Cardiac Arrhythmias, Pacing & Electrophysiology

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CARDIAC ARRHYTHMIAS, PACING & ELECTROPHYSIOLOGY

The Expert View

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Dedicated
to those who inspired me and encouraged me in this endeavour
and especially to my beloved Anastasia, Katerina and Emmanuel.

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FOREWORD

Europace '97 was held in Athens, Greece, on 8–11 June 1997 in the city of classical civilisation and learning. Though now held in modern surroundings and meeting facilities, the influence of the ancient city-state was unmistakable, with the architecture and learning of antiquity looming over the city, by its influence over the intellectual activities of the symposium. The ancient magnificence of the site was matched by the novelty of modern art and science, Europace is a European symposium, begun in 1979, and has occurred every second year since. Consistent with its importance and continental reach the actual symposium has moved to different cities throughout Western Europe. The first symposium was held in London and subsequent symposia have been held in Torremolinos, Ostend, Florence, Istanbul and other cities. Because of the ease of modern travel it rapidly became a truly international conference, with participation from the entire European continent and from every continent of the world. It has always served as a common ground for meeting of Europeans from East and West, and North and South Americans, at a site of mutual interest.

Unlike the administration of meetings of specific national and international organisations, Europace, under the auspices of the European Working Groups on Cardiac Pacing and Arrhythmias, has been administratively decentralised. Both the venue of the meeting and its organisation have constantly moved. In 1997 the organisation and conduct of Europace was conducted ably and efficiently by Professor P.E. Vardas of the Department of Cardiology of Heraklion University Hospital, Heraklion, Crete, Greece. Europace has always represented a most modern presentation of cardiac pacing techniques, and from the very beginning has mirrored the progressive expansion of the field.

One need only review the contents of the European pacing conferences over the years to note the evolution of arrhythmia diagnosis and management. The first congress dealt with pacing alone, and discussion of the classic indications for pacing of atrioventricular (AV) block and sinus node dysfunction and the haemodynamics of pacing those two conditions. At that time haemodynamics largely dealt with rate change and the effect of exercise with single rate pacing. Artificial sensors in pacing were so new as not to be discussed. Leads were, as usual, an important topic, with the earliest mention of the then-new polyurethane leads. Future conferences elaborated on these basic topics while progressively adding sensors and sensor function, dual-chamber pacing, and recognising the development of clinical cardiac electrophysiology.

Clinical cardiac electrophysiology and comprehension of arrhythmias has been largely a development of the twentieth century. With the description and recording of the bundle of His depolarisation, by direct access and by catheter, modern clinical investigation of arrhythmias and cardiac electrophysiology began. The disciplines of cardiac stimulation and of investigation of arrhythmias, impulse formation and AV conduction were essentially separate for many years. Investigators in the two areas appeared at different meetings and seldom corresponded with each other. In 1980 the first human implantation of an implantable cardioverter/defibrillator (ICD) occurred. That became an epochal event in this work, though unrecognised at the time. The defibrillator managed ventricular tachyarrhythmia, a capability which cardiac pacing did not have, other than indirectly, where the establishment of a regular and consistent ventricular rate might suppress the tachycardia by suppressing the escape ventricular arrhythmias which caused a small portion of Morgagni-Adams-Stokes episodes. With the presentation of the complexities of ICD therapy it progressively became clear that this therapy combined the capabilities and problems of cardiac stimulation while directed at management of the two most lethal of cardiac arrhythmias, ventricular tachycardia and ventricular fibrillation. The European and other world symposia then began to present pacing and defibrillation, especially as it became clearer that pacing was an integral component in overall tachyarrhythmia management when combined with the ICD. During the mid-1980s world symposia dealt with pacing, defibrillation and more and more with interventional cardiac electrophysiology. Even as late as the mid-1980s pacemaker and ICD programmability was relatively rudimentary compared to what it has become in 1997.

With the development of highly complex programmability and the transvenous approach to ICD implanta-

tion a truly new era has occurred. The ICD is now suitable for any patient, can manage both tachyarrhythmias and bradyarrhythmias and has begun to exercise increasing competitiveness with medications. Stimulation of yet another portion of the heart, the atrium, is now being evaluated for the management of atrial fibrillation, an arrhythmia beginning to receive closer scrutiny for its effect on cardiac health and its ability to be restrained and effectively reversed. With ablation of ventricular and atrial foci and the AV conduction system, there are now a range of powerful interventions in the management of cardiac arrhythmias. All bradyarrhythmias can be managed with an implantable pacemaker, either single- or dual-chamber, either pacing the ventricle alone and disregarding a chronically fibrillating or fluttering atrium or with dual-chamber pacing which restores the normal AV sequence. Even the intermittently fibrillating or fluttering atrium can be paced with a dual-chamber device because of sensor availability, which permits the automatic change of mode from dual-chamber to single-chamber pacing in the presence of an atrial arrhythmia. Reentry tachyarrhythmias and those dependent on a ventricular or atrial pathological focus can be managed by ablation techniques and drugs which still play a major, though diminishing, role. Ventricular tachyarrhythmias and fibrillation can be managed with the ICD and with drugs. Atrial arrhythmias may yet fall to the atrial defibrillator. The overall management of cardiac arrhythmias has progressed immeasurably in the past two decades. It is unrecognisable compared to management at the time of the first European Symposium on Cardiac Pacing.

The new frontiers of arrhythmology now deal with the use of pacing for management of hypertrophic obstructive cardiomopathy, the management of vagal syndromes and further expansion of non-invasive electrocardiology, in order to enhance diagnostic capability at minimum patient discomfort and cost. In cardiac pacing new areas presented included the pacing techniques to resynchronise the atria and further evaluation of the technique of single-lead VDD pacing. The discussion of randomised prospective trials in cardiac pacing and ICD therapy were also presented and discussed. Without doubt the technique of the randomised prospective trial is of immense value in discerning differences between therapeutic approaches. It is as new an approach as is the field itself. The power of the statistical technique has brought clarity to many investigations, and has enabled the detection of therapeutic directions which are sufficiently subtle so that they are not immediately obvious. This tool is one which will continue to thrive, and will expand in its value, as the years pass.

Europace '97, a superbly executed and scientifically distinguished international symposium, reflected credit upon its organisers, the European Working Groups and its immediate Greek organisers. It continued the line of European symposia in a way which makes the high quality of the next congress a necessity. It has also advanced the dissemination of the art and science of arrhythmia management throughout the world, but especially to those portions of Europe which are still unable readily to access symposia in other parts of the world. Everyone involved in the event is to be congratulated and commended.

Seymour Furman

PREFACE

Cardiology as a whole, and in particular cardiac arrhythmias, electrophysiology and pacing, are developing so rapidly in both the diagnostic and therapeutic fields that even the many associated publications barely manage to keep up with scientific progress.

Scientific congresses and symposia, as components of continuing medical education, provide a bridge between established medical knowledge and future groundbreaking research. This volume includes articles on a large number of topics which were presented at the recent congress on arrythmias, electrophysiology and pacing, Europace '97.

The main purpose of this publication is to provide an up to date presentation of aspects of arrhythmiology, clinical electrophysiology, internal defibrillation and pacing by pioneers in these fields. The book is aimed principally at specialised cardiologists and is not intended to cover the daily needs of patient care.

The advantages of this publication are undoubtedly the large number of chapters, 62 in all, the in depth analysis of particular scientific topics and the presentation of the clinical and research experience of many of the authors. I would like to take the opportunity to thank all the contributors especially for their willingness to contribute to this volume, as well as for the efforts they have made towards progress in their particular fields.

I would also like to thank my colleagues in our own cardiology department for their contribution to the development of the academic, research and authoring activities of the department. In particular, I would like to mention the contribution made by the head of the department's computer section, Mr. Philip Lees, and to thank him for his ideas and initiative.

Finally, I would like to express my gratitude to the staff of Kluwer Academic Publications, in particular Nettie Dekker, for their valuable cooperation and their assistance in the preparation of this book.

P.E. Vardas

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PART ONE

CARDIAC ARRHYTHMIAS AND CLINICAL ELECTROPHYSIOLOGY

Chapter 1

Sinus Node Reentrant Tachycardia versus Ectopic Atrial Tachycardia: Where Lies the Difference?

Hein Heidbüchel

Introduction

So-called "sinus node reentrant tachycardia" (SNRT) looks like a vanishing arrhythmia. In pre-ablation era textbooks and articles, it was reported to represent a significant proportion of paroxysmal supraventricular tachycardia, ranging from 3.2% to 16.9% of patients with supraventricular tachycardia[1–3]. There is the impression however that the reported incidence is lower in more recent papers since there are only few reports, each with few patients, on SNRT or its treatment by radiofrequency catheter ablation[3–7]. Another illustration is the complete absence of abstracts dealing with this arrhythmia during the NASPE meeting of May 1997 and only a single presentation during the 1996 meeting.

On the other hand, ectopic atrial tachycardia (EAT) is recognised more often than before. During the same NASPE meetings, more than 10 abstracts concerning EAT were presented. This may be over-diagnosis due to the fact that cure of an arrhythmia by a small radiofrequency lesion is falsely deduced to be indicative of elimination of a focal arrhythmia. There is an increased awareness of a predilection for this type of arrhythmia to reside on the crista terminalis (where the sinus node also resides). Hence, although a whole world lies between the mechanisms of SNRT and EAT, reentry versus a focal mechanism, their anatomical localisations are not far apart.

Although there are theoretical criteria to differentiate the reentrant mechanism of SNRT from the focal mechanism of EAT, correct differentiation during daily practice is often difficult. Moreover, from a purely pragmatic ablation standpoint, the two entities come very close to each other. It is the purpose of this chapter to review how far the two arrhythmias lie from each other conceptually (and how they can possibly be separated), but how close they are in practical terms of localisation and treatment.

Sinus node reentrant tachycardia and ectopic atrial tachycardia

Sinus node reentrant tachycardia

The concept of reentry within the sinus node area dates back to 1943, as it was originally suggested by Barker et al[18]. By extracellular mapping and by recording intracellular action potentials in the area of the sinus node in rabbit hearts, it became clear that reentry could indeed occur in a small region in or near the sinus node[9,10]. Interestingly however, these authors concluded that the wavelength of the arrhythmia precluded sustained

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SNRT in rabbits, which was never seen during their experiments. On the other hand, the larger size of the human sinus node could theoretically accommodate a reentrant circuit. After Narula et al in 1974 reported for the first time atrial complexes possibly due to sinus node reentry[11], numerous reports have described this arrhythmia in humans. Single sinus node echo beats during programmed atrial stimulation in humans are not uncommon, and may be present in more than 10% of patients[12], although much less frequently than isolated AV nodal reentrant beats[13]. However, as noted earlier, the incidence of clinically significant *sustained* SNRT remains controversial, ranging from 1.8%[13] to 16.9%[2] of patients presenting with supraventricular tachycardia. Reported cases have shown that its rate is usually slow (120–140 bpm), and that it may vary largely with autonomic tone. Therefore, it is also possible that some patients with this arrhythmia remain undiagnosed. There seems to be a higher incidence of structural heart disease in patients with SNRT, being present in 30–70%[2,3,5,14,15]. The significance of this association is unknown.

In some series reporting on patient groups with SNRT, it became clear that a significant proportion of these patients also had another arrhythmia[3,14]. One could therefore question whether the SNRT was indeed the clinical arrhythmia. Indeed, Wellens reported that in only three of seven patients with induced SNRT during an electrophysiological study was the arrhythmia the same as the clinically documented one[13]. Therefore, it actually accounted for only < 1% of clinical arrhythmias. Curry et al also reported that only five out of nine patients with induced SNRT in the electrophysiological (EP) laboratory had spontaneous palpitations[14]. Even if induced in the clinical EP laboratory, most episodes of SNRT are unstable and spontaneously terminate after a short time[13,14]. On the other hand, in other series on SNRT, long R-P tachycardias were recorded during the clinical event, suggesting that SNRT may indeed have been the clinical arrhythmia.

Ectopic atrial tachycardia

It has become clear over recent years that EAT is relatively common. Moreover, there seems to be a predilection for these foci to be situated on the crista terminalis, and therefore the term "cristal arrhythmias" has been coined. In a compilation by Goldberger et al, 85% of the ectopic foci seem to be right-sided, and approximately 15% originate from the sinus node area[16]. These foci may be located very close to the sinus node[17]. It was even reported in series on SNRT that some of these patients also had EAT (e.g. two out of the 12 patients in Sanders' series, one with a focus mid-lateral in the right atrium, and the other one with even multiple foci in both atria). This suggests that the presumed SNRT may also have been a focal arrhythmia, although with a localization very close to the sinus node[3].

"Ectopic atrial tachycardia" in itself is not only a heterogeneous group concerning its localization, but also mechanistically: it may be due to enhanced automaticity or to a triggered arrhythmia based on early or late afterdepolarisations.

Differentiating SNRT from EAT: theory and practice

Theoretical means to differentiate ...

In the discrimination between the two forms of arrhythmia, the importance of invasive electrophysiological testing is usually stressed. However, Holter monitoring may reveal important diagnostic information, since it may show multiple episodes of non-sustained tachycardia or even frequent atrial premature beats with P-wave morphology similar to that of the presenting – possibly sustained – arrhythmia[18]. Moreover, there may be a wide variation of atrial rate exhibiting "warm-up" at initiation and "cool-down" at termination. These features most likely point to a focal *automatic* origin as the mechanism of the arrhythmia, and virtually exclude SNRT.

Typically the criteria for diagnosis of SNRT during an EP study are summarised as follows: (1) identical P-wave morphology and intra-atrial activation sequence during sinus rhythm and tachycardia; (2) reproducible induction, resetting and termination by (single) atrial premature beats over an echo zone, independent of AV nodal conduction slowing; (3) termination of the tachycardia by vagal manoeuvres or adenosine; (4) exclusion of an atrioventricular accessory pathway.

In general, one can state that extrastimuli are more effective for the initiation of reentrant arrhythmias, and rapid pacing for triggered mechanisms. Enhanced automaticity may be transiently suppressed by overdrive stimulation, but cannot be initiated by pacing[19]. Initiation and termination by premature atrial stimulation virtually rules out enhanced automaticity as the cause of tachycardia. On the other hand, triggered rhythms, especially those based on delayed afterdepolarisations, may be inducible and can even be stopped by extrastimuli or

burst-pacing. If the focus of this triggered arrhythmia is located close to the sinus node, differentiation from SNRT may become very difficult. Additional findings may favour a reentrant arrhythmia:

(a) An inverse relation between the tachycardia initiating extrastimulus and the return cycle on induction (i.e. the interval between the extrastimulus and the first tachycardia beat) could differentiate a reentrant mechanism (with prolongation of the return cycle on shortening of the coupling interval) from a triggered rhythm (vice-versa)[20]. A nice example of this is shown in a paper by Breithardt and Seipel[21].
(b) The relation of the return cycles versus the coupling intervals of the extrastimuli during resetting of the tachycardia, the so-called resetting response curve, can also be used in the differentiation[22]. When the slope of the curve is increasing or mixed (flat + increasing), reentry is likely. Triggered rhythms usually have resetting response curves with a flat or a decreasing pattern.
(c) Theoretically, entrainment pacing could be very valuable to positively diagnose a reentrant arrhythmia. It has however never been reported on in series of patients with SNRT. This may be due to the fact that decremental conduction (for reentrant arrhythmias), and changing degrees of acceleration or overdrive suppression (for triggered arrhythmias) may be present, precluding consistent interpretation of the pacing protocol.

On the other hand, dependence on autonomic tone for induction or termination of the arrhythmia during an EP study cannot reliably be used for differentiation of reentrant and triggered mechanisms. Whereas ectopic rhythms due to enhanced automaticity may show a catecholamine-related increase in the frequency of isolated atrial premature beats or in he length of non-sustained runs of tachycardia (as well as in their rate), arrhythmias based on delayed afterdepolarisations may present in an all-or-none fashion and hence be indistinguishable from reentrant arrhythmias. Both often require isoproterenol for induction[3,23]. The mechanism of facilitation is however completely different: catecholamines increase the cellular calcium load which facilities delayed afterdepolarisations, whereas their enhancement of conduction with resulting shortening of the wavelength and shortening of the refractory period is the mechanism by which reentry arrhythmias are facilitated. Unfortunately, the mechanism of facilitation cannot be determined by routine electrophysiological means. Hence, it does not help in the differentiation.

The same holds true for the termination by vagal manoeuvres (carotid sinus massage or intravenous adenosine)[5], or by verapamil[24]. Engelstein et al nicely showed that adenosine both terminated SNRT and triggered atrial tachycardias, but again, by different mechanisms reversing the different effects of catecholamines which cannot easily be distinguished clinically or by invasive testing[25]. This was confirmed by Chen et al[23]. On the other hand, it is clear that automatic atrial tachycardia will only be suppressed transiently, so this response can lead to the diagnosis of a focal automatic arrhythmia.

An interesting new approach, be it more experimental, is the recording of delayed afterdepolarisations in monophasic action potentials. Chen et al showed that they were more prominent in the recordings just before onset of atrial tachycardia, and that their disappearance was coincident with the termination by verapamil or adenosine[23]. The question remains whether the presence of delayed afterdepolarisations in the recordings was purely coincidental or causally related with the presence and termination of arrhythmia.

If during radiofrequency application an acceleration is seen before termination of the tachycardia, a focal mechanism is more likely than a reentrant one. Acceleration has repeatedly been described during successful ablation of EAT[18,26], but it has not been reported during ablation for SNRT.

... and their usefulness in practice

In some reports on "SNRT", frequent spontaneous initiation and termination of the arrhythmia has been described (as can be recorded by Holter monitoring), even in the absence of antecedent premature atrial extrasystoles[5,14]. One can wonder how many of these patients in fact had an automatic rhythm and no SNRT.

In daily practice, reproducible induction and termination are not possible in all patients with an arrhythmia in the region of the sinus node. In some patients only rapid pacing is able to initiate the arrhythmia, which could point to a triggered rhythm. Sanders et al reported that in their series only in seven out of 12 patients could sustained SNRT be induced by single atrial extrastimuli[3]. Changes in autonomic tone may also prevent repetitive and consecutive measurements. This may explain why, in most reports, no relation between coupling intervals and return cycles was determined[3,5].

The same holds true for resetting response curves. Moreover, some triggered arrhythmias may have a resetting response curve where a flat part is followed by an increasing part, so that a definitive diagnosis again may not be made in all cases[27]. Also in a study by Chen et al an equal number of increasing or mixed curves was found among both groups[23].

The difficulty of differentiating triggered from reentrant mechanisms has been described in three patients with atrial tachycardia by Wen et al[28]. There was reproducible induction and termination by extrastimuli, with a flat relation between initiating coupling interval and return cycle. On the other hand, entrainment pacing was not possible and all were terminated by adenosine. Their exit sites were located at different right atrial locations. No resetting response curves were determined.

Per definition, the P-wave should be identical during SNRT and sinus rhythm. However, it was reported that not uncommonly it is slightly different[2,14]. Moreover, in many patients the P-wave during tachycardia superimposes on the T-wave, making detailed comparisons even more difficult. During an EP study, premature atrial or ventricular stimulation may unmask the P-wave, allowing more reliable comparisons. But even with very similar P-wave morphologies, the intracardiac activation and electrograms may be different on closer scrutiny[3,14]. The importance of detailed mapping for the differentiation of real SNRT from a nearby located ectopic focus or reentrant circuit has been reported by others[17,29]. In a well-documented study, Chen et al reported on six patients with 10 atrial tachycardias (which they did not label as "SNRT"). They showed in all: (1) reproducible induction and termination; (2) an inverse relation on initiation; and (3) an increasing part of the resetting response curves[29]. They even showed concealed entrainment. None of the patients had previously undergone cardiac surgery or had demonstrable congenital heart disease. However, none had a P-wave configuration and atrial activation sequence identical to sinus rhythm. Six of the 10 had exit sites in the right atrial free wall. Therefore, it is likely that these arrhythmias were based on reentry in the crista terminalis. It may be that so-called SNRT is similar, but with an exit site closer to that of the normal sinus node. One may wonder, however, whether the arrhythmia encompasses mainly atrial tissue without involvement of the sinus node proper, or whether it is (partly) located in the sinus node. Only detailed mapping of the crista terminalis can discriminate apparently similar atrial activation patterns and P-waves. It may therefore be more prudent to label "SNRT" at least as "sino-atrial reentrant tachycardia", as was also suggested by Gomes et al[17], and in some well-documented cases simply as "intra-atrial reentrant tachycardia" as labelled by Chen et al.

Institutional experience

During 513 EP studies performed over the past 2 years in our institution (from which 260 were for documented supraventricular arrhythmias), we incidentally induced an atrial tachycardia with origin in the region of the sinus node in six patients (1.2% of all studies, 2.3% of all SVT studies). Five of the six patients with induced "SNRT" were studied and ablated for Slow/Fast AV nodal reentrant tachycardia (two), atrio-ventricular reentrant tachycardia over a concealed bypass tract (one), a septal intra-atrial reentrant tachycardia (one), and VT in the setting of right ventricular dysplasia (one). One patient was studied for the presumed presence of an accessory pathway in the setting of an Ebstein malformation and congenitally corrected transposition of the great arteries without clinical arrhythmia. In one of these patients was there any evidence that the arrhythmia was clinically relevant. Hence, "SNRT" constituted 0% of the SVT patients presenting to our institution. Four of these six patients required 1 or 2 μg/min isoproterenol, and in five patients this "sinus nodal region tachycardia" could reproducibly be induced by a single extrastimulus. Cycle lengths ranged from 375 to 550 ms (110 to 160 bpm). None of the tachycardias lasted more than 40 s in baseline. Three were sustained after administration of isoproterenol (used for evaluation of non-inducibility of the ablated primary arrhythmia). In all these three, however, the P-waves and intra-atrial activation sequences were slightly but clearly different from sinus rhythm. One arrhythmia could be stopped by single extrastimuli; the other two required bursts. Interestingly, one of these three arrhythmias could not be reset by single extrastimuli (even if delivered in the high right atrium and preexciting both atria): this could indicate compensatory decremental slowing of the reentrant circuit over a wide range of coupling intervals (although this is unlikely over a zone of 100 ms), or the impossibility of reaching a protected focus or micro-reentrant circuit. Summarised, one can conclude that although these arrhythmias originated from the region of the crista terminalis, none of them really came from the sinus

node, and that differentiation of the mechanism was much more difficult than theoretically anticipated (three seemed to be based on reentry, two on a focal mechanism and one unknown). Since none of these arrhythmias was considered as a clinical problem, no ablation attempt was made. After a mean follow-up of 18 ± 6 months, no patient has presented with a clinical episode of this arrhythmia, nor if its initial presenting tachycardia.

In contrast, during the same 2-year period, 10 patients presented with clinically documented arrhythmias suggestive of EAT (one with two foci). In all, automatic firing from a focus influenced by autonomic tone was strongly suggested by the Holter recordings. This was confirmed during EP study, which could in no patient find indications for a reentrant mechanism. Ten foci were located in the right atrium (of which six were on the superior aspect of the crista terminalis, in the region of the sinus node). Ablation was not performed in four patients because the arrhythmia was not the clinically relevant one (one patient with PJRT and one patient with RVOT-VT each), or because only sporadic single beats during the procedure precluded adequate mapping (two patients). Ablation was successful in all other patients (seven tachycardias). There was recurrence in two, one of which had only received very limited power delivery out of concern for a directly underlying phrenic nerve.

Moreover, seven patients with manifest intra-atrial reentrant tachycardias (with P-waves different from sinus P-waves) were also ablated over the same time period, of whom five had underlying congenital heart disease and previous corrective surgery.

Reentry or a focus in the region of the sinus node? No difference as ablation target

The previous discussion illustrates how difficult it may be to exactly classify an atrial arrhythmia with earliest activation in the vicinity of the sinus node. On the other hand, whatever the arrhythmia mechanism may be, successful radiofrequency catheter ablation is directed by the same type of electrograms and seems to be equally effective for both reentrant or automatic tachycardias[6,23].

There have been numerous reports on successful treatment by radiofrequency catheter ablation of presumed SNRT, though always in a very limited number of patients with not always fully authenticated diagnoses[3–7,30]. In total, ablation in about 24 patients had a success rate of ± 90%. Generally, early and fractionated electrograms served as a guide to the successful ablation site[3,5,7]. The local atrial electrogram preceded the onset of the P-wave by at least 35 ms, and the mean duration of the local electrograms was about 85 ms. However, exactly the same local prematurity[18] and fractionation have been described for the successful ablation of EAT[19,23,31]. Goldberger et al reported earlier activation times and more fractionation at successful ablation sites for presumed reentrant arrhythmias than for automatic arrhythmias[16]. Walsh also reported absence of fractionation, which may indicate that this could be a discriminator between SNRT and EAT[18]. In contrast, Chen et al reported early potentials but no local fractionation at the successful ablation sites of proven atrial reentrant tachycardias[29]. Comparison of the paced activation sequence with the activation during tachycardia was also reported to be helpful for both[16,19].

Interestingly, in no patient has damage to normal sinus node function been described, secondary to catheter ablation. This could be another indication that in many patients the arrhythmia is not really located on the sinus node itself.

Kay et al reported shifting of the site of earliest atrial activation over several millimetres after unsuccessful radiofrequency applications during the ablation of SNRT[4]. This was interpreted as a different exit site of the same reentrant circuit or as a slight modification of the reentrant circuit itself. However, the same can be seen with an automatic arrhythmia comprising a somewhat larger area of origin and a shift to slower cells after ablation of the fastest ones, or with a shift in exit site of an unablated focus. It has also been shown that the automaticity of the sinus node is not just focal but more like regional, with shifts of the primary pacemaker site under different autonomic conditions[32].

Conclusions

In 1977 Waldo et al cautioned in an editorial against overdiagnosis of SNRT, and urged for refinement of the diagnostic criteria[33]. They stated that the P-wave itself is an unreliable indicator of the site of origin of atrial activation, and that even a high-to-low right atrial activation does not prove origin of the impulse from the sinus node *per se*[33]. Even with the refined mapping possibilities of today, the same caution remains true.

Reentry within the sinus node is possible, as has been experimentally shown. Presuming, however, that every atrial tachycardia with earliest activation in the vicinity

of the sinus node is SNRT is certainly incorrect. Automatic and triggered activity from an ectopic focus on the crista terminalis, in the vicinity of the sinus node, is proven to be rather prevalent and can be very hard to distinguish from reentry. Although there are clear theoretical arguments to distinguish such an arrhythmia as automatic, triggered, or reentrant, differentiation is often unpractical and unreliable. A simple Holter proves to be the most useful tool to discriminate automatic from reentrant tachycardia in the region of the sinus node. Other invasive techniques are difficult, time-consuming, and of no unequivocal value in the distinction. Moreover, careful mapping indicates that, although many of these arrhythmias originate from the crista terminalis, they do not have exactly the same site of origin as the sinus impulse. Therefore, in the absence of unequivocal arguments for one or the other arrhythmia mechanism, it may be better to describe the tachycardia as an "atrial tachycardia with origin in the vicinity of the sinus node" or at least as "sino-atrial reentrant tachycardia" (SART).

Finally, the incidence of sino-atrial reentrant tachycardia is rare, even during thorough EP studies with systematic atrial premature stimulation. Moreover, in most patients in whom it is induced, it is a clinically non-relevant finding that differs from the presenting arrhythmia. Its prevalence may have been over-estimated as an aetiological entity in the past. Most atrial arrhythmias in patients without underlying heart disease are ectopic in origin, or have a reentrant circuit located elsewhere in the atrium (maybe often incorporating the anisotropic crista terminalis).

Focal and reentrant mechanisms may be representing two ends of an aetiologicl spectrum, but the targets for effective cure by radiofrequency catheter ablation are very close, as are the approaches to localise them and their respective success rates. So in fact, for the clinical electrophysiologist and the patient, it does not really matter where the difference lies ...

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Chapter 2

Atrioventricular Nodal Reentry; What Have We Learned From Ablation Techniques?

Mark E. Josephson

Introduction

While atrioventricular (AV) nodal modification is highly successful in curing AV nodal reentry controversy remains as to the functional and/or anatomical nature of the reentrant circuit. The concept of dual AV nodal pathways as the underlying physiology of AV nodal reentry has focused attention on the fact that successful selective "fast" and/or "slow" pathway ablation can be accomplished by delivering radiofrequency (RF) energy at spatially separate sites (the apex and base of the triangle of Koch). The ability to selectively ablate these two pathways has led to the concept that the fast pathway and slow pathway are discrete anatomical structures with the intervening atrium required to complete the circuit. The proposed route would be from the compact AV node to the atrium over the fast pathway with sequential atrial activation from the fast to the slow pathway and then back to the compact node at the apex of the triangle of Koch. However, much evidence is available to suggest that this construct is too simplistic and that AV nodal reentry is far more complex. As will be noted below, there has never been documentation of sequential activation of the atrium that is compatible with this simple construct. The purpose of this chapter is to review the data obtained over the past decade during mapping and ablation of AV nodal tachycardia and experimental studies of the AV junctional region that suggest the need to reconsider our concepts of AV nodal reentry and to accept the fact that, just because ablation at apparently disparate sites is successful, this provides limited information as to the underlying mechanism of the arrhythmia. Recent data to be reviewed below suggest the primacy of the roles that atrionodal coupling and non-uniform anisotropy must play in the mechanism of AV nodal reentry.

Anatomical pathophysiological substrates of AV reentry

The AV node is a complex structure, both anatomically and electrophysiologically. Many years ago, Paes de Carvalho and Almeida[6] identified three functional regions of the AV node: the so-called AN, N, and NH regions. More recently, Anderson et al[7] classified the AV node into a compact, enclosed AV node, which was located towards at the apex of the triangle of Koch, and a more open or posterior node at the base of the triangle of Koch. They, as did Paes de Carvalho and, Almeida, divided the AV node into three cells types, called transitional, mid-nodal, and lower nodal cells. The electrophysiological characteristics of these cells corresponded

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to Paes de Calvalho and Almeida's AN, N, and NH regions. Of note they observed that the transitional cells in the posterior triangle of Koch are parallel to the annulus of the tricuspid valve. Anderson and his colleagues[7] really did the first anatomical electrophysiological correlates. They demonstrated that there was some variability of cell types in the transitional zone such that different cell types (AN, N, NH) were occasionally seen in different areas. In addition, slowing of conduction could also be noted in the transitional zone depending upon where the stimulated wavefront came from. It is of note that there have never been any documented histological correlates of discrete fast or slow pathways.

So-called slow pathway potentials as initially described by Jackman et al[1], as well as by Haissaguerre et al[3], can be found in virtually all patients with and without AV nodal reentry, and are widespread throughout the posterior half of the triangle of Koch. While some have theorized that these potentials represent activation of discrete slow pathway conduction, many observations suggest this is not so. Ablation in regions from which such potentials are recorded may result in fast pathway ablation or, on rare occasions, third degree AV block despite the fact that this may occur 2–3 cm away from where the compact node is supposedly located. Josephson[4] reported that, in approximately 30% of his patients, ablation at sites just above the coronary sinus in the region of the posterior triangle of Koch, the region from which slow pathway potentials are often recorded, could result in elimination of, or damage to, the fast pathway. A recent pathophysiological evaluation of this region, by McGuire et al[8], suggested that the slow pathway potentials described by Jackman et al[1] actually represented composite signals of activation of the sinus septum and the deep local potentials of the transitional cells, or perhaps atrial cells near the tricuspid annulus, and did not correspond to an area of slow conduction at all. In fact, these investigators found transitional cells could not only be found in the posterior region of the triangle of Koch running parallel to the tricuspid annulus but, in fact, ran circumferentially around the entire tricuspid annulus. Microelectrode recordings demonstrated a gradation of both the amplitude and *V*max of these potentials, with a decrease in amplitude and *V*max as the cells moved from approximately 1 cm away from the annulus towards the tricuspid annulus. This band of cells which runs parallel to the tricuspid annulus has marked non-uniform anisotropic properties which potentially could facilitate reentry as described by Spach and Josephson[9]. This will be discussed later in this chapter. In summary, no pathological or electrophysiological data have been able to describe discrete fast and slow pathways. The ability to ablate fast pathways in regions of slow pathway potentials, the ability to abolish slow pathway conduction without abolishing such potentials, and conversely, the failure to abolish slow pathway conduction (i.e., persistence of dual pathway physiology) despite eliminating slow pathway potentials all suggest that AV nodal reentry is far more complex that the simple construct of fixed, structurally distinct, fast and slow pathways.

Is the atrium necessary for AV nodal reentry?

Initial results of ablation of the "fast" pathway at the apex of the triangle of Koch at which earliest activation is frequently recorded when single His bundle recording electrograms are used and slow pathway conduction is abolished by ablating in regions from which slow pathway potentials occur (i.e., the posterior triangle of Koch) has suggested the simple construct of a circuit that involves the atrium depolarised at the apex of the triangle of Koch with sequential spread to the atrium at the base of the triangle of Koch either around or through the coronary sinus and back up along the slow pathway to the compact node[10–12]. This construct was based on the fact that slow pathway ablation can cure AV nodal reentry and can be performed 2–3 cm away from the fast pathway. These investigators[1,10] also showed that the tachycardia could be reset from the region of the posterior triangle of Koch (slow pathway region) with orthodromic activation of the fast pathway. We believe that these findings do not prove any mechanism, but only suggest that the circuit either has a significant dimension or has differential inputs and outputs which are more or less easy to engage depending upon where stimulation is carried out. These data are just as compatible with an anisotropic subatrial reentrant circuit, using deep transitional cells and the compact node. Separation of the so-called fast and slow pathways may be due to the non-uniform anisotropy of the transitional cells and the atrio-nodal connections, and is not proof of atrial participation. Several lines of evidence have become available that suggest that in many cases the atrium is not necessary, while to date there has been no demonstrated proof that the atrium is necessary. One piece of evidence is the fact that AV nodal reentry

may be initiated without the atrium being activated. While this is more common with ventricular stimulation for both typical and atypical AV nodal reentry[9] (Fig. 1), it has long been recognised that ventricular echoes due to AV nodal reentry can occur during ventricular pacing in the presence of atrial fibrillation[11]. AV nodal reentry can also be initiated during atrial flutter or fibrillation, with the first complex demonstrating a lack of atrial activation (Fig. 2).

