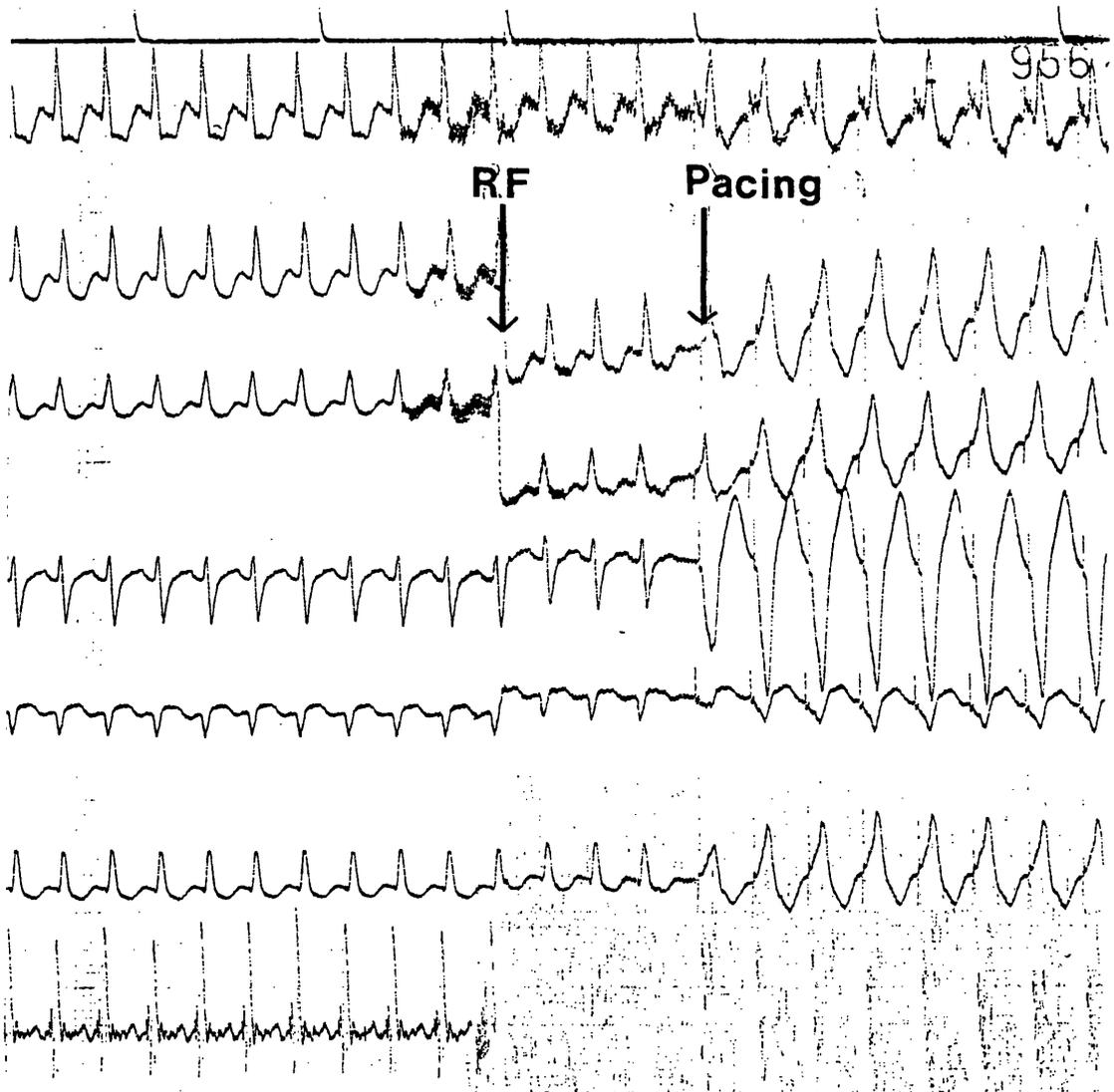
site. Thus, although subthreshold stimulation had no effect on the tachycardia at that site, the site was ideal for accessory pathway ablation by radiofrequency energy.

Radiofrequency catheter ablation was successful in five of the six patients, but in no patient was atrioventricular reentrant tachycardia reset or terminated by subthreshold stimulation at the successful ablation site (or at any other site).

Protocol 3

Attempts at termination of atrioventricular nodal reentrant tachycardia were made in two patients who were undergoing attempted radiofrequency catheter ablation of the slow atrioventricular nodal pathway for cure of this tachycardia. Details of the two patients are given in Table 7.3.

Figure 7.4 shows the electrograms recorded from patient 84 during sinus rhythm at the site of delivery of subthreshold stimuli and subsequent catheter ablation. The ablation catheter was positioned on the septal aspect of the tricuspid valve ring, between the His bundle electrode and the ostium of the coronary sinus. The three lower channels in figure 7.4 show (from above downwards) the bipolar electrogram from the distal two electrodes of the ablation catheter, and unipolar electrograms (with respect to a vascular indifferent in the inferior vena cava) from the distal and proximal of these two electrodes. A discrete sharp potential (arrowed) was recorded both on the bipolar signal and on the distal unipole, which preceded the His bundle potential by 10 ms, and at that point the ablation electrode was more than 1.5 cm inferior to the His bundle catheter. The threshold for atrial capture during sinus rhythm at that point was 1.6 mA. Atrioventricular nodal reentrant tachycardia was induced, with a cycle length of 285 ms. Unipolar cathodal stimuli with a duration of 350 ms were delivered to the distal pole of the ablation catheter, beginning synchronous with the local ventricular electrogram, and with an initial amplitude of 0.2 mA. Stimuli of up to 2.5 mA had no effect on the cycle length of the tachycardia. Stimuli of 3.0 mA and 3.5 mA resulted in atrial capture and resetting of the

tachycardia (figure 7.5), although stimuli of amplitude 4.0 to 9.0 mA had no effect. Stimuli of 10 mA also reset the tachycardia as a result of local capture. Termination of tachycardia did not occur with long duration stimuli, nor did reset occur without local capture.

Radiofrequency energy was delivered at that site, resulting in termination of tachycardia, after which the atrioventricular nodal reentrant tachycardia was no longer inducible. Similar results were obtained in the other patient, subthreshold stimuli at the successful ablation site having no effect on the tachycardia.

Table 7.3. Long Pulse Delivery at Atrioventricular Nodal Reentrant Tachycardia Ablation Sites.

Patient	Age	Ablation Site	SP Potential	AV interval (ms)	TCL (ms)	Ablation Success?
84	64	LSRA	Yes	150	285	Yes
86	49	LSRA	Yes	90	360	Yes

Key: AV interval = atrioventricular interval during sinus rhythm recorded at site of ablation;. LSRA = low septal right atrium; SP Potential = presence of putative slow pathway potential at site of ablation; TCL = tachycardia cycle length.

Figure 7.4. Recordings during sinus rhythm in patient 84, showing putative atrioventricular nodal slow pathway potential.
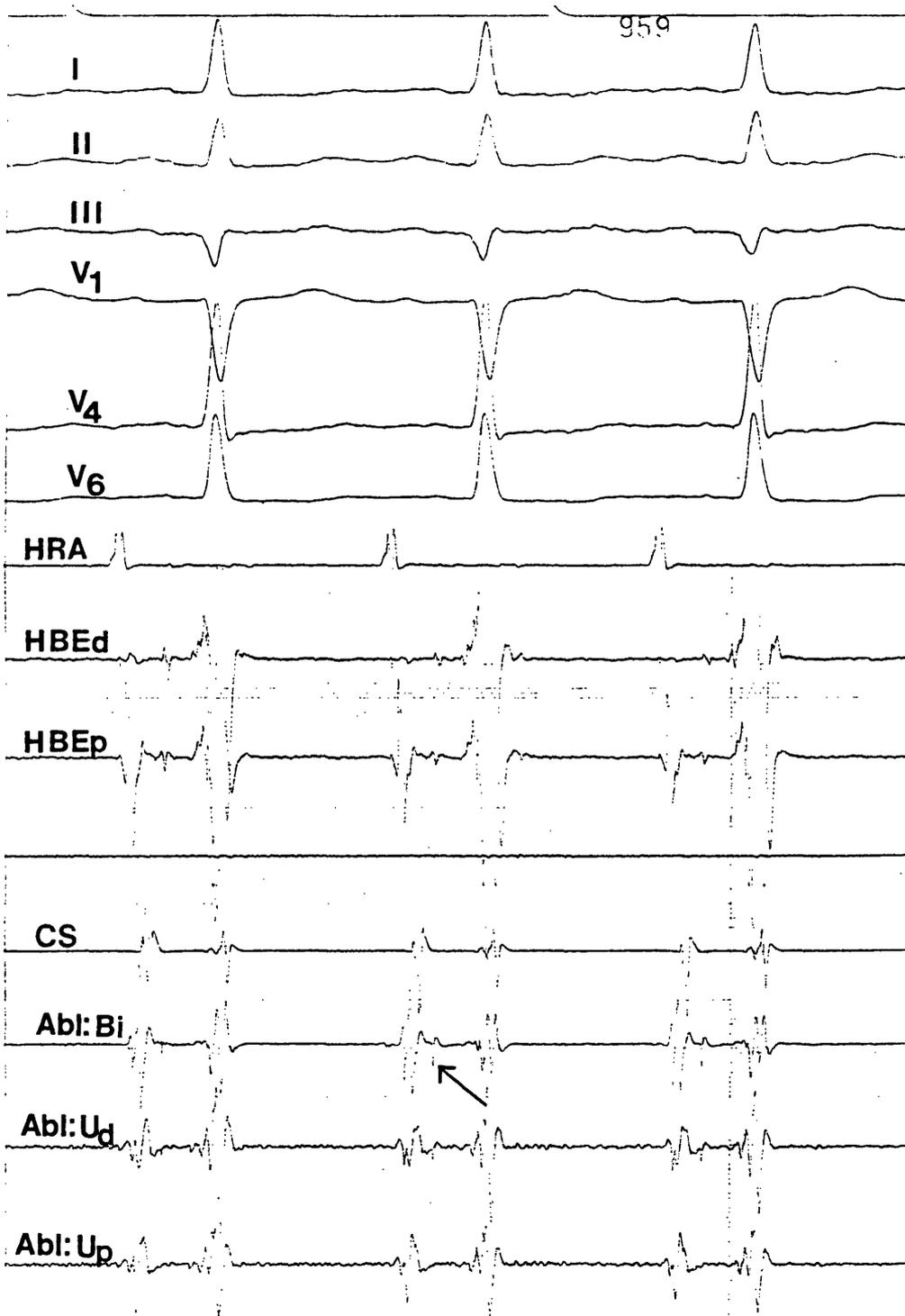
Figure 7.5. Effect of Long Duration (350 ms) Pulse (Amplitude 3.5 mA) During
Atrioventricular Nodal Reentrant Tachycardia in Patient 84.

Protocol 4

In one patient with ventricular tachycardia, an attempt was made to terminate the tachycardia by long duration subthreshold stimuli during a catheter ablation procedure. The patient (patient 80) was a 57-year-old man who had presented five years previously with an acute myocardial infarction complicated by ventricular septal rupture. He underwent emergency repair of the ventricular septum, and remained well for five years until he developed recurrent sustained monomorphic ventricular tachycardia which could not be suppressed by several antiarrhythmic drugs. The ventricular tachycardia was haemodyamically stable and was shown to arise from the interventricular septum. At catheter ablation, a site was found on the left side of the septum which fulfilled the following mapping criteria: perfect 12-lead pace mapping with stimulus-QRS delay of 130 ms; mid-diastolic low amplitude fractionated signals; and concealed entrainment (figure 7.6). The cycle length of the tachycardia was 430 ms, and unipolar cathodal subthreshold stimuli with a duration of 500 ms were delivered at this site via the distal pole of a National Heart Hospital low energy ablation catheter, the anodal indifferent electrode being the distal pole of a bipolar catheter in the inferior vena cava. Local unipolar electrograms were recorded between the proximal pole of the ablation catheter and the proximal pole of the catheter in the inferior vena cava. The threshold for late diastolic capture was 2.0 mA.

Figure 7.7 shows the effect of a pulse of amplitude 1 mA (50% of late diastolic threshold) and duration 500 ms (25% longer than the tachycardia cycle length, which

Figure 7.6. Pace Mapping and Concealed Entrainment During Ventricular Tachycardia at Site of Slow Conduction in Patient 80.
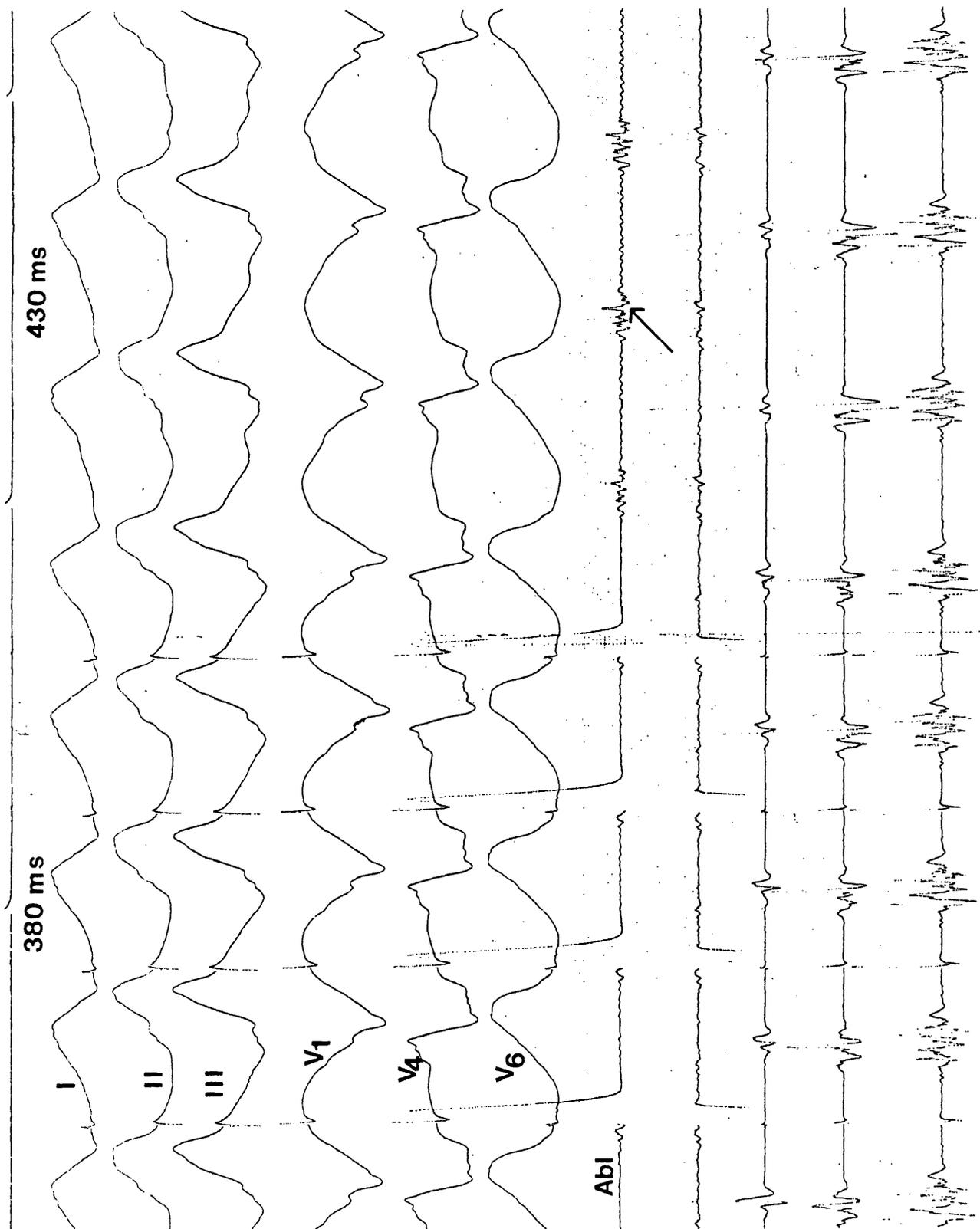
Figure 7.7. Effect of Subthreshold Long Duration Pulse During Ventricular Tachycardia in Patient 80
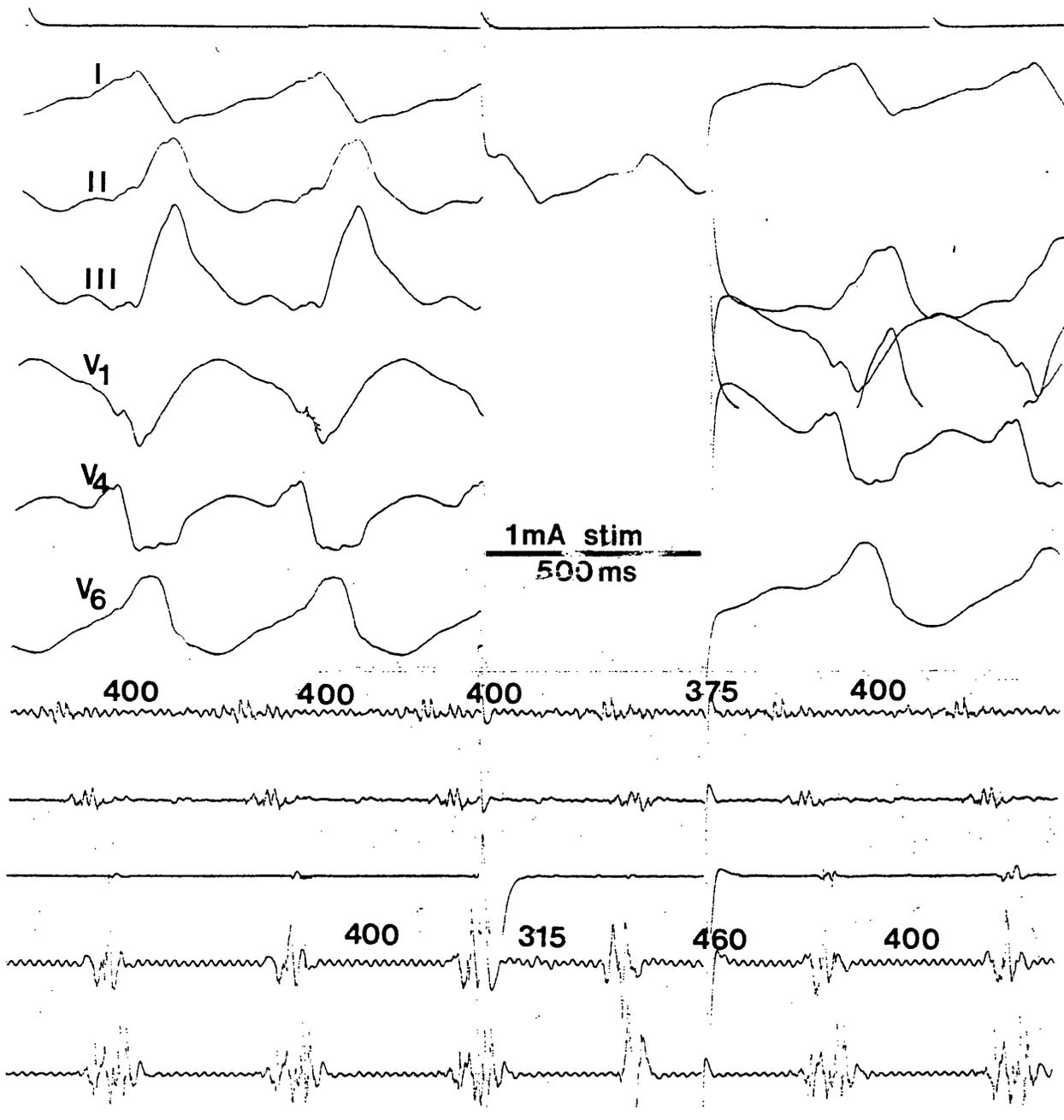
had by that time accelerated to 400 ms). The top intracardiac tracing shows the unipolar electrogram recorded adjacent to the stimulation site, and the other signals were recorded at other sites in the left and right ventricles. The stimulus reset the tachycardia, as seen most clearly in the electrograms recorded from the left side of the septum, where the electrogram during the pulse was 85 ms earlier than expected. The next electrogram on the same channel showed a pause which was not fully compensatory. However, the electrogram recorded adjacent to the stimulation site was not altered during the pulse, although the following cycle shortened by 25 ms. The electrograms at that point (the proximal pole of the ablation electrode) were not as distinct as those on the distal pole (figure 7.6), and the precise mechanism of the effect is open to speculation. Stimuli of larger amplitude produced similar effects, but also produced further distortion of the surface electrocardiogram and intracardiac electrograms. At no time was the ventricular tachycardia terminated by a pulse of up to 5 mA in amplitude, and on no occasion was reset of tachycardia seen without evidence of ventricular capture.