A second piece of evidence showing that the atrium is not necessary is that on occasions retrograde block to the atrium may be noted during AV nodal reentry[14,9,12]. Although this is uncommon (we have seen five examples in approximately 520 cases of AV nodal reentry), its demonstration suffices to demonstrate that the atrium may not be necessary. Two-to-one block may be noted at slow rates, in which case atropine can facilitate 1:1 conduction at a faster rate (Fig. 3) or may be noted at very rapid rates of AV nodal reentry, in which case slowing the tachycardia can result in 1:1 conduction (Fig. 4). Somewhat analogous to this is the ability to occasionally reset AV nodal tachycardia

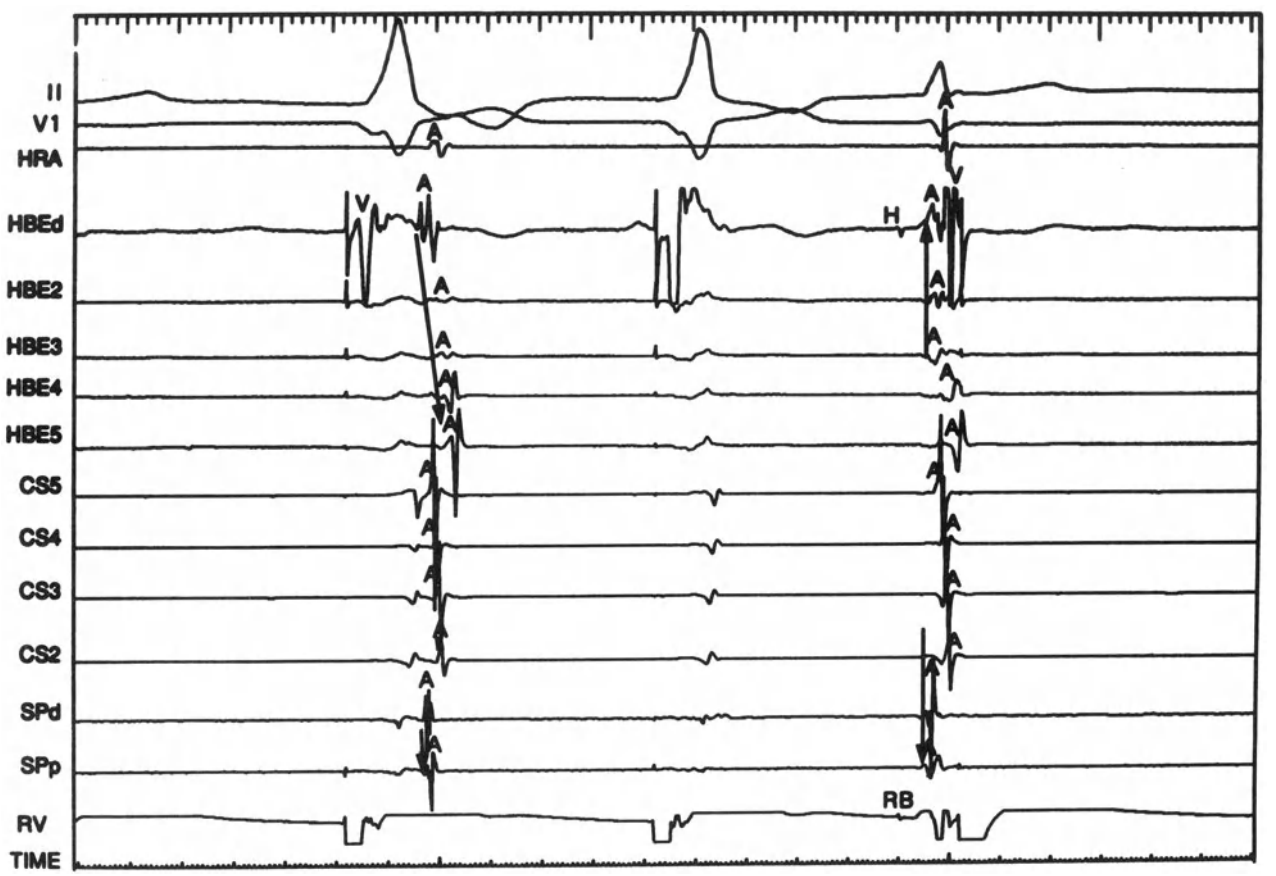

Figure 1. Initiation of AV nodal echoes during ventricular stimulation in the absence of atrial activation. Surface leads II and V_1 are shown with electrograms from the high right atrium (HRA), the His bundle electrogram from the distal (HBE_d) to most proximal (HBE_5), os of the coronary sinus (CS_5), two more distal sites, the slow pathway region distally (Sp_d), and the slow pathway proximal (Sp_p), right ventricle (RV), and time lines. During ventricular pacing at a cycle length of 500 ms, there is ventriculoatrial conduction with a left complex. Following the first complex shown on the figure, the second paced complex is associated with retrograde block to the atrium and initiation of a typical AV nodal echo with conduction down the slow pathway and returning up the fast pathway. Initiation of this AV nodal reentrant echo in the absence of atrial activation suggests it is a subatrial circuit. Note also that the distal His bundle atrial electrograms occur simultaneous with the slow pathway electrograms at the base of the triangle of Koch – (see text for discussion). (With permission from ref. 9.)

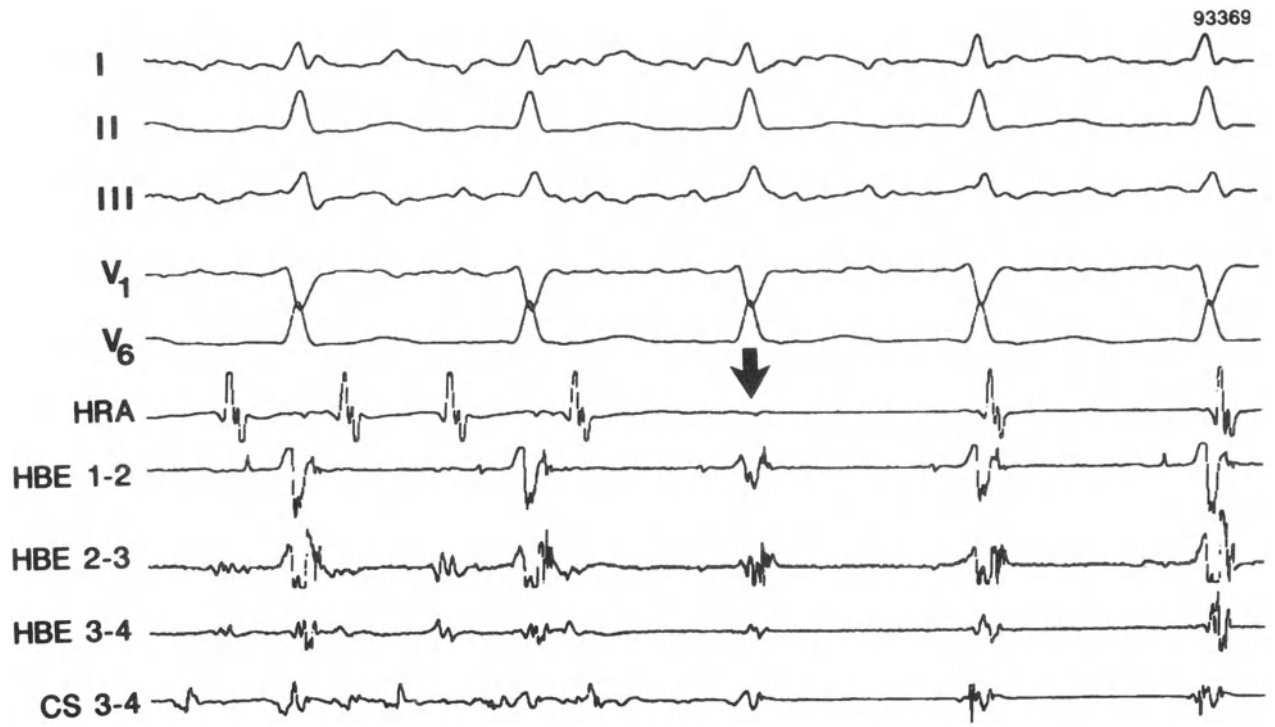

Figure 2. Initiation of AV nodal tachycardia by atrial flutter in the absence of atrial activation. Surface leads I, II, III, V_1, V_6 are shown with electrograms from HRA, HBE and CS. The first two complexes on the surface ECG are ventricular responses during atrial flutter. Following the last flutter complex, AV nodal reentry is initiated. The last flutter complex conducts down the AV nodal slow pathway but fails to visibly activate the atrium before returning down the slow pathway to initiate AV nodal reentry. Absence of atrial activation (arrow) suggests that the circuits are atrial (see text for discussion).

without atrial activation (Fig. 5). Recently Scherlag et al[13] demonstrated retrograde block between the slow pathway and the atrium during rapid activation of the slow pathway. They also noted that the conduction time from the region of the slow pathway to the atrium was longer than conduction time from the atrium to the transitional cells of the slow pathway. This is compatible with the difference in the voltage and resting membrane potential of the two structures, as well as the influence of coupling between the atrium and the node.

Stimulation during AV nodal tachycardia (primarily atrial, but also ventricular) has also supplied information suggesting that the atrium is not necessary. Josephson and Kastor[14], more than two decades ago, described the ability to capture the atrial recording in the His bundle region and at the os of the coronary sinus and mid-coronary sinus without affecting the tachycardia as long as stimulation was given greater than 2 cm from the region of the AV node in order to exclude non-local stimulation of the AV node or vagus stimulation (Fig. 6). This is most readily shown from stimulation of the high right atrium in which wavefronts can reach the AV junctional region without the possibility of local stimulation. While this most commonly occurs using single atrial stimuli, occasional double atrial extrastimuli or stimulation of the summit of the ventricular septum[15] can be used to demonstrate the same phenomenon. Interpretation of results of stimulation of the slow pathway region and the fast pathway region are difficult to assess, since it is highly likely that depolarisation of AV node (compact and/or transitional) occurs when stimulation is applied at these sites[16].

Objections have been raised to the interpretation of failure to reset AV nodal tachycardia by stimulation. Failure to reset may merely be due to compensatory delay in the "slow pathway". The model upon which this objection is based is AV reentry. This is an inappropriate model since response to atrial extrastimuli differs

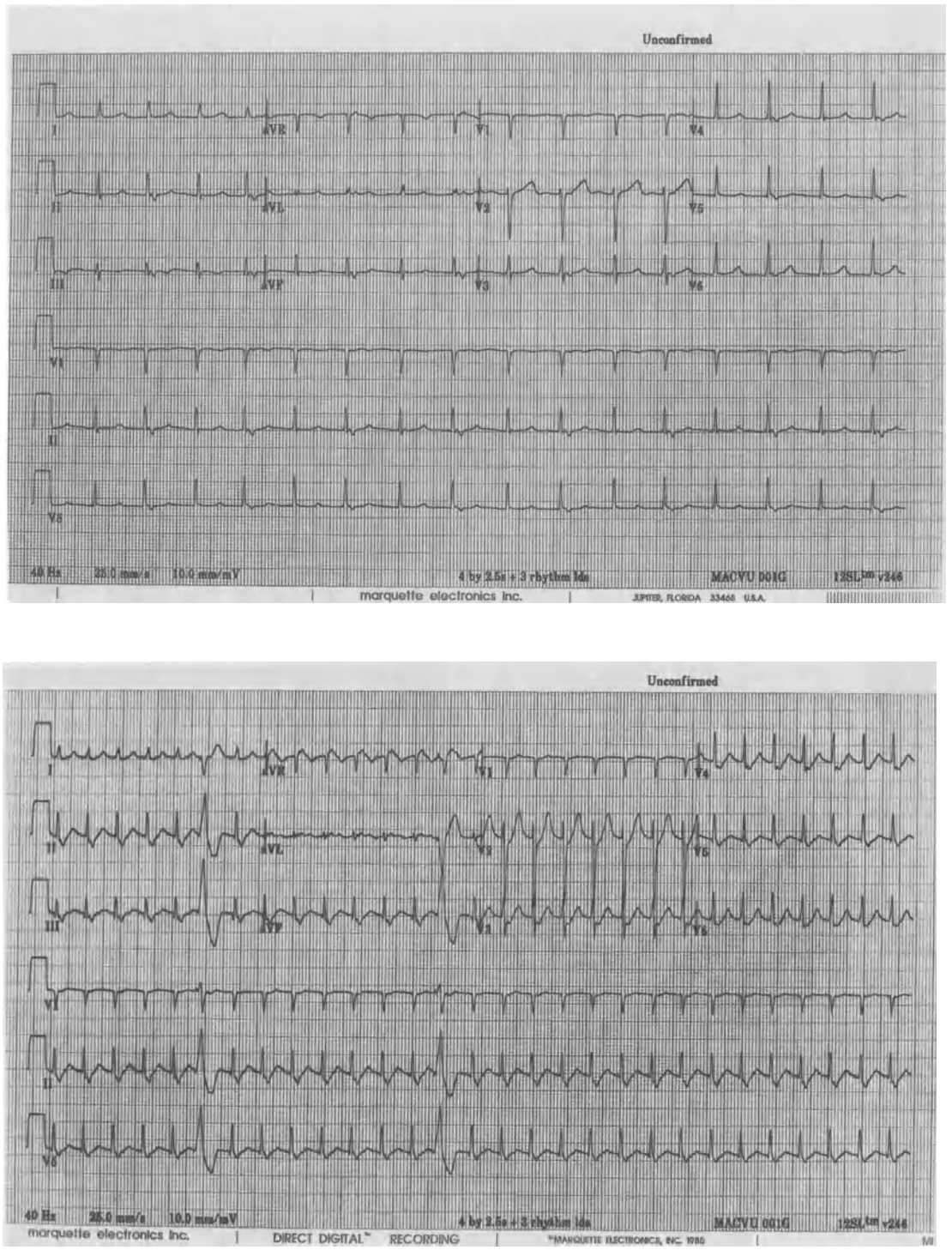

Figure 3. Retrograde block during AV nodal reentrant tachycardia. The panel on the top demonstrates AV nodal tachycardia with 2 : 1 retrograde conduction. In the presence of atropine, the tachycardia not only accelerates but conduction to the atrium is now 1 : 1. Improvement of conduction by atropine confirms the nodal location of the site of block (see text for discussion).

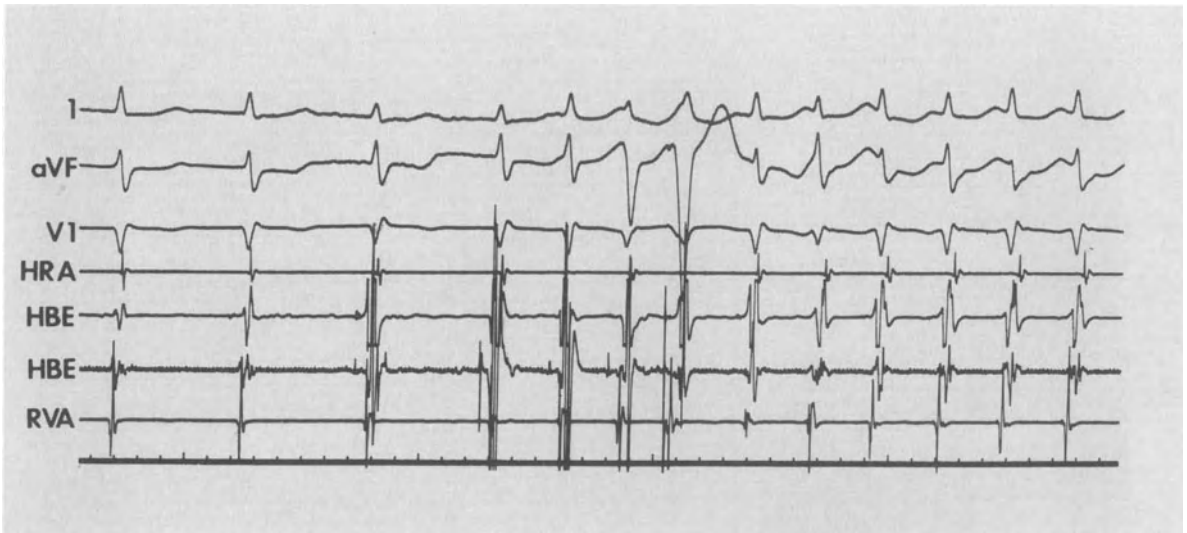

Figure 4. AV nodal reentry with 2 : 1 antegrade and retrograde block in the AV node. The first four complexes show AV nodal reentry with 2 : 1 conduction antegradely and retrogradely. With slight slowing of the tachycardia, 1 : 1 antegrade conduction initially develops, followed by the development of 1 : 1 retrograde conduction. (With permission from ref. 18.)

from that in AV nodal reentry, i.e., the slope of slow pathway conduction response to an atrial stimulus during AV nodal reentry is not the same as the slope of the AV nodal response during AV reentrant tachycardia in the absence of dual pathways. Moreover, if compensatory delay were present, the first observed reset should actually demonstrate a delay in H-H and V-V intervals. Thus, an atrial stimulus induced shortening of the H-H interval in response to earlier coupled atrial extrastimuli would militate against this hypothesis.

Scherlag et al[13] had demonstrated that atrial stimulation can produce block between the atrium and the fast pathway, supporting the concept that block may occur between the atrium and the AV nodal tissues, either due to a weak link in atrio-nodal coupling or non-uniform anisotropy or both. The most recent evidence described, suggesting that the atrium is not necessary, is by Loh et al[17]. These investigators performed high-density mapping (192 electrodes) of the triangle of Koch and left atrium during AV nodal echoes. Incisions (1–3 mm) were then made perpendicular to the tricuspid annulus and the ten-don of Todoro from the posterior end of the compact node to the os of the coronary sinus and two in between. These four incisions failed to prevent AV nodal reentrant echoes. This suggests that the atrial tissue in the region of the triangle of Koch, and perhaps even the superficial transitional cells, do not participate in this form of AV nodal reentry. The compact node and deeper transitional tissue, including those that might give rise to left atrial activation, must be source of these echoes.

Two other pieces of information support lack of atrial participation in AV nodal reentry. These are related to both the timing and sequence of atrial activation during AV nodal tachycardia. At the onset of AV nodal tachycardia it is very common to note changing VA relationships with minimal or no change in the cycle length of the ventricular response of AV nodal tachycardia, suggesting that atrial activation was functionally determined by output from the circuit[4]. This is even more clearly demonstrated when tachycardias with identical cycle lengths have different RP relationships (Fig. 7)[18]. Such phenomena are being noted more often after ablation, suggesting that ablation effects can affect the atrial activation sequence without affecting the underlying AV nodal circuit. Moreover, transient AV dissociation may be seen following atrial stimulation during AV nodal reentry[14,19]. Such AV dissociation may continue until the tachycardia terminates or results in continuous resetting of tachycardia depending upon where the sinus impulse falls[4].

Most recently, detailed activation mapping of the triangle of Koch and the coronary sinus during AV nodal tachycardia has been performed in the catheterization laboratory[20–22] as well as intraoperatively[23]. In no

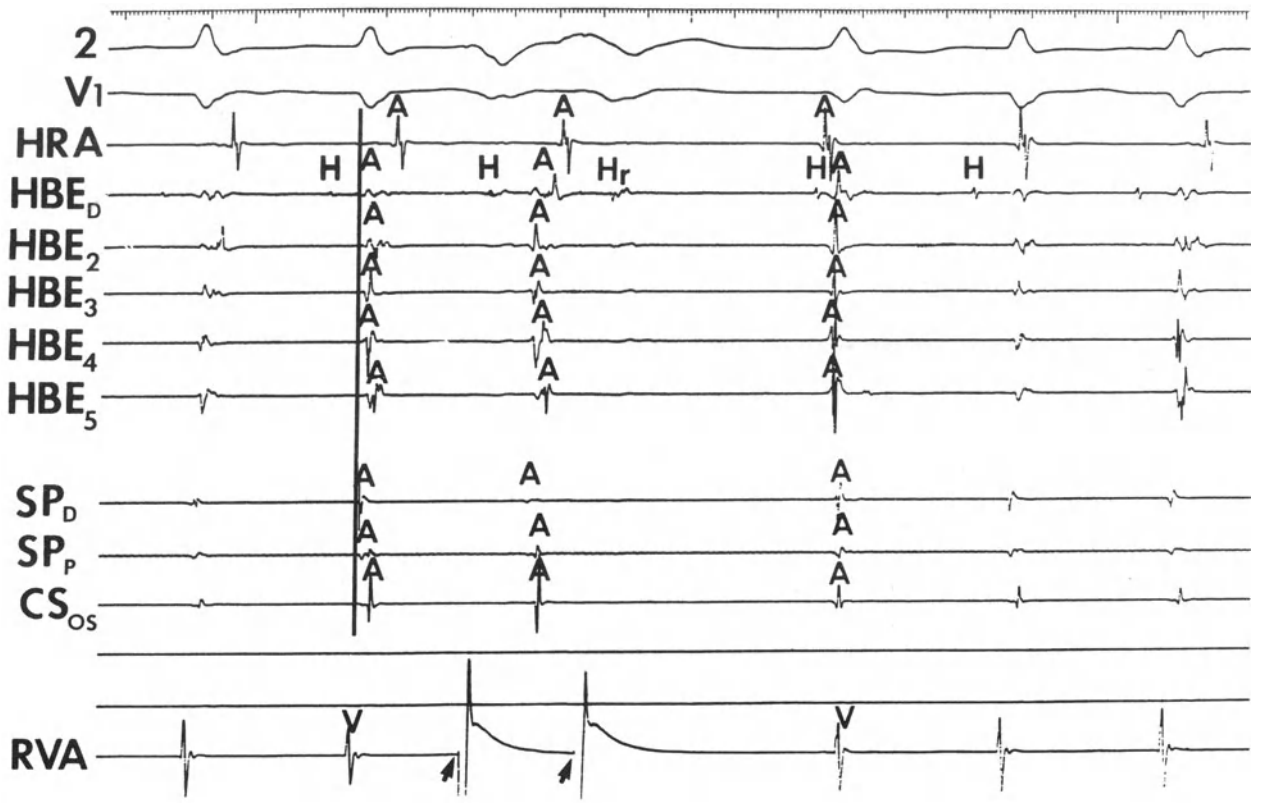

Figure 5. Resetting of ventricular tachycardia without atrial participation. Surface leads are shown with electrograms from the HRA, His bundle region, slow pathway region, os of the coronary sinus, as well as the RVA. During AV nodal reentrant tachycardia, two ventricular premature beats are delivered. The first fails to affect the tachycardia. The second ventricular extrastimulus resets the tachycardia, advancing the His. This extrastimulus conducts to the His but fails to demonstrate atrial activation. Transient AV dissociation is noted on the first return cycle. Thus, resetting of AV nodal tachycardia in the absence of atrial activation suggests the circuit is subatrial.

instance was a sequential activation from the fast pathway to the slow pathway observed. McGuire et al[23] used unipolar recordings to map the entire triangle of Koch with an additional series of electrodes placed in the coronary sinus. In nine of 10 patients the earliest activation was recorded at the apex of the triangle of Koch, but the entire triangle of Koch was activated almost simultaneously in one patient, and two sites of early activation were observed in two patients during ventricular pacing. Closer inspection of the data revealed that the earliest retrograde atrial activation was actually recorded over an area of 6 mm or more with simultaneous activation in three poles 3 mm apart. This relatively broad wavefront is similar to what was recently described by Anselme et al[20]. Although McGuire et al[23] did not address multiple breakthroughs in addition to the two patients with discrete breakthroughs in the triangle of Koch, in many of their examples an additional breakthrough was noted in the coronary sinus electrodes. This finding has been corroborated with detailed mapping of the triangle of Koch in the electrophysiology laboratory. The studies done by Anselme et al[20–22] from our laboratory, used a decapolar catheter with 2 mm interelectrode distance to record the His bundle along with the tendon of Todoro, a quadripolar catheter to record in the "slow pathway" between the coronary sinus and the tricuspid valve, and a decapolar catheter with a 5 mm interelectrode distance to record from within the coronary sinus with the proximal pole placed within 1 cm of the os of the coronary sinus (Fig. 8). Multiple patterns of atrial activation were observed during AV nodal tachycardia and were compared during ventricular stimulation. These investigators characterised the pattern of atrial activation into several

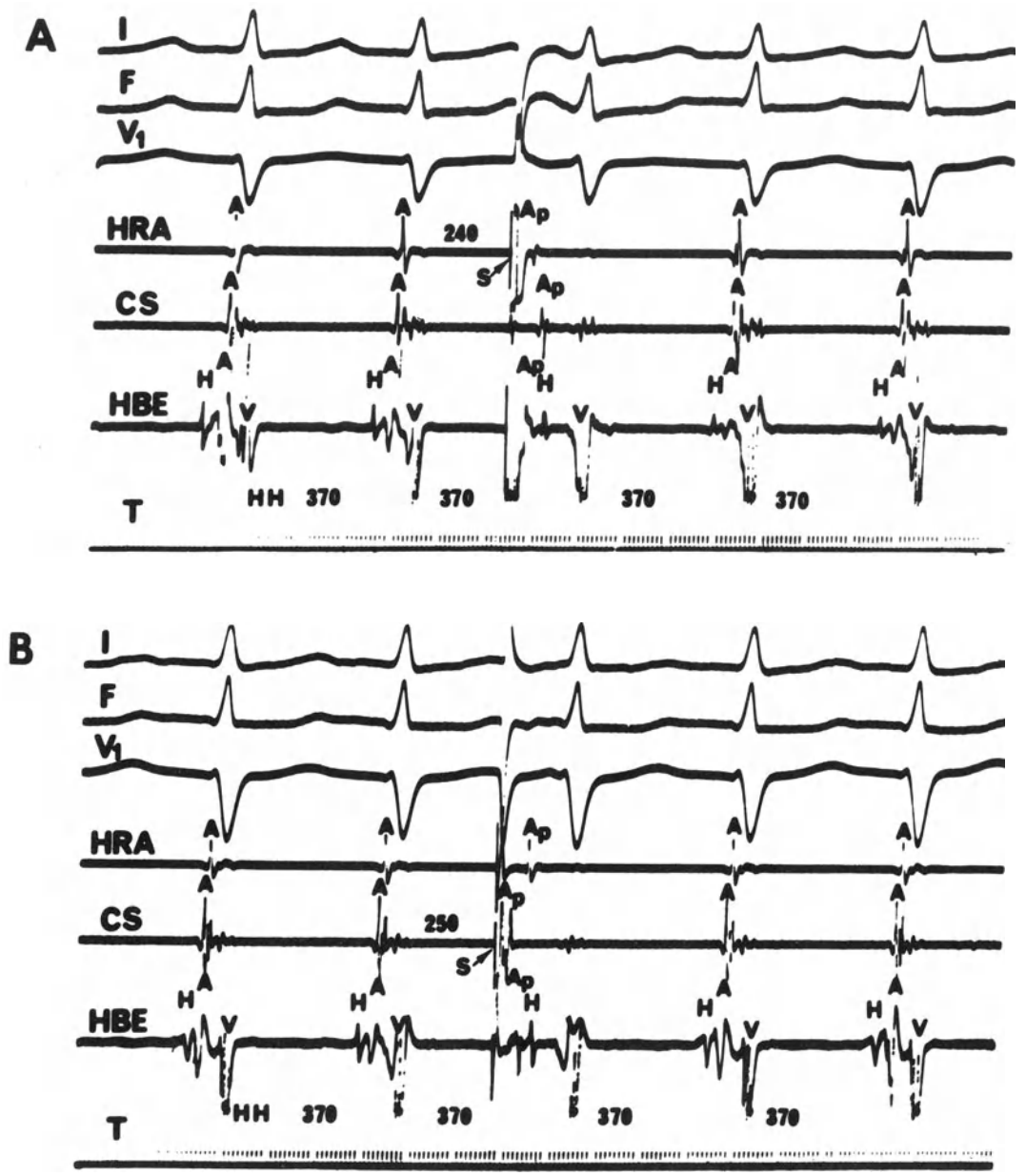

Figure 6. Failure to reset AV nodal reentry by atrial extrastimuli from the right atrium and left atrium. In panel A, during AV nodal reentry, an atrial premature beat is delivered at a coupling interval of 240 ms from the HRA. This premature beat depolarises the HRA, the CS at the os, and at the His bundle recording site 70–130 ms early without affecting the original tachycardia. At the bottom, in panel B, stimulation from the os of the CS at coupling intervals of 250 ms, prematurely depolarises all these atrial tissues around the AV junction 60–120 ms early without affecting the tachycardia. The ability to depolarise all the atrial tissue surrounding the AV node from the HRA and left atrium without affecting the tachycardia suggests that the atrial tissue is not necessary for persistence of the tachycardia. (With permission from ref. 14.)

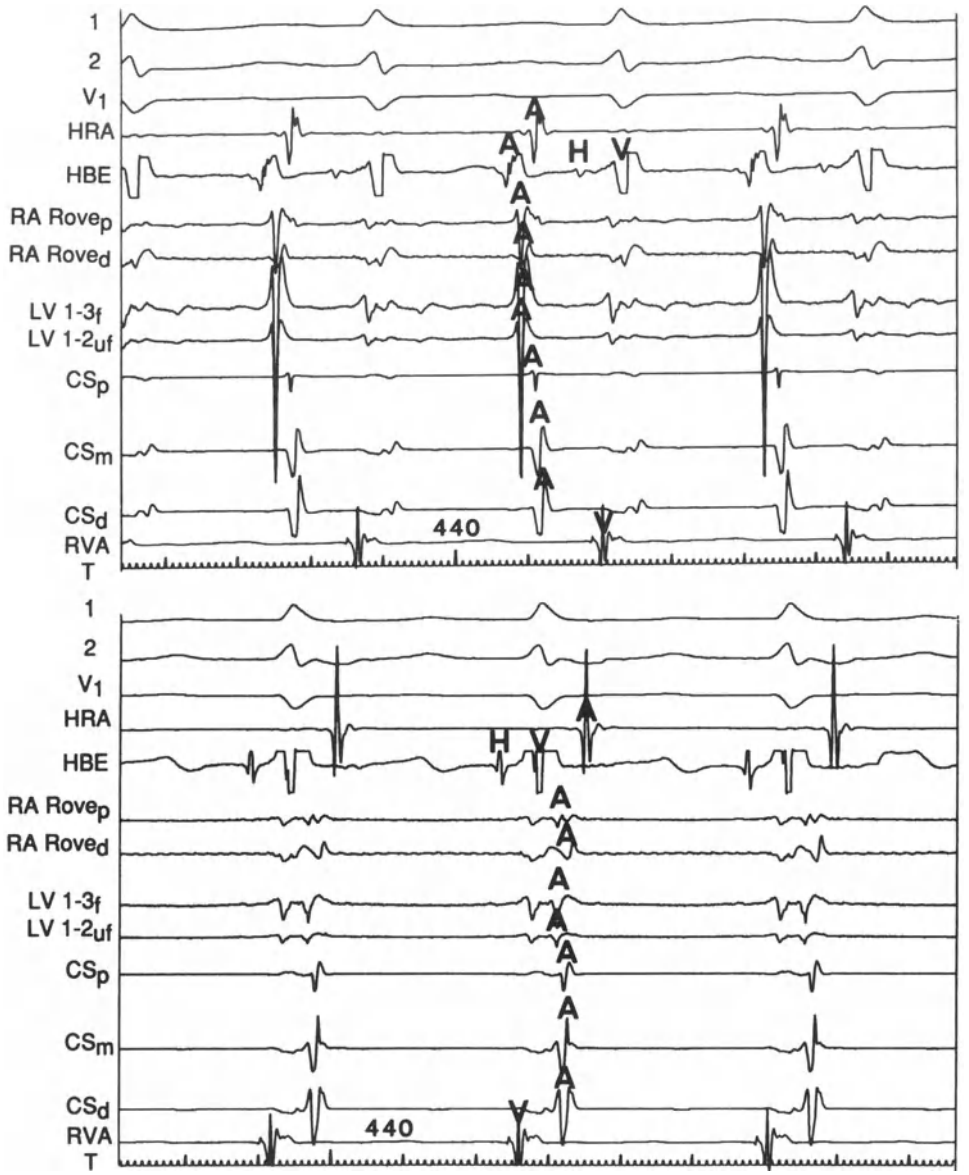

Figure 7. AV nodal tachycardias with different V-A intervals. All three panels are arranged similarly, with surface leads I, II, III, HRA, HBE, RA distal and proximal rove catheter, a left ventricular AV ring recording (LV), CS and RVA. In all three panels, AV nodal tachycardia was proven to be present at a cycle length of 440 ms. However, each of these tachycardias has a different V-A relationship. On top, one would consider this a long R-P tachycardia. At the bottom the atrial activation sequence and timing would be classified as typical AV nodal tachycardia. In the middle panel, an intermediate V-A relationship is noted. The absence in changes in tachycardia cycle length through varying V-A intervals suggests that the atrium is an innocent bystander with the timing influence by the determinants of nodoatrial conduction, (see text for discussion). (With permission from ref. 18.)

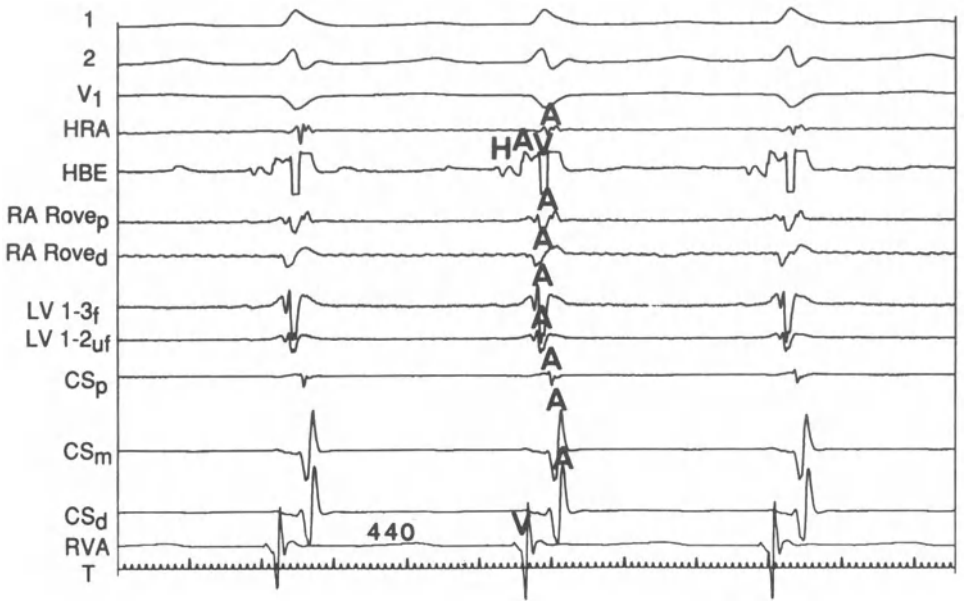

Figure 7. *Cont'd.*

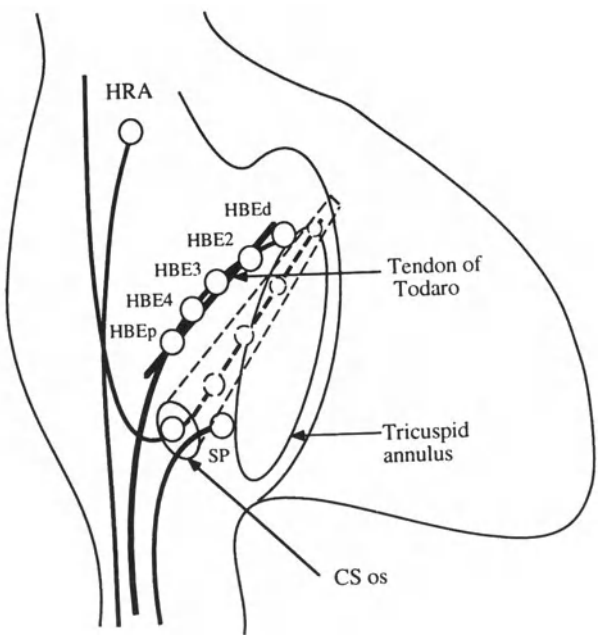

Figure 8. The schema of recordings of catheters in the AV junction. Atrial activation was recorded using a quadripolar catheter in the HRA, a quadripolar deflectable catheter in the slow pathway region, a decapolar catheter (2 mm interelectrode distance) to record the His bundle positioned along the tendon of Todoro, and a catheter placed in the CS (decapolar; 5 mm interelectrode distance) with proximal pair at the os of the CS. (With permission from ref. 20.)

categories. Along the His bundle catheter a sequential wavefront (Se) was defined when the earliest activation was recorded at one or two adjacent poles with sequential spread throughout the remaining electrode poles on the decapolar catheter. A broad wavefront required that three or more adjacent bipolar pairs on the His bundle catheter were activated within 5 ms of each other. This was comparable to the broad wavefront noted in McGuire et al's intraoperative study[23]. Over the entire triangle of Koch, multiple early sites were stated to be presented when two or more activation times along the His bundle catheter within 5 ms of each other were separated by two later sites, or one or more sites on the His bundle catheter and any other catheter (slow pathway or coronary sinus) occurred within 5 ms of one another. A single early site was said to be present if no criteria for multiple early sites were seen. Additional breakthroughs in the coronary sinus were said to occur if any coronary sinus site was activated prior to a His bundle site or poles within the coronary sinus were activated earlier than surrounding poles. These are schematically shown in Fig. 9. Our results demonstrated that multiple sites of early atrial activation were present in 21.7% of patients during ventricular pacing and 17.4% of patients during typical AV nodal reentry, with only a 39.1% concordance in the site of earliest activation. Multiple sites of breakthrough is defined as a pattern in which atrial depolarisation at the coronary sinus or slow