Discussion

In view of the spatial limitations of subthreshold stimuli, termination of a reentrant tachycardia by electrotonic inhibition would only be feasible were propagation of the arrhythmia to be dependent on conduction through a relatively narrow isthmus of excitable tissue which could not be 'bypassed" by the advancing wavefront. Such a situation exists in many clinically important tachycardias, especially atrioventricular reentrant tachycardia, where both the normal conduction system (atrioventricular node and bundle of His) and the accessory pathway represent critical sites in the circuit which, if transiently blocked, would cause the tachycardia to terminate. A similar situation is likely to exist in atrioventricular nodal reentrant tachycardia, although the precise anatomical correlates of the fast and slow pathways, and the

importance of intervening atrial myocardium, have not yet been fully evaluated. Sustained monomorphic ventricular tachycardia in patients with coronary artery disease and previous myocardial infarction usually involves as part of the reentrant circuit a region of myocardium (often, but not exclusively, endocardial) bordered on each side by scar tissue. Specific ventricular tachycardias such as bundle branch reentrant tachycardia or fascicular tachycardia may be critically dependent on an even narrower isthmus of specialised conduction tissue (the right bundle branch or left posterior fascicle respectively), but are relatively uncommon in clinical practice. Other reentrant arrhythmias, such as atrial flutter, may be less dependent on a narrow area of conduction, as it is uncertain whether the precise circuit of the tachycardia is a fixed circuit around an area of anatomical conduction block or is capable of shifting from beat to beat around an area of depressed excitability (the 'leading circle" hypothesis).

Stimulation in Coronary Sinus

The studies described under Protocol 1 are similar to those reported by Gang *et al.* (1988), who used rapid trains of subthreshold stimuli rather than long duration stimuli. They reported several instances of termination of atrioventricular reentrant tachycardia by stimuli with amplitudes less than the late diastolic threshold. What has not been clearly defined, either in the study of Gang *et al.* or in the present study, is the amount of variability in the late diastolic threshold for atrial capture by stimuli delivered in the coronary sinus, and whether the late diastolic threshold, as measured during sinus rhythm, is always lower in magnitude than the threshold in mid or early diastole, during sinus rhythm or tachycardia. As the coronary sinus is relatively large in diameter when compared to the diameter of a pacing catheter, the electrode is unlikely to be in constant close apposition to the wall of the vessel; furthermore, as the catheter tends to move within the coronary sinus, the electrode-tissue contact may vary markedly at different stages of the cardiac cycle, and it is quite feasible that an electrode might make better contact with the atrial aspect of the coronary sinus

during early diastole than during late diastole is certain patients, resulting in a lower threshold earlier in the cycle. Variations in catheter position at different phases of the respiratory cycle are likely to compound the difficulty in measuring accurately the threshold for capture. When these factors are considered, the observations that a stimulus with an amplitude less than the late diastolic threshold might occasionally result in atrial capture during atrioventricular reentrant tachycardia (as was observed in the present studies and in those of Gang *et al.* (1988)), and that the premature atrial beat might terminate the tachycardia, can be readily explained without resort to concepts such as summation of subthreshold impulses. In neither the present studies nor those of Gang *et al.* was there any instance of tachycardia termination or reset without atrial capture.

Studies During Catheter Ablation of Accessory Pathways

Mapping techniques for catheter ablation of accessory pathways have improved significantly in recent years, and success rates of 80-99% have been quoted for radiofrequency ablation of accessory pathways (Jackman *et al.*, 1991; Kuck *et al.*, 1991b; Schluter *et al.*, 1991; Calkins *et al.*, 1991, 1992a). However, even when an apparently suitable electrogram is recorded, the success rate for a particular pulse of radiofrequency energy is likely to be low (Calkins *et al.*, 1992b; Haissaguerre *et al.*, 1992a; Silka *et al.*, 1992; Bashir *et al.*, 1993). The purpose of the present study was to determine whether long duration subthreshold stimulation at a site close to an accessory pathway, which on conventional electrogram criteria would be considered suitable for radiofrequency ablation, would be able to terminate tachycardia without local capture, and if so whether this technique would be useful for identifying suitable sites at which ablation could be attempted. In none of the six patients studied in this way, however, could atrioventricular reentrant tachycardia be terminated with a subthreshold pulse.

These results are at variance with those of Shenasa and colleagues (Shenasa *et al.*, 1991, 1992; Hindricks *et al.*, 1992), who found that both rapid trains of stimuli and long duration stimuli delivered close to the site of an accessory pathway could occasionally result in termination of atrioventricular reentrant tachycardia.

Studies During Catheter Ablation for Atrioventricular Nodal Reentrant Tachycardia

Atrioventricular nodal reentrant tachycardia can be cured by catheter ablation techniques either by ablation of the fast atrioventricular nodal pathway (anterior approach: Lee *et al.*, 1991; Calkins *et al.*, 1991), or by slow pathway ablation (posterior approach). The latter technique can be attempted by an anatomical approach, delivering lesions to the low septal right atrium close to the ostium of the coronary sinus (as described by Wathen *et al.*, 1992), or by a systematic search for signals thought to originate from either the slow pathway itself (Haissaguerre *et al.*, 1992b) or the atrial insertion of the slow pathway (Jackman *et al.*, 1992). Of the two techniques (fast versus slow pathway ablation), slow pathway ablation leaves the patient with a normal PR interval and is thought to result in a more physiological outcome (Jazajeri *et al.*, 1992; Mitrani *et al.*, 1993). Both the patients with this arrhythmia had radiofrequency ablation of the slow atrioventricular nodal pathway, using the technique described by Jackman *et al.* (1992). In each case, delivery of long duration subthreshold stimuli at the site of recording of slow pathway potentials did not affect the cycle length of the tachycardia and did not terminate the tachycardia. By contrast, Fromer and Shenasa (1992) were able to terminate atrioventricular nodal reentrant tachycardia in fifteen out of seventeen patients, using rapid subthreshold stimuli (at cycle lengths of 20-100 ms) applied to the low septal right atrium or the proximal coronary sinus (i.e. sites close to the slow pathway). They did not attempt to record slow pathway potentials at these sites. In all their patients the stimuli were bipolar, the distal pole being positive. They did not observe any instance of atrial capture during rapid subthreshold pacing. The amplitudes of the effective pulses \ranged from 0.3 mA to 1.5 mA. The authors drew attention to the fact that

thresholds were only measured during sinus rhythm, and slight catheter movement during tachycardia might alter the threshold, making some stimuli suprathreshold during tachycardia. The tachycardia might then be terminated as a result of concealed conduction within the atrioventricular nodal slow pathway.

Study During Attempted Catheter Ablation of Ventricular Tachycardia

In the one patient in whom catheter ablation of ventricular tachycardia was attempted, subthreshold stimulation did not terminate the tachycardia. Stimuli which were "subthreshold" in sinus rhythm were effective in altering the cycle length of the tachycardia, as shown in figure 7.7, but this only occurred with evidence of local ventricular capture. This shows conclusively that, at least under these circumstances, a stimulus which is apparently subthreshold during sinus rhythm may be suprathreshold during tachycardia.

The mapping techniques used to determine the suitability of the site chosen for catheter ablation in this case are fairly well established. Pace mapping often gives a reasonable approximation to the site of origin of ventricular tachycardia, but other techniques are necessary for more precise mapping. Concealed entrainment is a modification of the classical technique of entrainment as developed by Waldo and others (1977, 1983, 1984). Whereas classical entrainment involves the demonstration of progressively increasing fusion of QRS complex morphology (or P wave morphology in atrial arrhythmias) as the pacing rate increases, concealed entrainment only occurs when the pacing site is within or very close to the area of slow conduction, so that at faster pacing rates the QRS morphology remains identical to that of the tachycardia (Morady *et al.*, 1988). Although this technique has been useful in identifying the area of slow conduction in ventricular tachycardia (Stevenson *et al.*, 1987b;Kay *et al.*, 1988), it is complementary to, and probably no more useful than other mapping techniques such as the identification of localised mid-diastolic potentials (Fitzgerald *et al.*, 1988; Morady *et al.*, 1991; Morady *et al.*, 1993).

Despite apparently optimal mapping techniques, catheter ablation was unsuccessful in this patient, presumably because the lesion produced by the low energy ablation system was not large enough to produce complete block in the reentrant circuit at that site. It may be that the substrate for that particular ventricular tachycardia was not entirely subendocardial, but may have been arising from deeper layers of myocardium within the interventricular septum (Kaltenbrunner *et al.*, 1991). Alternatively, the ablation site may have been within the area of slow conduction, but not close enough to the exit site of the slow conduction area to be effective (Stevenson *et al.*, 1993). The fact that subthreshold stimulation was effective in resetting the tachycardia at that site suggests that local capture may have occurred during the long duration pulse, and this serves to emphasise the difficulty in accurately measuring threshold during tachycardia at an area of slow conduction.

Chapter 8

General Discussion

In the studies described in Chapters 3 and 4, pronounced changes were observed in the effective refractory period of human atrial and ventricular myocardium as a result of subthreshold stimulation. The use of unipolar stimulation demonstrated that cathodal stimuli always produced inhibition (shortening of effective refractory period), whereas anodal stimuli had varying effects, producing inhibition on some occasions and summation (shortening of effective refractory period) on others. The cellular mechanisms for these effects were not clear, and their elucidation was considered to be beyond the scope of these studies on human patients, but possible effects on either sodium channels (I_{Na}) or potassium channels (I_K) were considered, and the results were not incompatible with results obtained previously by other investigators.

The temporal and spatial effects of long duration subthreshold pulses were assessed in the studies described in Chapter 5. Although changes in effective refractory period could be demonstrated several milliseconds after the end of a subthreshold conditioning stimulus, the current and delivered charge required to produce the same effect increased with the length of the gap after the end of the stimulus. Furthermore, although it remained possible to demonstrate profound changes in refractory period at the site of stimulation, no effect could be demonstrated at sites one milllimetre or more away, and only in about 50% of cases studied could an inhibitory effect be demonstrated 0.4 mm from the stimulation site. In accordance with this were the results of studies using monophasic action potential recordings. In these studies (described in Chapter 6), no consistent effect was seen, presumably because the monophasic action potential recording site was a few millimetres from the site of subthreshold stimulation. These results on the spatial effects of subthreshold stimulation are in agreement with those of Paya et al. (1991), who demonstrated prolongation of refractoriness by up to 50 ms in canine ventricular myocardium, but could not demonstrate any effect 3 mm away from the stimulation site. The same authors (Paya et al., 1992, Chorro et al., 1992) demonstrated inhibition at a point 3

mm from the stimulation site when the subthreshold stimuli were delivered to an array of six electrodes surrounding a central electrode, or to a circular electrode. Similar studies were not performed in the present series of studies. If subthreshold stimuli were to be delivered to multiple electrodes, then in theory it would be necessary to measure the threshold precisely at each of those electrodes, and use separate stimulators for each electrode in order to deliver stimuli at a given percentage of the threshold value to each electrode. Chorro's (1992) studies in canine atria with a ring electrode, in which inhibition was demonstrated at an electrode at the centre by delivery of subthreshold current to the ring electrode surrounding that point, solved that problem, although it remains uncertain where precisely on the ring the effective current was being delivered. As discussed previously (Introduction, page 31), a propagated response tends to occur when a critical current density is reached at one particular point on the electrode-tissue interface (Lindemans 1975, Lindemans & Denier van der Gon, 1978). Whether subthreshold stimuli exert their spatial effects in a similar way, or by a more diffuse effect throughout a larger area of the electrode-tissue interface, remains unknown.