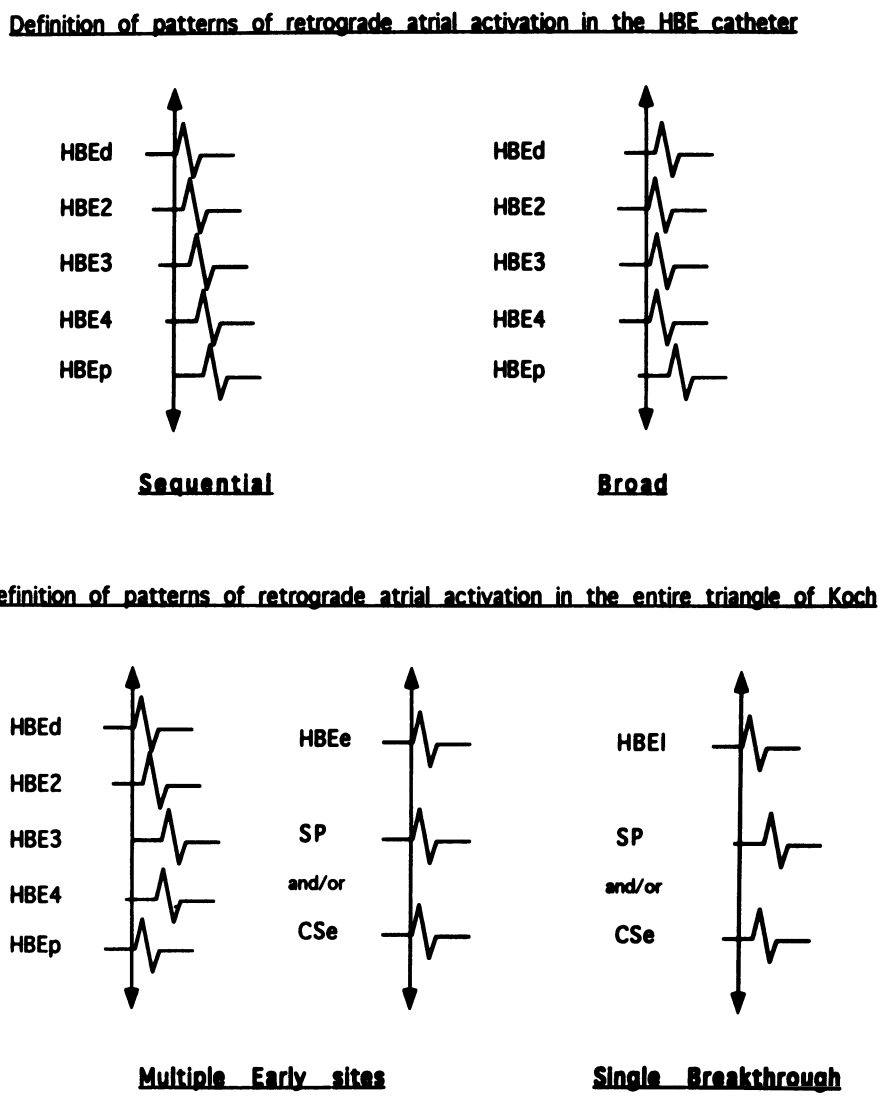

Figure 9. Schema of activation patterns during AV nodal reentry. Sequential and broad activation patterns along the His bundle catheter are shown on the top and multiple early sites and single breakthrough sites at all other sites are shown at the bottom. (From ref. 21 with permission.)

pathway region was recorded too early to have been a consequence of sequential activation from the apex of the triangle of Koch; in other words, earlier than two or more of the proximal His bundle electrodes. By this definition, multiple sites of early breakthrough were recorded in two-thirds of the patients during both AV nodal reentry and ventricular pacing. Moreover, a broad wavefront of His bundle activation was recorded in 37% and 56.5% of patients during ventricular pacing and AV nodal reentry respectively. Concordance in the pattern of activation was present in only 45% of our patients. It must be stated that not only was there discordance in the *pattern* of activation, but the *exact timing and relationship* of electrical activation at the different sites varied in the majority of patients. These differences suggest: (1) that so-called fast and slow pathway activation are not fixed but vary depending upon difference of activation (in our study, ventricular pacing or AV nodal tachycardia) and (2) that patterns of activation, including nearly simultaneous activation of the triangle of Koch (Fig. 10), are incompatible with a large reentrant circuit with sequential activation from the apex of the triangle of Koch around to the coronary sinus and back up the so-called slow pathway region. The activation patterns noted by both Anselme and colleagues[20] and McGuire et al[23] are more consistent with an anisotropic activation

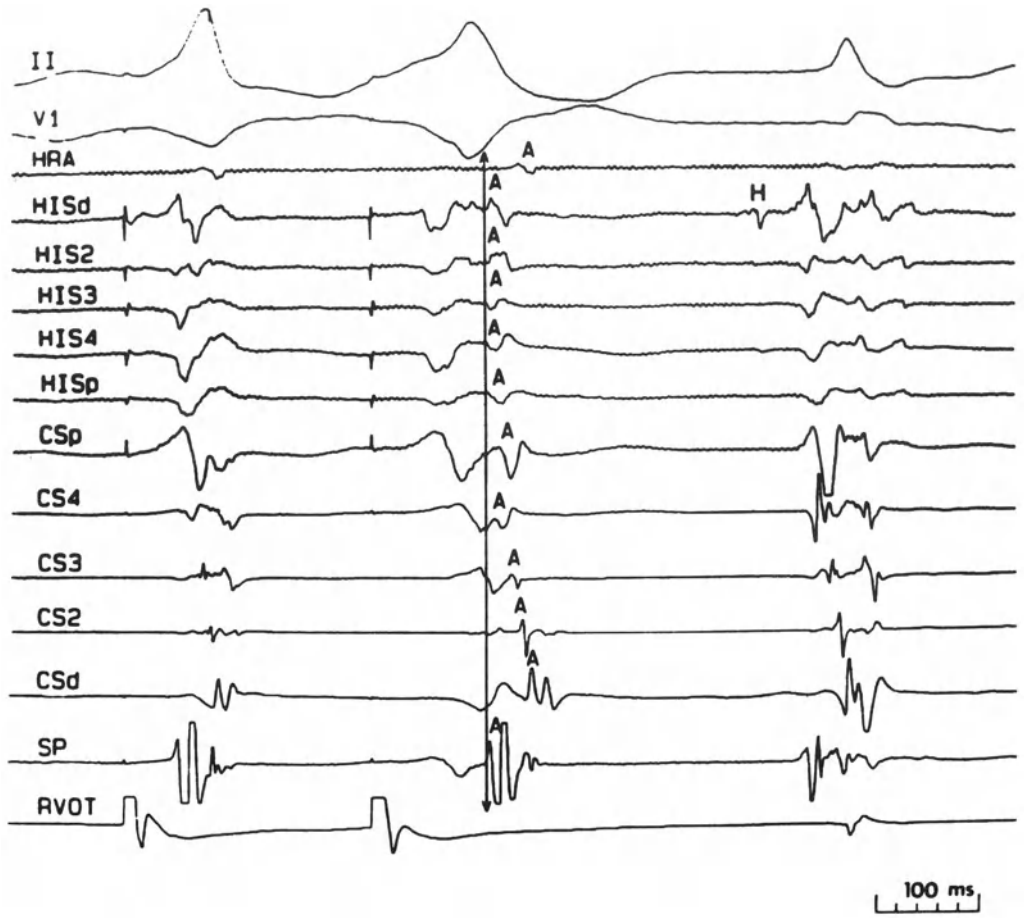

Figure 10. Retrograde atrial activation consistent with anisotropic reentry during AV nodal tachycardia. Leads II and V_1 with recordings from the HRA, HBE, CS, and slow pathway area along with RVOT. Two VPDs are delivered during AV nodal tachycardia to allow for demonstration of the atrial activation sequence. It can be seen that there is a broad band of activation in the His bundle catheter with all five electrodes being activated almost simultaneously. The slow pathway region is also activated simultaneously. Activation of both the apex and the base of the triangle of Koch is nearly simultaneous with a broad activation pattern in the His bundle catheter, suggesting an anisotropic pattern of atrial activation (see text for discussion).

of the atrium from the subjacent transitional cells. Absence of a discrete, definable, sequential atrial activation sequence in every attempt to demonstrate this suggests that it is untenable to continue to believe in such a simplistic mechanism of AV nodal reentrant tachycardia.

Role of anisotropy in AV nodal tachycardia

Several items of information suggest an important role of non-uniform anisotropic conduction in the genesis of AV nodal tachycardia. These include experimental studies and clinical observations. The transitional cells in the posterior triangle of Koch are arranged parallel to the tricuspid annulus as they approach the compact node. Spach and Josephson[9] recently evaluated whether or not this transitional region of the AV node has non-uniform anisotropic electrical properties. They measured extracellular potential waveforms and their derivatives on a microscopic level in this region, using a microarray of extracellular electrodes in a rabbit atrial preparation. The electrodes were positioned in the posterior transitional zone of the AV node of the rabbit and stimulation was performed perpendicular to and

parallel to fibre orientation. When propagation was parallel to fibre orientation, conduction velocity was rapid (0.39 m/s) and was associated with a smooth, large extracellular electrogram. In contrast, when propagation was perpendicular to the fibre orientation, the extracellular waveforms were markedly fragmented and conduction velocity was very low at 0.07 m/s. Thus, conduction could be slow or rapid in the same tissue, depending upon the propagating wavefront direction. This confirmed that the large posterior zone of transitional fibres in the triangle of Koch was associated with markedly non-uniform anisotropic properties in which fast or very slow conduction is purely dependent upon the relationship of fibre orientation to the direction of the activating wavefront.

Thus the normal properties we attribute to the AV node in patients with AV nodal tachycardia are compatible with tissue having non-uniform anisotropic properties. This has led to the concept of AV nodal reentry as an example of anisotropic reentry. In such a construct, slow conduction can be seen both in the compact node and when propagation moves perpendicular to the deep transitional tissues in the posterior triangle of Koch. In fact, in this model, conduction along the so-called "slow pathway", parallel to the tricuspid annulus, would actually be more rapid. This is finding which has been

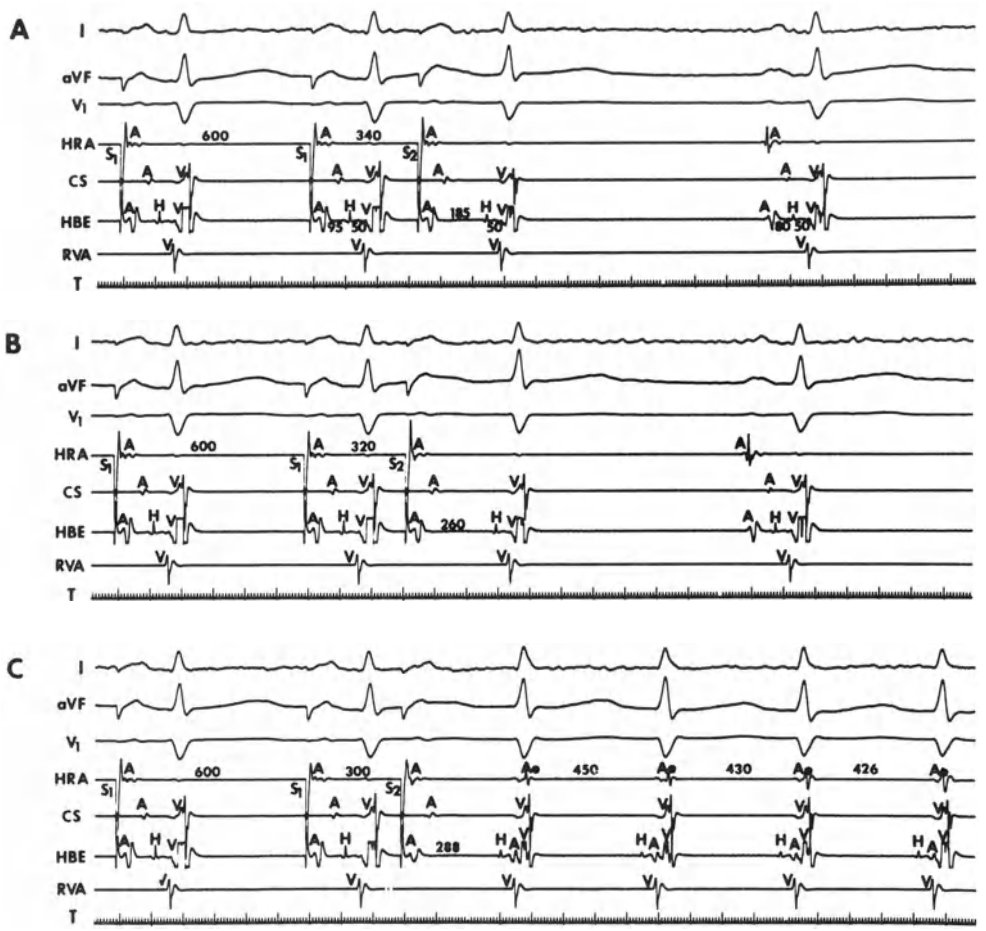

Figure 11. Initiation of AV nodal tachycardia from the HRA. Panels A, B, and C demonstrate the response of progressively premature HRA stimulation. In panel A, at coupling intervals of 340 ms, conduction precedes over the fast pathway. In panel B a jump exists with conduction now over the slow pathway, an A-H interval at 260 ms, yet no retrograde conduction over the fast pathway is noted. In panel C, at coupling interval of 300 ms, a critical A-H of 200 ms is achieved, which allows retrograde fast pathway activation and induction of the tachycardia. (From ref. 4 with permission.)

noted during resetting of AV nodal reentry; greater delays are seen when the activating wavefront moves down the septum perpendicular to the transitional cells when compared to when the region of the slow pathway is stimulated parallel to the transitional cell fiber orientation[16]. Another observation which is compatible with anisotropic reentry is the fact that it is more difficult to initiate reentry from the coronary sinus than from the anterior septum or high right atrium[4]. Even when AV nodal reentry can be initiated from both, frequently the critical A-H interval which is required to initiate reentrance and the cycle length of the tachycardia differ, depending upon the site of stimulation (Figs 11 and 12)[4]. In fact, the critical A-H is usually shorter during coronary sinus stimulation than A-Hs which failed to demonstrate retrograde conduction over the fast pathway during high right atrial stimulation (see Figs 11 and 12). This suggests functional differences both in initiation of the arrhythmia and potentially of the paths through which the impulses travel both at initiation

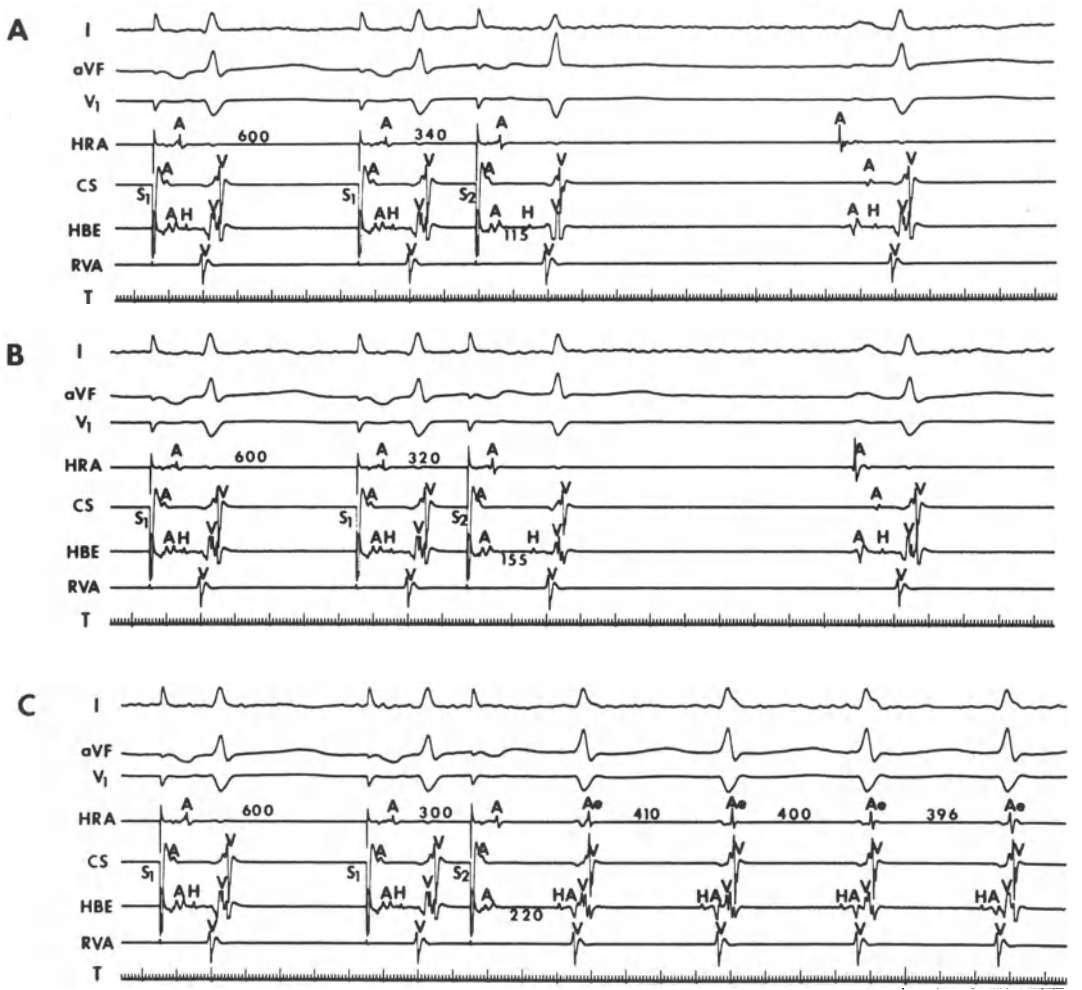

Figure 12. Induction of AV nodal reentry by CS stimulation. This figure is from the same patient as in Fig. 11, only stimulation is carried out from the CS. At comparable intervals as those seen in Fig. 11, conduction is different. At 340 and 320 ms, the A-H interval is increased only slightly and persists along the fast pathway. At a coupling interval of 300 ms fast pathway refractoriness is encountered, resulting in a jump with dual pathway physiology but the A-H is only 220 ms. Despite the fact that the A-H is 40 ms shorter than in panel B of Fig. 11, in which retrograde fast pathway conduction was possible, following CS stimulation retrograde fast pathway activation and AV nodal tachycardia develops at a shorter A-H interval. This difference in A-H intervals and, in fact, tachycardia cycle length, suggests the functional nature of fast and slow pathways (see text for discussion.) (With permission from Fig. 4.)

and during maintenance of the arrhythmia. Since the intervals of AV nodal conduction delay that are required to initiate AV nodal reentry far exceed atrial refractoriness, the underlying mechanism for such criticality must be related to the non-uniformity of anisotropic conduction in the AV junctional region and/or the heterogeneity of atrionodal coupling, or both.

Other features of AV nodal reentry which suggest subatrial non-uniform anisotropic propagation come from activation sequence mapping of the triangle of Koch and coronary sinus during AV nodal reentry. Detailed activation mapping during AV nodal reentry in the clinical electrophysiology laboratory from Anselme et al[20–22], as well as detailed mapping intraoperatively from McGuire et al[23], and more recently, experimental mapping of this region with 192 electrodes in experimental canine AV nodal reentry[16], have failed to demonstrate reentrant excitation in the atrial activation pattern. In most cases the activation pattern of isochrones was most consistent with anisotropic propagation, which may have been purely a reflection of the subatrial propagation to the transitional fibres.

Another item of evidence which suggests that both atrionodal coupling and non-uniform anisotropy play an important role is analysing the accelerated junctional rhythms during RF ablation of the AV node. According to the conventional hypothesis in which antegrade conduction moves parallel to fibre orientation over a so-called slow pathway and retrograde activation exits the compact node along the fast pathway with a large

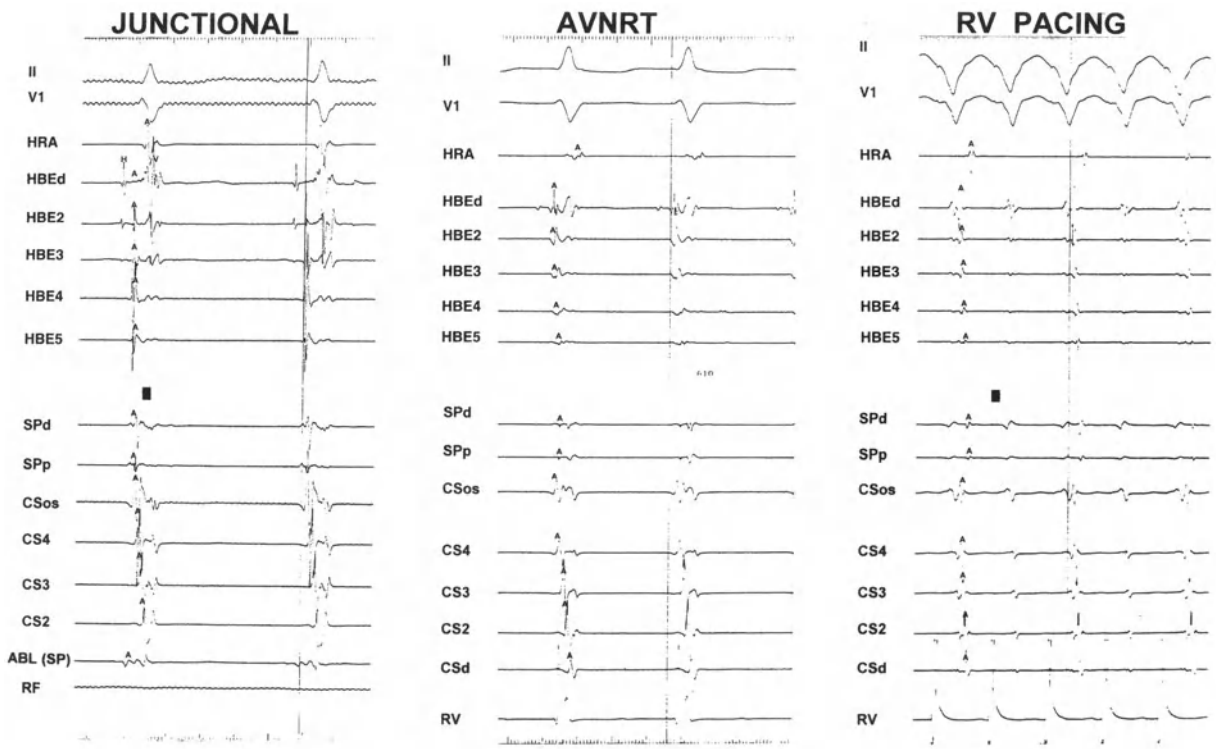

Figure 13. Atrial activation pattern during radiofrequency-induced junctional rhythm. Leads II and V_1 and electrograms from the HRA, HBE, SP and CS are shown along with electrograms from the ablation catheter which is just below the slow pathway catheter at the inferior aspect of the CS. During RF-induced junctional rhythm, the atrial activation pattern demonstrates broad activation along the His bundle and earliest activation posterior to the site of ablation noted in the proximal ablation catheter. Slow pathway is activated nearly simultaneously with the His bundle electrogram. This pattern of activation is incompatible with orthodromic activation of AV nodal reentrant circuit. The activation pattern during AV nodal reentry is different, as can be seen in the middle panel; furthermore, it is still different from that noted during ventricular pacing in the right-hand panel (see text for discussion). (Adapted with permission from ref. 24.)

macro-reentrant circuit, RF stimulation produces conduction along the slow pathway to the compact node with orthodromic activation of the fast pathway, producing an activation pathway identical to that seen during AV nodal reentry. If AV nodal reentry were unrelated to this mechanism, RF-induced junctional rhythm could be due to single or multiple automatic foci within the compact or transitional AV node caused by both RF-induced atrionodal uncoupling and RF stimulation-enhanced abnormal automaticity. Anisotropic propagation from these sites would lead to the subsequent atrial activation. We[24] have analysed atrial activation during RF-induced junctional rhythm in 18 patients: 10 had multiple sites of early activation in both the mid and/or distal His bundle catheter and the proximal coronary sinus; seven had early activation recorded only along the mid-distal coronary sinus and one had earliest activation recorded in the distal His and posterior to the ablation site in the slow pathway region (Fig. 13). [24]. This was in contrast to that fact that earliest activation was observed in the mid to distal. His electrograms in 12 of 18 patients during AV nodal tachycardia[24]. Thus, there were disparate qualitative patterns of activation of the junctional rhythms as well as quantitative differences in relative activation time during these accelerated rhythms produced by RF ablation. These data suggest that the junctional rhythms induced by RF ablation are unlikely to present direct stimulation of the AV node/His bundle over a discrete "slow pathway". We believe that junctional rhythm most likely represents enhanced automaticity from one or more sites in the AV node transitional zone at the site of ablation which are uncoupled from the atrium by RF energy. The atrial activation sequence which ensues results from anisotropic spread from these sites. These data taken as a whole suggest that AV nodal reentrant tachycardia may be another example of anisotropic reentry.

Conclusion

Much information has been learned in the era of ablation of AV nodal tachycardia. Our concepts of fixed, fast and slow pathway and macroreentrant circuits need to be challenged and revised. The inability to record reentrant atrial excitation during AV nodal reentry, the activation of patterns during AV nodal reentry, the ability to demonstrate block between the atrium and the tachycardia circuit during AV nodal reentry, as well as the ability to initiate and reset AV nodal reentry without atrial activation all suggest a sub-atrial location for the circuit. The anatomical structure of the AV node is markedly anisotropic and, we believe, provides the substrate for reentry. More detailed intraoperative mapping and studies similar to those of Loh et al[17] would further confirm the role, or lack thereof, of the atrium in AV nodal tachycardia, and may help us to understand the site of the circuit in this arrhythmia.

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Chapter 3

Severe Paroxysmal Atrial Fibrillation: Atrioventricular Junction Ablation and DDDR Mode-switching Pacemaker Versus Pharmacological Treatment

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Numbers of potential candidates for ablate and pace treatment

Atrial fibrillation (AF) is by far the most frequent arrhythmia. It has been calculated that it accounts for 1.6–2% of the general population. It is particularly frequent in the elderly, in males and in patients with heart disease; the prevalence of AF is 9.1 in men and women with cardiovascular disease over 65 years of age[1,2]. Given this high incidence, even if catheter ablation therapy were prescribed for a minority of drug refractory patients[3], the total number of potential candidates for this treatment would be very high. For example, we have calculated that in Europe about 396 000 patients (216 000 over 65 years) are affected by intolerable paroxysmal AF (Fig. 1).

The PAF study in brief

While a few, small, uncontrolled studies[4–7] have suggested the beneficial effect of AV junction ablation in patients with symptomatic paroxysmal AF, these did not include a control group of patients with similar arrhythmias treated without catheter ablation. The main aim of the paroxysmal atrial fibrillation study (PAF study)[8] was to compare AV junction ablation and DDDR

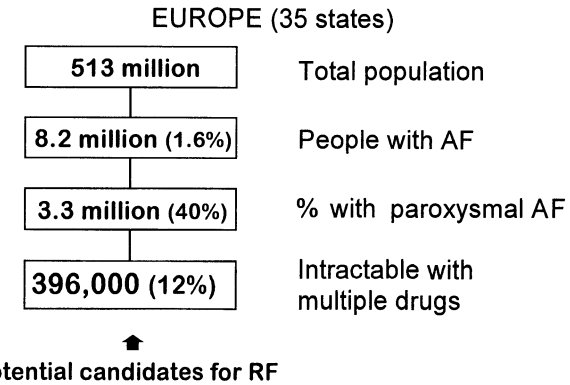

Figure 1. Ablate and pace for paroxysmal atrial fibrillation.

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mode-switching pacemaker (Diamond, Vitatron, The Netherlands) (Abl&Pm) with pharmacological therapy (Drugs) in regard to quality of life and control of specific symptoms in patients affected by severely symptomatic paroxysmal AF not controlled by pharmacological therapy.

We performed a multicentre randomised 6-month evaluation of the clinical effects of Ab1&Pm versus pharmacological treatment in 43 patients with intolerable, recurrent paroxysmal AF (≥ 3 episodes/last 6 months), not controlled with three or more antiarrhythmic drugs. Before completion of the study, withdrawals occurred in three patients of the Drug group because of the severity of their symptoms and in one patient assigned to the Abl&Pm group in whom the ablation procedure failed. A comprehensive evaluation of the patient's quality of life was made using the Minnesota Living with Heart Failure Questionnaire[9] and the Specific Symptoms Scale, developed as a disease-specific instrument to measure the patient's perception of the frequency and severity of arrhythmia-related symptoms[10].

Main results of PAF study

At the end of the 6-month study period the Ab1&Pm group patients showed significantly lower scores in LHFQ (–53%), palpitations (–71%), effort dyspnoea (–36%), exercise intolerance (–46%) and easy fatigue (–51%) in comparison with those of the Drug group (Table 1). The intrapatient comparisons between enrolment and month 6 are shown in Table 1. In the Ab1&Pm group all variables decreased significantly, except for chest discomfort; in the Drug group only palpitation scores decreased significantly. Clinical events occurring during the study period are reported in Table 2. Both the documented episodes of AF and the number of patients with permanent AF were higher in the Abl&Pm group. By contrast, the subjective perception of atrial tachyarrhythmias and the number of hospitalisations or electrical cardioversions were higher in the Drug group.

What have we learnt from the PAF study

Main aims

To date, no non-pharmacological treatments of paroxysmal AF have been evaluated against a control group of medically treated patients. The main result of this study is that, in patients affected by severely symptomatic paroxysmal AF which is not controlled by pharmacological therapy, Ab1&Pm treatment is highly effective and superior to drug therapy in controlling symptoms and improving quality of life during the following 6 months. Palpitations, the most specific symptom of paroxysmal AF, were virtually abolished in 81% of patients at the end of the 6-month study period. Although arrhythmia is paroxysmal, patients are also expected to report a great improvement in general, physical, emotional and social indexes of their health-related quality of life and not only in arrhythmia-specific parameters. Moreover, the discontinuation of drug therapy exposes patients to further recurrences of

Table 1. Results of quality of life measurements

Symptoms (score)	Enrolment			Month 6				Difference enrolment/month 6*			
	Abl & Pm (n = 22)	Drugs (n = 21)	p	Abl & Pm (n = 21)	Drug (n = 18)	p	Percentage reduction	Abl & Pm Percentage	p	Drugs Percentage	p
LHFQ questionnaire	50 ± 16	50 ± 19	1	20 ± 16	43 ± 22	0.006	–53%	–59%	0.000	–16%	0.12
Specific Symptoms Scale											
Palpitations	7.5 ± 2.1	7.2 ± 2.5	0.67	1.5 ± 2.4	5.1 ± 2.0	0.0000	–71%	–75%	0.0000	–31%	0.005
Effort dyspnoea	5.8 ± 3.9	6.7 ± 2.4	0.36	3.7 ± 3.0	5.8 ± 3.0	0.04	–36%	–35%	0.04	–15%	0.21
Rest dyspnoea	3.8 ± 3.5	2.0 ± 2.5	0.05	0.8 ± 1.4	1.8 ± 2.6	0.13	–56%	–79%	0.0003	–22%	0.56
Exercise intolerance	7.0 ± 2.9	6.5 ± 2.6	0.56	3.7 ± 3.0	6.8 ± 2.5	0.001	–46%	–46%	0.004	+8%	0.33
Easy fatigue	4.6 ± 3.6	3.8 ± 3.3	0.46	2.1 ± 2.5	4.3 ± 2.9	0.02	–51%	–55%	0.006	–2%	0.84
Chest discomfort	1.8 ± 3.0	1.2 ± 1.6	0.41	0.5 ± 1.5	1.0 ± 2.4	0.42	–50%	–72%	0.10	–17%	0.78
NHYA class	2.9 ± 0.7	2.7 ± 0.7	0.35	1.9 ± 0.7	2.3 ± 0.8	0.08	–17%	–34%	0.0002	–12%	0.10

* The intrapatient difference between enrolment and month 6 was calculated for the 21 patients of the Abl & Pm group and the 18 patients of the Drug group who completed the study period (paired t test).
Values are mean ± SD; Abl & Pm means AV junction ablation and DDDR automatic mode-switching pacemaker.

Table 2. Clinical events during the 6-month study period (as derived from monthly visits)

Event	Abl&Pm (n = 21	Drugs (n = 18)	p
Atrial fibrillation at the time of monthly visit			
Total number of visits	122*	107*	
Visit 1	3	3	
Visit 2	5	1	
Visit 3	5	1	
Visit 4	4	1	
Visit 5	7	2	
Visit 6	7	1	
Overall	31 (25)	9 (8)	0.0005
Permanent atrial fibrillation at the end of the study	5 (24)	0 (0)	0.04
Subjective perception of atrial tachyarrhythmia			
Visit 1	11 (52)	15 (83)	0.04
Visit 2	8 (38)	14 (78)	0.01
Visit 3	9 (43)	17 (94	0.0003
Visit 4	5 (24)	14 (78)	0.001
Visit 5	7 (33)	15 (83)	0.002
Visit 6	4 (19)	16 (89)	0.0000
Hospitalization or electrical cardioversion, n	1 (5)	6 (33)	0.03

Numbers indicated in parentheses are percentages.
Abl&Pm means AV junction ablation and DDDR automatic mode-switching pacemaker.
* Data unavailable in four and one patient, respectively.

paroxysmal AF and the risk of developing permanent AF, though these events do not have a negative impact on the short-term outcome.

Use of drugs

The use of antiarrhythmic drugs has been demonstrated to significantly increase the probability of maintaining sinus rhythm. For example, in seven comparative trials[11–17] in which a no-drug or placebo regimen was compared with active drug therapy after cardioversion for AF, the use of quinidine, disopyramide, flecainide, or amiodarone increased the proportion of patients remaining in sinus rhythm. Sotalol and propafenone have been found to have efficacy comparable to that of quinidine[18,19]. Several studies[20–25] have suggested that amiodarone may be effective where other agents have failed. Crijns et al[3] and Antman et al[26] have suggested that the sequential use of flecainide, quinidine, propafenone, sotalol and amiodarone, when one has failed to maintain sinus rhythm, increases the proportion of patients successfully treated. In the present study, patients were treated in a similar manner; the results suggest that the sequential antiarrhythmic drug therapy was superior to no-drug treatment in preventing recurrences of paroxysmal AF and the development of permanent AF, even in a selected population with very severe AF which had been considered to be resistant to multiple pharmacological treatment. On 6-month intrapatient comparison, the Drug group patients showed a significant improvement in palpitation score and a trend towards improvement in some other symptoms (Table 1). The final effects of antiarrhythmic drugs on outcome probably depend on the sum of various factors, including a better control of arrhythmic recurrences, more thorough examinations during the study than before, higher motivation of the patients to treat their disease, the negative impact (as perceived by the patient) of antiarrhythmic drugs on quality of life and the potential toxicity and side-effects of the drugs. The study was not designed to investigate whether the better outcome observed in the Abl&Pm group was due to the beneficial effect of the non-pharmacological treatment *per se* or also to the discontinuation of the antiarrhythmic drugs.

Which mode of pacing?

The pacing modalities after ablation are likely to have influenced the clinical outcome. In the literature, various pacing modes (VVI, VVIR, DDD, DDDR),

algorithms of recognition of atrial tachyarrhythmias, and modes of switching have been proposed[4–6, 27–32]. This study was not designed to compare different devices or different modalities of pacing; therefore, the results do not necessarily apply to other pacing modes and algorithms. In patients with paroxysmal AF, AV junction ablation creates an iatrogenic effect only rarely found in patients without ablation; namely the presence, at one and the same time, of total AV block and paroxysmal atrial tachyarrhythmias[27,28]. We preferred DDDR to the VVIR and DDD modes, since it theoretically restores AV synchrony during sinus rhythm, prevents the development of atrial fibrillation and provides adequate ventricular rate increase during physical activity in the presence of atrial tachyarrhythmias. To overcome ventricular tracking of rapid atrial activity, various mode-switching algorithms have been developed which are able to change pacing modality automatically from an AV synchronous mode during sinus rhythm to a non-AV synchronous mode during AF. For this purpose the pacemakers must have an algorithm which is able to identify pathological atrial arrhythmias and to differentiate them from physiological variations in rate. The fast mode-switching devices have been reported to be more effective than the medium and slow mode switching devices[33]. We preferred a fast mode-switching system, which is able to identify pathological atrial rhythms on a beat-to-beat change in atrial rate. In an acute study[27], this system proved to be able to lower the percentage of abnormal ventricular tracked beats during AF to $\leq 4\%$ of total ventricular beats.

Future perspectives

At present, in patients in whom drugs are unable to maintain a stable sinus rhythm the control of rapid heart rate achieved by ablation and pacemaker treatment can be proposed as the preferable mode of treatment. Owing to the higher rate of recurrences of AF (both paroxysmal and permanent) in patients off drugs, one could infer that the results of ablation and pacemaker treatment may be improved by adding pharmacological therapy or by developing more sophisticated pacing modalities able to reduce the recurrence rate of AF. Whether this approach is cost-effective remains to be demonstrated. New non-pharmacological approaches to the prevention of AF, including surgery and endocardial catheter ablation, atrial pacing or implantable atrial defibrillators, or control of rapid ventricular rate by means of AV junction modulation are encouraging, but too few data are available and their recommendation for use awaits results from clinical trials[34]. Their efficacy should probably be compared with the definitively proven treatment, namely Ab1&Pm. Several unresolved issues remain regarding the efficacy and safety of Ab1&Pm treatment in the long term.

The first concerns the long-term effect of the haemodynamic modifications caused by asynchronous ventricular activation as a result of right ventricular apex stimulation and the loss of AV synchrony in the cases in which chronic AF develops. Although some data indicate no increased risk of death or complications during long-term follow-up[35], and cardiac performance has proved unchanged or improved, during an intermediate follow-up, especially in those patients with pre-ablation left ventricle dysfunction[5,6,10,35], too few data are available on the long-term outcome of these patients to recommend a larger prescription of this treatment in cases with less severe or short-duration AF.