Attempts were made to reset or terminate reentrant tachycardias in thirteen patients using long duration subthreshold stimulation. This represents a very small number of patients, particularly in view of the vast number of ablation procedures currently being performed (Scheinman, 1992; Zipes, 1993), and it would be premature to conclude that subthreshold stimulation is useless as a mapping tool in patients undergoing radiofrequency ablation for reentrant tachycardias. All the studies presented in Chapter 7 were performed during the early part of our experience with radiofrequency ablation (and in the case of ventricular tachycardia, low energy direct current was used rather than radiofrequency energy), and it was not thought appropriate to prolong the procedure significantly by searching for a site at which subthreshold stimuli terminated the tachycardia. Accordingly, if a site appeared to be suitable using standard electrographic criteria, the effects of subthreshold stimuli

were studied, and ablation attempts were made irrespective of whether the subthreshold stimuli had any effect on the tachycardia. It is certainly possible that more prolonged mapping with subthreshold stimuli would have yielded sites at which tachycardias could have been terminated in this way. However, the fact that atrioventricular reentrant tachycardia could be successfully treated in five of six patients at sites unresponsive to subthreshold stimulation, and atrioventricular nodal reentrant tachycardia could be similarly treated in two patients, suggests that subthreshold mapping is unlikely to be a useful tool for location of accessory pathways or atrioventricular nodal slow pathways.

These results are at variance with the studies of Shenasa and others (1991,1992; Fromer & Shenasa, 1992; Hindricks *et al.*, 1992), as described in Chapter 7. The published studies of these investigators have not described in detail their techniques for measuring threshold, and in at least one study (Fromer & Shenasa, 1992) in patients with atrioventricular nodal reentrant tachycardia they measured threshold during sinus rhythm rather than during tachycardia. In all their studies they have used bipolar subthreshold stimuli, but have not always specified which pole was distal and what interelectrode distance was used. Furthermore, the thresholds obtained were considerably higher than those obtained in the studies described here (often greater than 5 mA), and the stimulus durations used were considerably longer than those used in this study (often up to 5 seconds). It has been pointed out that such stimuli are likely to have other effects on excitable tissue, induced by electrolysis at the catheter tip and subsequent changes in local pH (Donaldson, 1993). Furthermore, other effects such as local heating at the catheter tip using such prolonged stimuli of relatively high intensity have not been quantified. Whether the effects observed by Shenasa and colleagues represent a genuine electrotonic effect on pathway conduction or an unspecified biophysical effect is therefore uncertain. Finally, recent evidence from the same group has shown that, in at least some of the cases of tachycardia termination by apparently subthreshold stimuli, the observed effect may

be due to capture of the accessory pathway by the (supposedly subthreshold) stimulus (Chen *et al.*, 1993; Hindricks *et al.*, 1993).

Conclusions

The studies presented here have described the effects of long duration subthreshold stimuli on human atrial and ventricular refractory periods, the spatial and temporal effects of these stimuli, and the lack of effect of subthreshold stimulation on termination of tachycardias. The precise cellular effects of long duration subthreshold stimuli have not been determined. The use of antiarrhythmic drugs given acutely during electrophysiological studies, with determination of the effects of subthreshold pulses before and after a drug (particularly Class I agents, which block sodium channels, and the newer investigational Class III agents which block the delayed inward potassium current I_K), might give some information, but this was not performed in the studies described here. It seems likely, however, that the full elucidation of the cellular mechanisms will be beyond the scope of currently available *in vivo* techniques in humans.

Whether the technique will be useful as a mapping tool for identification of suitable sites for catheter ablation remains a point of controversy. The evidence presented here suggests that it will not be useful, and in view of the high success rates already obtained in expert centres for accessory pathway ablation, further studies using subthreshold stimuli to aid localisation are unlikely to be productive. However, if the results of Shenasa and colleagues can be reproduced by other centres, and if the mechanism of action can be determined, it is possible that the technique might find a use in mapping and ablation of ventricular tachycardia, where despite currently available mapping techniques it may still remain uncertain whether a point on an area of slow conduction is genuinely critical for the maintenance of the tachycardia.

Appendix 1

Consent Form for Studies

(ADULT CONSENT FORM)

NATIONAL HEART AND CHEST HOSPITALS

FORM OF CONSENT

TITLE OF PROJECT The influence on myocardial tissue of electrical current
delivered during refractoriness

EXPLANATION OF PROJECT

As you know, you have a tendency to an abnormal heart rhythm and we propose
to investigate this by performing an electrical test. During this test
small wires are inserted through the veins and positioned inside the heart.
We will be able to use very small electrical voltages passed along these wires
to alter the rhythm of your heart. This helps us to test whether the response
of your heart is normal and also to bring on your abnormal heart rhythms in
order to determine why they occur and what form of treatment would be appropriate.

The size and duration of the voltages used has not changed for some years.
We believe that the electricity of the heart may react differently to voltages
that last longer and this may be of use in understanding abnormal heart rhythms
and how special pacemakers can prevent fast heart rhythms. We would like
to gain extra information during your test on how these longer impulses can
help. If carried out, the test does not involve the insertion of any additional
needles or the taking of extra blood samples. It will add approximately 20
minutes to the length of the study and will be performed at the end. It will
not entail any additional risk. As with the routine test, all the voltages
will be delivered at a low level and you should not be aware of them. If
you do feel any discomfort or are not prepared to continue with the test,
please inform the doctor and the test will be stopped immediately. It is
possible that the information gained from this research may help to develop
more effective pacemakers for the control of your abnormal heart rhythm.

Signed by the person in charge of the project: X _____ Date 16/2/90

The ethics committee of The National Heart & Chest Hospitals has approved the above statement.
Signed by the chairman/representative of that committee:

_____ Date 8/3/90

DOCTOR'S DECLARATION

I have explained the project to the participant as outlined above in the presence/absence* of a
witness**

Signed: _____ Date: _____ Time: _____

* delete as appropriate

** every effort should be made to give the explanation in the presence of a witness

NOTES FOR PATIENTS

1. Please do not hesitate to ask the Doctor any questions you may have about this project before you decide whether you wish to participate.

2. If you decide, now or at any other stage, that you no longer wish to participate in the project, this will not in any way prejudice your future treatment.

3. If you decide to take part in this project, you will be given a copy of this form for your information.

==

FORM OF CONSENT

(for use by adult patients undergoing investigations connected with clinical research)

I, _____ of _____

_____

give my consent to undergo the procedures described overleaf. The nature, purpose and possible consequences have been fully explained to me.

Signed: _____   Date: _____

** WITNESS (See Note 1)

I am satisfied that the procedures have been fully explained to the Patient. The Patient has given consent in my presence.

Name of Witness:_____   Position: _____

Address: _____

Signed: _____   Date:_____

==

NOTES

1. **WITNESS: Wherever possible, a witness should be present whilst the doctor/sponsor explains the procedures to the patient. If this is impractical, complete the "Doctor's Declaration" accordingly. In the case of a patient, the witness should not be a doctor if the sponsor is a doctor. If the witness is a nurse, he or she must be a ward sister or senior nurse in charge of the ward who is not undertaking a post-basic course.

2. SAFE-KEEPING OF THIS FORM: In the case of a patient, a copy of this signed form must be kept in the patients case-notes, and the sponsor should retain a copy for subsequent examination if required by the Ethics Committee.

Appendix 2

The Constant Current Stimulator

This section describes in more detail the design, construction and programming of the stimulator which was built specifically for the purposes of the present series of studies. Further details are available from Spicer & Boone (1990), Boone (1989), and Spicer *et al.* (1992).

Although the Constant Current Stimulator was designed primarily to generate long duration pulses of constant current, a wide variety of pulse shapes and durations can be programmed. The pulse shape is specified to the Constant Current Stimulator as a series of segments, each of which lasts at least 100 ms. The system allows a pulse to be built from up to 25 segments, each of which corresponds to a constant current or a ramp. The maximum current at any point is 51 mA, provided that the tissue impedance does not rise above 1 kΩ. The stimulator can be programmed from any computer with a standard RS232 interface. The stimulator contains a built-in microprocessor with its own memory, which means that it can be delivering one pulse shape while another is being received from the computer. Error checking software prevents bad or corrupted pulse data from being delivered to the patient.

Synchronisation is provided either from an amplified ECG signal (1V/mV) or any equipment which can generate a Transistor-Transistor Logic (TTL) (5V) level pulse. If an ECG signal is used to trigger the pulse, the pulse can be programmed to start at any point in the cardiac cycle, and to hold off from delivering further pulses for any length of time.

Two outputs are provided for monitoring the voltage and current supplied by the unit. These outputs are electrically isolated from the output to the patient, so they can be connected to an appropriate recording device.

Setting up and Operation

Figure A2.1 shows the typical installation and connections for the Constant Current Stimulator. The computer connection is a standard RS232, using a 3-wire connection. The computer transmits data on pin 2 and receives data on pin 3. The computer connection is on the rear of the Constant Current Stimulator, and is a 25-way "male" D-plug. The RS232 interface should be set up as follows: 9600 baud, 1 stop bit, 8 data bits, no parity.

The trigger input can be either a TTL-level signal from a pacing stimulator which senses the QRS complex, or an amplified ECG or intracardiac electrogram of about 1V positive. TTL or ECG operation is selected by a switch on the front panel. With ECG operation, triggering is effected when the amplified signal exceeds 0.5V. In TTL mode, triggering is on the leading edge of the TTL signal. The trigger input is supplied to a standard BNC socket on the front panel of the stimulator.

Patient connections are provided on two 2 mm sockets on the front panel. These are connected to the pacing catheter(s), either directly or through a switch box.

Mains power supply is connected by a standard IEC mains lead to a socket on the rear of the unit.

Front panel controls and connections

Range high/Range low lamps - these indicate which current range (0 - 5.1 or 0 - 51 mA) has been specified; either one lamp or the other should be lit when a pulse is being delivered.

Output A /Output B lamps - these indicate from which of the two internal memories the current pulse is being delivered.

Figure A2.1. Installation and Connections for the Constant Current Stimulator
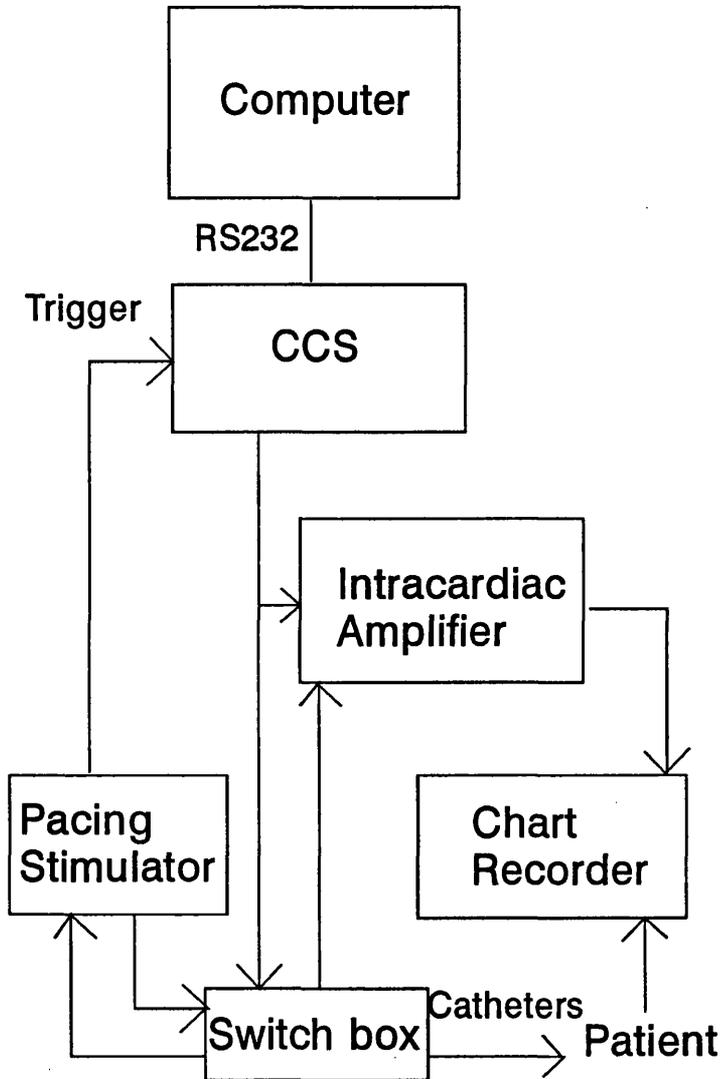
Open circuit lamp - this will come on if, during delivery of a pulse, the resistance rises to such a level that an output of over 50V would be required to keep the current constant. The pulse will be stopped and can be restarted from memory once connections have been checked.

Max current - indicates that the full current of 50 mA is being delivered.

Error lamp - this lamp comes on under error conditions, such as a syntax fault in the RS232 communications or a request to perform an action which cannot be accepted. The error lamp will remain illuminated until the next valid message is received.

V and I monitor outputs - these allow connection of recording equipment for monitoring voltage and current supplied by the unit.

Trigger input - used for connecting a trigger source.

Trigger selector - for selecting an amplified ECG (or intracardiac electrogram) or a TTL level pulse as trigger.

Trigger lamp - indicates that a valid trigger signal has been received.

Overcurrent lamp - this lamp, if illuminated, indicates that a fault has occurred in the hardware. The unit may be restarted by switching off then switching on again, but it is advisable to send a test pulse before stimulating the patient, since overcurrent usually only occurs when the unit has been damaged.

Main output switch - when open, this switch isolates the output from any other circuitry. When this switch is closed it allows pulses to be delivered to the patient. It is recommended that this switch be opened if a defibrillator is to be used, although defibrillator protection is provided in the unit.

Patient outputs - two 2 mm sockets for connection to the catheter electrodes.

Mains switch - controls mains poser to the unit.

Mains lamp - indicates that the mains power is on.

Rear Panel Connections

Mains input - an IEC mains socket is provided with separate live and neutral fuses.

Computer connection - a 25-way male D-plug for connection to the RS232 port of a computer.

Trigger sync output - A BNC socket is used to deliver a 5V, 10ms pulse at the start of the trigger cycle. This pulse is intended for oscilloscope synchronisation.

Operation of the Constant Current Stimulator

The computer should be switched on and its RS232 socket connected to the Constant Current Stimulator before the stimulator is switched on. The control software for the Constant Current Stimulator should be started, and if no error messages are displayed the stimulator mains switch should be switched on. If a trigger signal from a pacing unit is being used to trigger the stimulator's output and a suitable trigger signal is being generated, the trigger light on the front of the stimulator should flash with each trigger. The main output switch should then be switched on, the appropriate pulse shape programmed, and the appropriate "start" command selected (as described in "Software" section below).

Programming

The Constant Current Stimulator has no control panel *per se,* and can only be used in conjunction with a suitable computer. All data transferred to and from the unit is in ASCII format, using only letters and numerals. The data is framed in small (64 character) packets, each with a checksum to protect against data corruption. All

numerical data is transmitted in hexadecimal format, each digit being an ASCII character.

For the purposes of the studies described in this thesis, the software used was that supplied for test and evaluation purposes as described below. Other users may wish to write other software appropriate to their uses, and if so they are advised to consult the operating and programming manual by Spicer & Boone (1990).

Technical Description of Hardware

The following is a brief summary of the detailed description of the hardware by Spicer & Boone (1990). It is intended as a general guide to the components of the Constant Current Stimulator, and is not intended as an aid for repair or servicing of the unit, for which the full technical reference should be consulted.

Output stage

This consists of an isolated digital-analog converter, a controlled current source, current feedback circuit, current overload protection, range switching, output circuit, and defibrillator protection.

Isolated Digital-Analogue Converter (DAC) - this takes the 8-bit output from the microprocessor board which represents the amplitude of the output current. Each bit increment on the digital scale represents a current step of 0.2 mA in high range and 0.02 mA in low range. Optical isolation is used between the microprocessor board and the DAC.

Controlled current source and current feedback - the output current generated in the current source is proportional to the output of the DAC. The input to this circuit is an analogue signal of 0-1V, representing zero output to full output. A current

mirror output stage is used to ensure fast response to load fluctuations (low compliance), while feedback is used to ensure accuracy.

The current source is designed to operate into loads of up to 1 kW, and to supply current up to 50 mA. This implies that a voltage swing of up to 50 V is needed at the output terminals. The supply voltage is in fact 65 V, to account for voltage drops in the output current path, which includes the current sensing network and the defibrillator protection. The ratio of output current to control voltage has to be constant to such a degree of accuracy as to be compatible with the 8-bit resolution of the digital control circuit (i.e. within 200 mA of the reference level in high range or 20 mA in low range, corresponding to 0.4% of full scale) while being able to slew at 5 V/ms over a 50 V range. The overall accuracy is virtually independent of gain, and the gain has been set to give the best compromise between speed of response and stability. The load applied to the output terminals (i.e. myocardial tissue) has a variable impedance, and has a capacitive as well as a resistive element. In addition, the connecting cables will introduce an inductive element into the circuit. The high slew rate demands a fast response, particularly when a step change in output is required, and this is provided in the circuitry of the Constant Current Stimulator.

Current overload protection - The output current should not exceed 60 mA under any circumstances. A 62 mA fuse is fitted to protect against serious circuit failure, and normal overload protection is provided by a small high voltage field effect transistor which switches off the output current path if the sensed current is above the set level. Under these circumstances the overcurrent indicator light will be turned on.

Range switching - selection of high (0-51 mA) or low (0-5.1 mA) is carried out by switching the resistance in the current path between 19.61 Ω and 196.1 Ω . Thus the feedback voltage is 1 V at full output current in both ranges. Range selection is carried out by a relay.

Output circuit and defibrillator protection - There are two levels of output switching - a large switch on the front panel which completely isolates both patient terminals from anything else in the circuit, and a relay which switches the current output circuit from the internal test load to the patient circuit in response to software control. The power-up circuit ensures that this relay cannot be closed for a few seconds after power-up. Defibrillator protection is included, and has been tested up to 360 J, but it is recommended that the main output switch is turned off before defibrillation is undertaken. The defibrillator protection circuit absorbs the energy applied in the event of a full defibrillator discharge in the vicinity of the patient connections. This energy is absorbed in a large 50 Ω resistance and a 200 V spark gap.

Trigger Circuit

The unit can be triggered by an ECG signal or intracardiac electrogram ('ECG') or by the output of another unit ('TTL'). A switch on the front panel enables the choice of trigger. The ECG input has a slew-rate detector to prevent triggering on T waves. the trigger circuit detects the leading edge of a QRS complex. The sensitivity is *not* adjustable, so the user must make sure that the input is amplified sufficiently to allow triggering to occur. The trigger must be positive and have an amplitude of about 1 V and a slope of greater than 20 V/s. The trigger circuit consists of a level comparator for the analogue input, a slope comparator, a level comparator for the TTL input, TTL logic and defibrillator protection. The trigger circuit has an isolated power supply.

Monitor Amplifiers

These are provided in order that the output voltage and current may be measured by monitoring equipment which is not isolated from the mains without compromising medical specifications. A current signal is derived by monitoring the voltage across the current-sensing resistor, and a voltage signal is derived by subtraction of this current signal from the voltage at the high end of the output. Both these signals are

then divided down by resistor networks, and are fed to a pair of isolation amplifiers. Both the current and voltage signals are transferred across the isolation barrier by these devices so that a ground referenced recorder or oscilloscope can be used to monitor the output. The input signal level should have a maximum amplitude of about 2 V to achieve the best compromise between bandwidth and noise, since the bandwidth of the device is lower for higher signal levels.

Microprocessor Interface

This comprises the power-on reset circuit, parallel interphase buffers, trigger bleeper and trigger flasher.

Reset circuitry - following a power-on, or reset, the parallel input-output outputs are undefined and the Digital-Analogue output is also high. The isolated power supplies also need a few seconds to settle. It is therefore important to prevent the passage of any current through the patient connections at this time. To prevent this, the input voltage to the current output stage is clamped to zero volts, and the isolation relay is held off, connecting the current output to the test load rather than to the patient connections.

Parallel interphase opto-coupler drivers - the eight-bit message representing the current to be delivered is transferred from the parallel interphase across the isolation barrier by opto-couplers. The parallel interphase outputs have a source capability of about 250 mA and a sink capability of about 2 mA, and are buffered in order to drive the opto-coupler's LED's.

Range selection and indication - one parallel interphase output line is used to drive the range relay of the output stage. The range is also shown on the front panel range lights.