Conclusion

In patients with paroxysmal AF not controlled by pharmacological therapy, Ab1&Pm treatment is highly effective and superior to drug therapy in controlling symptoms and improving quality of life. The discontinuation of drug therapy exposes patients to further recurrences of paroxysmal AF and the risk of developing permanent AF.

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Chapter 4

Mechanisms of Drug Action in Atrial Fibrillation

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Introduction

Atrial fibrillation was first described electrocardiographically in 1909[1]. Recently its important role as a cause of morbidity and mortality has become apparent. More than 3 million cases of atrial fibrillation are currently present in the United States[2] and the number will increase further with the ageing of the population. The condition accounts for approximately 75 000 strokes per year in the United States[3].

The prevalence of atrial fibrillation rises steadily with age, from 0.2% to 0.3% in individuals less than 40 years of age, to 5% to 9% in those between 60 and 90 years old[4].

The most important advances in the therapy of cardiac arrhythmias made during the past 30 years are electrical devices such as pacemakers and defibrillators. However, substantial progress has also been recorded in the pharmacological treatment of arrhythmias. In the past, the use of antiarrhythmic drugs has been largely empirical. Since the 1980s, however, huge strides have been made in understanding the basis and mechanisms of arrhythmias, and this situation has been paralleled by the recognition of the mode of action of antiarrhythmic drugs.

This chapter will focus on the pharmacological treatment of atrial fibrillation and, in particular, on the mechanisms of drug action in the relatively neglected, for many years, case of arrhythmia.

Drug therapy of atrial fibrillation

The electrophysiological substrates responsible for the atrial vulnerability to atrial fibrillation are shortening of atrial refractoriness[5], inhomogeneity in atrial refractory periods, slow conduction[6] and atrial size[7]. Autonomic factors are also involved in the mechanisms of atrial fibrillation. Coumel[8] has postulated two different patterns: one of predominantly vagal aetiology and another in which adrenergic mechanisms induce atrial fibrillation.

The understanding of the basis and mechanisms of arrhythmias made possible the identification and selection of drugs that are likely to be effective in particular situations, rather than empirically searching for one to achieve suppression of the arrhythmia.

The Sicilian Gambit approach to antiarrhythmic drug action offers this opportunity[9,10]. It utilises four steps: (1) the mechanism of a particular arrhythmia is identified, if possible; (2) the vulnerable parameter, defined as the electrophysiological property of the arrhythmia most susceptible to modification and whose modification will suppress arrhythmia, is also identified; (3) the target (channel, pump, receptor, etc.) that influences the vulnerable parameter is selected; and (4) the antiarrhythmic drug that modifies this target is chosen. In the case of atrial fibrillation, therapy has two goals. The first is to slow the ventricular response and

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the second, especially when the atria are of approximately normal size, to restore sinus rhythm.

Digoxin, β-adrenergic receptor blocking drugs and calcium channel blockers (verapamil and diltiazem), singly or in combination, are effective in controlling the ventricular rate at rest and during exercise in patients with atrial fibrillation.

Drugs that slow ventricular rate in atrial fibrillation

Digoxin: mechanisms of action in atrial fibrillation

Digoxin depresses atrioventricular (AV) conduction and thus slows the ventricular rate by a direct depressant effect on the AV node and, more importantly, by increasing vagal activity and reducing both sympathetic activity and catecholamine sensitivity. The refractory period of the atrial muscle shortens as a result of the increase in vagal activity (Table 1). Digoxin enhances the slope of phase 4 of the action potential, thus atrial tissue and Purkinje fibres become automatic. In addition, the increase in intracellular calcium leads to propagation of delayed afterdepolarisations[11]. In patients with preexcitation and atrial fibrillation digoxin may be life-threatening, especially when the antegrade refractory period of the accessory pathway is short. The electrophysiological mechanisms include shortening of the refractory period of the accessory pathway[12], and increased AV nodal blockade[13].

Although atrial fibrillation frequently converts to sinus rhythm after digoxin, the conversion rate parallels that of placebo[14].

Beta-adrenoceptor blocking agents: mechanisms of action in atrial fibrillation

Beta-adrenergic receptor blockers (e.g. esmolol, metoprolol, propranolol) have proved highly effective in achieving rate control in patients with atrial fibrillation. They slow AV conduction by blocking the effect of catecholamines on the Ca^{2+} channels via the β-adrenergic cascade.

Although extensive data on the effects of β-blockers on ionic currents in different myocardial fibres are available, these data cannot be extrapolated to the *in-vivo* experimental and clinical contexts in which the autonomic nervous system is intact and there is variable adrenergic tone[15]. These agents, structurally a somewhat homogeneous group, do not exhibit specific antifibrillatory properties in the atria as opposed to the ventricles[16]; thus, β-blockade has no significant effect on conversion of atrial fibrillation to sinus rhythm. They are effective in reducing the ventricular response at rest, as well as during exercise. Their electrophysiological profile in atrial fibrillation is shown in Table 2. In a placebo-controlled study, acute heart rate control was achieved in 72% of patients treated with esmolol, compared with 6% treated with placebo ($p < 0.001$)[17]. In another trial intravenous esmolol was compared with intravenous propranolol. An initial therapeutic response was achieved in 72% and 69% of patients, respectively, and a sustained response in 67% and 59% of patients. Sinus rhythm was restored in only 14% and 16% of patients, respectively[18].

Calcium channel blockers: mechanisms of action in atrial fibrillation

As a class, calcium channel blockers are not effective in inducing conversion to sinus rhythm, nor are they effective in maintaining sinus rhythm, either when given alone or in combination with other drugs. Intravenous calcium antagonism with verapamil or diltiazem is effective in achieving rate control acutely. Calcium channel blockers slow AV conduction by decreasing inward Ca^{2+} current (Table 3).

Three types of response to intravenous verapamil have been reported in atrial fibrillation. The first and

Table 1. Digoxin: mechanisms of action in atrial fibrillation

Direct depressant effect on AV node ↑ Vagal activity ↓ Sympathetic activity ↓ Cathecholamine sensitivity	↓ AV conduction

AV: atrioventricular.

Table 2. Beta-adrenergic channel blockers: mechanisms of action in atrial fibrillation

APA/APD	0 or ↓
d*V*/d*t*	0 or ↓
ERP-A/ERP-AVN/ERP-AP	0/↑/0 or ↑
Conduction velocity	0
Autonomic nervous system	Antisympathetic

APA = action potential amplitude; APD = action potential duration; ERP = effective refractory period; A = atrium; AVN = atrioventricular node; AP = accessory pathway.

Table 3. Calcium channel blockers: mechanisms of action in atrial fibrillation

APA/APD	0/↓
d*V*/d*t*	0
ERP-A/ERP-AVN/ERP-AP	0/↑/0 or ↓
Conduction velocity	0
Autonomic nervous system	?block α-receptors; enhance vagal

Abbreviations as in Table 2.

most common is a brief inhibition of AV conduction with subsequent slowing of the ventricular response. The ventricular response gradually accelerates after 30 min. The second type of response is described in 25% of patients as regularisation of ventricular response[19]. The third type of response is reversion to sinus rhythm, which is unusual and may occur in patients with recent-onset atrial fibrillation.

Intravenous diltiazem was given in 44 patients to establish its utility in slowing the ventricular response in atrial fibrillation or flutter[20]. The proportion of patients maintaining a response to 24-h infusion of diltiazem was 83%; the drug was significantly more effective than placebo.

Control of ventricular response follows oral therapy with verapamil and diltiazem. This effect is mediated by the modulation of AV nodal conduction by combined calcium channel blocking actions and those due to the associated non-competitive adrenergic inhibitory effects.

Calcium channel blockers and β-blockers are becoming first-line therapy for rate control in the absence of severe impairment of ventricular function when digoxin is preferred. When verapamil is used together with digoxin, their depressant effects on the AV node may sum. Careful monitoring of serum drug concentration versus response is then necessitated. Similarly, diltiazem effectively controlled the ventricular response in atrial flutter and fibrillation when combined with digoxin[21].

Drugs that convert atrial fibrillation

The second goal in atrial fibrillation is restoration of sinus rhythm. Atrial fibrillation is identified as a Na^+ channel-dependent reentrant arrhythmia with a short excitable gap. The vulnerable parameter is the atrial refractory period, which needs to be prolonged. The drugs that are empirically administered for clinical cardioversion are quinidine, procainamide, disopyramide, flecainide, propafenone, amiodarone, sotalol and ibutilide.

Quinidine, procainamide and disopyramide: mechanisms of action in atrial fibrillation

Quinidine. For many years quinidine has been the principal drug used for chemical cardioversion of atrial fibrillation. Quinidine prolongs the duration of action potential of atrial muscle while also prolonging the effective refractory period (Table 4). Because of its significant anticholinergic effect and reflex sympathetic stimulation resulting from α-adrenergic blockade, quinidine can increase sinus nodal discharge rate and can improve AV nodal conduction. Refractoriness is prolonged in atrial, AV and accessory pathways.

Quinidine has been used for many years in the management of atrial fibrillation. Flecainide was compared with quinidine in a study group consisting of 60 patients with atrial fibrillation[22]. The incidence of conversion to normal sinus rhythm was similar in the two groups (60% in the quinidine versus 67% in the flecainide group). A meta-analysis of six studies involving over 800 patients evaluated the efficacy and safety of quinidine in maintaining sinus rhythm. The proportion of patients remaining in sinus rhythm 3, 6 and 12 months

Table 4. Quinidine, procainamide and disopyramide: mechanisms of action in atrial fibrillation

	Quinidine	Procainamide	Disopyramide
APA/APD	↓/↑	↓/↑	↓/↑
d*V*/d*t*	↓	↓	↓
ERP-A/ERP-AVN/ERP-AP	↑/0 or ↑/↑	↑/0 or ↑/↑	↑/↑ or 0/↑
Conduction velocity	↓ or ↑	↓	↓
Autonomic nervous system	Antivagal; α-blocker	Slight antivagal	Central: antivagal, antisympathetic

Abbreviations as in Table 2.

following cardioversion was 69%, 58% and 50% for quinidine and 45%, 33% and 25% for the control group[23]. However, the total mortality at 12 months was 2.9% in the quinidine-treated patients compared with only 0.8% in controls. An excess mortality was also found in patients receiving predominantly quinidine antiarrhythmic therapy for atrial fibrillation in the Stroke Prevention in Atrial Fibrillation Trial[24].

Procainamide. The direct electrophysiological effects of procainamide are similar to those of quinidine (Table 4). Atrial and accessory pathway refractory periods are prolonged while AV nodal refractory periods are variably affected. Conduction through the AV node is prolonged[25]. Unlike quinidine, procainamide has little effect on the parasympathetic nervous system. Procainamide can be used to convert atrial fibrillation of recent onset to sinus rhythm[26]. Intravenous procainamide is the drug of first choice for treatment of atrial fibrillation with conduction over an accessory pathway. Drug-induced lupus erythematosus syndrome with procainamide has been recognised since 1962[27]. The incidence of torsades de pointes with procainamide is probably lower than with quinidine. However, it becomes paramount to monitor the QT interval during therapy with procainamide.

Disopyramide. The *in-vitro* electrophysiological effects of disopyramide are similar to those of quinidine and procainamide, although structurally these compounds are different (Table 4). Disopyramide slows conduction in atrial tissue by blocking the fast sodium current. V_{max} is suppressed. Action potential duration is prolonged while conduction is slowed through the atria. In humans the net effect of disopyramide on AV conduction depends on the level of parasympathetic tone. Accessory pathway refractoriness and conduction are lengthened[28]. Disopyramide exerts greater anticholinergic effects than quinidine and does not appear to affect α- or β-adrenoceptors.

Disopyramide is effective in the treatment of atrial fibrillation with efficacy rates for the conversion to, and maintenance of, sinus rhythm ranging from 37% to 72%[29,30]. The combination of disopyramide and digoxin was found to be as effective as intravenous sotalol in the conversion of atrial fibrillation after open-heart surgery[31].

Side-effects of disopyramide include those related to the drug's potent parasympatholytic properties, QT prolongation and reduction of contractility of the ventricle[32,33]. Quinidine, procainamide and disopyramide need to be administered in conjunction with an AV nodal blocking drug before cardioversion to avoid acute increases in ventricular rate.

Flecainide and propafenone: mechanisms of action in atrial fibrillation

Flecainide. Flecainide is a potent sodium channel blocker resulting in marked slowing of V_{max}[34]. Conduction through the AV node is slowed and refractoriness is prolonged (Table 5). The prolongation of atrial refractoriness is probably the mechanism by which flecainide terminates atrial fibrillation[35]. Flecainide also prolongs the conduction and refractoriness of the accessory pathway[36].

Intravenous flecainide was compared to placebo in a study by Donovan et al[37]. Atrial fibrillation was converted to sinus rhythm within 30 min in 50% of patients receiving flecainide versus 5% receiving placebo. Flecainide may be more effective than procainamide in the acute termination of atrial fibrillation[38].

Proarrhythmia is the most important side-effect of flecainide. In the Cardiac Arrhythmia Suppression Trial, patients treated with flecainide had 5.1% mortality or

Table 5. Flecainide and propafenone: mechanisms of action in atrial fibrillation

	Flecainide	Propafenone
APA/APD	↓/0 or ↑	↓/0 or ↑
d*V*/d*t*	↓	↓
ERP-A/ERP-AVN/ERP-AP	↑/↑/↑	0 or ↑/0 or ↑/↑
Conduction velocity	↓↓	↓↓
Autonomic nervous system	0	Antisympathetic

Abbreviations as in Table 2.

non-fatal cardiac arrest compared with 2.3% in the placebo group over 10 months[39]. Because of the significant use-dependent effects of the drug, pro-arrhythmia can sometimes occur with exercise[40].

Propafenone. Propafenone blocks the fast sodium current in a use-dependent manner[41]. It lengthens the AV node conduction time and prolongs the effective refractory periods of the atria, AV node and accessory pathways[36].

Propafenone demonstrates non-selective β-adrenergic block (Table 5). Structurally, it is similar to propranolol.

The conversion rates of propafenone were compared to those of propafenone plus digoxin, quinidine plus digoxin and placebo in a multicentre randomised study in 246 patients[42]. The most successful regimen was the combination of propafenone plus digoxin, with a success rate of 50% at 3 h and 82% at 12 h. The corresponding success rates for placebo were 27% and 58%, respectively ($p < 0.05$).

Amiodarone, sotalol and ibutilide: mechanisms of action in atrial fibrillation

Amiodarone. Amiodarone acts by all major electrophysiological mechanisms; thus it blocks sodium channels, has antiadrenergic actions, lengthens action potential duration and blocks calcium channels. Amiodarone modifies the autonomic nervous system and also inhibits thyroxine action on the heart. Amiodarone does not prolong repolarisation more at slow than fast rates, but exerts time-dependent effects on refractoriness. Thus, the low incidence of torsades de pointes, and the high efficacy rate, may in part be explained by the above[43]. Its electrophysiological profile is shown in Table 6.

Several studies have looked at the use of amiodarone in converting atrial fibrillation to sinus rhythm and the subsequent maintenance of normal sinus rhythm[44–46]. Conversion rates ranged from 17% to 100%. The effects of amiodarone in converting chronic atrial fibrillation to sinus rhythm were compared with those of quinidine and verapamil[47]. Quinidine restored sinus rhythm in 25% of patients, the combination of quinidine and verapamil in 55% and amiodarone alone in 60% of patients.

Amiodarone may facilitate defibrillation experimentally[48] but increases the electrical defibrillation threshold[49]. Because of the unusual pharmacokinetics of the drug[50,51] and its adverse effects amiodarone therapy should possibly be started with the patient hospitalised. Adverse effects are frequently reported in patients treated with amiodarone. Pulmonary toxicity, hyperthyroidism, hypothyroidism and symptomatic bradycardias are among those uncommonly reported[52,53].

Sotalol. Sotalol is a selective β-adrenoceptor blocker without intrinsic sympathomimetic activity and with little or no sodium channel blocking actions. Sotalol does not exhibit any effect on conduction velocity. It prolongs atrial repolarization time[54] and the atrial refractory period (Table 6).

Intravenous sotalol was tested in a placebo-controlled multicentre study in 48 patients with atrial fibrillation[55]. Sotalol was highly effective in slowing heart rate compared with placebo; however, it was no more effective than placebo in achieving sinus rhythm at 30 min. In another study the efficacy of sotalol was compared with that of quinidine plus digoxin in converting acute atrial fibrillation to sinus rhythm. Conversion of atrial fibrillation to sinus rhythm occurred in 52% of patients taking sotalol and 86% taking quinidine ($p < 0.0001$)[56].

Table 6. Amiodarone, sotalol: mechanisms of action in atrial fibrillation

	Amiodarone	Sotalol
APA/APD	0/↑	0 or ↓/↑
d*V*/d*t*	0 or ↓	0 or ↓
ERP-A/ERP-AVN/ERP-AP	↑ / ↑ / ↑	↑ / ↑ /↑
Conduction velocity	↓	0
Autonomic nervous system	Antisympathetic	Antisympathetic

Abbreviations as in Table 2.

Table 7. Ibutilide: mechanisms of action in atrial fibrillation

APD	↑ (at 10^{-8}, 10^{-7} mol/L) ↓ (at 10^{-5}, 10^{-4} mol/L)
ERP-A	↑
Conduction velocity	0
Autonomic nervous system	0

Abbreviations as in Table 2

Proarrhythmia is the most serious adverse effect occurring as wide complex tachycardia in 13% of patients taking sotalol for conversion of atrial fibrillation to sinus rhythm[56]. Other adverse effects, although frequent, were generally not dangerous[57,58].

Ibutilide. Ibutilide fumarate is a novel intravenous antiarrhythmic agent that has been approved by the Food and Drug Administration for the conversion of atrial fibrillation or atrial flutter to sinus rhythm. Electrophysiologically, ibutilide lacks activity at β-adrenergic receptors or independent actions upon the autonomic nervous system (Table 7). Ibutilide prolongs atrial refractoriness with little change in conduction velocity[59].

Ibutilide was tested in 133 patients with sustained atrial fibrillation of 3 h to 45 days duration[60]. Patients were randomised to receive ibutilide or placebo. Atrial fibrillation was converted to sinus rhythm in 31% of patients. Polymorphic ventricular tachycardia developed in 8.3% of treated patients.

Conclusions

Given the prevalence of atrial fibrillation it is likely that pharmacological therapy will continue to play an important role in the management of the disease. The Sicilian Gambit approach to the treatment of an arrhythmia, taking into account the mechanism, the critical components and the vulnerable parameter of the arrhythmogenic substrate, helps in selecting the antiarrhythmic agent most likely to be successful.

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Chapter 5

Conclusions and Questions from Large Trials of Anticoagulants in Patients with Atrial Fibrillation

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Introduction

Atrial fibrillation (AF) is a common dysrhythmia, affecting 2–5% of the general population over the age of 60[1–3]. It can be found in about 15% of all stroke patients[4,5], and in about 2–8% of transient ischaemic attack (TIA) patients[6–8]. The incidence of ischaemic stroke in AF patients without rheumatic heart disease (RHD), so called non-rheumatic atrial fibrillation (NRAF), is about 4.5% per year. Following an initial embolism, the stroke recurrence rate is 12% per year, and the annual mortality rate is 5%[9].

Since the early 1990s several large clinical trials have investigated the value of anticoagulation in the prevention of stroke and other vascular complications in patients with NRAF[10–15]. In addition, trials have studied the value of antiplatelet drugs[10,11,15–17]. Several studies have focused on stroke prevention in NRAF patients without a recent TIA or minor stroke (primary prevention)[10–14], whereas others have specifically addressed the prevention of recurrent vascular events in NRAF patients with recent cerebral embolism (secondary prevention)[15–17].

Primary prevention

As summarised in Table 1, all primary prevention trials have shown a significant risk reduction in patients treated with anticoagulants, ranging between 42% and 86% in the intention-to-treat analysis. The risk of significant bleeding, defined as bleeding severe enough to require hospitalisation, blood transfusion, or surgery, was low, ranging between 0.4 and 1.7 per 100 patient-years. Table 2 shows the results of aspirin in the prevention of cerebral embolism. Of the two primary prevention studies, the AFASAK trial showed a small and not significant 16% risk reduction against a significant 42% risk reduction in the SPAF study. The overall risk reduction for primary prevention by aspirin was 35% (95% confidence interval 5–56%). In SPAF-I, the benefit of aspirin applied especially to patients under the age of 70. A prolongation of this study, SPAF-II, showed that anticoagulants were 30% (95% CI 14–57%) more effective than aspirin in the prevention of embolic events[18]. This difference was not statistically significant, probably due to the small number of embolic events. The low absolute risk of embolic

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Table 1. Results of randomised clinical trials in patients with non-rheumatic atrial fibrillation; warfarin versus placebo

Study	Type of prevention	Embolic events (*n*)		RR (%)	95% CI
		Warfarin	Placebo		
AFASAK[10]	Primary	9	22	59	11–89
SPAF-I[11]	Primary	6	18	67	27–85
BAATAF[12]	Primary	2	13	86	51–96
SPINAF[14]	Primary	4	19	79	52–90
CAFA[13]	Primary	6	11	37	–64–76
EAFT[15]	Secondary	20	50	66	43–80
Aggregate	Both	47	133	67	59–78

RR = risk reduction; CI = confidence interval.

Table 2. Results of randomised clinical trials in patients with non-rheumatic atrial fibrillation: aspirin versus placebo

Study	Type of prevention	Embolic events (*n*)		RR (%)	95% CI
		Aspirin	Placebo		
AFASAK[10]	Primary	19	22	16	–53–60
SPAF[11]	Primary	26	46	42	9–63
EAFT[15]	Secondary	88	90	14	–15–36
Aggregate	Both	133	158	23	2–45

RR = risk reduction; CI = confidence interval.

complications also explains that the absolute difference between the two treatments was very small. The risk of intracranial bleeding varied between 0.2 and 0.9 per 100 patient-years (Table 3).

In a meta-analysis of all clinical trials in NRAF patients the following independent risk factors for embolism were identified: history of hypertension, diabetes, and prior thromboembolism[19]. The results of SPAF-II[18] suggested that patients with clinical risk factors benefited more from anticoagulants than those without. This was further investigated in SPAF-III, in which patients with any of the above clinical risk factors, or female sex or congestive heart failure, were randomised to the combination of aspirin and a fixed low dose of warfarin with a target intensity international normalized ratio (INR) 1.2–1.5, or titrated warfarin with an INR range of 2.0–3.0. The mean follow-up was 1 year. The annual stroke risk in patients on full-dose warfarin was 2.6% versus 8.6% in patients with combination, a relative risk reduction of 70% (95% CI 44–83).

In summary, primary prevention studies completed to date show that anticoagulation with a target intensity of INR 2.0–3.0 is the therapy of first choice in AF patients with clinical risk factors, whereas aspirin can be given to patients without risk factors, because it is cheaper and

Table 3. Risk of bleeding complications in patients treated with anticoagulants

Study	Mean age	INR	Major bleed (%/year)	Intracranial (%/year)
AFASAK[10]	74	2.8–4.2	0.8	0.4
SPAF[11]	67	2.0–3.5	1.7	0.9
BAATAF[12]	68	1.5–2.7	0.9	0.5
SPINAF[14]	67	1.5–2.7	1.5	0.2
CAFA[13]	68	2.0–3.0	2.5	0.5
EAFT[15]	73	2.5–4.0	2.8	0.0
SIFA[16]	72	2.0–3.5	1.4	0.9

INR = International normalised ratio.

easier to administer, and has a lower risk of bleeding complications. In patients with echocardiographic indications of cardiac abnormalities, particularly impaired left ventricular function[20], anticoagulants can probably also be recommended, although this has not been addressed specifically in clinical trials. In the near future the results of a Dutch primary prevention study among general physicians, the PATAF study, and the Danish AFASAK-II trial, may further help to establish the optimal therapeutic approach in the primary prevention of thromboembolic complications in NRAF patients.

Secondary prevention

For neurologists, secondary prevention is of more importance than primary prevention, since NRAF patients with a recent TIA or minor stroke are primarily referred to them. Until the early 1990s the optimal treatment for the secondary prevention of embolism in patients with NRAF was uncertain[9]. In the absence of direct data supporting the value of anticoagulants or aspirin in secondary prevention, many physicians have probably extrapolated the results of the primary prevention trials. This may not be justified, however. Firstly, NRAF patients with a recent TIA or minor ischaemic stroke are likely to have more advanced atherosclerosis of extra- and intracranial blood vessels. Together with a fresh ischaemic lesion and higher mean age this may lead to a much higher risk of intracerebral bleeding. Secondly, in at least a third of NRAF patients with recent cerebral ischaemia, the stroke is related to an arterial lesion rather than to embolism from the heart[21], and aspirin may be the most effective drug in such patients. In 1993 the results of a large multicentre secondary prevention trial, the European Atrial Fibrillation Trial (EAFT), were published[15]. In this study 1007 NRAF patients with a TIA or minor stroke within the preceding 3 months were randomised to open treatment with anticoagulants (target INR 2.5–4.0) or double-blind treatment with 300 mg aspirin or placebo (group 1; n = 669). Patients with contraindications to anticoagulants were randomised to aspirin or placebo (group 2; n = 338). The primary measure of outcome was the composite event of vascular death, non-fatal stroke, non-fatal myocardial infarction or systemic embolism, whichever occurred first. During a mean follow-up of 2.3 years the annual rate of primary outcome events was 8% in patients assigned to anticoagulants versus 17% in placebo-treated patients of group 1 (hazard ratio [HR] 0.53, 95% CI 0.36–0.79). The risk of stroke alone was reduced from 12% to 4% per year (HR 0.34; 95% CI 0.20–0.57). In absolute terms, 90 vascular events (mainly strokes) are prevented if 1000 patients are treated with anticoagulants for 1 year. These findings are remarkably similar to those of the primary prevention studies. The most important difference is the much higher absolute risk of subsequent stroke. Among all aspirin-treated patients (groups 1 and 2 combined), the annual incidence of primary outcome events was 15%, against 19% in those on placebo (HR 0.83; 95% CI 0.65–1.05). Anticoagulants were significantly more effective than aspirin (HR 0.60; 95% CI 0.41–0.87. The aggregate results of all three AF trials which directly compared aspirin with placebo show that the effect of aspirin is statistically significant, but is considerably smaller than of anticoagulants (unpublished data from the Atrial Fibrillation Investigators database). This treatment prevents about 50 vascular events (of all types) per 1000 patients treated for 1 year. This benefit is of similar magnitude to that found in an overview of studies in patients with a variety of arterial diseases, including patients with a recent TIA or minor stroke without atrial fibrillation. The incidence of bleeding events in the EAFT was low, both on anticoagulation (2.8% yearly) and on aspirin (0.9% yearly). No intracranial bleeds were identified in patients using anticoagulation. In a secondary analysis of EAFT data the optimal level of anticoagulation was found to be INR 2.0–4.0. No treatment effect was found below INR 2.0 and most bleedings occurred at INR above 5.0. These findings are in keeping with those of a recent case control study which showed that below INR 2.0 the risk of ischaemic events rapidly increased, and that above INR 3.0 no further benefit was obtained while the risk of bleeding sharply increased at INR 4.0 and above[22].

Very recently, the results of the Studio Italiano Fibrillazione Atriale (SIFA) were published. In this multicentre, randomised study, 916 patients with NRAF and recent (< 15 days) minor stroke or TIA were treated with indobufen 200 mg b.i.d. or warfarin (INR 2.0–3.5) for a period of 12 months[16]. The incidence of any vascular event was 10.6% in the indobufen group versus 9.0% in the warfarin group (not statistically significant), and that of any stroke 5% and 4%, respectively (not significant). The incidence of major bleeding complications was very low in both groups: in the warfarin group, four intracerebral haemorrhages (0.9%/year) and four major systemic bleeds (1.4%) occurred. These interesting findings, which need to be

confirmed in another trial, suggest that indobufen is a valuable alternative in case anticoagulants are contra-indicated, and may be more efficacious than aspirin.

The above studies do not definitively answer the question of when antithrombotic treatment should be started after a cerebral ischaemic event in a patient with atrial fibrillation, since in both trials a minority of patients were randomised within 2 weeks after onset of neurological symptoms. Given the high efficacy of anti-coagulation it may be that treatment should be started as soon as possible. However, several studies have recommended withholding anticoagulants during the first few days after suspected cardiogenic emboli to the brain, especially in patients with large infarcts[23,24]. Very recently the results of a large trial in patients with acute stroke, the International Stroke Trial, have been published[17]. In this study 19, 435 patients were randomised within 48 h of onset, to treatment during 14 days with aspirin alone, 5000 E or 12 500 E standard unfractionated heparin b.i.d. subcutaneously, the combination of either dose of heparin and aspirin, or neither. A total of 3153 patients, or 16% were in AF. Of AF patients treated with heparin, 44 suffered a recurrent ischaemic stroke versus 79 of those not receiving heparin. However, recurrent haemorrhagic stroke occurred in 32 patients on heparin versus seven in those without. The benefit of heparin regarding the prevention of ischaemic events was therefore completely offset by bleeding complications. In aspirin-treated patients the numbers of ischaemic and haemorrhagic stroke were 53 and 22, respectively, versus 70 and 17 in those without aspirin. This difference was not statistically significant. In conclusion, the IST results show that in AF patients with large acute ischaemic stroke early treatment with subcutaneous heparin or with aspirin is not beneficial within the first 14 days.

In summary, with the completion of the studies described above, the optimal treatment for secondary prevention of thromboembolic complications in patients with non-rheumatic atrial fibrillation and a recent TIA or minor ischaemic stroke has now been defined: such patients should be treated with anticoagulants with an intensity of INR 2.0–3.0 if at all possible. In case of a contraindication to anticoagulants, aspirin and ibuprofen are safe, but less effective, alternatives. During the first 2 weeks following AF-related major stroke the benefit of subcutaneous heparin is offset by a higher risk of secondary cerebral bleeding, and the procedure therefore cannot be recommended at present during that period.

Remaining questions

The International Stroke Trial has shown that early heparin in AF patients with major stroke is associated with an unacceptable risk of bleeding complications. The timing of the secondary bleeding complications is yet unknown, however, and it is therefore unknown when it is safe to start. Furthermore, although still not investigated specifically, it seems very probable that massive strokes were particularly prone to haemorrhagic transformation. The risk of early haemorrhage in patients with TIA or minor stroke is probably much lower, and these patients can therefore be anticoagulated immediately. This issue has to be sorted out in the near future.

It is unknown how long antithrombotic treatment should be continued when given for secondary prevention. Survival curves from EAFT dispel the common notion that the risk of recurrent events is confined to the early period after the initial event. Both risk and benefit of treatment remained fairly constant during the relatively short period of follow-up (mean follow-up 2.3 years). In the primary prevention studies a previous thromboembolic event was identified as an important risk factor for thromboembolic complications even if it had occurred years earlier. Thus, the available data suggest that both anticoagulant and aspirin treatment should be given for as long as possible; that is, until a contraindication or a serious bleeding complication occurs.

Another important question is whether the results of clinical trials discussed above also apply to patients of 80 years old or more[25]. Although the mean age in the EAFT was 71 years there were only 79 patients of 80 years or over. This subgroup is definitely too small for a reliable subgroup analysis, apart from general objections one may have against such analyses. The combined evidence of all clinical trials in AF patients does not suggest a substantial difference in efficacy of anticoagulants in patients under or over 75 years[19]. However, if anticoagulants are equally effective in preventing embolic stroke in both age groups, it may be much more difficult to improve the very elderly's quality of life, since this would require the prevention of falls, arthritis, dementia and many other

diseases as well. Data from the EAFT show that increasing age is indeed an independent risk factor for thromboembolic events. This finding is in keeping with the results of a pooled analysis of five primary prevention trials in AF patients. In EAFT the increased risk in the elderly mainly applied to cardiac events, and less to ischaemic stroke. Although there is no consensus on whether the elderly have an increased risk of bleeding complications from anticoagulants, most studies suggest that the risk is indeed considerably higher. This seems logical in view of the expected lower patient compliance, greater difficulty in anticoagulation monitoring and increased comorbidity. In the EAFT the risk of any bleeding complication was 3.6-fold increased in patients over 75 years. Surprisingly, no intracranial bleeding was observed among the 225 patients using anticoagulants. The aggregate results of all primary prevention AF trials did not show a significant difference in mean age between those with and without an intracranial bleed. The small number of patients with intracranial bleeding did not allow us to draw a reliable conclusion about the effect of age, however. In contrast, findings of SPAF-II showed a higher risk of intracranial haemorrhages in patients over 75. In fact, in very elderly patients these bleeding complications negated the beneficial effect of anticoagulants. Previously identified risk factors for anticoagulant-associated intracranial bleeding include excessive anticoagulation and poorly controlled hypertension. Furthermore, elderly patients especially should be very carefully monitored to minimise the risk of bleeding complications. In conclusion, very elderly AF patients have most to win, but also most to lose from anticoagulant treatment. We definitely need more data, since most of the questions addressed above cannot be answered with sufficient certainty. However, the experience from the large clinical trials performed so far is that very few patients of 80 years or over are randomised. It is hoped that an increased involvement of geriatricians in future trials may help to overcome this problem. Until more data become available, the treatment of elderly AF patients with a recent TIA or minor ischaemic stroke should be tailored individually. There is no good reason to deny anticoagulants to an 85-year-old AF patient with a recent stroke who has no contraindication for anticoagulants, and whom one expects to be compliant and able to visit the hospital regularly for anticoagulation monitoring. In many patients, however, it will be very difficult to balance the potential benefit and risk. The decision to give anticoagulants to fibrillating stroke patients over 80 years is a persisting dilemma.

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Chapter 6

Role of the Autonomic Nervous System in Sustained Ventricular Tachycardia after Myocardial Infarction

Maurizio Landolina, Ruggero Manfredini, Massimo Mantica and Gaetano M. De Ferrari

Introduction

The analysis of the autonomic control of the heart, by means of indirect markers, may represent a new approach for the identification of patients at high risk of sudden death after a myocardial infarction.

Baroreceptor reflexes and heart rate variability are both indexes of vagal activity, but whereas heart rate variability reflects the continuous sympatho-vagal modulation of sinus activity, baroreflex sensitivity (BRS) is correlated mainly with the capability of the parasympathetic nervous system to react to a sudden stimulus and thus concerns primarily vagal reflexes.

In this chapter we will discuss some recent experimental and clinical observations that may offer insights into the pathophysiology of the onset and of the haemodynamic tolerability of malignant ventricular arrhythmias, and that may suggest new approaches for the risk stratification of patients with a previous myocardial infarction. We will focus our attention mainly on baroreceptor reflexes.

Background: experimental studies

The idea of using baroreceptor reflexes in risk stratification is based on the evidence originating from experimental studies showing that the autonomic responses occurring during acute myocardial ischaemia are a major determinant of the likelihood of malignant arrhythmias[1–4]. Indeed, sympathetic activation can trigger ventricular arrhythmias, whereas vagal activity may exert a protective effect.

The availability of an experimental model for sudden cardiac death[5], which combines three elements relevant to the occurrence of malignant arrhythmias in humans (i.e. previous myocardial infarction, acute myocardial ischaemia, and elevated sympathetic activity), has represented a critical step. In this conscious animal model, dogs with a previous myocardial infarction underwent a submaximal exercise stress test. When the heart rate reached nearly 220 bpm, a 2-min occlusion of circumflex coronary artery was performed and the exercise was stopped after 1 min. This test induced ventricular fibrillation in slightly more than 50% of the dogs

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("susceptible" dogs). At variance with "susceptible" dogs, those resistant to ventricular fibrillation showed an unexpected trend towards a reduction in heart rate, despite continuation of exercise; this reduction was clearly dependent on a vagal reflex, since it could be prevented by atropine. Thus, it was evident that, among the two groups of dogs, resistant and "susceptible", the dominant autonomic reflex responses were opposite.

This observation has represented the starting point to analysing whether the study of cardiac reflexes at rest might provide useful information for the early recognition of the dogs that were likely to develop ventricular fibrillation during an episode of acute myocardial ischaemia. With this aim baroreflex sensitivity (BRS) was used as a marker of vagal reflexes. According to the method described by Smyth et al[6], BRS was calculated as the slope of the linear regression line relating RR interval changes to blood pressure changes induced by the pressor agent phenylephrine. The changes at sinus node level reflect mainly vagal activity but also, even if to a much lesser extent, sympathetic activity (Fig. 1)[7].

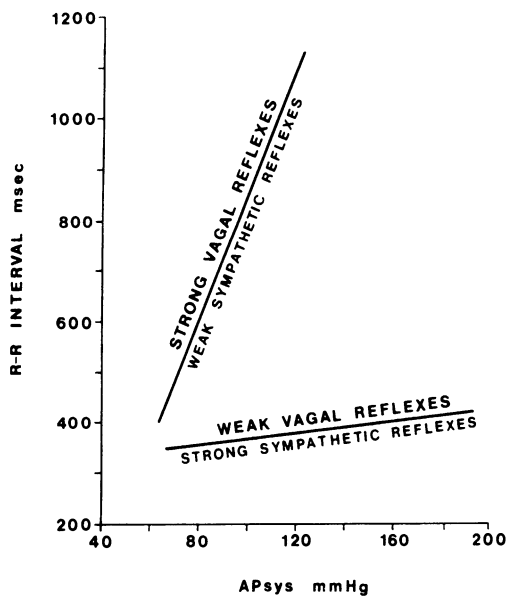

Figure 1. An example of the relation between RR interval lengthening (y axis) and blood pressure increases (x axis) induced by the pressor agent phenylephrine. The lower curve represents a depressed BRS whereby marked increases in blood pressure are accompanied by small increases in RR interval. The upper curve represents the opposite response. As indicated, the changes at sinus node level reflect mainly vagal activity but also, even if to much lesser extent, sympathetic activity. (Reproduced with permission from ref. 7.)

A large-scale experimental animal study[8] demonstrated that BRS was significantly lower in dogs that developed ventricular fibrillation during the exercise and ischaemia test compared to the resistant group (9.1 ± 6.5 vs 17.7 ± 6 ms/mm Hg, $p < 0.001$). At a value of BRS < 9 ms/mmHg, 91% of the dogs developed ventricular fibrillation during the exercise, whereas at a value of BRS > 15 ms/mm Hg, 80% of the dogs survived. This indicated that the capability to activate powerful vagal reflexes had potentially beneficial effects in the prevention of sudden cardiac death.

Background: clinical studies

The applicability of the experimental findings to the clinical setting had to be demonstrated in clinical studies in patients with a previous myocardial infarction. As in the experimental studies[8], BRS was significantly lower in patients with a recent myocardial infarction than in the control group[9]. An interesting finding was that this reduction in BRS lasted for a few months and then subsided. A prospective clinical study[10] evaluated 78 post-myocardial infarction patients to assess if BRS was correlated to cardiac mortality in humans. The 2-year mortality was rather low (seven cardiac deaths, four sudden); nevertheless BRS was significantly lower in the seven patients who died compared with the survivors (2.4 ± 1.5 vs 8.2 ± 5 ms/mmHg, $p = 0.004$). Moreover, the presence of markedly depressed BRS (≤ 3 ms/mmHg) identified a group of patients at high mortality risk (50% vs 3%).

A recent international multicentre prospective trial (Autonomic Tone and Reflexes After Myocardial Infarction)[11] evaluated in 1284 post-myocardial infarction patients, BRS and various measures of heart rate variability, in addition to the traditional clinical variables for risk stratification. During a follow-up of 21 ± 8 months, 45 patients had a cardiac death and five additional patients had a non-fatal cardiac arrest due to documented ventricular fibrillation. One-year mortality was significantly higher (9% vs 2%, $p < 0.0001$) in patients with depressed BRS (< 3 ms/mmHg) compared to those with preserved BRS (> 6.1 ms/mmHg) as well as in patients with reduced standard deviation of RR interval (SDNN) (< 70 ms) compared to patients with preserved (> 105 ms) SDNN (10% vs 2%, $p < 0.0001$). The study demonstrated that BRS was a strong predictor of cardiac mortality, and that it was independent of left ventricular ejection fraction (LVEF) and ventricular

arrhythmias; moreover, the presence of depressed BRS and LVEF identified a group at high risk (relative risk = 11.9).

These data are in agreement with the hypothesis that subjects with higher BRS are able of activating more powerful vagal reflexes in response to acute myocardial ischaemia, thus counteracting the detrimental effects of sympathetic hyperactivity and decreasing the likelihood of cardiac death and ventricular fibrillation.

Relevant to the present topic is the existence of a relationship between baroreceptor reflexes and the occurrence of monomorphic sustained ventricular tachycardia (VT) early after myocardial infarction, in the likely absence of active myocardial ischaemia.

An important support for this relationship was provided by a study by Farrell et al[12]. The authors assessed BRS, heart rate variability, the presence of late potentials and the inducibility of sustained monomorphic VT by programmed ventricular stimulation in 68 patients 1 week after myocardial infarction. A depressed BRS (< 3 ms/mmHg) was found to be the most significant predictor of induction of sustained monomorphic VT at programmed ventricular stimulation (relative risk 36.3).

A prospective trial of risk stratification[13] assessed BRS, heart rate variability, 24-h ECG recordings, exercise stress testing and LVEF in 122 post-myocardial infarction patients. During a 1-year follow-up period there were 10 arrhythmic events including five sudden deaths; BRS was significantly depressed in those patients suffering arrhythmic events (1.75 vs 7.89 ms/mmHg, p = 0.0001) and sudden deaths (2.34 vs 7.54 ms/mmHg, p = 0.001).

Autonomic nervous system and ventricular tachycardia long after myocardial infarction

Susceptibility to ventricular tachycardia

It has been demonstrated that myocardial infarction creates a derangement in the autonomic balance[8,9] characterised by a shift towards a sympathetic dominance that lasts for a few or several months after the infarction and then subsides[9,14]. After this early post-infarction period little is known of the role of the autonomic balance and specifically of vagal tone and reflexes in the occurrence of monomorphic sustained VT.

This is the reason why we designed a study[15] to assess whether heart rate variability and BRS would differ between patients with clinical episodes of symptomatic sustained VT occurring more than 1 year after myocardial infarction and a control population with similar characteristics but without ventricular arrhythmias.

The study was performed in 28 patients. The ventricular tachycardia/ventricular fibrillation (VT/VF) group consisted of 14 patients (12 with sustained monomorphic VT, and two with ventricular fibrillation). No difference was seen in age, site of previous myocardial infarction, presence of left ventricular aneurysm, LVEF between the two groups. All patients had a previous myocardial infarction but no patient was enrolled in the first year, to avoid transient alteration in the autonomic balance induced by the infarction. No significant difference was found in SDNN (25.1 ± 3.7 ms in the VT/VF group vs 29.6 ± 3.1 ms in the control group) as well as in the other time-domain indexes of heart rate variability. Similarly, frequency-domain analysis did not disclose any difference between the two groups of patients. At variance with heart rate variability, BRS was found to be significantly different in the two groups. Patients in the VT/VF group had a mean BRS of 4.2 ms/mmHg, whereas patients in the control group had a mean value of 8 ms/mmHg (p = 0.008) (Fig. 2).

Findings similar to those of this study were reported by Hohnloser et al[16], although with two main differences: every patient had a history of aborted sudden death

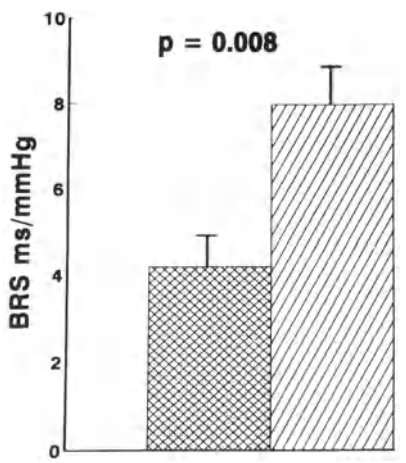

Figure 2. Patients in VT/VF group (cross-hatched bars) had significantly lower BRS value compared with patients in control group (hatched bars). Mean ± SEM values are shown. (Reproduced with permission from ref. 15.)

(a ventricular fibrillation was documented in 50% of them), the control group enrolled patients in the first 25 days after an acute myocardial infarction. BRS was markedly depressed in patients with a history of cardiac arrest compared to the control group (1.8 vs 9.2 ms/mmHg; p = 0.0002); moreover only three patients in the group with cardiac arrest had a BRS > 3 ms/mmHg.

These two studies, taken together, suggest that a sustained depression of vagal reflexes may play a role in the occurrence of sustained VT well beyond the first year after an episode of myocardial infarction.

The mechanism(s) by which powerful vagal reflexes may exert a protective effect against the occurrence of sustained monomorphic VT is (are) not yet fully understood. A reasonable possibility involves the presence of a trigger, such as premature ventricular contractions, known to cause an increase in sympathetic outflow[17,18]. It is conceivable that, in the presence of premature ventricular contractions, the capability to activate more effective vagal reflexes can counteract the sympathetic dominance at the cardiac level[18], thus resulting in an autonomic condition less favourable for the development of malignant arrhythmias. Patients with a marked depression of vagal reflexes, on the other hand, may leave completely unopposed the increase in sympathetic activity, and would be more susceptible to sustained ventricular arrhythmias.

Haemodynamic tolerability of sustained ventricular tachycardia

Poorly tolerated sustained VT is associated with an unfavourable prognosis[19]; several factors may play a role in the haemodynamic response to VT[20]. A fast heart rate decreases cardiac output, mainly because of the shortening of diastole, and this effect is markedly exaggerated in patients with impaired left ventricular function. Other factors considered to play a role in haemodynamic status during VT include the potential occurrence of myocardial ischaemia at high heart rates and the neurohormonal response to VT[20,21].

We studied 24 consecutive patients with a previous myocardial infarction a few days after an episode of sustained monomorphic VT, and evaluated several clinical and autonomic variables related to haemodynamic tolerability[22]. Mean age was 66 years, mean LVEF 37%. Patients were assigned to group 1 if the VT was well tolerated (n = 11) or to group 2 if faintness or syncope occurred or if systolic blood pressure was < 90 mmHg with clinical signs of shock (n = 13).

No difference was observed between the two groups in age, mean left ventricular ejection fraction, presence of left ventricular aneurysm, or cycle length of the clinical VT (Fig. 3). Analysis of the rest 10-min RR recordings disclosed no differences between groups in time and frequency domain heart rate variability. At variance with the results of heart rate variability, patients in group 2 (poorly tolerated VT) had a significantly lower BRS (3.4 vs 7.1 ms/mmHg, p = 0.003) (Fig. 4). Notably, only three patients in group 1 (well-tolerated VT) had a BRS < 5 ms/mmHg, whereas no patient in group 2 (poorly tolerated VT) had a BRS > 5 ms/mmHg. A multiple logistic regression analysis showed that only BRS (p = 0.0003), but not age, LVEF, VT cycle length or standard deviation of the RR interval correlated with the tolerability of the VT.

During an average follow-up of 24 months after the index arrhythmia, six patients had a cardiac death (documented ventricular fibrillation or sudden death in three), and four others had a non-fatal recurrence of VT (in two the arrhythmia was associated with haemodynamic deterioration). Patients with either cardiac death or haemodynamically unstable VT during the follow-up period (n = 8) had a lower LVEF (27 ± 5% vs 42 ± 11%, p = 0.001) and lower BRS (2.9 ± 1.1 vs 5.9 ± 3.3 ms/mmHg, p = 0.003) than did patients with neither of these events (n = 15). No difference was found in any other clinical or autonomic variable (Fig. 5).

This study suggests that patients with higher BRS have more flexible cardiovascular reflexes to compensate for the haemodynamic disturbances caused by VT. The hypothesis is in good agreement with the suggestion[20] that the flexibility of reaction to VT is decisive for the haemodynamic outcome during VT.

The unfavourable haemodynamic profile of patients with poorly tolerated VT may depend on inadequate sympathetic drive during the arrhythmia. This hypothesis is supported by both human and animal studies. Smith et al[23] suggested that, in humans, the preservation of arterial pressure during induced VT was directly related to the increase in muscle sympathetic nerve activity in response to the arrhythmia. Since a correlation exists between the extent of vagal activation in response to phenylephrine and the extent of sympathetic activation during baroreceptor unloading[24], it is likely that patients with a depressed baroreflex sensitivity do

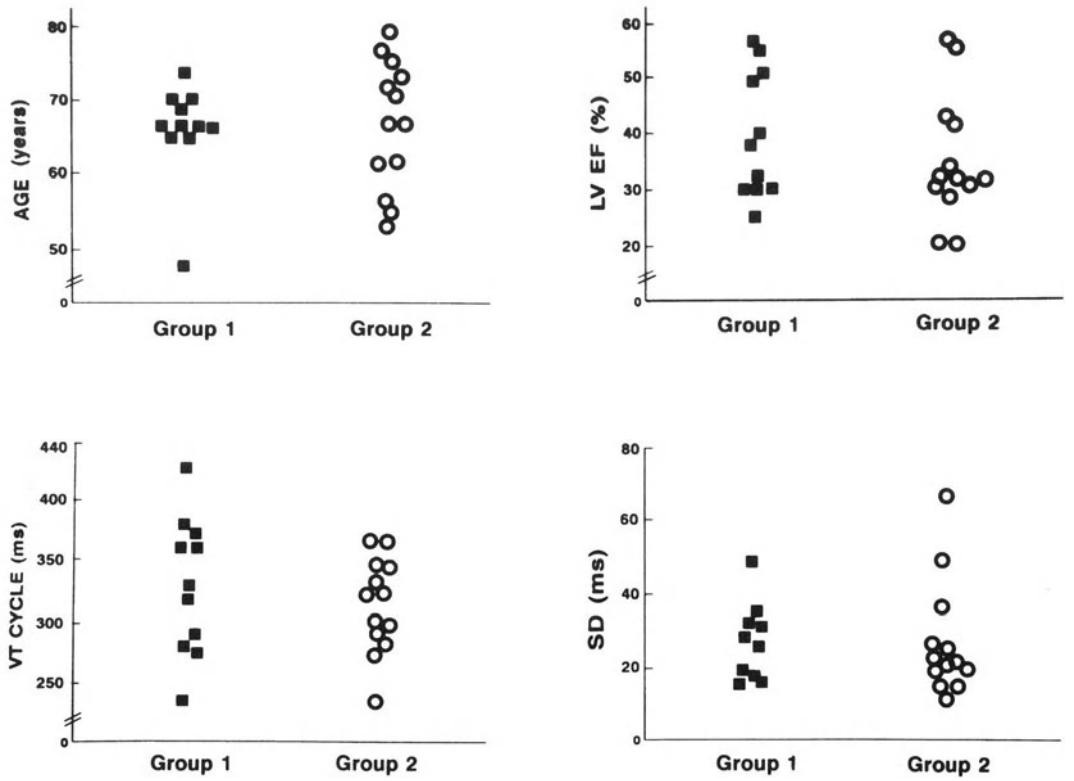

Figure 3. Plot of individual values for age, cycle length of ventricular tachycardia (VT cycle), left ventricular ejection fraction (LVEF) and standard deviation of the RR interval (SD) of patients in group 1 (well-tolerated VT) and group 2 (poorly tolerated VT). There is an almost complete overlap of values between the two groups. (Reproduced with permission from ref. 22.)

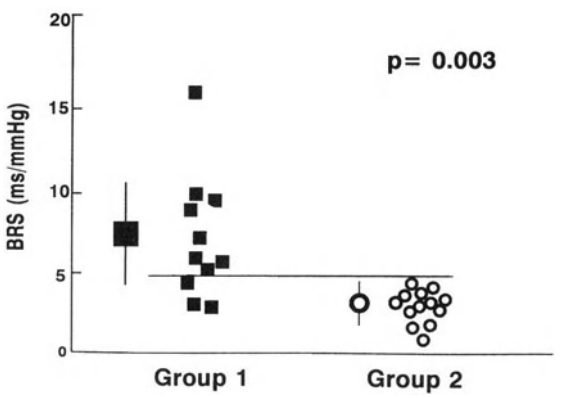

Figure 4. Plot of the individual values of BRS of patients in groups 1 and 2. Also shown is the mean value ± SD for both groups. The arbitrary cut-off line at 5 ms/mmHg shows that all patients with poorly tolerated VT had a BRS below this value, whereas this occurred in only three patients with well-tolerated VT. (Reproduced with permission from ref. 22.)

not tolerate the VT because of inadequate arterial baroreflex-mediated sympathoexcitation.

In agreement with this hypothesis, a recent animal study[25] suggests that arterial baroreflex-mediated sympathoexcitation plays the key role in determining the haemodynamic outcome during VT. Indeed, arterial baroreceptor denervation reduced both the sympatho-excitatory response to ventricular pacing and the attendant recovery of mean arterial pressure.

Conclusions

These findings suggest that the autonomic balance exerts an important influence on the arrhythmic substrate well beyond the first year after myocardial infarction and, specifically, that a sustained depression of vagal reflexes may have a role in the occurrence of malignant ventricular arrhythmias. Therefore, the

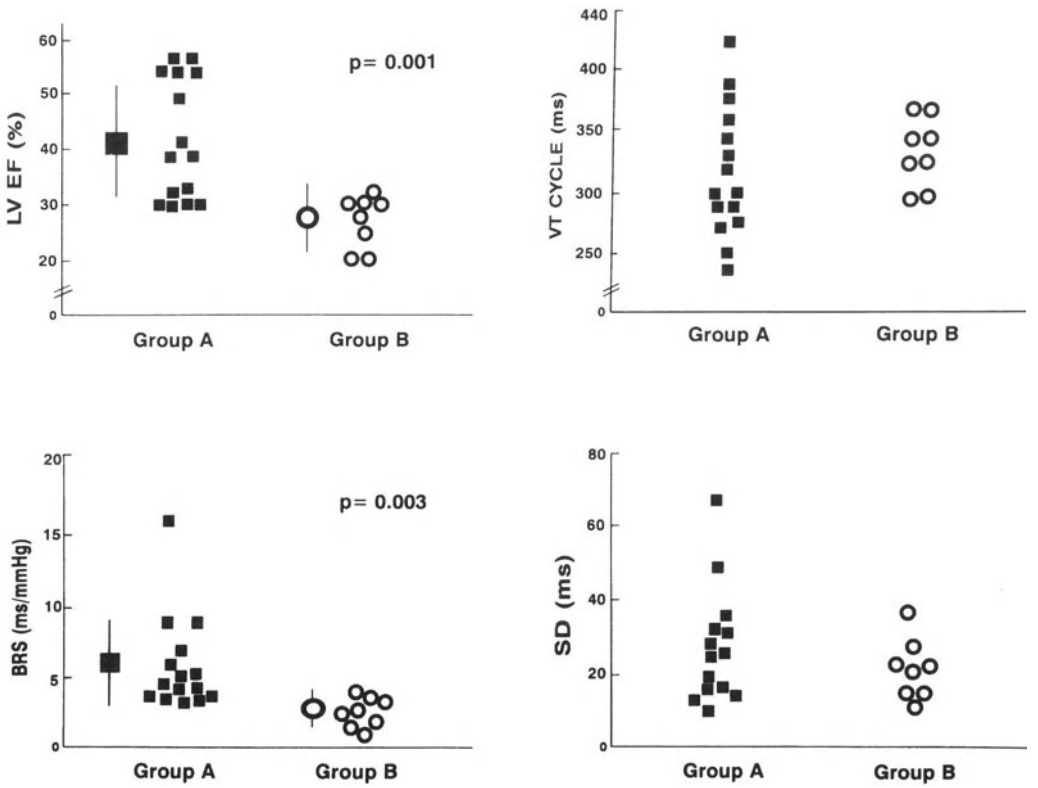

Figure 5. Plot of individual values for cycle length of ventricular tachycardia (VT cycle), left ventricular ejection fraction (LVEF), BRS and standard deviation of the RR interval (SD) of patients in group A and group B. Group B comprised patients with either cardiac death or unstable VT during follow-up; group A comprised patients with neither of these two end-points. Mean ± SD values are shown for significantly different variables. (Reproduced with permission from ref. 22.)

analysis of BRS may help in identifying patients at high risk of ventricular tachycardia/ventricular fibrillation long after myocardial infarction.

In patients with sustained VT and a previous myocardial infarction, low BRS values identify patients with a poor ability to tolerate VT haemodynamically and with a worse prognosis than that of patients with higher values. Thus, a better haemodynamic response during VT may be an additional mechanism underlying the relation between preserved BRS and a reduced incidence of cardiac death after myocardial infarction.

The evaluation of BRS in patients with a clinical episode of sustained VT may become useful both in the identification of patients at risk of major events and in the individualisation of treatment.

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Chapter 7

Does Assessment of Autonomic Tone Translate into New Therapeutic Approaches in Survivors of Myocardial Infarction?

Federico Lombardi

Introduction

Numerous observations indicate that evaluation of the autonomic nervous system by means of the analysis of heart rate variability and baroreflex sensitivity may facilitate the identification of patients at risk for increased cardiac mortality after myocardial infarction[1–4].

However, the mechanism by which a reduced heart rate variability or a reduced baroreflex sensitivity is associated with enhanced arrhythmic and total cardiac mortality is far from being defined[5]. This uncertainty prevents, on the one hand, greater utilisation of these non-invasive techniques in clinical practice; from the other hand a degree of scepticism regarding the future possibility of guiding patients' management according to results provided by the two methodologies.

In this chapter the physiological significance of both a reduced heart rate variability and baroreflex sensitivity as an expression of altered neural control of cardiovascular function will be revised in order to facilitate interpretation of a growing number of clinical studies.

Heart rate variability

The basic assumption is that the continuous beat-to-beat oscillations which characterise heart period also during resting controlled conditions are the result of a complex interaction between sympathetic and vagal efferent neural activities and sinus node responsiveness[6–9]. Thus, the identification and quantification of the most important oscillatory components can provide information on the neural mechanisms largely responsible for such a rhythmicity.

It is generally recognised[7–9] that, during short-term recordings obtained during resting controlled conditions, two major oscillatory components characterise heart rate variability in addition to a very low frequency component (VLF). A low frequency (LF ~0.10 Hz) component which corresponds to the low frequency oscillations of arterial blood pressure and which is considered to reflect, particularly when expressed in normalised units, sympathetic modulation of heart period and a high frequency (HF ~0.25 Hz) component which is a measure of the respiratory sinus arrhythmia and is largely mediated by vagal mechanisms. Thus, the

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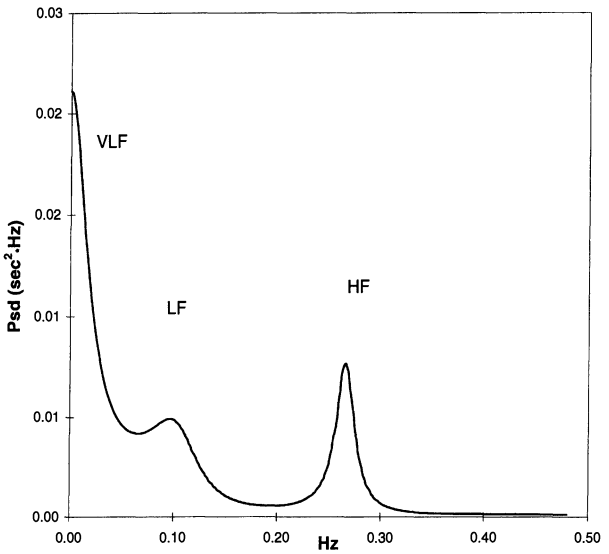

Figure 1. Spectral analysis of heart rate variability of a normal subject during resting conditions. The autospectrum was estimated from a time series of 250 RR intervals. In addition to a very low frequency component (VLF), a low (LF) and a high (HF) frequency components are clearly detectable. The order of the model for spectral decomposition was 10.

ratio between LF and HF has been proposed and utilised as an index of sympatho-vagal balance[7–9].

An increase in LF and in LF/HF ratio has been reported in most clinical conditions associated with a shift of sympatho-vagal balance towards a sympathetic activation and a reduced vagal tone, as in the acute and post-acute phase of an uncomplicated myocardial infarction[9–12], in congestive heart failure or in patients with mild to moderate essential hypertension[9]. On the contrary, values of LF/HF ratio smaller than 2 and a predominant HF component have been reported in conditions characterised by a vagal predominance[9].

More complex is the physiological interpretation of heart rate variability parameters derived from the analysis of 24-h recordings.

It is evident that beat-to-beat variations of heart period along the 24-h period are the results of several factors which cannot be clearly quantified. Amount of physical activity, respiratory pattern, environmental factors, and duration of sleep are only a few among the several factors which can influence heart period and its variability analysed over a 24-h period. Moreover it is an accepted opinion that the relation between neural effectors and sinus node responsiveness is linear, and that duration of the RR interval is positively correlated with magnitude of RR variability. Thus, sympathetic activation is reflected by a faster heart rate, which is generally associated with a reduction in heart rate variability, whereas a vagal predominance is reflected by sinus node bradycardia and by an increase in those time and frequency domain parameters such as standard deviation of normal RR intervals or total power which provide a measure of total heart rate variability.

According to this interpretation a reduced heart rate variability such as the one occurring in high-risk postmyocardial infarction patients[1–4], has been considered to reflect a shift of sympatho-vagal balance towards a sympathetic predominance and a reduced vagal tone: an autonomic disturbance leading to cardiac electrical instability and favouring the occurrence of malignant ventricular arryhthmias.

It was also reported[3] that a reduction in total as well as in fractional power of the four frequency bands in which a 24-h autospectrum is generally subdivided (ultra-low, very low, low and high frequency components) was also detectable in a subgroup of postmyocardial infarction patients with an increased cardiac mortality. Thus, a reduction in either a time domain parameter or in the power of spectral components of heart rate variability seems to provide similar prognostic information, leaving unsolved, however, our interpretation of the mechanisms responsible for such a negative predictive value.

Baroreflex sensitivity

The evaluation of baroreflex sensitivity is based on the quantification of the slope of the relationship between lengthening of heart period and increase in systolic arterial pressure induced by a vasoactive drug such phenylephrine[13].

As the increase in RR interval is largely mediated by a reflex activation of efferent vagal activity, and by a reflex inhibition of efferent sympathetic neural activity directed to the sinus node, this methodology has been proposed as a tool to quantify the individual capability of activating vagal reflexes. In an initial study[14] it was reported that increased cardiac mortality characterised patients with a marked depression of baroreflex sensitivity. Subsequently[15], it was also reported that postmyocardial infarction patients with a reduced baroreflex sensitivity presented an enhanced susceptibility to sustained monomorphic ventricular tachycardia during

electrophysiological testing. Thus, the link between cardiac electrical instability and alterations of neural control found additional support by these clinical findings.

Also in this case, a reduced baroreflex sensitivity was considered to reflect an alteration of autonomic control characterised by an enhancement of sympathetic mechanisms and by a reduction of vagal mechanisms. However, at variance with the analysis of heart rate variability which can and should be performed under resting controlled conditions to obtain appropriate information on autonomic modulation of sinus node, baroreflex sensitivity is based on a stimulus-response analysis which explores an aspect of autonomic control which is complementary to that addressed by heart rate variability. It is therefore not surprising that preliminary data from the ATRAMI study[4] have confirmed the negative prognostic values of both methodologies, and that their combined use may further facilitate the identification of patients at higher risk.

Heart rate variability and pharmacological interventions

Although several reports[1–4] indicate the possibility and clinical utility of evaluating autonomic tone after an acute myocardial infarction, the impossibility of utilising information derived by these methodologies to guide therapy in these patients is somewhat intriguing.

The case of β-blockers represents a typical example. There is no doubt that β-blocker administration in the acute and post-acute phase of myocardial infarction represents the only pharmacological intervention capable of reducing arrhythmic and total cardiac mortality[16]. These drugs have been proven to be effective in almost all patients after an acute myocardial infarction. The beneficial effect was also evident in patients with an inferior localisation, where a vagal predominance is often suspected, and in patients with a depressed ventricular function where β-blockers are likely to exert their maximal protective effect.

As indicated above, the analysis of heart rate variability and baroreflex sensitivity has been largely utilised in these patients, and has been demonstrated to be effective in identifying patients at higher risk[1–4,14,15]. However, some of the reported results[9] are difficult to explain, due to the limited effect of this pharmacological intervention on those parameters whose reduction is definitely associated with increased mortality after a myocardial infarction.

Signs of sympathetic activation, indicated by a predominant LF component and by a LF/HF ratio greater than 2, have been reported in most patients after an uncomplicated myocardial infarction, independent of its localisation. Similarly a depressed baroreflex sensitivity has not been associated with infarct localisation[14]. Both findings suggest that a common pattern of autonomic alteration can be recognised in most postmyocardial infarction patients with signs of a sympathetic predominance and of a reduced vagal tone.

Available data, mostly concerning heart rate variability, indicate that β-blocker administration has minimal effects on time and frequency domain parameters of heart rate variability. Drug-induced bradycardia is associated with an increase in RR variance, which is somehow limited by a lesser day–night difference in mean RR interval, i.e. one of the factors which most contributes to overall RR variability. Thus, the final result is significant but small, and in some cases not even observed[9].

As to the effects of β-blockers on spectral indices of sympathetic and vagal modulation of heart period, a reduction in LF and an increase in HF (only if expressed in normalised units) has been reported[9,12,17]. However, the most interesting result was the drug-induced attenuation of the early-morning increase in spectral indices of sympathetic modulation; a finding which is consistent with the well-known protective effects of β-blockers at this part of the day characterised by signs of sympathetic activation and by a greater cardiovascular morbidity and mortality.

In addition, the amount of drug-induced changes in time and frequency domain parameters of heart rate variability appears too small to identify subgroups of patients in whom β-blockers could be particularly effective, or to explain their protective action.

This problem is made even more complicated by the fact that in patients who from a clinical point of view appear at higher risk, and who almost always have a drastic reduction in heart rate variability, signs of sympathetic activation as reflected by a predominant LF and by a LF/HF ratio greater than 2, are often undetectable[12,18]. These patients are often characterised by a depressed ventricular function, by a larger infarct dimension and by a higher level of ventricular arrhythmias. In these subjects we expect β-blockers to exert their most protective action, yet the effect of the drug on heart rate variability is variable and minimal. A possible explanation of this unexpected finding is to consider

the drug-induced effects on heart rate variability as further evidence of the diminished responsiveness of sinus node to neural inputs as a manifestation of a more complex derangement of autonomic modulation of cardiac function in these high-risk patients.

It is unlikely that, in these patients, who often present clinical signs of sympathetic activation, β-blockers could not exert their antiadrenergic effect. A reduction in heart rate is frequently observed, but not associated with a consistent change in heart rate variability and, in particular, in the absolute and normalised power of spectral indices of sympathetic and vagal modulation of heart period. Thus, in these patients the heart rate variability pattern appears more as a manifestation of what can be defined as the result of the complex interaction of the mechanical and electrophysiological events associated with an acute myocardial infarction than a parameter on which we have to target our pharmacological and non-pharmacological interventions.

The limited effects on heart rate variability of other pharmacological interventions proven to be effective in post-myocardial infarction patients, such as ACE inhibitors, are well in agreement with this interpretation.

In conclusion, it seems impossible at the moment to target our therapy and to evaluate its efficacy in relation to the observed values of the different parameters of heart rate variability. Nevertheless, time and frequency domain analysis of heart rate variability and the assessment of baroreflex sensitivity stand as the two non-invasive techniques capable of providing relevant clinical information for an early stratification of those patients who, after myocardial infarction, are at increased risk for arrhythmic and cardiac death.

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Chapter 8

Mechanisms of Ventricular Arrhythmias in Ischaemic Heart Disease

Nabil El-Sherif

Introduction

Ventricular tachycardia and ventricular fibrillation are serious complications of myocardial infarction and ischaemic heart disease. Different electrophysiological mechanisms may give rise to ventricular arrhythmias in myocardial ischaemia and infarction. A better understanding of these mechanisms will provide a basis for improved management. More precise information is difficult to obtain from clinical electrophysiological studies because of the limitations of the experimental protocols and techniques that can be utilised. This information could be obtained, however, from successful extrapolations from experimental studies on appropriate animal models to humans. In this chapter the electrophysiological mechanisms of ventricular arrhythmias in myocardial ischaemia and infarction are reviewed.

Following coronary artery occlusion, the area that was originally perfused becomes ischaemic. Due to diffusion and collateral circulation, irreversible cell damage spreads from the central zone into the border zone. Most infarctions will have one or more areas of necrosis surrounded by ischaemic border zones. Purkinje and ventricular muscle fibres in the ischaemic zone develop abnormal electrophysiological properties and generate ventricular arrhythmias at various stages following infarction[1]. Since the classic experiments on the dog heart by Harris, it is known that ventricular arrhythmias after coronary artery occlusion occur in two distinct phases. The first phase corresponds to the acute phase of ischaemia and lasts until 15–30 min after coronary occlusion; the second starts 4–8 h after occlusion and lasts 24–48 h. The early phase of ventricular arrhythmias is more serious, can degenerate into rapid ventricular tachycardia and ventricular fibrillation, and has been attributed to reentrant excitation in ischaemic myocardium. The second phase, which is more benign, consists of spontaneous multiform ventricular rhythms having about the same rate as the sinus rhythm, and represents ectopic discharge from electrophysiologically abnormal Purkinje fibres. It is not known whether such a distinct bimodal distribution of arrhythmias occurs in other animals, including humans. Furthermore, El-Sherif and associates have shown that during the second phase of spontaneous ventricular rhythms, as well as following the subsidence of this phase, fast ventricular tachyarrhythmias and ventricular fibrillation could be induced by programmed electrical stimulation of the heart[2]. These tachyarrhythmias, similar to those in the first phase, were attributed to reentrant excitation in ischaemic myocardial border zones[3].

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Ventricular arrhythmias in the early phase of myocardial ischaemia

Within minutes of coronary artery occlusion the cells in the centre of the ischaemic zone show progressive decrease in resting membrane potential, action potential amplitude, duration, and upstroke velocity[4]. In the first 1–3 min of ischaemia the refractory period changes concomitantly with the changes in action potential duration. After a brief initial shortening, the refractory period begins to lengthen, even though action potential duration continues to shorten. El-Sherif and colleagues used the term "post-repolarisation refractoriness" to indicate that at certain stages of ischaemia the membrane may remain inexcitable even when it has been completely repolarised[5]. The marked dependence of recovery of excitability on the resting potential in partially depolarised ischaemic myocardial cells is probably the most important determinant for the occurrence of slow conduction and conduction block in the acute phase of ischaemia[6].

Cellular K^+ loss and extracellular K^+ accumulation has been considered to be a major determinant of the electrophysiological changes that underlie the early phase of malignant ventricular arrhythmias following acute myocardial ischaemia. However, the depolarisation and depressed action potential characteristics of ischaemic cardiac cells cannot be attributed solely to changes in K^+. Other components of ischaemia, particularly amphipathic lipid metabolites, free radicals, and locally accumulating catecholamines, may play a significant role in ischaemic injury, and electrophysiological alterations associated with ischaemia[1].

Isochronal mapping of ventricular activation has allowed the demonstration of circus movements around areas of conduction block having a diameter of 1–2 cm on the epicardial surface of the ischaemic zone during ventricular tachycardia occurring between 2 and 10 min after coronary occlusion[7]. The localisation, revolution time, and size of the circus movements changed from beat to beat. Ventricular tachycardia, which could terminate spontaneously or degenerate into ventricular fibrillation, was characterised by the presence of basically one fairly large circus movement. During ventricular fibrillation, reentrant circuits were multiple, were seldom completed, and had small diameters, on the order of 0.5 cm.

Other studies that have utilised tridimensional mapping techniques with improved spatial resolution have shown that, during early ischaemia in the cat heart, ventricular tachycardia could be initiated, maintained, or terminated by either reentrant or non-reentrant mechanisms[8]. Micro-reentry or reflection involving a small myocardial region could not be ruled out, and the nature of the non-reentrant ectopic activity was not determined. However, Janse and associates have proposed that injury currents flowing between ischaemic and non-ischaemic myocardium could initiate premature beats, either by directly stimulating the non-ischaemic myocardium at the end of the refractory period or by enhancing the amplitude of delayed afterdepolarisations[7].

Sudden release of coronary artery occlusion is known to be a potent arrhythmogenic stimulus, often leading to ventricular fibrillation. The incidence and severity of reperfusion arrhythmias seem to correlate with the duration of occlusion before release and the amount of myocardium at risk. Other variables, such as heart rate and reperfusion blood flow, also influence outcome. The electrophysiological mechanisms underlying reperfusion arrhythmias have not been fully elucidated.

Triggered ventricular rhythms in the subacute phase of myocardial infarction

Approximately 4–8 h following coronary artery occlusion, spontaneous ventricular rhythms develop. The spontaneous multiform activity peaks 1–2 days post-infarction and usually subsides by the third day. These rhythms arise from surviving subendocardial Purkinje fibres overlying the infarction. *In-vitro* studies of these surviving subendocardial Purkinje fibres have suggested that two mechanisms may be responsible for the activity: (1) abnormal automaticity[9] and (2) triggered activity[10]. However, the preponderance of evidence favours the second mechanism.