Trigger bleeper and trigger flasher - the trigger bleeper is a TTL monostable driving a piezo transducer. The monostable has a time constant of about 100 ms, and it is

driven by one of the PIO units. The trigger flasher is similar, but has a longer time constant (150 ms), and is driven from the trigger circuit via an optocoupler.

Memory output and error lights - Three other LED's are connected to the PIO lines - output from memory A, output from memory B, and message error. Buffer transistors drive the front panel LED's from the PIO.

Self test switch - this switch normally connects the parallel interphase input line to 0 V. To initiate a self test the switch should be open circuited, and the system then powered on.

"Voltage delivered" and "current delivered" circuits - the "voltage delivered" signal, an analogue signal from the isolation amplifier board, is amplified to the required level (i.e. 0 - 5.1 V for 0 to maximum output for the given range). The signal is buffered to the front panel BNC connector. In the event of the output being short circuited, the output current into the short circuit is limited to 12 mA. The signal is also fed to a comparator, which compares the signal level with the preset value. The "current delivered" signal works in a similar way.

Microprocessor Board

This is a pre-assembly unit ('Firefly') from Silicon Data Systems. It is based on the Z80 processor and includes random access memory, parallel interfaces, counter timer chip, serial interface and support logic. System software is contained in an 8k x 8 read-only memory. The board includes RS232 interface. It requires a power supply of +12 V and +5 V, 600 mA.

Microprocessor Power Supply Unit

This is a proprietary module ('RAM-15') supplied by Powersolve. The unit has been modified to reduce the earth leakage current, by removal of the filter capacitor which connected the main transformer to earth.

Output Power Supply Unit

This supplies the output circuit at +65 V, +12 V and +5 V. Since the output stage is connected to the patient, it has to conform to class CF standard isolation (British Standards Institution, 1988). The power supply unit is a flyback type, in which current only flows in the primary of the transformer or the secondary, never both together (except during switching). When the primary coil is energised, current builds up and magnetises the core; when the main transistor is switched off, the core demagnetises through the secondary winding.

The dimensions of the core and the other circuit parameters are a compromise between isolation and efficiency. For good isolation, the transformer should be constructed with the primary and secondary coils physically separated by as large a distance as possible. Separation, however, increases the leakage resistance, which leads to inefficiency and heating of the transistor. In the circuit in the Constant Current Stimulator, the space between the windings is about 12 mm, and the efficiency is about 50%. The output voltage is stabilised by closed-loop feedback, which is applied through an optocoupler.

Software

The software used in the project (Boone, 1989) was written for an IBM PC/AT-compatible computer with at least 512 Kbytes of random access memory and a free COM 1 serial port. The software was installed on the hard disc of a Dell 200 microcomputer (Dell Computer Corporation, Austin, Texas) running under MS-DOS version 3.3 (Microsoft Corporation).

Operation

The software is stored in a directory on the hard disc named 'CCS", which is entered from the DOS prompt (C>). Typing the letters 'CCS" will then initiate the startup file CCS.EXE which initiates the program.

The main screen display is in colour, and has three main areas. The top lines constitute the 'menu area", where options are displayed which may be selected by the user. The first letter of any option is displayed in yellow if it is currently selectable. The middle section of the screen displays the pulse shape table, with one line for each section of the pulse. This area is enclosed in a box, with the current filename at the top. One of the data items is highlighted with a red background, this being the 'active field" which will be modified by any keyboard entry. The active field can be changed with the arrow (cursor) keys. The bottom three lines are used for status information and messages received from the Constant Current Stimulator.

Any key pressed by the user is interpreted as data to enter into the active field in the main display, unless the "ALT" key is pressed in combination with another key, or a function key is pressed. A command from the main menu is selected by pressing the "ALT" key in combination with the first letter of the command. If this command opens up other subordinate commands, these will be displayed, and can be selected by pressing the first letter of the subordinate command (without the "ALT" key).

The data appearing on the main part of the screen is altered by moving the cursor to the appropriate place and typing in new data. Sections can be added to or removed from the pulse shape by specifying the 'Edit" command followed by the 'Insert" or 'Delete" options. The 'Range" field accepts anything beginning with 'h" or 'l" (upper or lower case) for high or low range. All other data is numeric, and must consist of numbers with an optional decimal point. Duration of each section of a pulse is specified in milliseconds, to one decimal place if desired. Amplitude of each section (in milliamperes) can be specified to one decimal place in high range and to

two decimal places in low range. Anything entered in a numeric field which is not a number will be interpreted as zero. If the amplitude of a pulse is too high for the chosen range it will not be possible to send this pulse shape to the Constant Current Stimulator. If too high a resolution is specified, it will be rounded down to the nearest permitted figure. The 'delay' and 'holdoff' times (in milliseconds) are periods of no output immediately after the trigger and at the end of the pulse respectively. These can be set to zero if required, or varied to produce a gap before or after each pulse. A warning message will be generated if the holdoff time is less than the total pulse length.

The pulse data displayed on screen can be sent to the Constant Current Stimulator by selecting the 'Go" command or pressing the F1 key. If there are no errors it will be stored in one of the stimulator's buffers, and delivered to the patient at the next trigger. Output to the patient can be prevented by selecting the 'Stop" command or pressing the F2 key. The bottom area of the screen will display error messages if there is a communication error between the computer and the stimulator (e.g. if the stimulator is not switched on, or the cable between the computer and stimulator is not connected). The 'Exchange" option ('Control" menu or F7 key) causes the previous pulse to be delivered again. The 'Test" output delivers the pulse to the internal test load rather than to the patient.

The pulse data displayed at any time can be saved on disk by selecting 'File" and 'Save". The session can be ended by selecting the 'Quit" command. This returns control to DOS.

Status Display

The bottom three lines of the screen display information about the operation of the system. The 'CCS Status" field shows whether the Constant Current Stimulator is delivering a pulse, stopped, or waiting for a trigger. The 'Output" field reports whether the main output isolator switch is open or closed. The 'Session Time"

records the time elapsed in hours, minutes and seconds since the program was started, or since the Constant Current Stimulator unit was switched on or a reset command issued.

The program calculated the energy delivered to the patient in each pulse, in mJ or mJ per ohm of tissue resistance (square milliamp-seconds) and the total energy delivered in a session. The number of triggers received during the session is also displayed and updated every five seconds.

Fault Finding, Calibration and Servicing

These aspects of the use of the stimulator are covered in the Operating Manual (Spicer & Boone, 1990), to which reference should be made. Calibration and servicing should be carried out at least every six months, or every 1000 hours of use, or whenever a major repair has been carried out.

When set up and used correctly, the Constant Current Stimulator conforms to BS5724 (British Standards Institution, 1988, 1989) and is classified as class 1, type CF.

References

Aidley DJ (1971). *The Physiology of Excitable Cells*. Cambridge: Cambridge University Press.

Antzelevitch C, Moe GK (1983). Electrotonic inhibition and summation of impulse conduction in mammalian Purkinje fibres. *American Journal of Physiology* **245**: 1142-1153.

Bashir Y, Heald SC, Katritsis D, Hammouda M, Camm AJ, Ward DE (1993). Radiofrequency ablation of accessory atrioventricular pathways: predictive value of local electrogram characteristics for the identification of successful target sites. *British Heart Journal* **69**: 315-321.

Boone K (1989). Constant current stimulator control software for IBM PC/AT: Operating manual. Department of Biomedical Engineering, Royal Brompton National Heart & Lung Hospital, London, UK.

British Standards Institution (1988). BS 5274: Medical Electrical Equipment. Part 2: Particular Requirements for Safety. Section 2.10: Specification for nerve and muscle stimulators. London: British Standards Institution.

British Standards Institution (1989). BS 5274: Medical Electrical Equipment. Part 1: General Requirements for Safety. London: British Standards Institution.

Calkins H, Sousa J, El-Atassi R, Rosenheck S, de Buitleir M, Kou WH, Kadish AH, Langberg JJ, Morady F (1991). Diagnosis and cure of the Wolff-Parkinson-White syndrome or paroxysmal supraventricular tachycardia during a single electrophysiologic test. *New England Journal of Medicine* **324**: 1612-1618.

Calkins H, Langberg J, Sousa J, El-Atassi R, Leon A, Kou W, Kalbfleisch S, Morady F (1992a). Radiofrequency catheter ablation of accessory atrioventricular

connections in 250 patients: abbreviated therapeutic approach to Wolff-Parkinson-White syndrome. *Circulation* **85**: 1337-1346.

Calkins H, Kim YN, Schmaltz S, Sousa J, El-Atassi R, Leon A, Kadish A, Langberg J, Morady F (1992b). Electrogram criteria for identification of appropriate target sites for radiofrequency catheter ablation of accessory atrioventricular connections. *Circulation* **85**: 565-573.

Castellanos A, Lemberg L, Johnson D, Berkovits BV (1966). The Wedensky effect in the human heart. *British Heart Journal* **28**: 276-283.

Chen X, Shenasa M, Willems S, Kottkamp H, Rotman B (1993). Subthreshold stimulation in catheter ablation of accessory pathway: evidence of concealed capture of the pathway (Abstract). *Circulation* **88**: I-61.

Chorro FJ, Sanchis J, Lopez-Merino V, Burguera M, Martinez-Mas ML, Cortina J, Such L (1992). Effects of subthreshold stimuli trains on atrial refractoriness (Abstract). *European Heart Journal* **13** (Abstract Supplement): 207.

Connelly DT, Cunningham D, Boone KG, Spicer M, Rowland E (1991a). Summation and inhibition in the human heart are dependent on polarity of conditioning stimuli (Abstract). *Journal of the American College of Cardiology* **17** (Supplement A): 387A.

Connelly DT, Cunningham D, Spicer M, Boone KG, Rowland E (1991b). Inhibition and summation in the human heart by long duration subthreshold conditioning pulses (Abstract). *British Heart Journal* **66**: 62.

Connelly DT, Cunningham D, Spicer M, Boone KG, Rowland E (1991c). Inhibition in the human heart using long duration subthreshold conditioning pulses (Abstract). *Pacing and Clinical Electrophysiology* **14**: 625.

Connelly DT, Cunningham D, Rowland E (1992a). Spatial and temporal effects of long duration subthreshold conditioning stimuli (Abstract). *British Heart Journal* **68**: 122.

Connelly DT, Cunningham D, Rowland E (1992b). Inhibition in the human heart by long duration subthreshold pulses - spatial and temporal effects (Abstract). *Pacing and Clinical Electrophysiology* **15**: 521.

Connelly DT, Cunningham AD, Rowland E (1992c). Inhibition in the human heart by long duration subthreshold stimuli - spatial and temporal effects (Abstract). *European Heart Journal* **13** (Abstract Supplement): 207.