Delayed afterdepolarisations (DAD) giving rise to triggered activity were recorded in depolarised ischaemic Purkinje fibres from a 1-day-old canine infarction[10]. The amplitude and rate of rise of the DAD were a function of both the cycle length and the number of impulses in a stimulated train. A critically timed premature impulse may be followed by a DAD that triggers activity. However, in contrast to other preparations demonstrating triggered activity, one stimulated action potential during quiescence was often able to generate a suprathreshold DAD, which in turn initiated triggered activity (Fig. 1). The ease of inducing triggered activity in ischaemic Purkinje fibres may explain the persistence

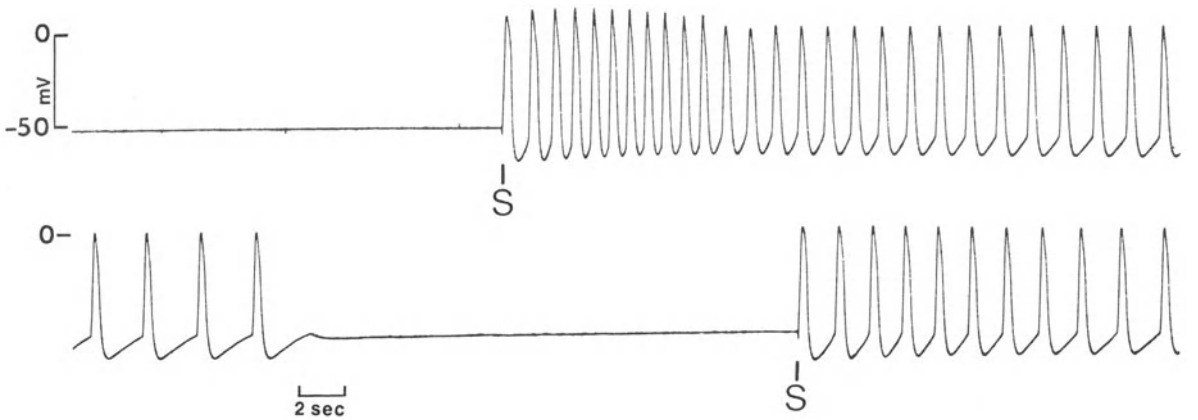

Figure 1. Initiation of triggered activity by a single stimulated action potential. Transmembrane recordings are from a Purkinje cell in the ischaemic zone of an endocardial preparation from 1-day-old canine infarction. The depolarised cell (resting membrane potential, –53 mV) was quiescent. A single stimulated action potential initiated a run of triggered activity. In the bottom tracing the activity slowed gradually and terminated following a subthreshold afterdepolarisation. Following another quiescent period, triggered activity was again initiated by a single stimulated action potential. (Reprinted by permission of W.B. Saunders, from ref. 1.)

of multiform ventricular rhythms *in vivo* in 1-day-old canine infarctions.

Two mechanisms have been proposed to explain the transient inward current giving rise to DAD in ischaemic Purkinje fibres[11]. The first mechanism is a non-specific cation channel, activated by a phasic rise in intracellular Ca^{2+}, which had significant permeability to Na^+, K^+ and Ca^{2+}. The inward current is thought to be carried predominantly by Na^+ with some Ca^{2+} contribution. The second proposed mechanism for transient inward current is the electrogenic Na^+-Ca^{2+} exchange pump driven by the transmembrane electrochemical gradient for Na^+ and Ca^{2+}. The stoichiometry for charge translocation is 3 Na^+ to 1 Ca^{2+}. Ca^{2+} overload produces a phasic release of Ca^{2+} from the sarcoplasmic reticulum into the myoplasm. This produces a transient decrease in the transmembrane Ca^{2+} gradient, which in turn facilitates Ca^{2+} extrusion and Na^+ entry by the exchanger. The electrogenicity of the exchange produces a transient inward current.

Reentrant ventricular rhythms in the subacute phase of myocardial infarction

In 1977 El-Sherif and associates made the observation that, in dogs that survived the initial stage of myocardial infarction arrhythmias, and that were studied 3–5 days post-infarction, reentrant ventricular rhythms occurred spontaneously, but were more commonly induced by programmed electrical stimulation[2]. The anatomical and electrophysiological substrates for the reentrant rhythms were later characterised in a series of reports[3,12]. These studies have shown that reentrant excitation occurred around zones (arcs) of functional conduction block. The arcs were attributed to ischaemia-induced spatially non-homogeneous lengthening of refractoriness. Sustained reentrant tachycardia was found to have a figure-eight activation pattern whereby clockwise and counterclockwise wavefronts were oriented around two separate arcs of functional conduction block. The two circulating wavefronts coalesced into a common wavefront that conducted slowly between the two arcs of block (Fig. 2). Using reversible cooling, reentrant excitation could be successfully terminated only from localised areas along the common reentrant wavefront[13].

Intracellular recordings from the surviving "ischaemic" epicardial layer show cells with variable degrees of partial depolarisation, reduced action potential amplitude, and decreased upstroke velocity. Full recovery of responsiveness frequently outlasts the action potential duration, reflecting the presence of post-repolarisation refractoriness[14]. In these cells, premature stimuli could elicit graded responses over a wide range of coupling intervals. Isochronal mapping studies have shown that both the arcs of functional conduction block

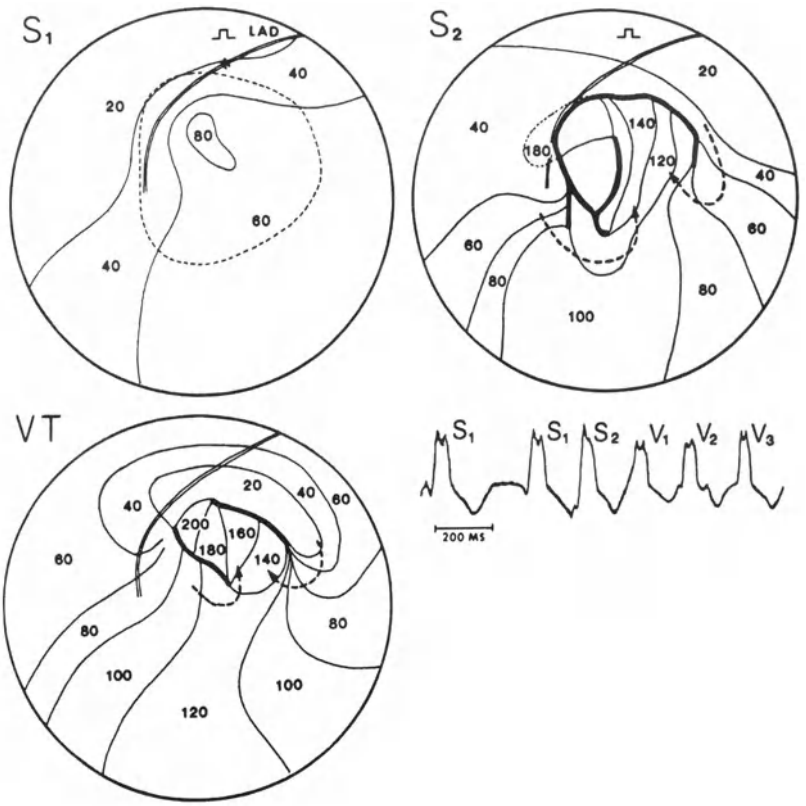

Figure 2. Epicardial isochronal activation maps during a basic ventricular stimulated beat (S_1) initiation of reentry by a single premature stimulus (S_2), and sustained monomorphic reentrant ventricular tachycardia (VT). A representative electrocardiogram is shown in the lower right panel. The recordings were obtained from a dog 4 days post-ligation of the left anterior descending artery (LAD). Site of ligation is represented by a double bar. Epicardial activation is displayed as if the heart is viewed from the apex located at the centre of the circular map. The perimeter of the circle represents the AV junction. The outline of the epicardial ischaemic zone is represented by the dotted line. Activation isochrones are drawn at 20-ms intervals. Arcs of functional conduction block are represented by heavy solid lines and are depicted to separate contiguous areas that are activated at least 40 ms apart.

During S_1 the epicardial surface was activated within 80 ms with the latest isochrone located in the centre of the ischaemic zone. S_2 resulted in a long continuous arc of conduction block within the border of the ischaemic zone. The activation wavefront circulated around both ends of the arc of block and coalesced at the 100-ms isochrone. The common wavefront advanced within the arc of block before reactivating an area on the other side of the arc at the 180-ms isochrone to initiate the first reentrant cycle. During sustained VT the reentrant circuit had a figure-eight activation pattern in the form of a clockwise and counter clockwise wavefronts arounds two arcs of functional conduction block before coalescing into a slow common wavefront that conducted between the two arcs of block. (Printed with permission of W.B. Saunders from ref. 1.)

and the slow activation wavefronts of the reentrant circuit develop in the surviving electrophysiologically abnormal epicardial layer overlying the infarction.

The ionic changes induced by ischaemia that explain abnormal transmembrane action potentials of myocardial cells in the subacute phase of myocardial infarction have not been fully explored. Some studies suggest that ischaemic transmembrane action potentials may be generated by a depressed fast Na^+ channel. This was based on experiments that showed that ischaemic cells are sensitive to the depressant effect of the fast channel blocker tetrodotoxin (TTX), but not to the slow channel blocker methoxyverapamil (D600)[14]. The fast channel may be depressed in ischaemia for various reasons. This can be only be partly explained by cellular depolarisation, because the depression is usually out of

proportion to the degree of depolarisation of the resting potential. The Na^+-K^+ pump may be depressed in surviving ischaemic myocardial cells, leading to intracellular Na^+ loading. This can diminish the electrochemical driving force for the inward Na^+ current.

Abnormal membrane properties of ischaemic myocardial cells may not be the only cause for slowed conduction and block in the surviving ischaemic epicardial layer. Electrical uncoupling and increase of extracellular resistance after ischaemia have also been suggested[15]. Ischaemia-induced increase in intracellular Ca^{2+} and low pH may increase the resistance of the gap junctions of the intercalated disc. Changes in gap-junctional distribution in the border zone of healing canine infarcts may define the locations of reentrant ventricular tachycardia in the surviving epicardial layer[16].

Another factor that was considered by some authors is the anisotropic structure of the surviving epicardial layer. The normal uniform anisotropic conduction properties of the epicardial layer may be altered further following ischaemia. It was suggested that the site of conduction block of premature stimuli in the ischaemic epicardial layer may be determined by its anisotropic properties (i.e. premature stimuli block along the long axis of epicardial muscle fibres)[17]. We have shown that functional conduction block of premature stimuli in the ischaemic epicardial layer is due to abrupt and discrete change in refractoriness. The spatially non-uniform refractory distribution occurs both along and across fibre direction, the same as the arcs of conduction block[18].

We have also shown that, during sustained figure-eight monomorphic reentrant tachycardia, the two arcs of functional conduction block around which the reentrant wavefronts circulate are usually oriented parallel to the long axis of the epicardial muscle fibres. Other investigators have suggested that these areas represent apparent or pseudo-block, and are in fact due to very slow and possibly discontinuous conduction across the myocardial fibres. Restivo et al have analysed close bipolar electrograms obtained at high resolution (1-mm interelectrode distance) from sites of the arcs of block during sustained stable reentry. Electrograms recorded at each side of the line of block showed two distinct deflections; one represented local activation, and the second an electrotonus corresponding to activation recorded a 1-mm distance away. Both deflections were separated by a variable isoelectric period that correlated with the isochronal difference across the arc. In recordings obtained from the centre of the arc, local activation and electrotonus were separated by 90–110 ms. This interval successively decreased towards both ends of the arc (Fig. 3). These observations provide evidence that circus movement reentry is sustained around a continuous arc of abrupt functional conduction block and not very slow conduction across fibres.

Cellular, ionic and molecular basis of arrhythmias in post-infarction remodelled ventricular myocardium

In recent years the importance of ventricular remodelling following myocardial infarction (MI) on long-term survival has been better appreciated. The structural remodelling of the left ventricle post-MI involves both the region of necrosis and the non-infarcted myocardium. The non-infarcted myocardium undergoes significant hypertrophy, which is considered an adaptive universal response of the heart to increased workload from whatever cause. Clinical and experimental data strongly suggest that the risk of ventricular arrhythmias correlates with the degree and characteristics of post-MI remodelling[19]. Although post-MI remodelling is a complex time-dependent process that involves structural, biochemical, neurohumoral, and electrophysiological alterations, there is considerable evidence that electrophysiological changes associated with the hypertrophied non-infarcted myocardium play a key role in the arrhythmogenicity of the post-MI heart. For example, although β-blockers and angiotensin-converting enzyme (ACE) inhibitors have very different effects on ventricular dilatation, both agents have been shown to prevent the development of myocardial hypertrophy, and may thus decrease the susceptibility to ventricular arrhythmias[19]. On the other hand, there is a considerable amount of data from other models of hypertrophy showing that hypertrophied myocardium can generate arrhythmias more readily than can normal tissue[20].

The most consistent electrical abnormality which has been described in association with myocardial hypertrophy is prolongation of action potential duration (APD). We have recently shown that remodelled hypertrophied left ventricular myocytes from rats 3–4 weeks post-MI have prolonged APD with marked heterogeneity of the time-course of repolarisation across the left ventricular wall. The prolongation of APD could be

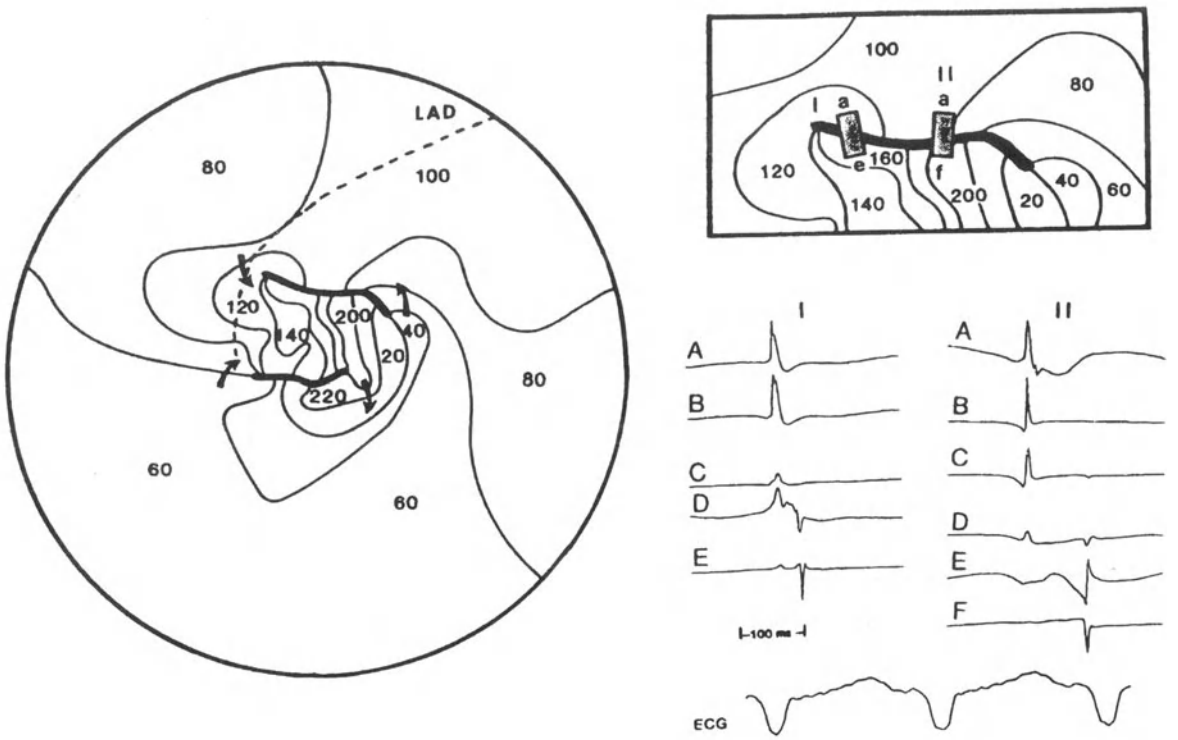

Figure 3. High-resolution recordings of activation across one of the two ars of functional conduction block around which sustained figure-eight reentrant activation occurred. The left panel illustrates the epicardial activation pattern during a figure-eight reentrant tachycardia as obtained from a sock electrode array with 5–10-mm interelectrode distance. A high-density electrode plaque (1-mm interelectrode distance) was positioned at two locations across the upper arc of block. Shown on the right are an expanded map of the counterclockwise circuit around the upper arc of block and the electrograms along one row of bipolar electrodes at each location.

Plaque location II was situated near the centre of the arc of block. Conduction between sites A and C during the left to right wavefront on the upper side of the arc was fast. Conduction block probably occurred between sites C and D. Similarly, conduction between sites F and E during the returning wavefront on the distal side of the arc was fast, and conduction block probably occurred between sites E and D. The two deflections recorded at site D were separated by an isoelectric interval of 85 ms, which corresponded to isochronal activation difference across the site of 81–100 ms. Both deflections most probably represented electrotonic potentials. (Modifed from ref. 18.)

explained by the decreased density of the two outward K^+ currents $I_{to\text{-}fast}$ and $I_{to\text{-}show}$ rather than by changes in the density or kinetics of $I_{Ca\text{-}L}$.

Although there are some similarities with other models of hypertrophy, it has been suggested that myocardial hypertrophy post-MI, which compensates for a lack of substance, may involve different sets of signal transduction pathways as compared to hypertrophy secondary to mechanical overload[13]. Some of our recent data seem to support this view. For example, we have shown that the T-type Ca current, present in neonatal rat, but not in adult ventricular myocytes, is reexpressed in post-MI remodelled myocytes[21]. Similarly, the fetal isoforms of the α_1 subunit of the L-type Ca current are reexpressed in post-MI myocardium[22]. None of these changes were described in other models of hypertrophied rat myocyte.

Cardiac hypertrophy is associated with both quantitative and qualitative changes in gene expression, the latter usually represents a shift towards reexpression of fetal isogenes. Although alterations in expression of contractile and other intracellular proteins has been well characterised in a variety of experimental models of hypertrophy, little is known regarding changes in gene expression in post-MI remodelled myocardium. This is especially so regarding sarcolemmal ion channel

proteins that may explain the electrophysiological alterations in these hearts. We have examined the changes in mRNA levels of the α_1 subunit of the L-type Ca channel and the five K channels shown to be expressed in adult rat ventricular myocytes, in remodelled myocardium from rats 3 weeks post-MI, and compared the results with sham-operated rats. There was no statistical difference in the expression of mRNA of the α_1 subunit of L-type Ca channel between sham and 3 weeks post-MI ventricular tissues[22]. These results are consistent with our electrophysiological studies that showed no change in the density of $I_{Ca\text{-}L}$ in ventricular myocytes obtained from sham and 3 weeks post-MI rat hearts[23].

We have also compared the mRNA expression of Kv1.2, Kv1.4, Kv1.5, Kv2.1, and Kv4.2 in ventricular tissue from sham-operated rats and from rats 3 weeks post-MI. There was a statistically insignificant increase in the expression of Kv1.2 mRNA and an insignificant decrease in the expression of Kv1.5 mRNA in post-MI hearts. On the other hand, the expression and protein levels of the Kv2.1 and Kv4.2 were significantly reduced (Fig. 4)[24]. These data illustrate the occurrence of transcription regulation of voltage-gated K channels that is distinct for each channel. Recent studies suggest that the Kv4.2 is the likely candidate for the native $I_{to\text{-}fast}$ while Kv2.1 is the likely candidate for the $I_{to\text{-}slow}$ (also called I_K)[25]. Our data showing significant decrease in the expression and protein levels of the Kv4.2 and Kv2.1 in 3 weeks post-MI remodelled ventricular myocardium correlate remarkably well with our electrophysiological observations showing significant reduction of both $I_{to\text{-}fast}$ and $I_{to\text{-}slow}$ in myocytes abstained from rats 3 weeks post-MI.

Three potential electrophysiological mechanisms for tachyarrhythmia generation in the post-MI remodelled ventricular myocardium have been demonstrated[23]. The increased heterogeneity of APD in the remodelled hypertrophied left ventricle can result in dispersion of refractoriness, a critical substrate for the development of circus movement reentrant tachyarrhythmias. Hypertrophy-induced increase in interstitial tissue with possible impairment of cellular coupling, as well as quantitative and/or qualitative changes in gap junction proteins, can also contribute to the occurrence of reentry. Another potential mechanism for ventricular tachyarrhythmias in the hypertrophied myocardium is triggered activity from EAD (Fig. 5). Prolongation of APD is considered the priming step for the development of EAD. The *in-vivo* representation of EAD-induced triggered activity is a prolonged QT interval associated with polymorphic VT. Triggered activity from DAD is yet another potential mechanism of arrhythmias in the post-MI heart. DAD could be induced in hypertrophied post-MI myocardium in the presence of β-adrenergic agonists[23].

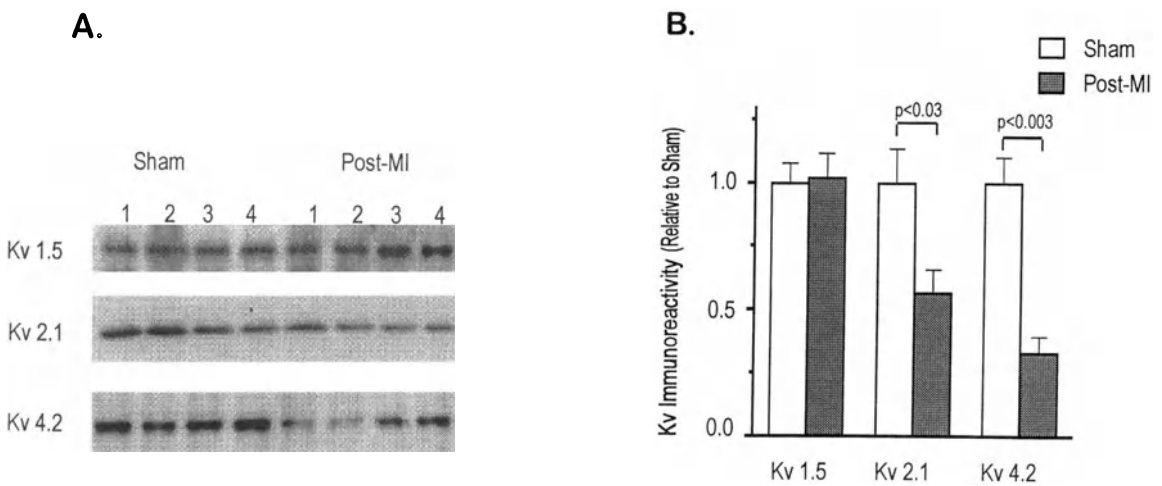

Figure 4. Action potential (AP) of an isolated post-infarction hypertrophied myocyte (MI) superimposed on AP of an isolated sham myocyte (S) cell to illustrate the changes in action potential duration (APD) in MI cells. Note that APD25, APD50, APD75 and APD90 of the MI cell were all prolonged compared to the S cell. Section B shows the development of multiple early afterdepolarisation (EAD) in an isolated MI myocyte. The EAD were more easily induced at 0.2 Hz stimulation than at 1 Hz. (Modified from ref. 21, with permission.)

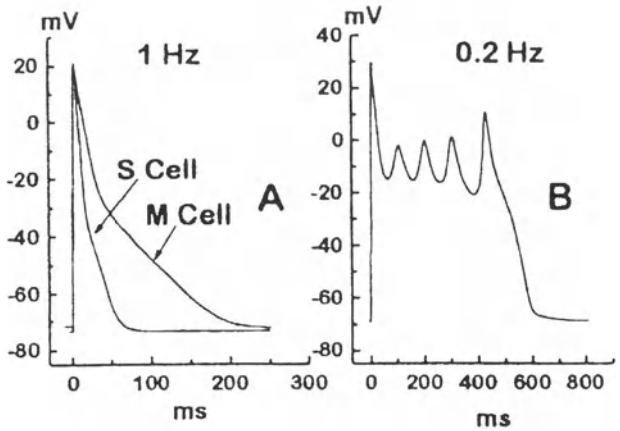

Figure 5. Western blot analysis of Kv channel subunit immunoreactive proteins (Kv1.5, Kv2.1, and Kv4.2) in left ventricular (LV) myocardium from post-MI (n = 4) and sham-operated (n = 4) animals. Note that different proteins were investigated in different blots. **B**: Bar graph showing Kv immunoreactivity by measuring the signal for the protein (Kv1.5, Kv2.1, and Kv4.2) by densitometry. Columns represent the immunoreactivities relative to the mean of the sham group, with error bars indicating SEM (n = 4). Immunoreactivity of Kv2.1 and Kv4.2 proteins was significantly decreased in the LV myocardium of post-M1 animals compared with sham-operated animals ($p < 0.03$ and $p < 0.003$, respectively). There was no significant change in the Kv1.5 immunoreactive protein level between the two experimental groups. (Reprinted with permission of the American Heart Association from ref. 24.)

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Chapter 9

Basic Mechanisms of Vulnerability to Ventricular Fibrillation

Michiel J. Janse

Introduction

It has been known since 1850 that the normal heart can be made to fibrillate when exposed to strong electrical shocks[1], and since 1899 that such fibrillating hearts can return to beating normally after similar shocks[2]. These experimental findings became of importance when in the early decades of this century electrical devices were increasingly installed in households, and more and more people were accidentally electrocuted. Electricity companies gave grants to academic centres to study the effects of electrical currents on the heart[3], and one of these was the laboratory of Dr Carl Wiggers at Western Reserve University in Cleveland.

Wiggers and Wégria[4] demonstrated in 1940 that normal hearts have a vulnerable period in late systole during which single induction shocks or condensor discharge induce ventricular fibrillation. The vulnerable period is that part of the cardiac cycle "during which some fibers are in and others have passed out of a refractory state"[5]. The duration of the vulnerable period in the dog heart[5] is in the order of 10–20 ms. Thus, the normal heart is vulnerable during a small part of the cardiac cycle, albeit only to strong electrical shocks, and this vulnerability seems to be related to inhomogeneities in excitability. It can therefore be expected that an increase in such inhomogeneity would increase the vulnerability. Han and Moe in 1964 were the first to test the hypothesis that "any agency which increases the temporal dispersion or asynchrony of excitability recovery should increase the likelihood of fibrillation"[6]. They concluded that "those agencies known to favour the development of ventricular fibrillation were found to increase the temporal dispersion of recovery of excitability, whether the average refractory period was reduced (sympathetic nerve stimulation, ouabain intoxication, ischaemia) or increased (chloroform, quinidine in high dosage, or hypothermia). The results emphasize the importance of nonuniformity of excitability and conduction velocity during the relative refractory period in the induction of turbulent impulse propagation"[6].

Although this paper can be criticised on some details (e.g. how reliably can one measure the refractory period at 12 ventricular sites during short-lasting interventions such as stellate ganglion stimulation or during ischaemia where electrophysiological parameters change quickly?), the basic concept still holds. In the following I will concentrate on the electrophysiological changes that occur during acute ischaemia, and how they increase vulnerability to fibrillation.

Ventricular fibrillation during acute ischaemia

There may be more than one mechanism causing ventricular fibrillation, such as a single, or two, wandering

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spiral waves or a rapidly firing focus, but most experimental studies support the concept that multiple wavelet reentry underlies both atrial and ventricular fibrillation[7–10]. Unidirectional block is a prerequisite for the induction of reentry, and to maintain fibrillation, a minimum number of independent reentrant wavefronts must be present. The wavelength for a reentrant circuit is given by the product of conduction velocity and refractory period, and a short wavelength favours the presence of multiple wavelets in a given tissue mass necessary to maintain fibrillation, Two conditions must therefore be met to allow fibrillation to develop: (1) there must be a certain spatial and temporal dispersion for unidirectional block to occur; and (2) wavelength must be short, either due to a low conduction velocity, a short refractory period or both.

Inhomogeneity in recovery of excitability

Figure 1 shows in a schematic fashion the effect of varying K^+ concentrations in a severely hypoxic and acidotic milieu on action potential configuration and recovery of excitability[11]. At a K^+ concentration of 5 mmol/L, hypoxia caused a marked shortening of the action potential, but the recovery of excitability, measured as the return of maximal upstroke velocity of premature action potentials induced by electrical stimulation at varying intervals following complete repolarisation to control values, is similar to that during control conditions. When extracellular K^+ is increased, marked postrepolarisation refractoriness occurs. It can intuitively be appreciated that a premature beat occurring at a certain coupling interval may be conducted at normal velocity in ischaemic cells with a K^+ of 5 mmol/L, slowly in zones with a K^+ of 10 mmol/L, and will be blocked in areas where K^+ has risen to 12 mmol/L. Studies using K^+ sensitive electrodes have shown distinct spatial inhomogeneity in extracellular K^+ in hearts with regional ischaemia[12,13]. In a zone of 1 cm extending from the border between normal and ischaemic myocardium towards the central ischaemic zone, differences in extracellular K^+ at different recording sites in the order of 8 mmol/L were found[12]. In fact, it was found that when extracellular K^+ concentration in this lateral border zone was between 8 and 13.5 mmol/L, ventricular fibrillation could easily be induced by premature stimulation of the non-ischaemic part of the ventricle[14]. This critial range had to be present in a zone that comprised between 20% and 35% of the total ischaemic zone. This situation is present between 3 and 8 min following occlusion of the left anterior descending coronary artery in the pig heart, and it is precisely during this period that ventricular fibrillation could easily be induced, and often occurred spontaneously. When extracellular K^+ became higher than 13.5 mmol/L the tissue became inexcitable, and reentrant circuits could no longer be induced. Thus, cells within this zone have different degrees of postrepolarisation refractoriness. The fact that action potential characteristics are cycle length dependent has several important consequences: (1) during regular rhythms that are relatively fast, full recovery time may exceed the basic cycle length; this results in alternation, Wenckebach type of block, 2:1 block, or even higher degrees of block; and (2) The degree of postrepolarisation refractoriness is very sensitive to small changes of resting membrane potentials caused by relatively small changes in extracellular K^+ (Fig. 1). Thus, a mere increase in sinus rate or a single premature beat may unmask the inhomogeneity in recovery of excitability and produce conduction block and reentry at sites which are conducting homogeneously at longer cycle lengths. An example is shown in Fig. 2. It is of interest that the only drugs that have been shown to reduce the incidence of sudden death are β-adrenergic blocking agents, particularly those that reduce heart rate[15].

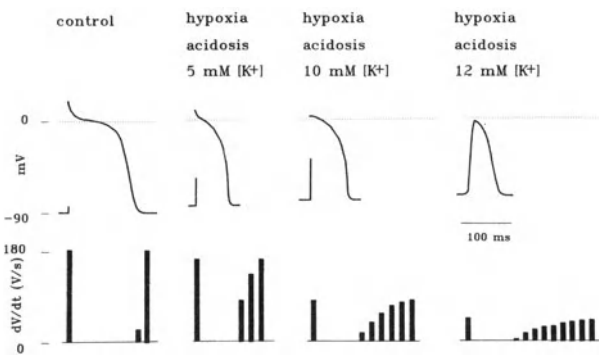

Figure 1. Schematic illustration of the changes in transmembrane potentials (top trace) and the recovery of the maximal upstroke velocity, dV/dt_{max} (bottom trace), following an action potential in normal ventricular myocardium (control) and in three different conditions of simulated ischaemia in which the extracellular K^+ is increased.

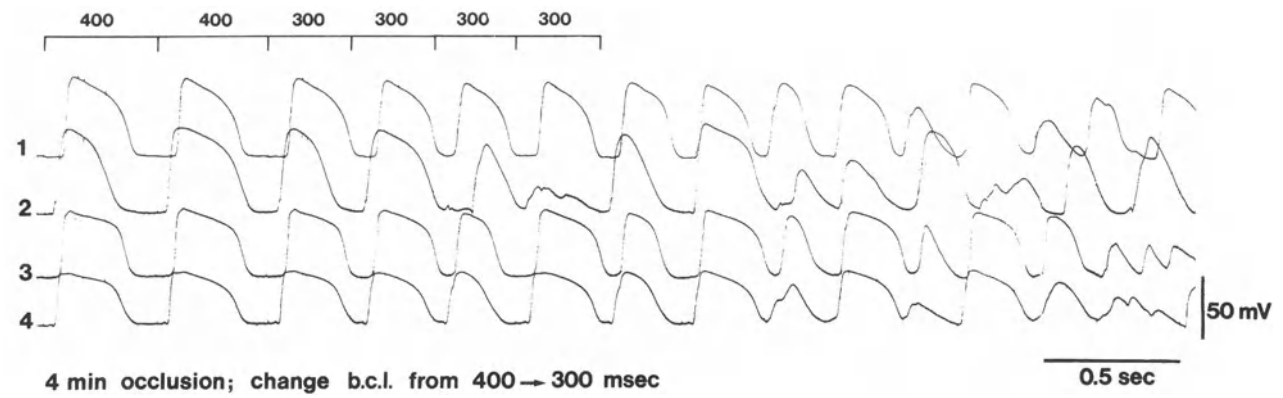

Figure 2. Increase in heart rate unmasks inhomogeneity in recovery of excitability and induces fibrillation. Four action potentials were recorded simultaneously from acute ischaemic myocardium. The atria were paced at a cycle length of 400 ms. At this driving rate, the four cells are activated rather synchronously. The synchronicity is lost when the pacing cycle is reduced to 300 ms. Cell 2 becomes activated with delay (beat 5) and shows conduction block (beat 6) because of a greater degree of postrepolarisation refractoriness than the other cells. This sets the stage for unidirectional block and reentry.

Changes in conduction velocity

During the first 2 min after onset of ischaemia, conduction velocity remains fairly constant, to decrease rapidly thereafter. For conduction velocity along the longitudinal axis of myocardial fibres the following values have been measured: control situation to 2 min after coronary artery occlusion: 50 cm/s; after 3 min of ischaemia: 40 cm/s; and after 4–5 min: 30 cm/s. After 5 min of ischaemia conduction velocity could no longer accurately be determined because of the development of regional conduction clock, shortly followed by inexcitabilty[16]. The major reason for the early decrease in conduction velocity is the decrease in action potential amplitude and upstroke velocity. Passive electrical properties, particularly changes in extracellular and intracellular longitudinal resistance, have been measured in isolated, arterially perfused papillary muscle placed in a H_2O-saturated gaseous environment[17]. In such a preparation, arrest of coronary flow, in addition to changing the gaseous environment to 94% N_2 and 6% CO_2, resulted in an immediate increase in extracellular resistance (related to loss of intravascular volume) followed by a secondary slower increase, most likely caused by osmotic cell swelling. Intracellular resistance remained constant during the first 10–15 min. Thereafter, ischaemic cells rapidly uncoupled and intracellular longitudinal resistance increased by 400% within 5 min. Thus, during the first 10 min of ischaemia, electrical uncoupling is unlikely to play any role in the slowing of conduction. However, in a later period, 15–20 min after coronary occlusion, electrical uncoupling may cause slow and inhomogeneous conduction, and thus may be an arrhythmogenic factor for arrhythmias occurring at that time.

Activation patterns

During the first 30 min of ischaemia, spontaneous ventricular fibrillation occurs in two distinct phases[18]. The first phase (phase 1a) occurs between 3 and 8 min, and is due to the changes in excitability and conduction velocity described above. The second phase (phase 1b) is associated with the period during which electrical uncoupling occurs[19].