Coombs JS, Eccles JC, Fatt P (1955a). Excitatory synaptic action in motoneurones. *Journal of Physiology* **130**: 374-395.

Coombs JS, Eccles JC, Fatt P (1955b). The inhibitory suppression of reflex discharges from motoneurones. *Journal of Physiology* **130**: 396-413.

Coumel P, Cabrol C, Fabiato A, Gourgan R, Slama R (1967). Tachycardie permanente par rhythme reciproque. I. Preuves du diagnostic par stimulation auriculaire et ventriculaire. *Archives des Maladies du Coeur et des Vaisseaux* **60**: 1830-1849.

Cranefield PF, Hoffman BF (1971). Conduction of the cardiac impulse. II. Summation and inhibition. *Circulation Research* **28**: 220-233.

Cranefield PF, Hoffman BF, Siebens AA (1957). Anodal excitation of cardiac muscle. *American Journal of Physiology* **190**: 383-390.

Cunningham AD, Kennedy JA (1985). Atrioversion: conversion of atrial flutter in man using a long constant current pulse. *British Heart Journal* **53**: 93.

Cunningham AD (1988). Atrioversion: mechanism of atrial flutter in man and a new technique for electrical conversion of atrial flutter. PhD Thesis, University of Glasgow.

Curtis DR, Eccles JC (1959). The time course of excitatory and inhibitory synaptic actions. *Journal of Physiology* **145**: 529-546.

Dekker E (1970). Direct current make and break thresholds for pacemaker electrodes on the canine ventricle. *Circulation Research* **27**: 811-823.

Donaldson PEK (1993). Letter to the Editor. *Medical and Biological Engineering and Computing* **31**: 30.

Drury AN, Love WS (1926). The supposed lengthening of the absolute refractory period of frog ventricular muscle by veratrine. *Heart* **13**: 77-85.

El-Sherif N, Gough WB, Restivo M (1987). Reentrant ventricular arrhythmias in the late myocardial infarction period: 14. Mechanisms of resetting, entrainment, acceleration, or termination of reentrant tachycardia by programmed electrical stimulation. *Pacing and Clinical Electrophysiology* **10**: 341-371.

Fatt P, Katz B (1952). Spontaneous subthreshold activity at motor nerve endings. *Journal of Physiology* **117**: 109-128.

Fitzgerald DM, Friday KJ, Yeung Lai Wah JA, Lazzara R, Jackman WM (1988). Electrogram patterns predicting successful catheter ablation of ventricular tachycardia. *Circulation* **77**: 806-814.

Franz MR (1983). Long term recording of monophasic action potentials from human endocardium. *American Journal of Cardiology* **51**: 1629-1634.

Franz MR, Burkhoff D, Spurgeon H, Weisfeldt ML, Lakatta EG (1986). In vitro validation of a new cardiac catheter technique for recording monophasic action potentials. *European Heart Journal* **7**: 34-41.

Franz MR, Swerdlow CD, Liem LB, Schaefer J (1988). Cycle length dependence of human action potential duration in vivo. Effects of single extrastimuli, sudden sustained rate acceleration, and different steady-state frequencies. *Journal of Clinical Investigation* **82**: 972-979.

Franz MR, Chin MC, Sharkey HR, Griffin JC, Scheinman MM (1990). A new single catheter technique for simultaneous measurement of action potential duration and refractory period in vivo. *Journal of the American College of Cardiology* **16**: 878-886.

Frazier DW, Krassowska W, Chen PS, Wolf PD, Danieley ND, Smith WM, Ideker RE (1988a). Transmural activations and stimulus potentials in three-dimensional anisotropic canine myocardium. *Circulation Research* **63**: 135-146.

Frazier DW, Krassowska W, Chen PS, Wolf PD, Dixon ED, Smith WM, Ideker RE (1988b). Extracellular field required for excitation in three-dimensional anisotropic cardiac muscle. *Circulation Research* **63**: 147-164.

Fromer M, Shenasa M (1992). Ultrarapid subthreshold stimulation for termination of atrioventricular node reentrant tachycardia. *Journal of the American College of Cardiology* **20**: 879-883.

Gang ES, Peter T, Nalos PC, Meesmann M, Karagueuzian HS, Mandel WM, Oseran DS, Myers MR (1988). Subthreshold atrial pacing in patients with a left-sided accessory pathway: an effective new method for terminating reciprocating tachycardia. *Journal of the American College of Cardiology* **11**: 515-521.

Garan H, Ruskin JN (1988). Reproducible termination of ventricular tachycardia by a single extrastimulus within the reentry circuit during the ventricular effective refractory period. *American Heart Journal* **116**: 546-550.

Goto M, Brooks CMcC (1969). Membrane excitability of the frog ventricle examined by long pulses. *American Journal of Physiology* **217**: 1236-1245.

Haissaguerre M, Fischer B, Warin JF, Dartigues JF, Lematayer P, Egloff P (1992a). Electrogram patterns predictive of successful radiofrequency catheter ablation of accessory pathways. *Pacing and Clinical Electrophysiology* **15**: 2138-2145.

Haissaguerre M, Gaita F, Fischer B, Commenges D, Montserrat P, d'Ivernois C, Lematayer P, Warin JF (1992b). Elimination of atrioventricular nodal reentrant tachycardia using discrete slow potentials to guide application of radiofrequency energy. *Circulation* **85**: 2162-2175.

Hindricks G, Shenasa M, Borggrefe M, Haverkamp W, Chen X, Willems S, Karbenn U, Breithardt G (1992). Subthreshold stimulation as a key for the precise localization and catheter ablation of accessory pathways (Abstract). *European Heart Journal* **13** (Abstract Supplement): 432.

Hindricks G, Shenasa M, Chen X, Willems S, Haverkamp W, Kottkamp H, Lubinski A, Borggrefe M (1993).Emergence of preexcitation during constant current subthreshold stimulation at the ventricular insertion of accessory pathways (Abstract). *Circulation* **88**: I-65.

Hodgkin AL, Huxley AH (1952). A quantitative description of membrane current and its application to conduction and excitation in nerve. *Journal of Physiology* **117**: 500-544.

Hodgkin AL, Rushton WAH (1946). The electrical constants of a crustacean nerve fibre. *Proceedings of the Royal Society* B **133**: 444.

Ideker RE, Frazier DW, Krassowska W, Chen PS, Wharton JM (1990). Physiologic effects of electrical stimulation in cardiac muscle. In: *Electrical Therapy for Cardiac Arrhythmias* (eds. Saksensa S, Goldschlager N). Philadelphia: Saunders.

Inoue H, Saihara S, Toda I, Sugimoto T (1989). Summation and inhibition by ultrarapid train pulses in dogs: effects of frequency and duration of trains, lidocaine, and beta blockade. *Pacing and Clinical Electrophysiology* **12**: 1777-1786.

Jackman WM, Wang X, Friday KJ, Roman CA, Moulton KP, Beckman KJ, McClelland JH, Twidale N, Hazlitt HA, Prior MI, Oren J, Overholt ED, Lazzara R

(1991). Catheter ablation of accessory atrioventricular pathways (Wolff-Parkinson-White syndrome) by radiofrequency current. *New England Journal of Medicine* **324**: 1605-1611.

Jackman WM, Beckman KJ, McClelland JH, Wang X, Friday KJ, Roman CA, Moulton KP, Twidale N, Hazlitt HA, Prior MI, Oren J, Overholt ED, Lazzara R (1992). Treatment of supraventricular tachycardia due to atrioventricular nodal reentry by radiofrequency catheter ablation of slow-pathway conduction. *New England Journal of Medicine* **327**: 313-318.

Jalife J, Antzelevitch C (1979). Phase resetting and annihilation of pacemaker activity in cardiac tissue. *Science* **206**: 695-697.

Jazajeri MR, Hempe SL, Sra JS, Dhala AA, Blanck Z, Deshpande SS, Avitall B, Krum DP, Gilbert CJ, Akhtar M (1992). Selective transcatheter ablation of the fast and slow pathways using radiofrequency energy in patients with atrioventricular nodal reentrant tachycardia. *Circulation* **85**: 1318-1328.

Kadish AH, Schmaltz S, Morady F (1991). Variability in the measurement of human ventricular refractoriness. *Pacing and Clinical Electrophysiology* **14**: 1393-1401.

Kaltenbrunner W, Cardinal R, Dubuc M, Shenasa M, Nadeau R, Tremblay G, Vermeulen M, Savard P, Page PL. Epicardial and endocardial mapping of ventricular tachycardia in patients with myocardial infarction. Is the origin of the tachycardia always subendocardially localized? *Circulation* 1991; **84**: 1058-1071.

Kavanagh KM, Duff HJ, Clark R, Robinson KV, Wyse DG (1990). Monophasic versus biphasic cardiac stimulation: mechanism of decreased energy requirements. *Pacing and Clinical Electrophysiology* **13**: 1268-1276.

Kay GN, Epstein AE, Plumb VJ (1988). Region of slow conduction in ventricular tachycardia: direct endocardial recordings and functional characterization in humans. *Journal of the American College of Cardiology* 11: 109-116.

Kennedy JA, McAlpine HM, Rae AP, Cunningham D, Christie J (1986). Termination of ventricular tachycardia by a long duration, low energy, constant current endocardial pulse. *Circulation* 74: II-388.

Kuck KH, Schluter M, Geiger M, Siebels J (1991a). Successful catheter ablation of human ventricular tachycardia with radiofrequency current guided by an endocardial map of the area of slow conduction. *Pacing and Clinical Electrophysiology* 14: 1060-1071.

Kuck KH, Schluter M, Geiger M, Siebels J, Duckeck W (1991b). Radiofrequency current catheter ablation of accessory atrioventricular pathways. *Lancet* 337: 1557-1561.

Langberg JJ, Calkins H, Sousa J, El-Atassi R, Morady F (1991a). Effects of drive train stimulus intensity on ventricular refractoriness in humans. *Circulation* 84: 181-187.

Langberg JJ, Calkins H, Sousa J, El-Atassi R, Morady F (1991b). Noncapturing stimuli during the basic drive shorten ventricular refractoriness. *American Journal of Cardiology* 68: 1094-1096.

Langendorf R (1948). Concealed A-V conduction: The effect of blocked impulses on the formation and conduction of subsequent impulses. *American Heart Journal* 35: 542-552.

Langendorf R, Pick A (1956). Concealed conduction. Further evaluation of a fundamental aspect of propagation of the cardiac impulse. *Circulation* 13: 381-399.

Lee MA, Morady F, Kadish A, Schamp DJ, Chin MC, Scheinman MM, Griffin JC, Lesh MD, Pederson D, Goldberger J, Calkins H, de Buitleir M, Kou WH, Rosenheck S, Sousa J, Langberg JJ (1991). Catheter modification of the atrioventricular junction with radiofrequency energy for control of atrioventricular nodal reentrant tachycardia. *Circulation* **83**: 827-835.

Lewis T, Drury AN (1926). Revised views of the refractory period, in relation to drugs reputed to prolong it, and in relation to circus movement. *Heart* **13**: 95-100.

Lindemans FW, Heethaar RM, Denier van der Gon JJ, Zimmerman ANE (1975). Site of initial excitation and current threshold as a function of electrode radius in heart muscle. *Cardiovascular Research* **9**: 95-104.

Lindemans FW, Denier van der Gon JJ (1978). Current thresholds and liminal size in excitation of heart muscle. *Cardiovascular Research* **12**: 477-485.

Liu Y, Zeng W, Delmar M, Jalife J (1993). Ionic mechanisms of electrotonic inhibition and concealed conduction in rabbit atrioventricular nodal myocytes. *Circulation* **88**: 1634-1646.

Love WS (1926). The effect of quinidine and strophanthidin upon the refractory period of the tortoise ventricle. *Heart* **13**: 87-93.

Malik M, Camm AJ (1990). Termination of macro-reentrant tachycardia by a single extrastimulus delivered during the `effective' refractory period: a computer modeled `case report'. *Pacing and Clinical Electrophysiology* **13**: 103-109.

Mitrani RD, Klein LS, Hackett K, Zipes DP, Miles WM (1993). Radiofrequency ablation for atrioventricular node reentrant tachycardia: comparison between fast (anterior) and slow (posterior) pathway ablation. *Journal of the American College of Cardiology* 1993; **21**: 432-441.

Morady F. Frank R, Kou WH, Tonet JL, Nelson SD, Kounde S, de Buitler M, Fontaine G (1988). Identification and catheter ablation of a zone of slow conduction in the reentrant circuit of ventricular tachycardia in humans. *Journal of the American College of Cardiology* 11: 775-782.

Morady F, Kadish AH, Rosenheck S, Schmaltz S, de Buitleir M (1990). Effect of the intertrain pause on the ventricular effective refractory period measured by the extrastimulus technique. *Pacing and Clinical Electrophysiology* 13: 405-409.

Morady F, Kadish A, Rosenheck S, Calkins H, Kou WH, de Buitler M, Sousa J (1991). Concealed entrainment as a guide for catheter ablation of ventricular tachycardia in patients with prior myocardial infarction. *Journal of the American College of Cardiology* 17: 678-689.

Morady F, Harvey M, Kalbfleisch SJ, El-Atassi R, Calkins H, Langberg JJ (1993). Radiofrequency catheter ablation of ventricular tachycardia in patients with coronary artery disease. *Circulation* 87: 363-372.

Morgan JM (1991). MD thesis, University of Cambridge.

Morgan JM, Cunningham AD, Rowland E (1990). Relationship of the effective refractory period and monophasic action potential duration after a step increase in pacing frequency. *Pacing and Clinical Electrophysiology* 13: 1002-1008.

Paya R, Chorro FJ, Sanchis J, Alberola A, Dalli E, Lopez-Merino V (1991). Changes in canine ventricular refractoriness induced by trains of subthreshold high-frequency stimuli. *Journal of Electrocardiology* 24: 63-69.

Paya R, Chorro FJ, Sanchis J, Gil F, Burguera M, Quesada A, Lopez-Merino V (1992). Inhibition by trains of subthreshold high-frequency stimuli: an experimental study in spatial limitation. *European Heart Journal* 13: 544-549.

Podczeck A, Borggrefe M, Martinez-Rubio A, Breithardt G (1988). Termination of re-entrant ventricular tachycardia by subthreshold stimulus applied to the zone of slow conduction. *European Heart Journal* **9**: 1146-1150.

Prystowsky EN, Zipes DP (1983). Inhibition in the human heart. *Circulation* **68**: 707-713.

Roberts DE, Hersh LT, Scher AM (1979). Influence of cardiac fiber orientation in wavefront voltage, conduction velocity, and tissue resistivity in the dog. *Circulation Research* **44**: 701-712.

Roberts DE, Scher AM (1982). Effect of tissue anisotropy on extracellular potential fields in canine myocardium in situ. *Circulation Research* **50**: 342-351.

Rothschild R, Stevenson WG, Klitzner T, Weiss J (1987). Enhancement of conduction in an accessory pathway by local noncaptured stimuli. *Journal of the American College of Cardiology* **9**: 455-458.

Ruffy R (1990a). Subthreshold stimulation of the heart: small but important. *Pacing and Clinical Electrophysiology* **13**: 110-118.

Ruffy R (1990b). Termination of ventricular tachycardia by nonpropagated local depolarization: further observations on entrainment of ventricular tachycardia from an area of slow conduction. *Pacing and Clinical Electrophysiology* **13**: 852-858.

Ruffy R, Friday KJ, Southworth WF (1983). Termination of ventricular tachycardia by single extrastimulation during the ventricular effective refractory period. *Circulation* **67**: 457-459.

Rush S, Abildskov JA, McFee R (1963). Resistivity of body tissues at low frequencies. *Circulation Research* **12**: 40-50.

Saihara S, Inoue H, Toda I, Usui M, Sugimoto T (1990a). Summation of excitation with a single conditioning stimulus in the canine heart. *Pacing and Clinical Electrophysiology* **13**: 52-58.

Saihara S, Inoue H, Toda I, Usui M, Sugimoto T (1990b). Reappraisal of inhibition and summation with a single conditioning stimulus in man. *Pacing and Clinical Electrophysiology* **13**: 151-157.

Scheinman MM (1992). Catheter ablation for carfiac arrhythmias, personnel, and facilities. *Pacing and Clinical Electrophysiology* **15**: 715-521.

Schluter M, Geiger M, Siebels J, Duckeck W, Kuck KH (1991). Catheter ablation using radiofrequency current to cure symptomatic patients with tachyarrhythmias related to an accessory atrioventricular pathway. *Circulation* **84**: 1644-1661.

Shenasa M, Cardinal R, Kus T, Savard P, Fromer M, Page P (1988). Termination of sustained ventricular tachycardia by ultrarapid subthreshold stimulation in humans. *Circulation* **78**: 1135-1143.

Shenasa M, Fromer M, Borggrefe M, Breithardt G (1991). Subthreshold electrical stimulation for termination and prevention of reentrant arrhythmias. *Journal of Electrocardiology* **24** (Supplement): 25-31.

Shenasa M, Borggrefe M, Shenasa J, Hindricks G, Chen X ,Haverkamp W, Willems S, Breithardt G (1992). Subthreshold electrical stimulation: a novel method for prevention and termination of reentrant arrhythmias (Abstract). *European Heart Journal* **13** (Abstract Supplement): 293.

Silka MJ, Kron J, Halperin BD, Griffith K, Crandall B, Oliver RP, Walance CG, McAnulty JH (1992). Analysis of local electrogram characteristics correlated with successful radiofrequency catheter ablation of accessory atrioventricular pathways. *Pacing and Clinical Electrophysiology* **15**: 1000-1007.

Skale BT, Kallok MJ, Prystowsky EN, Gill RM, Zipes DP (1985). Inhibition of premature ventricular extrastimuli by subthreshold conditioning stimuli. *Journal of the American College of Cardiology* 6: 133-140.

Spicer M, Boone K (1990). Constant current stimulator: Operating manual, programming guide and technical reference. Department of Biomedical Engineering, Royal Brompton National Heart & Lung Hospital, London, UK.

Spicer M, Pitty DL, Boone K, Obeyesekara P, Connelly DT, Logan-Sinclair RB, Cunningham AD (1992). Cardiac stimulator for the study of refractory period control using current pulses of programmable duration and shape. *Medical and Biological Engineering and Computing* 30: 377-384.

Stevenson WG, Wiener I, Weiss J (1987a). Limitations of bipolar and unipolar conditioning stimuli for inhibition in the human heart. *American Heart Journal* 114: 303-310.

Stevenson WG, Weiss J, Wiener I, Wohlgelernter D, Yeatman L (1987b). Localization of slow conduction in a ventricular tachycardia circuit: implications for catheter ablation. *American Heart Journal* 114: 1253-1258.

Stevenson WG, Khan H, Sager P, Saxon L, Middlekauff HR, Natterson PD, Wiener I (1993). Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. *Circulation* 88: 1647-1670.

Swerdlow CD, Liem LB, Franz MR (1987). Summation and inhibition by ultrarapid train pacing in the human ventricle. *Circulation* 76: 1101-1109.

Tamargo J, Moe B, Moe GK (1975). Interaction of sequential stimuli applied during the relative refractory period in relation to determination of fibrillation threshold in the canine ventricle. *Circulation Research* 37: 534-541.

Waldo AL, MacLean WAH, Karp RB, Kouchoukos NT, Jones TN (1977). Entrainment and interruption of atrial flutter with atrial pacing. Studies in man following open heart surgery. *Circulation* **56**: 737-745.

Waldo AL, Plumb VJ, Arciniegas JE, MacLean WAH, Copper TB, Priest MF, Jones TN (1983). Transient entrainment and interruption of the atrioventricular bypass type of paroxysmal atrial tachycardia. A model for understanding and identifying reentrant arrhythmias. *Circulation* **67**: 73-83.

Waldo AL, Henthorn RW, Plumb VJ, MacLean WAH (1984). Demonstration of the mechanism of transient entrainment of ventricular tachycardia with rapid atrial pacing. *Journal of the American College of Cardiology* **3**: 422-430.

Wathen M, Natale A, Wolfe K, Yee R, Newman D, Klein G (1992). An anatomically guided approach to atrioventricular node slow pathway ablation. *American Journal of Cardiology* **70**: 886-889.

Weidmann S (1951). Effect of current flow on the membrane potential of cardiac muscle. *Journal of Physiology* **115**: 227-236.

Wedensky NE (1886). Uber die beziehung zwischen reizung und erregung im tetanus. *Ber Acad Wiss* **54**: 96.

Wellens HJJ, Lie KI, Durrer D (1974). Further observations on ventricular tachycardia as studied by electrical stimulation of the heart. Chronic recurrent ventricular tachycardia and ventricular tachycardia during acute myocardial infarction. *Circulation* **49**: 647-653.

Windle JR, Miles WM, Zipes DP, Prystowsky EN (1986). Subthreshold conditioning stimuli prolong human ventricular refractoriness. *American Journal of Cardiology* **57**: 381-386.

Wit AL, Cranefield PF (1976). Triggered activity in cardiac muscle fibers of the simian mitral valve. *Circulation Research* **38**: 85-98.

Zipes DP (1993). Arrhythmias on the endangered list. *Journal of the American College of Cardiology* **21**: 918-919.