Figure 3 shows the activation pattern of part of the left ventricle during the last sinus beat, a spontaneous premature ventricular beat and the first "beat" of ventricular fibrillation induced by the premature impulse, 3 min after occlusion of the left anterior descending coronary artery in a porcine heart. Within the octagonal surface 60 electrodes simultaneously registered the extracellular electrograms. The premature impulse originates at the border between ischaemic and normal myocardium, 280 ms after the P wave of the last sinus beat (B). It is blocked in part of the ischaemic zone (the T symbol indicates conduction block) and slowly conducted via two semicircular wavefronts

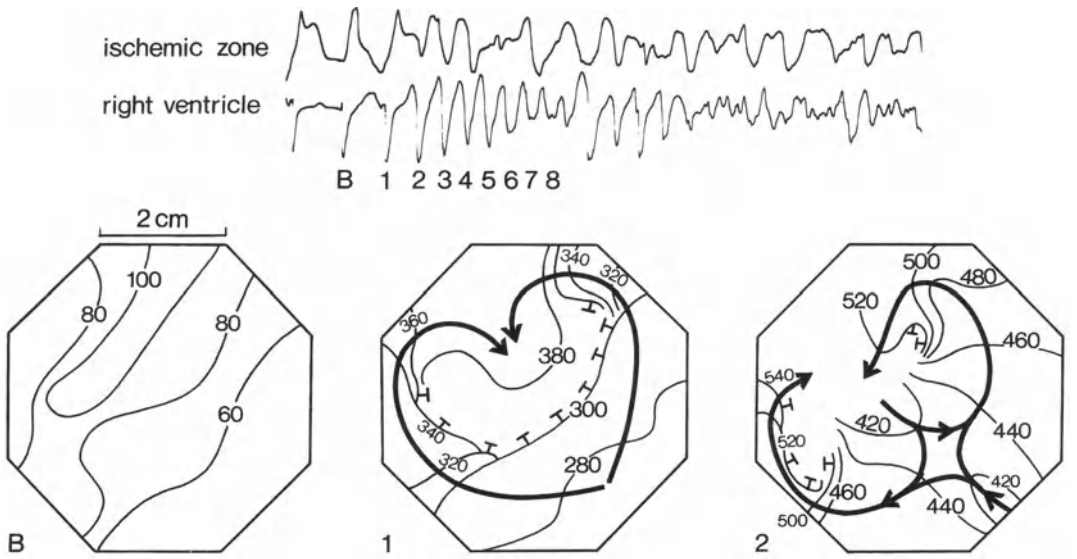

Figure 3. Electrograms from ischaemic myocardium and normal right ventricle during the spontaneous occurrence of ventricular fibrillation, 3 min after occlusion of the left anterior descending coronary artery in an isolated pig heart. In the lower panel, activation patterns of the last sinus beat (B) and the first two ectopic beats are shown. These isochronal maps were based on simultaneous recordings of 60 electrograms from the anterior surface of the left ventricle within the octogonal surface shown. Isochrones separate areas activated within the same 20-ms interval. Time zero is the P wave of the last sinus beat;numbers are in milliseconds; the T symbol indicates conduction block; arrows indicate general spread of excitation. A premature beat originates at 280 ms at the border between ischaemic and normal myocardium. Note figure-of-eight reentry between first and second ectopic beats.

around the zone of block. These two wavefronts unite at 380 ms and reenter the area where the ectopic beat originated after 420 ms. In the second ectopic beat two circus movements are set up that combine at 520 and 540 ms to continue in the next beat (not shown). The characteristics of the initiation of ventricular fibrillation are: (1) the occurrence of a spontaneous premature impulse at the border of the ischaemic zone (most likely caused by reexcitation of normal myocardium close to the border by injury currents[9]; (2) unidirectional block and reentry.

In Fig. 4 activation patterns are shown when ventricular fibrillation has developed fully; in the left panels during ischaemia, in the right panel after reperfusion (following defibrillation during ischaemia).

The characteristics of multiple wavelet reentry are clearly visible: (1) multiple wavelets are simultaneously present; (2) reexcitation frequently occurs and is indicated by asterisks; (3) circus movements are seldom completed and sites are usually reexcited by a different wavefront than the one which activated that site before.

The activation pattern during occlusion VF and reperfusion VF are similar, but there are also differences. First, conduction during reperfusion is more rapid: the difference between earliest and latest activity during the four "beats" shown is 460 ms during ischaemia, and 400 ms during reperfusion VF. Second, refractory periods are shorter during reperfusion since reexcitation occurs at shorter coupling intervals. For example, in the upper left panel reentry is attempted, but the wavefront at 140 ms fails to reexcite the region at which block had occurred after 20 ms (coupling interval 120 ms). In the same area during reperfusion successful reentry occurs at a coupling interval of 140 – 80 = 60 ms (asterisks at A and B).

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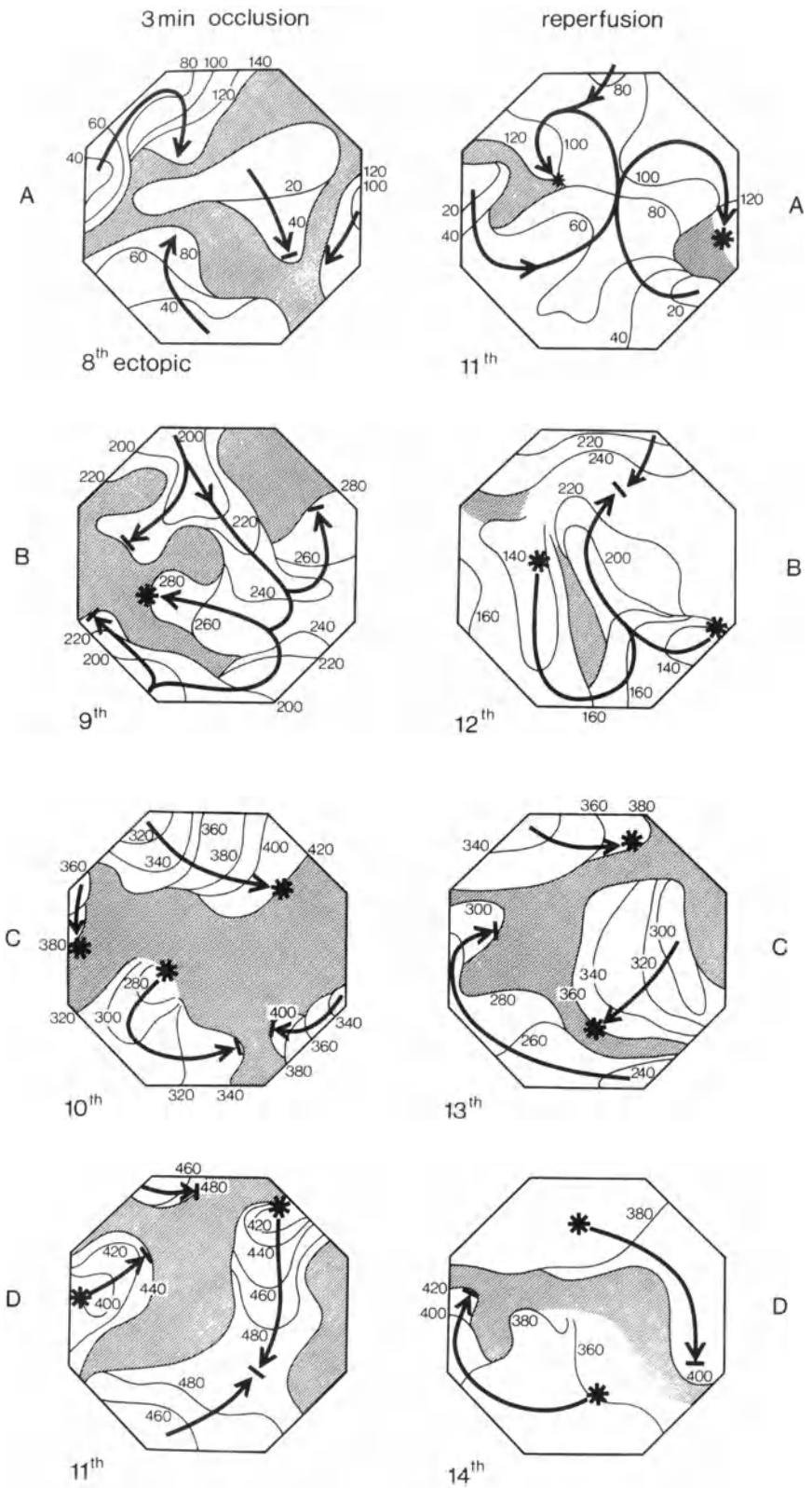

Figure 4. Comparison of patterns of excitation during fully developed ventricular fibrillation during ischaemia (left) and following reperfusion (right). Shaded areas are zones of conduction block, asterisks indicate reentry. See text for further discussion.

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Chapter 10

Molecular and Electrophysiological Mechanisms of Arrhythmias in Hypertrophic Cardiomyopathy

Dan M. Roden

Introduction

The entity of idiopathic cardiac hypertrophy has been recognised for over a century[1,2] and that of autosomal dominant familial cardiac hypertrophy for over 40 years[3,4]. While symptoms are often attributable to the direct haemodynamic consequences of massive hypertrophy, sudden death due to arrhythmias is, in fact, the common mode of death in such patients[5,6]. Moreover, it is now increasingly clear that while patients with massive hypertrophy are at high risk for sudden death, this catastrophic event can also occur in patients with familial hypertrophic cardiomyopathy (HCM) and near-normal ventricular thickness. Thus, management of the patient with HCM may necessitate a consideration of antiarrhythmic therapy separate from therapy directed at improving symptoms.

Clinical features of hypertrophic cardiomyopathy that may impact on an understanding of mechanisms

The mechanisms whereby patients die suddenly in HCM are not well established. In cases in which the terminal arrhythmia has been recorded, ventricular fibrillation is common. However, whether ventricular fibrillation is a primary event or due to superimposed ischaemia is usually uncertain[5,7]. Ischaemia in patients with HCM is common[8], and may be exacerbated or triggered by "benign" arrhythmias, such as sinus tachycardia or atrial fibrillation with rapid ventricular responses to which these patients appear particularly subject[9]. In occasional instances, sudden death due to bradyarrhythmias has been recorded[5].

Certain clinical features appear to identify patients as being at risk for sudden death[6]. These include relatively obvious markers, such as surviving an episode of out-of-hospital cardiac arrest or the presence of sustained ventricular tachycardia. A strong family history of sudden death, the onset of clinical symptoms in childhood, and the presence of massive hypertrophy are also thought to be high risk markers, as is exercise-induced hypotension. Whether the latter indicates a primary ischaemia-related arrhythmia in such patients, or whether the development of myocardial ischaemia and associated hypotension with exercise serves a trigger for arrhythmias in an electrophysiolgocially abnormal milieu, is not known. As discussed below, emerging molecular genetic information may eventually shed some light on the mechanisms whereby some patients develop severe disease.

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Other potential risk factors have been identified but their role in predicting outcome in an individual patient remains unknown or controversial. These include syncope, the presence of asymptomatic non-sustained ventricular tachycardia on a Holter monitor, the presence of inducible polymorphic ventricular tachycardia with triple extrastimuli during programmed stimulation, and the presence of atrial fibrillation. Patients with HCM also display abnormal repolarisation. In one study, QTc among HCM patients was 465 ± 24 ms, compared to 410 ± 20 ms in gender- and age-matched controls[10]. QTc dispersion was also increased (71 ± 21 vs 35 ± 11 ms). In another study, QTc and QT dispersion were greater in subjects who had non-sustained ventricular tachycardia on Holter monitor compared to those who did not[11]. As in other patient groups[12], amiodarone increased the QTc, but reduced dispersion[11,13]. It is uncertain whether these QT abnormalities are at all useful in identifying high-risk patients in HCM.

Since, as described below, the myocardial disarray typically seen in HCM may be a substrate for arrhythmias, methods to determine the extent of such disarray have been assessed as prognostic markers in HCM. One such technique, signal-averaged electrocardiography, has proven ineffective in identifying those patients at risk for sudden death. For example, in one study, abnormal signal-averaged electrocardiograms were identified in only six of 121 patients with HCM, while nine of the 121 – all with normal signal-averaged electrocardiograms – suffered sudden death or were resuscitated from out-of-hospital ventricular fibrillation[14]. More recently, a method based on assessment of electrograms recorded at multiple sites in the right ventricle during right ventricular pacing has suggested that inhomogeneities in conduction times assessed in this fashion may be a predictor of risk[15].

Potential mechanisms of arrhythmias in HCM

There are very few data that refer directly to basic mechanisms of arrhythmogenesis in HCM. Therefore, the mechanisms underlying the arrhythmias remain largely speculative, and based on emerging information in other forms of cardiomyopathy in which hypertrophy and arrhythmias are common features. As described below, animal models of HCM are now being developed, so this situation may change soon. There are two fundamental electrophysiological pertubations in HCM that may contribute to arrhythmias: myocardial disarray and changes in the individual channels or other proteins whose function is necessary for the generation of normal cardiac action potentials.

Myocardial disarray has long been recognised as the histopathological hallmark of HCM. More recently, Sepp and colleagues[16] studied the extent to which microscopic evidence of abnormal fibre orientation was associated with abnormalities in cell-cell communications. There were both morphological abnormalities and changes in the distribution of desmosomes, the structures that mechanically couple cells to each other. In addition, gap junctions, the structures that provide electrical cell-cell coupling, were markedly abnormal. Under usual conditions, gap junctions are most localised to intercalated discs at the end of individual myocytes. In HCM hearts there appeared to be a more random distribution of connexin-43, the major gap junction protein, extending over the sides of cells as well as at their ends. The shapes of gap junctions were also thought to be abnormal. Such abnormal distribution of cardiac gap junctions is thought to be highly arrhythmogenic in other diseases (e.g. myocardial infarction[17], atrial fibrosis with atrial fibrillation[18]) as it provides for abnormal conduction pathways and fractionation of conduction, with the potential for subsequent reentrant arrhythmias[19].

As described above, QT prolongation and abnormal QT dispersion is present in HCM. These abnormalities are also common in other forms of cardiac hypertrophy and in cardiomyopathy, where their presence has been linked to the genesis of arrhythmias[20–22]. An increase in the normal heterogeneity of action potential durations (which may be reflected by "dispersion" of QT intervals) implies that a premature impulse could, under appropriate conditions, block in cells with long action potentials and propagate in ones with short action potentials, thereby setting up reentrant arrhythmias. This process would be facilitated by the abnormal conduction pathways provided by gap junction dysfunction described above. Another potential mechanism whereby abnormally long action potentials could be arrhythmogenic would be to promote the development of afterdepolarisation-related arrhythmias. Two types of afterdepolarisations have been described: early and delayed. Under most conditions, early afterdepolarisations (EAD) occur more frequently at slow heart rates, while delayed afterdepolarisations (DAD) occur under conditions of intracellular calcium overload, especially with fast heart rates. Bradyarrhythmias occasionally

developing in patients with HCM could predispose to EAD-mediated arrhythmias.

There are also abundant precedents from studies in other forms of cardiomyopathy (including cells isolated from human subjects) that intracellular calcium homeostasis is markedly abnormal in various forms of cardiomyopathy[23–25]. A common finding in such studies is up-regulation of the sodium-calcium exchanger. This up-regulation, which may be viewed as a defence mechanism to maintain contractility, may also account, in part, for action potential prolongation, as the exchange of one divalent Ca^{2+} moving into a cell in exchange for three Na^+ ions moving out results in a net outward current, prolonging repolarisation. In one study, in a strain of Syrian hamsters which develop a disease with some features in common with human HCM, delayed afterdepolarisations and DAD-related rhythm disturbances were common[26].

The mechanisms whereby action potentials are prolonged in cardiac hypertrophy and failure are uncertain. One possibility is a change in Na^+-Ca^{2+} exchange protein, described above. There are many other studies, in a variety of animal species and models of hypertrophy and/or failure, in which a range of abnormalities in individual ion currents have been described[21]. There are two general mechanisms whereby abnormalities of individual ion currents can prolong cardiac action potentials: an increase in inward current or a decrease in outward current. The most obvious inward current candidate (aside from Na^+-Ca^{2+} exchange) is the calcium current, but there is considerable disparity in experimental results reported with calcium current. In human cardiomyopathies, calcium current was found to be slightly, but not statistically, increased[23]. Changes in outward current have been more consistently reported, in humans and other species. The major currents reported to be decreased include the transient outward current (I_{TO}) and the inward rectifier current (I_{K1})[27–29].

Thus, in hypertrophy and heart failure, there are changes reported in the duration of the action potential that may be arrhythmogenic, and studies have identified some of the changes in membrane currents that may underlie action potential prolongation. However, very few data are available to address the mechanisms whereby abnormalities in membrane currents occur. In the case of the Na^+–Ca^{2+} exchanger, an increase in mRNA and protein is observed, suggesting an increase in gene transcription[24,25]. Similarly, in the case of I_{TO} in human heart failure, preliminary reports indicate a decrease in mRNA encoding the potassium channel Kv4.3, whose expression is thought to be responsible for I_{TO}[30]. Whether such abnormal gene transcription represents a response to the same stimuli as those causing hypertrophy and myocardial disarray, or whether these changes represent a secondary abnormality (for example in response to the haemodynamic changes consequent upon hypertrophy) remains uncertain.

Atrial fibrillation is a common arrhythmia in HCM. Whether atrial fibrillation reflects atrial dilation due to diastolic dysfunction, or whether the disease results in myofibrillar disarray in the atrium, is not known. In one study of cats with spontaneous cardiomyopathy resembling HCM, Boyden et al noted interstitial fibrosis and abnormal action potentials in the atria of affected animals[31]. The extent of both the pathological changes and the action potential changes was greater in animals with greater atrial dilatation. Similarly, other studies have suggested that hypertrophy leading to heart failure causes changes in expression not only of ion channel genes and of genes controlling intracellular calcium, but also genes whose expression results in proteins making up the interstitial matrix[32].

The genetics of hypertrophic cardiomyopathy

Mutations in at least seven genes can cause familial HCM[6]. Four of these are genes whose expression results in proteins that are part of the cardiac sarcomere: the β-myosin heavy chain, α-tropomyosin, myosin-binding protein C, and cardiac troponin T. Two other genes encode myosin light chains, and mutations in some families have not been linked to any of these loci, suggesting further genetic abnormalities can cause the disease. The identification of elements of the cardiac sarcomere as the major cause of HCM has suggested the working hypothesis that sarcomeric dysfunction results in impaired contractility, and that hypertrophy and disarray are a response to this stimulus.

In addition to providing clues to further study of the mechanism of HCM, the identification of specific gene defects offers the hope that genetic diagnosis can be used not only to identify affected and unaffected family members, but also to stratify risk However, it should be understood that information in this area is probably still too sparse to make any but tentative inferences on the potential importance of genetic diagnosis for prognosis and therapy.

One direct consequence of the identification of disease genes has been the realisation that HCM may be much commoner than previously thought, and more benign. A heightened awareness of the disease and the use of both genetic and echocardiographic screening techniques has led to the identification of patients not followed at tertiary referral centres who appear to have HCM and yet have no alterations in prognosis. Conversely, a number of groups have suggested that particular mutations cause a high incidence of serious arrhythmias. The St George's-Boston group has suggested that, among patients with β-myosin heavy chain mutations, the Val606Met mutation is especially benign, whereas other mutations (e.g. Arg403Gln, Arg453Cys, and Arg249Gln) carry a much worse prognosis, with 50% death rates by 40–60 years of age[33]. The Baylor Group similarly found a very poor prognosis for the Arg403Gln mutation, but suggested that the Val606Met mutation might also be associated with decreased survival[34]. In their analysis the probability of surviving to age 60 was 11% in subjects with the Arg403Gln mutation, and ~90% for subjects with the Val606Met mutation. The NIH Group has reported that the Arg403Gln mutation is also associated with a decreased survival (50% mortality by age approximately 30)[35]. However, their kindred with the Val606Met mutation had an even worse prognosis, with 50% survival of only approximately 25 years with sudden death in one subject as early as age 13. They identified two other mutations, Gly256Glu and Leu908Val, that appeared to be associated with an especially good prognosis with > 90% cardiac event-free survival to age 60. The identification of the mechanisms whereby families with HCM and identical mutations display such variable clinical presentations is an area of intense research interest.

Two families have been reported in which mutations in cardiac tropinin T were associated with a very high incidence of sudden death, especially among young men (64% mortality by age 28), but very little manifest cardiac hypertrophy[36]. In fact, only 33% of subjects had an abnormal echocardiogram and the mean left ventricular wall thickness was near-normal, at 11.3 mm. These subjects do apparently display myocardial disarray. The identification of a high-risk genetic abnormality in the absence of other manifestations reinforces the concept that hypertrophy *per se* is not the major mechanism underlying sudden death in HCM. This finding also suggests that, at least in some families, genetic-based screening with a view to trials of therapy in even asymptomatic subjects, may be considered.

A glimpse to the future

This summary has made clear that studies of the mechanisms underlying arrhythmias in HCM have suffered from lack of a credible animal model. In mice the major myosin heavy chain isoform is α, not β; nevertheless, in mice genetically engineered to carry the Arg403Gln mutation in one α-myosin heavy chain allele, cardiac hypertrophy does occur[37]. Affected animals displayed prolongation of sinus node recovery time, QT interval, and left ventricular effective refractory period[38]. Importantly, arrhythmias were readily inducible by programmed electrical stimulation or by isoproterenol infusion in the mutant, but not the wild-type mice, and occasionally the arrhythmias were relatively long-lasting. Further studies in these and other mice should provide further direct evidence of the mechanisms underlying the electrophysiological abnormalities in HCM.

Summary

HCM is a familial disease of the cardiac sarcomere. The histopathological hallmark of the disease is myocyte disarray, and the common clinical symptoms, such as breathlessness and chest pain, are related to diastolic dysfunction and/or outflow tract obstruction. However, the major cause of death in HCM is arrhythmias. Abnormalities in HCM that may account for arrhythmias include gap junction disarray as well as abnormalities in the ion currents that control action potential duration. Recent advances in molecular genetics have suggested that certain mutations may be associated with an especially high risk of sudden death. These molecular genetic findings should, in turn, provide the stimulus for further research into the mechanisms underlying arrhythmias in this syndrome.

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Chapter 11

Risk Stratification in Patients with Hypertrophic Cardiomyopathy

Perry M. Elliott and William J. McKenna

Introduction

Hypertrophic cardiomyopathy (HCM) is a primary heart muscle disorder caused by mutations in genes encoding cardiac sarcomeric proteins[1–3]. Its highly characteristic pathology, namely myocardial hypertrophy, myocyte disarray and fibrosis, contributes to a broad spectrum of functional abnormalities that includes myocardial ischaemia, diastolic dysfunction, congestive cardiac failure, arrhythmias and sudden death[1,4,5]. In spite of intensive research, there are a number of persisting controversies relating to the clinical management of the disease, the most important of which is the identification and treatment of patients at risk of sudden death. This chapter reviews published data on clinical risk stratification and gives a personal view on current options for prophylactic therapy.

Genetics

Six HCM-related loci have been identified in genes encoding for cardiac sarcomeric proteins; β-myosin (chromosome 14), Troponin-T (chromosome 1), α-tropomyosin (chromosome 15), myosin binding protein C (chromosome 11), and the essential and regulatory light chains[1,2]. A further locus on chromosome 7 has been identified in a family with Wolff–Parkinson–White syndrome[3].

Natural history

Data on the prevalence of HCM in most countries are sparse, but several studies from the United States and Japan suggest a figure of approximately 1:500 of the general population[6–10]. The natural history of the disease is, for most individuals, relatively benign, with a gradual age-related deterioration in functional class and left ventricular function. A more rapid decline in left ventricular function is sometimes observed, but symptoms and signs of overt congestive cardiac failure occur in less than 10% of patients[11]. Sudden death may occur at all ages, with an estimated annual frequency of 2–4% in tertiary referral centres and approximately 1% in outpatient-based populations[12–14]. Most deaths occur during adolescence, reaching 4–6% per annum in some series[15,16]. Sudden death in the first decade is probably uncommon, but data in this age group are limited.

Diagnostic criteria

The diagnosis of HCM in adults is based on the demonstration of unexplained left ventricular hypertrophy in the absence of any other discernible cardiac or systemic cause. It is increasingly recognised, however, that some individuals with the disease do not fulfil conventional diagnostic criteria; in particular diagnosis in children

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and adolescents, athletes, adults with hypertension and obese patients can be problematic.

The interpretation of minor electrocardiographic and echocardiographic abnormalities in first-degree relatives of patients can also be difficult, and this has led to a proposal for new diagnostic criteria[17]. A number of rare neuromuscular and metabolic syndromes overlap with "idiopathic" HCM, and should also be considered in the differential diagnosis.

Role for risk stratification in HCM

The relatively low annual incidence of sudden death in HCM has led some cardiologists to argue that clinical risk stratification has a limited role in the management of patients with the disease. However, as most deaths occur in young, asymptomatic individuals, the socio-economic and emotional impact of this complication is of disproportionate significance to affected families and the wider community.

Triggers for sudden death in HCM

As most deaths in patients with HCM are sudden and unexpected, only a few examples of the sequence of events leading up to cardiac arrest have been recorded. Data from case reports and anecdotal experience in referral centres suggest that a number of potential mechanisms may trigger a cascade of events that lead to sudden cardiac death. Suggested "triggers" include paroxysmal atrial fibrillation, sustained monomorphic ventricular tachycardia, atrioventricular block, accessory pathways and myocardial ischaemia.

Clinical markers of sudden death risk in hypertrophic cardiomyopathy

Genes and sudden death

While preliminary studies indicate that some sarcomeric protein mutations are associated with a high incidence of sudden death (Fig. 1)[18], the number of patients studied to date is small, and the expression of disease in individuals with the same mutation is highly variable, indicating that other genetic and/or environmental factors must have a role in determining the phenotype.

Symptoms and family history

In children and adolescents with HCM, recurrent unexplained syncope during exertion is an ominous symptom,

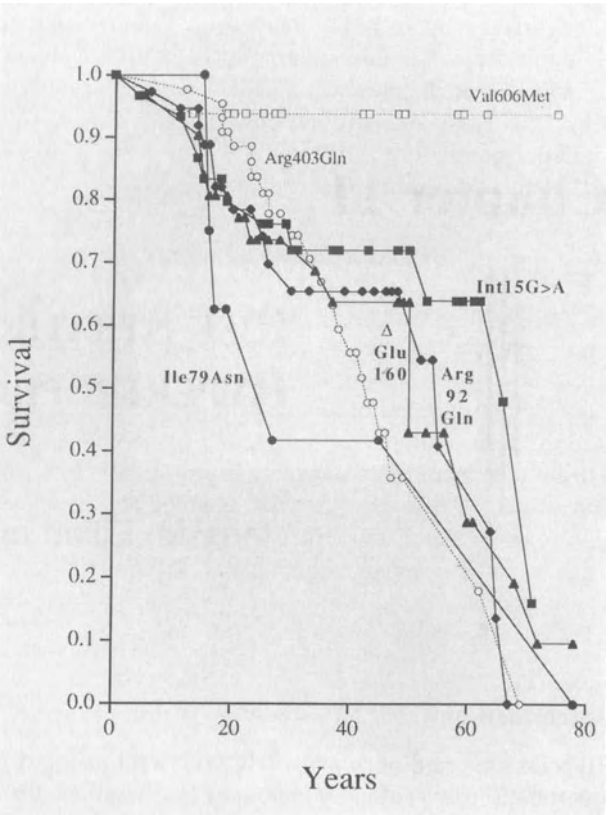

Figure 1. Kaplan-Meier survival curves in patients with ß-myosin heavy chain and cardiac Troponin T mutations. The incidence of sudden death in patients with a "benign" ß-myosin heavy chain mutation Val606Met is much less than in patients with either Troponin T mutations (Intron 15 G1-A, Ile79Asn, Δ Glu160 and Arg92Gln) or the "malignant" ß-myosin heavy chain mutation Arg403Gln. (From ref. 18, Copyright 1995 Massachusetts Medical Society. All rights reserved.)

particularly when it occurs in individuals with a family history of premature sudden death[12]. Young patients with severe symptoms are also a greater risk. Although a previous history of cardiac arrest is considered to be a highly significant risk factor, when treated in a non-systematic manner, the majority of patients do not have a further event in the short to medium term[19]. It is unclear whether this is a specific feature of ventricular fibrillation in HCM, or the effect of therapy.

Echocardiographic predictors of risk

The severity of left ventricular hypertrophy *per se* does not directly relate to prognosis[20,21], but symptomatic

patients with particularly severe (more than 3–3.5 cm) and diffuse hypertrophy may be at greater risk of sudden death. Similarly, while there is no conclusive evidence that the presence of a left ventricular outflow gradient is by itself of prognostic importance, substantial gradients (> 100 mmHg) may have a role in triggering fatal ventricular arrhythmias.

Exercise blood pressure responses

Twenty-five per cent of patients with HCM have either a flat or, less commonly, a hypotensive blood pressure response during symptom-limited upright exercise testing[22]. Abnormal blood pressure responses are more common in patients with a family history of sudden death and small left ventricular cavity dimensions, and in patients less that 40 years of age they are associated with an increased mortality (Fig. 2)[23]. The underlying cause for the abnormal response is uncertain, but inappropriate vasodilatation in non-exercising muscles may be responsible[24].

Non-sustained ventricular tachycardia

Two studies[25,26] have shown that patients with HCM and non-sustained ventricular tachycardia (NSVT) have an increased risk of sudden death (Fig. 3). However, the value of NSVT as a marker of risk is limited by a modest positive predictive accuracy of 22% and a low incidence in children. More recently some workers have suggested that NSVT is important only when repetitive, and when it occurs in symptomatic patients[27], but this hypothesis requires further evaluation.

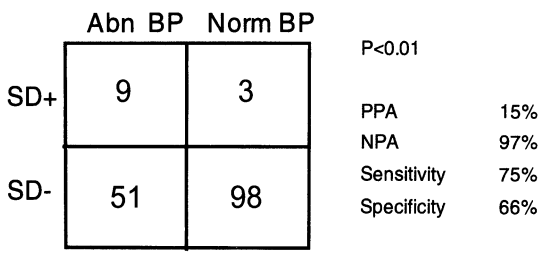

Figure 2. Schematic representation of the relation between the presence of an abnormal exercise blood pressure (Abn BP) and the occurrence of sudden death (SD) in a prospective study of 162 patients with hypertrophic cardiomyopathy. (PPA = positive predictive accuracy, NPA = negative predictive accuracy). (From ref. 23.)

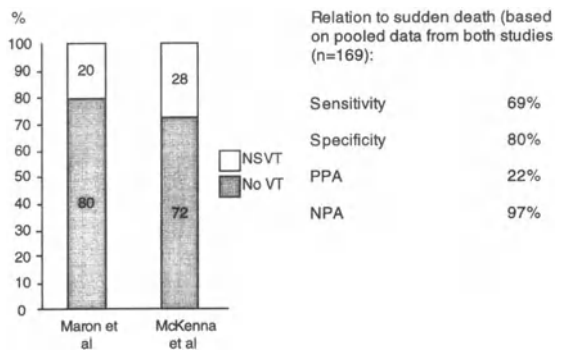

Figure 3. Schematic demonstrating the percentage of patients with non-sustained ventricular tachycardia (VT) detected during ambulatory electrocardiographic monitoring in two independent studies and its relation to the occurrence of sudden death (pooled data). (PPA = positive predictive accuracy, NPA = negative predictive accuracy). (From refs 25 and 26.)

Electrophysiological assessment in hypertrophic cardiomyopathy

Non-invasive

QT interval analysis. Both QT and QTc intervals may be increased in patients with HCM, but QT prolongation appears to relate more to maximal left ventricular wall thickness (possibly reflecting variable volumes of repolarising tissue) than to the risk of dying suddenly[28–30]. QT dispersion may be a more sensitive marker of the propensity to ventricular arrhythmia[31], but the available data in patients with HCM are contradictory and further study is required.

Signal-averaged electrocardiography. Abnormal signal-averaged electrocardiograms (SAECG) are more common in patients with HCM and NSVT, the best predictor being a reduced voltage in the initial portion of the high gain QRS complex[32]. Unfortunately, abnormal SAECG are associated with no other clinical risk factor or an increased incidence of sudden death[32].

Heart rate variability. Studies of heart rate variability (HRV) in patients with HCM are limited, but both global and specific vagal components of HRV are reduced in patients with NSVT[33]. Unfortunately, there are no differences in HRV in patients who die or survive out-of-hospital ventricular fibrillation, and at present HRV has no role in the routine evaluation of patients with the disease.

Invasive

Programmed electrical stimulation. Some studies have suggested that inducible VT in HCM is associated with a higher risk of cardiac events[34]. However, the response to ventricular stimulation in any patient depends on the protocol used, and while aggressive protocols using three or more premature stimuli produce sustained polymorphic ventricular tachycardia in 30–40% of patients, their predictive accuracy for sudden death is low[35]. As most high-risk patients can be identified non-invasively, the inherent risks associated with programmed stimulation mean that it cannot be routinely used to assess risk in HCM.

Electrocardiogram fractionation. It has been hypothesised that myofibrillar and myocyte disarray create a spectrum of conduction velocities and refractory periods within the myocardium that acts as a substrate for reentrant tachycardia[36]. This putative arrhythmogenic substrate has been studied by measuring individual paced electrocardiogram transitions in the right ventricle. In comparison with controls and HCM patients with no clinical risk factors for sudden death, patients with a history of ventricular fibrillation have marked prolongation ("fractionation") of the paced electrocardiogram at relatively long extrastimulus coupling intervals[36,37]. Patients with a family history of premature sudden death or NSVT exhibit responses that range from high risk (ventricular fibrillation) to low risk (no adverse prognostic features). Pooled data from two studies[36,37] indicate that patients with syncope also have a range of conduction responses. The incidence of syncope in patients with ventricular fibrillation is significantly higher, suggesting that the haemodynamic disturbance associated with syncope may act as a trigger for sudden death in those with the necessary electrical substrate.

Management of the high-risk patient

As stated earlier, less than a third of patients with a history of cardiac arrest have a further catastrophic event when treated in a non-systematic fashion[19]. Unfortunately, most patients with HCM do not survive their first episode of VF, making it vitally important to identify patients at risk of a catastrophic cardiac event. All patients should be assessed for the presence of "triggers" for sudden death and treated appropriately;

Table 1. Generally accepted markers of increased sudden death risk in patients with hypertrophic cardiomyopathy

1. Family history of premature sudden death
2. Recurrent syncope in the young
3. Non-sustained ventricular tachycardia (in adults)
4. Abnormal exercise blood pressure response

paroxysmal atrial fibrillation (amiodarone therapy with or without anticoagulation), sustained monomorphic ventricular tachycardia (amiodarone and/or implantable cardioverter defibrillator), conduction system disease (pacemaker), accessory pathways (radiofrequency ablation) and myocardial ischaemia (high-dose verapamil). Although conclusive data on the relative value of different markers of sudden death risk are not available, it has been our practice to consider patients with two or more conventional risk markers (Table 1) for prophylactic therapy. Low-dose amiodarone therapy has been shown to reduce the incidence of sudden death in patients with NSVT[38], the drug's potential side-effects minimised by using low doses (100–300 mg/day) and regularly assessing blood levels of the parent compound and its metabolites. An increasing number of high-risk patients receive implantable cardioverter/defibrillators, but these devices are costly, have important socioeconomic implications for patients, and are untested in prospective studies.

Summary

While further work is necessary to refine current diagnostic and treatment criteria in patients with HCM, clinical risk stratification not only facilitates the treatment of individuals who are at risk of dying but also allows clinicians to reassure those individuals who are at low risk. It is essential that the inevitable imperfections in the risk stratification algorithm are not seen as an excuse to do nothing, but are used as inspiration to improve on current medical practice.

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Chapter 12

Floppy Mitral Valve/Mitral Valve Prolapse: Cardiac Arrhythmias

Harisios Boudoulas, Stephen F. Schaal, and Charles F. Wooley

Introduction

Multiple clinical investigators contributed to our understanding of the floppy mitral valve/mitral valve prolapse (FMV/MVP), an important clinical entity in valvular heart disease[1–8]. FMV/MVP postural auscultatory phenomena (posturally mediated changes in timing and intensity of the systolic click-apical systolic murmur) were explained in haemodynamic terms in the 1970s as changes in timing and extent of MVP and the time of onset and duration of mitral regurgitation were related to postural changes in left ventricular volume and contractility[1–8]. Thus, by the late 1970s, clinical auscultatory, postural auscultatory dynamics and angiographic definition of FMV/MVP characteristics, with established pathological correlates, provided a reasonable clinical diagnostic profile of the FMV/MVP, mitral regurgitation triad. When M-mode echocardiography was introduced as the diagnostic standard for MVP, the auscultatory-phonocardiographic and angiographic diagnostic criteria and correlates that existed for FMV/MVP, mitral regurgitation, were relegated to a minority position[1–3]. Patients or individuals with small, hyperdynamic left ventricles had false-positive echocardiograms and were placed into the same category as patients with the FMV/MVP. As the MVP pendulum moves away from the exaggerated prevalence figures of the past two decades, it is apparent that the FMV occupies the high ground and is the central issue in the FMV/MVP, mitral regurgitation triad (Fig. 1).

Diagnostic considerations

The FMV/MVP is a common mitral valve abnormality with a broad spectrum of structural and functional changes. While the pathophysiology of the FMV/MVP has been reexamined, we continue to deal with gross structural and morphological characteristics at the clinical level. Distinguishing between the normal mitral valve with its minor variants, and a mitral valve with an intrinsic structural derangement, remains a difficult clinical problem (Fig. 2)[1–3]. We are more comfortable with the FMV/MVP, mitral regurgitation diagnosis when the clinical auscultatory phenomena are precisely described, preferably recorded, and dynamic auscultation has been performed; the clinical auscultatory phenomena are matched with an imaging procedure that captures and quantitates FMV morphology and function; and the imaging procedure demonstrates MVP and the presence or absence of mitral regurgitation. Clinical coherence should exist among the medical history, the physical examination, and the imaging procedure[2,3].

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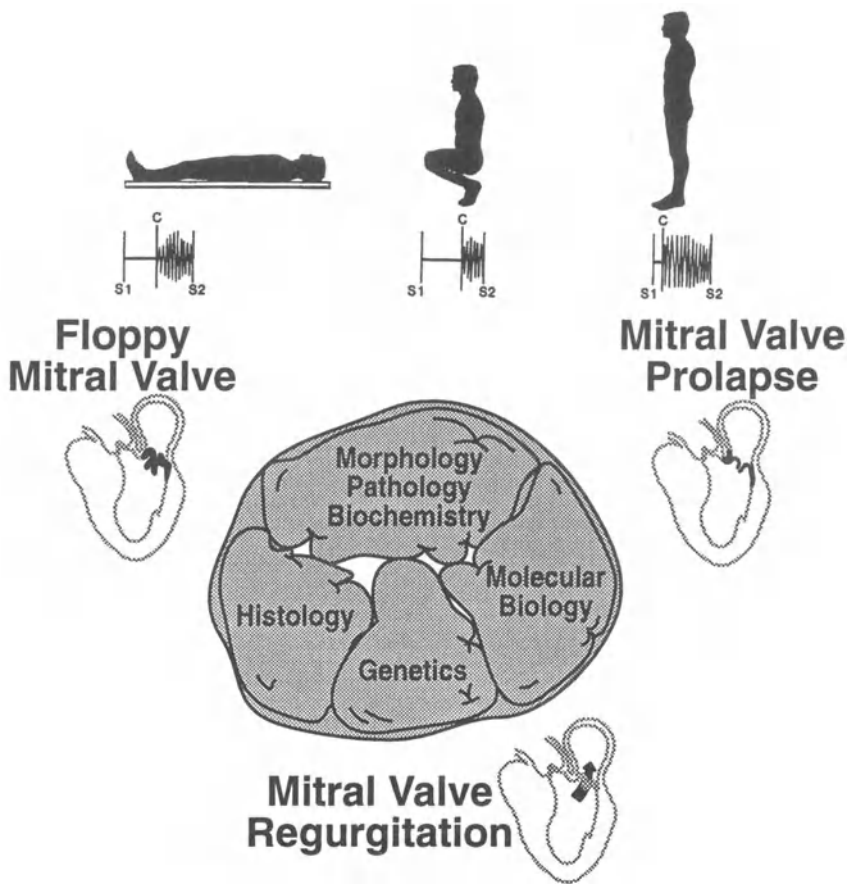

Figure 1. The floppy mitral valve-mitral valve prolapse-mitral valvular regurgitation triad. The floppy mitral valve occupies the central role in the triad. Postural auscultatory phonocardiographic changes are illustrated at the top of the figure. (From ref. 2, with permission.)

The FMV may be an inherited lesion, either as an isolated event or as part of the recognised or incompletely defined heritable disorders of connective tissue[2,3,7,8]. The FMV has gradually become recognised as the most common cardiac lesion in many heritable systemic disorders[7]. The FMV/MVP inheritance and phenotypic features have been well described. As yet, FMV genetic diagnostic testing has not entered clinical practice. Such approaches permit diagnostic pathways that will be part of the twenty-first-century cardiologist's armamentarium.

FMV/MVP – classification/natural history

At present the classification of patients with FMV/MVP involves two general categories. The first category places emphasis on the FMV anatomy and pathobiology, and includes those patients whose symptoms, physical findings, laboratory abnormalities and clinical course are directly related to the progressive mitral valve dysfunction and complications associated with the FMV/MVP mitral regurgitation. The second category includes those FMV/MVP patients whose symptoms cannot be explained on the basis of the valvular abnormality alone, but result from the occurrence of, or coexistence of, various forms of neuroendocrine or autonomic nervous system dysfunction. This group of patients we have referred to as patients with the mitral valve prolapse syndrome[1–3].

We have found this to be a clinically useful classification, but one that should be subject to regular revision or modification as we better understand the pathogenesis and mechanisms of symptoms in patients with FMV/MVP mitral regurgitation.

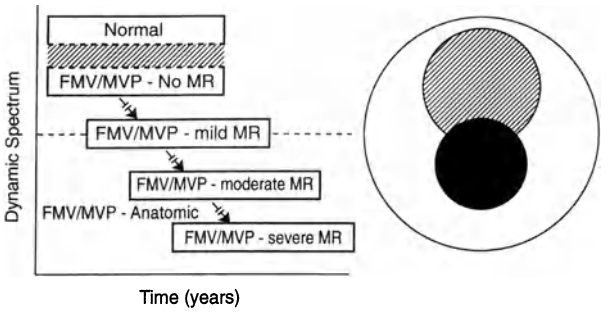

Figure 2. The dynamic spectrum and progression of mitral valve prolapse (MVP) are shown. A subtle gradation (hatched area) exists between the normal mitral valve and floppy mitral (FMV) that produces mild MVP without mitral valvular regurgitation (MVR) (MVP-No MR). The condition may remain at the level MVP-No MR or may progress. Most patients with MVP syndrome occupy the area above the dotted line, and patients with progressive mitral valve dysfunction occupy the area below. The large circle represents the total number of patients with FMV-MVP – symptomatic and asymptomatic. Symptoms may be related directly to the mitral valve dysfunction (black circle) or to autonomic dysfunction (dotted area). Some patients with symptoms directly related to mitral valve dysfunction may subsequently experience symptoms secondary to autonomic dysfunction. (From ref. 1, with permission.)

Profiles of the natural history of the FMV/MVP mitral regurgitation are gradually emerging, but have been limited by variations in diagnostic criteria, the nature of the populations studied and the duration of the clinical follow-up periods. The FMV/MVP association may lead to progressive mitral valvular dysfunction and severe mitral regurgitation over time; however, it may take several decades before the individual patient's natural history is developed. Hence, studies or evaluations at one point in time have limitations. Chordal rupture, progressive mitral regurgitation, left atrial and left ventricular failure, atrial and ventricular arrhythmias occur in varying combinations and permutations (Fig. 2)[1–3,9].

Valve surface phenomena occur in patients with FMV. The FMV is particularly vulnerable to infection and is a common site for infectious endocarditis. Thromboemboli are additional valve surface complications of FMV[1–3].

Floppy mitral valve/mitral valve prolapse: cardiac arrhythmias

Several studies have suggested that the incidence of cardiac arrhythmias in patients with FMV/MVP is greater compared to the general population[10–18]. The incidence of MVP among patients referred for electrophysiological studies and the incidence of electrophysiological abnormalities in symptomatic patients with FMV/MVP who had electrophysiological studies were analysed in a study from the Ohio State University Medical Center. During the period 1976 to 1986, 1856 patients were referred for electrophysiological studies; 271 patients (14.6%) had MVP without significant mitral regurgitation. One or more electrophysiological abnormalities were found in 220 patients with FMV/MVP (81.2%). Assuming that the prevalence of FMV/MVP in the general population is 5% or less, our data suggest that the incidence of symptomatic arrhythmias in patients with FMV/MVP is greater than that of the general population. A higher incidence of arrhythmias has also been reported in the younger age group[19].

The incidence of ventricular arrhythmias and sudden death is also higher in the FMV/MVP group. The incidence of sudden death during follow-up of clinically recognised patients with MVP has varied from 0% to 1.3% per year. Data reflect heterogeneous populations who are more likely to be highly symptomatic and have more complex arrhythmias than unselected patients with MVP. The most common cause of sudden death in MVP is ventricular fibrillation. Ventricular fibrillation is more likely to occur in patients with a history of syncope or significant ventricular arrhythmias[10,11,19,20].

The cause of ventricular arrhythmias in patients with FMV/MVP appears to be multifactorial (Table 1)[10,11,19]. Endocardial friction lesions resulting from friction between the chordae and left ventricular myocardium have been reported at autopsy studies in patients with FMV/MVP who died suddenly. It is possible that this pathology may be responsible for, or contribute to

Table 1. Floppy mitral valve/mitral valve prolapse: possible cause of ventricular arrhythmias

Likely multifactorial
Autonomic dysfunction (↑NE→ ↓K^+, postural phenomena)
Papillary muscle traction/ventricular stretch
QT dispersion
Mechanical stimulation of myocardium by leaflets
Abnormal innervation of floppy mitral valve
Endocardial friction lesions
Platelet aggregation – fibrin deposits (emboli of coronary arteries)
Myocardial fibrosis

the development of, ventricular arrhythmias. Platelet aggregation, haemorrhage and fibrin deposits have been observed in the angle between the left atrium and the posterior mitral leaflet, and microembolism from these deposits may involve the coronary circulation, with subsequent myocardial ischaemia and ventricular arrhythmias. Autonomic dysfunction may initiate, precipitate or contribute to arrhythmias in symptomatic patients with MVP. Increased sympathetic activity may intensify ventricular and supraventricular arrhythmias in patients with FMV/MVP[10,11,19–22].

Papillary muscle traction in FMV/MVP may also be responsible for ventricular arrhythmias. Membrane depolarisation is caused by both gradual and rapid ventricular stretch, but premature ventricular depolarisations are more readily elicited by rapid stretch. Recent studies have demonstrated the existence of stretch activated membrane channels in ventricular myocardium; these may contribute to ventricular ectopy under conditions of differential ventricular loading as in FMV/MVP. Echocardiographic data demonstrated that, in normal subjects, the distance between the papillary muscle tips and the mitral annulus during systole remains relatively constant. In contrast in patients with FMV/MVP, mitral valve leaflet displacement into the left atrium results in papillary muscle displacement that causes traction of the muscle (Fig. 3)[23–29].

Innervation of the mitral valve may also contribute to the genesis of cardiac arrhythmias in FMV/MVP. Human cardiac valves have distinct patterns of innervation that comprise both primary sensory and autonomic components. The presence of distinct nerve terminals suggests a neural basis for interactions between the central nervous system and the mitral valve. The subendocardial surface on the atrial aspect at the middle portion of the mitral valve is rich in nerve endings,

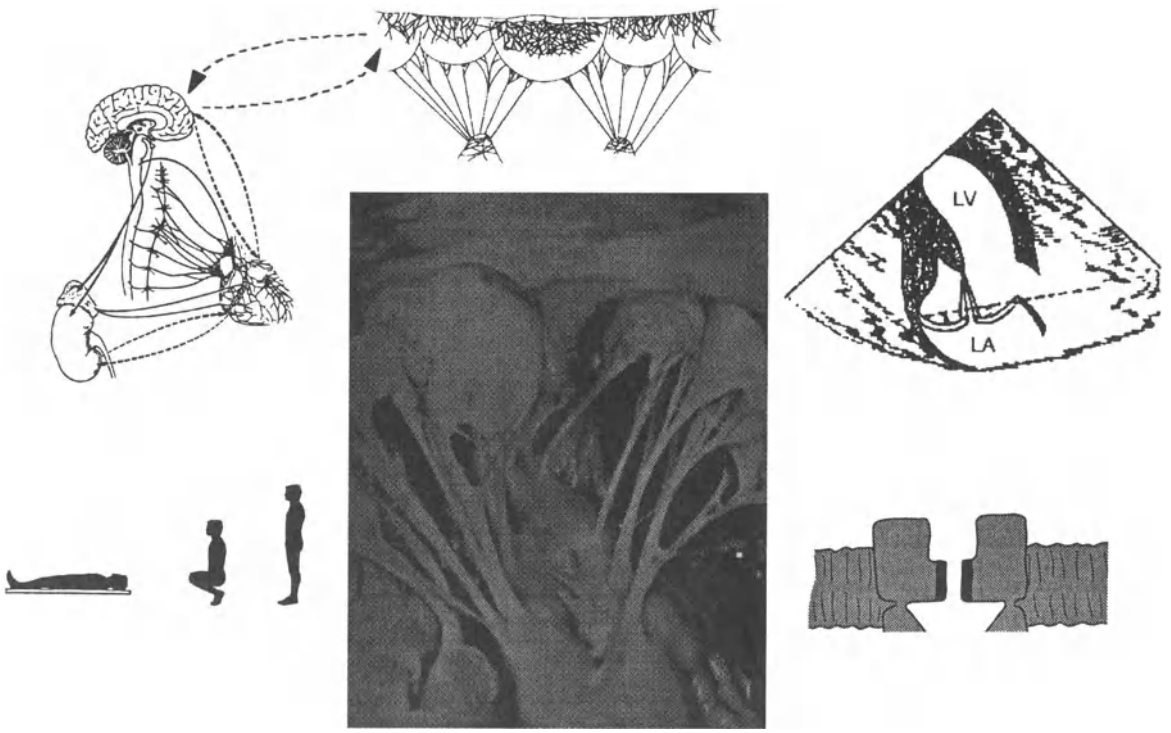

Figure 3. The cause of cardiac arrhythmias in floppy mitral valve/mitral valve prolapse is multifactorial. Autonomic dysfunction-neurohumoral abnormalities, papillary muscle traction/ventricular stretch-stretch receptors activation, orthostatic phenomena, innervation of the mitral valve, and mechanical stimulation of myocardium by mitral valve leaflets are contributory factors. Floppy mitral valve is shown in the middle; above the mitral valve innervation of the mitral valve is shown schematically; upper right shows papillary muscle tension during ventricular systole; lower right stretch-activated receptor is shown schematically. Left upper part shows schematically interactions between the brain-heart-kidneys and adrenals. Lower left part shows schematically orthostatic phenomena.

including afferent nerves; mechanical stimuli from this area caused by abnormal coaptation in MVP may cause abnormal autonomic nerve feedback between the central nervous system and mitral valve nervous system (Fig. 3)[30–33].

Increased adrenergic activity, catecholamine regulation abnormality, and adrenergic hyperresponsiveness has been observed in certain patients with FMV/MVP. Altered vagal tone or baroreceptor activity may also play a role in the pathogenesis of cardiac arrhythmias in certain patients[10,11].

Increased adrenergic activity associated with MVP in some instances may be associated with hypokalaemia which, in turn, may contribute to cardiac arrhythmias. Autonomic dysfunction and stretch-activated mechanoreceptors may contribute to QT disparity, which may cause ventricular arrhythmias in some patients with MVP. As a general rule, the duration of the QT interval is normal in patients with MVP. The incidence of QT disparity, however, has been reported to be higher in patients with MVP compared to the general population[20,21,32–42].

Patients with FMV/MVP often present with postural phenomena such as orthostatic decreases in cardiac output, orthostatic hypotension, tachycardia, and symptoms related to alterations in heart rate, blood pressure, and cardiac output. Orthostatic phenomena are multifactorial in origin. Decreased intravascular volume, an abnormal renin-aldosterone response to volume depletion, a baroreflex modulation abnormality, a hyperadrenergic state, or a parasympathetic abnormality may partially account for these phenomena. Further, inability of patients with FMV/MVP to maintain normal left ventricular diastolic volume in the upright posture will result in greater prolapse and papillary muscle traction; these changes in left ventricular size and mitral valve apparatus may contribute to orthostatic changes and cardiac arrhythmias[1,3].

In general, sudden death in patients with FMV/MVP without significant mitral valvular regurgitation has been almost exclusively reported in symptomatic patients with FMV/MVP[19,20]. Patients with a history of recurrent syncope, a history of complex ventricular arrhythmias or a family history of cardiac sudden death, appear to be at higher risk for sudden death.

We reported nine cases of resuscitated survivors of sudden death in patients with FMV/MVP, only one of whom had significant mitral regurgitation. All patients but one were symptomatic before the cardiac arrest; eight had long histories of palpitations with documented ventricular arrhythmias, and three of the eight had recurrent syncope[19].

Electrocardiographic ST segment and T wave changes are frequently present in patients with FMV/MVP and sudden death or ventricular fibrillation. Although the lack of data regarding the overall incidence of these electrocardiographic changes in patients with FMV/MVP limits the conclusions that may be drawn, at present it is probably important to regard these resting electrocardiographic changes with concern, particularly when present in symptomatic individuals. Cardiac arrest in patients with FMV/MVP is most often due to ventricular fibrillation. Among the patients with FMV/MVP-cardiac arrest reported from the Ohio State University Medical Center, ventricular fibrillation was documented in eight of nine patients.

Patients with FMV/MVP who are currently classified to the incompletely defined "high-risk" category (Table 2), should have further diagnostic studies such as ambulatory monitoring, exercise testing, transtelephonic electrocardiography, or electrophysiological studies in order to identify the potential for serious arrhythmias. Appropriate therapy would depend upon the outcome of such testing, and is subject to the same limitations and potential benefit of individualised antiarrhythmic therapy. Patients with significant mitral regurgitation should undergo valve replacement or reconstruction when indicated, to prevent irreversible ventricular damage[10,11,19].

Standard electrocardiography should be used to identify patients who have evidence of preexcitation or other anomalous atrioventricular pathways and prolongation of the rate-corrected QT interval. Since each of these subgroups may be at increased risk of sudden death, such patients should be separated from the general FMV/MVP population for more intensive evaluation[10,11]. Asymptomatic patients with QT prolongation should be

Table 2. Floppy mitral valve/mitral valve prolapse: ventricular arrhythmias: the high-risk patient

Past history compatible with cardiac arrhythmias (palpitations, premature ventricular beats, syncope)
Family history of sudden death
Autonomic dysfunction (orthostatic phenomena, syncope)
QT dispersion
Non-specific electrocardiographic changes

considered for a trial of β-blockade therapy, particularly when ventricular arrhythmias are present. Diuretics should be avoided to prevent hypokalaemia and hypomagnesaemia that might initiate or precipitate cardiac arrhythmias. Likewise, caffeine, alcohol, ephedrine-like drugs, or other stimulants should be avoided[1–3].

Abnormal atrioventricular pathways, when present and particularly when associated with supraventricular arrhythmias, warrant electrophysiological studies and ablation[10,11]. Patients with FMV/MVP who have recovered from cardiopulmonary resuscitation should undergo thorough non-invasive and invasive cardiac evaluation to define the nature of the arrhythmia and to exclude any other coexisting cardiac pathology[19]. Automatic defibrillator implantation may be necessary in selective cases. Although mitral valve reconstruction has been reported to provide the relief of symptoms including syncope and ventricular fibrillation, these studies involved relatively few, highly selected patients and should not be extrapolated to the general high-risk population.

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Chapter 13

Pathology of Arrhythmogenic Right Ventricular Cardiomyopathies, Dysplasia and Naxos Disease: Clinical, Pathological and Nosological Classification

G. Fontaine, N. Protonotarios, F. Fontaliran, A. Tsatsopoulou and R. Frank

Introduction

Arrhythmogenic right ventricular dysplasia (ARVD) is a clinical entity due to a disease of the heart musculature, identified in 1977, which was recognised because of its cardiac arrhythmias originating in the right ventricle. The arrhythmias that were not controlled by drug therapy were treated successfully by antiarrhythmic surgery[1]. Later it was observed that this disease was not limited to the right ventricle. In some cases the left ventricle was involved by the same disease process as was found in the right ventricle. It was clear that the ventricular arrhythmias were the result of the particular structure of the myocardium and that this entity should be classified as a cardiomyopathy.

In 1986 the World Health Organisation proposed a classification of cardiomyopathies in three main categories: hypertrophic, dilated and restrictive. Recently, a new World Health Organisation classification has been published incorporating ARVD in a larger category, called "arrhythmogenic right ventricular cardiomyopathy". This group has the advantage of including a wide spectrum of clinical entities, involving both right and left ventricles. Moreover in some cases the left ventricle may be the cause of the main clinical presentation. Nevertheless, all these right ventricular cardiomyopathies have the same basic histological structure which is typical of this group of diseases. This work summarises our knowledge on this subject and attempts to classify the different subgroups. The differential diagnoses of this new group of cardiomyopathies will also be discussed.

The structure of the normal right ventricle has some similarities to that observed in arrhythmogenic right ventricular dysplasia. This explains why ARVD has been recognised only recently by pathologists[2].

The normal right ventricle

Before description of ARVD it is appropriate to review the main features of normal myocardium as opposed to

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ARVD. Adipocytes are always present in the normal right ventricular free wall. In a large number of cases they are also observed in large clusters. This is independent of age and sex, although they seem to be seen more frequently in elderly women. This adipose tissue separates strands of cardiomyocytes. Therefore strands or sheets of myocardial fibres can be observed in the fat of the right ventricular epicardium. The boundary between subendocardial fibres and external layers is generally clear, but a fuzzy limit may also be observed in normal right ventricles[3].

Disorganisation of myocardial fibres, also called "disarray", is observed quite frequently in normals in the right ventricular free wall at its junction with the lower part of the right septum.

The normal left ventricle

In the left ventricle, adipocytes are observed only in the perivascular region at the epicardial level. The pattern of cardiomyocyte disorganisation "disarray" which is observed in hypertrophic cardiomyopathy, as well as in some places of the right ventricular free wall, is definitely abnormal in the free wall of the left ventricle. No fibrous tissue is observed.

Typical ARVD

In ARVD the isolated form is not the most common. It is generally discovered in teenagers or young adults who have ventricular arrhythmias that range from isolated extrasystoles to ventricular tachycardia. Almost invariably, the ventricular arrhythmias have a left bundle branch block pattern. Symptoms include palpitations or syncope that can be the harbinger of sudden death. In some cases sudden death may be the first presenting symptom of the disease[4].

Gross pathology

On gross pathology the right ventricle is dilated and covered by a thick layer of epicardial fat on most of its surface. In minor forms, and particularly at the beginning of the disease, the right ventricle is of normal size or slightly dilated. This large layer of epicardial fat is associated with a decrease in the thickness of the remaining myocardial muscle, which subsists only in the subendocardial layers and may be transilluminated. The papillary muscles or physiological trabeculations are hypertrophied and thicker than normal, particularly at the level of the moderator band[5]. In some cases the myocardium is visible in the subendocardial and subepicardial layers separated by a medio-mural layer of fat. The endocardium may look totally normal on gross pathological examination, although in some patients white fibrous plaques are observed. Their position is independent of the dysplastic areas. This endocardial fibrosis could embed papillary muscles. Generally, the left ventricle appears normal on gross pathology.

Microscopy

The visceral pericardium is frequently thick, suggesting an old pericardial reaction. The subepicardial layer contains a large amount of adipocytes, with subsequent reduction of cardiomyocytes, which are present only at the level of the subendocardium. Inside this adipous tissue it is possible to observe fibromyocytic fibres, defined as cardiomyocytes embedded in or bordered by a thick layer of fibrous tissue. This suggests its long-standing presence. The fibromyocytes appear as remnants of myocardium which have been spared and could be the substrate for the arrhythmogenicity of this tissue. Inside this adipous tissue there may be cardiomyocytes of normal appearance, which constitute a border parallel to the epicardium. This suggests the ruins of the external layers of the heart, progressively infiltrated and replaced by adipocytes. In the strands of fibromyocytes it is also possible to observe transitional forms, ranging from cardiomyocytes to adipocytes, due to a phenomenon of cell degeneration. In these cells, single or multiple vacuoles are clearly visible that seem to increase progressively up to complete replacement of cardiomyocytes by adipocytes. This aspect is frequently observed in zones of adipocytes made of cells of variable size mixed with fibrosis and cardiomyocytes without connective tissue. This pattern suggests an active phenomenon, and is frequently associated with a large amount of fibrous tissue.

The subendocardial layers are generally preserved despite a large decrease in their thickness. In some patients there is almost complete disappearance of this muscle layer. In addition, these myocytes are frequently interspersed by stands of interstitial fibrosis isolating muscular bundles.

Cardiomyocyte destruction leading to fibrosis formation is also suggested by some histological samples in which there is a decrease in the number of myo-

fibrils with a pattern of fragmentation progressively disappearing within a frame of collagen tissue. This pattern is similar to that observed in hypertrophic cardiomyopathy, whether obstructive or non-obstructive. At the present time we consider that the presence of fibrous tissue is essential for the diagnosis of ARVD, since strands of cardiomyocytes within adipous tissue are frequently observed in the right ventricular myocardium even in normal young individuals.

In this form there are no or few inflammatory cells. This structure, which is characteristic of the disease, has been sometimes named "myofat", which is an abbreviation of myo-fibro-fat[6]. The myofat is mostly observed in the infundibular and anterior area of the right ventricle, extending to the apex, as well as the diaphragmatic area under the tricuspid valve. This is consistent with the previously described "triangle of dysplasia"[7].

Coronary vessels are easy to identify in fatty tissue. In their distal trajectory, marked thickness of the media is frequently observed[8]. This is associated with a change in leiomyocytes which are arranged longitudinally, parallel to the axis of the vessels. In some places the media is so thick that the vascular lumen is no longer present. This pattern is frequently associated with a major increase in nerve fibres, and suggests a particular histological pattern, generally related to localised non-specific vascularisation trouble.

This may be correlated with findings at coronary angiography showing a stretch of the distal coronary vessels, which appears as straight and cylindrical. Atypical precordial pains observed in a large number of patients affected by ARVD may be related to these particular histological abnormalities.

Histologically, endocardial fibrosis is due to dense and thick collagen deposits with few cells. In some places there is a variable amount of elastic fibres (Fig. 1). The pattern of "disarray" of myocytes which may be observed frequently in normals in the right ventricular free wall is also present in ARVD. Therefore the typical pattern of ARVD consists of strands of cardiomyocytes, within adipose tissue, bordered by or embedded in fibrosis. However, this is not pathognomonic of ARVD, since it can also be observed in other situations such as scar tissue produced by ischaemia in coronary artery disease. However, the clinical presentation of the patient is different. Nevertheless a combination of these two causes of the pathological finding has been observed in some cases[9].

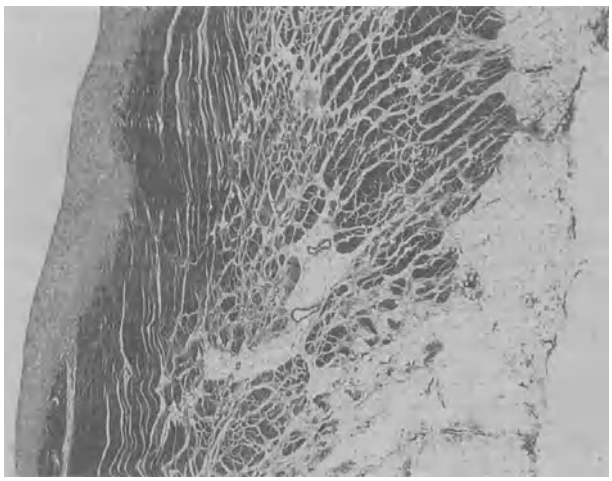

Figure 1. Cross-section of the right ventricle from a heart removed during cardiac transplant surgery in a patient who developed irreversible right heart failure. At the top the epicardium shows a large amount of fatty tissue, as well as fibromyocytes that are surrounded by fat in the mid-mural layers. The subendocardial layers are spared. The endocardium is covered by a thick layer of fibrous tissue. (HPS: G × 18.)

Left ventricular involvement

Shortly after the identification of ARVD attention was directed to the right ventricle to treat ventricular tachycardia by surgery and later by ablation. However, it has been observed that ventricular tachycardia could originate both from right and left ventricle in patients who had typical clinical features of ARVD. In addition, electrophysiological studies showed evidence of delayed activation on the left ventricle similar to that observed on the right[1]. It was only when a larger number of cases was studied systematically, with clinical presentation ranging from the "forme fruste" to the extensive diffuse form, that it became apparent that some of these patients had significant involvement of the left ventricle. The resulting decrease in cardiac function was frequently subclinical, and these individuals were able to engage in sports and even competitive sports. However, when it was possible to study the whole heart of ARVD cases who died suddenly, it became apparent that some of them had histological signs confirming extension of the same disease process to the left ventricle.

Left ventricular involvement typical of that seen in the right ventricle can be observed to a limited extent in ARVD. These areas of adipous tissue and interstitial

fibrosis isolating strands of cardiomyocytes may be observed in the apex of the left ventricle, and seem to be an extension of the disease in this area.

However, some zones showing the presence of fibrosis and fat may also be scattered in the left ventricular myocardium. They may constitute the substrate for abnormal electrical activity and reentrant phenomena originating in the left ventricle. These moderate abnormalities may explain the slight decrease of the LV ejection fraction observed in uncomplicated cases of ARVD.

Fetal dysplasia

We have observed one case in which the diagnosis was suspected by routine echosonography showing obvious dilatation of the anterior aspect of the right ventricle. This was associated with cardiac arrhythmias, but it was impossible to determine by retrospective analysis of tapes if these arrhythmias were of supraventricular or ventricular origin. Spontaneous abortion was observed at 27 weeks. At microscopic examination there was thinning of the anterior parietal wall. There were adipocytes in mediomural and subepicardial layers, as well as a small amount of collagen tissue.

Biventricular dysplasia

This is a rare clinical form with a poor prognosis. The same pathological process observed in the right ventricle also involves the left ventricle. Therefore the left ventricle is covered by a thick layer of fat and the subepicardial layers are largely replaced by fatty tissue which infiltrates and penetrates the muscle towards the endocardium. As we have stressed previously for the right ventricle, fibromyocytic layers should be present for a positive diagnosis. However, they are less frequently observed than on the right ventricle. The loss of a large amount of myocardium explains the progressive evolution towards left ventricular failure. The patient may be diagnosed as having idiopathic dilated cardiomyopathy.

Arrhythmogenic right ventricular dysplasia and myocarditis

It is frequent to observe histological evidence of signs of inflammation such as lymphocyte infiltrates compatible or strongly suggestive of old or healing myocarditis in typical cases of ARVD. There is frequently an increased thickness of the visceral epicardium, and inflammatory cells such as lymphoplasmocytes are frequently present. This has led us to speculate, at least for a while, that ARVD was the result of myocarditis, as recently suggested by other groups[10,11]. However, further experience gave us the impression that there was no correlation between the phenomenon of fatty replacement and the various patterns of myocarditis. These two components seem to have their own pattern of evolution.

It was later suggested that the frequency of signs of myocarditis, which does not exceed 10% in the population of normal subjects who died of trauma, could frequently be present in ARVD patients because of the particular sensitivity of an already-abnormal myocardium to environmental factors that have not been identified, acting directly on myocardial muscle or indirectly through an autoimmune phenomenon (Fig. 2). The important feature of myocarditis is to involve, in the vast majority of cases, both ventricles. This again favours the concept of a superimposed phenomenon on the genetically determined background of RV dysplasia. A similar phenomenon is well known in other cardiac diseases, such as subacute endocarditis.

In one case, who died in the clinical setting of fulminant heart failure, it was possible to observe a large component of acute myocarditis with

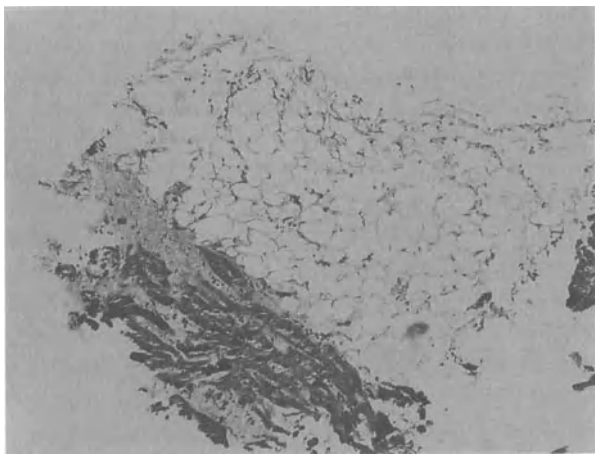

Figure 2. Biopsy sample of the right ventricle in a 50-year-old woman with Naxos disease. The left ventricular ejection fraction was 20%. The histology shows surviving endocardial fibres (in dark) covered by a layer of subepicardial fat. The presence of fibrosis, necessary for the diagnosis of dysplasia, is clearly visible (in grey). Lymphoplasmocytes and active cells are visible in the areas of fibrosis (HPS: G × 85.)

polymorphonuclear or a large predominance of eosinophils, and frequently the presence of histiomacrophages (Fig. 3). Both ventricles were involved in this process. However, careful study of histological slides identified the presence of fibrous tissue bordering or embedding cardiomyocytes inside fat in the right ventricular free wall. In this situation hyaline fibrosis was too old to be the consequence of acute myocarditis[12].

Other evidence concerning the role of a superimposed phenomenon in ARVD cases has recently been published from groups studying sudden death during sports. The presence of myocarditis alone, or superimposed on a structural heart disease such as ARVD or hypertrophic cardiomyopathy, was observed[13,14].

The role of an environmental factor has been also demonstrated by the study of identical twins with a diagnosis of ARVD in whom a clear difference of long-term evolution was documented[15].

When both ventricles are involved in myocarditis the late stage of the disease may look like idiopathic dilated cardiomyopathy[16].

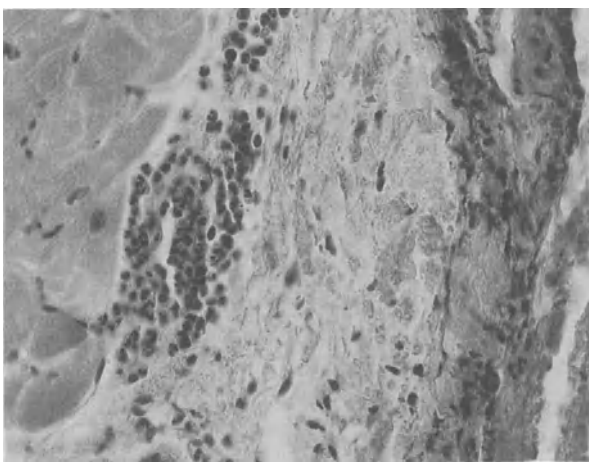

Figure 3. Surgical biopsy taken from the right ventricle in a 50-year-old man, referred for sustained monomorphic ventricular tachycardia of right ventricular origin resistant to medical therapy. The arrhythmia started after an acute episode of fever and intense pain, suggesting the diagnosis of acute myocardial infarction. The surgical sample shows active cells inside fibrous tissue bordering normal cardiomyocytes. The final diagnosis was acute myocarditis superimposed on the background of dysplasia, clearly seen on other histological slides. (HE: G × 204.)

Non-arrhythmogenic right ventricular dysplasia

Arrhythmogenicity is the result of critical electrophysiological conditions, probably rarely attained in the general population. Therefore, the non-arrhythmogenic forms of RVD are probably widespread. We have received data from forensic medicine showing typical aspects of RVD observed incidentally in patients who died of a different cause. It may be that, in those cases, ARVD was a contributory factor to the cause of death.

However, RVD patients may develop myocarditis, and some of them may have a poor prognosis. It is in this situation that a pattern of a late stage of generalised cardiomyopathy with left ventricular failure is observed; however, the diagnosis may be suspected by analysis of the 12-lead ECG[17].

Naxos disease

Naxos disease represents a specific clinical type of arrhythmogenic right ventricular dysplasia, being the most important part of a familial syndrome which combines ARVD, palmoplantar keratoderma and peculiar kinky hair[18]. It appears in families descending from the Hellenic island of Naxos with an autosomal recessive type of transmission[19]. The skin disorder becomes clinically apparent during the first year of life, but cardiac events, including ventricular arrhythmias, sudden death and heart failure, are not manifested until late puberty. Comparing Naxos disease to other clinical forms of ARVD, there is a higher incidence of sudden death and left ventricular involvement. The typical "myo-fibro-fatty" histological pattern of ARVD characterises the affected right ventricular myocardium in patients with Naxos disease[20].

ARVD in Naxos disease may progress in the right and/or left ventricle. In two patients who suffered severe rapid deterioration of cardiac condition at the ages of 50 and 43 years, respectively, endomyocardial biopsy during the acute phase revealed features of an active inflammatory process. The first patient with inflammatory findings in both ventricles (Fig. 2) had severe deterioration in left ventricular function and congestive heart failure. The second patient showed progression in right ventricular involvement with severe ventricular arrhythmias, and biventricular biopsy revealed inflammation restricted to the right side. These two cases support the hypothesis that the abnormal substrate of

ARVD predisposes the heart to a myocarditis, which can alter disease prognosis and evolution.

Histology and arrhythmogenic substrate

Anatomical structure

1. The histology provides some clues suggesting an arrhythmogenic substrate. Some myocardial cells are observed in bunches bordered by connective tissue, inside adipous tissue. This could represent "zones of slow conduction" for activation transmitted from normal myocardium. Therefore these fibres may play an important role in the reentrant phenomenon. This situation is similar to that observed at the border zone of a postmyocardial infarction scar. In these cases there are isolated fibres with an abnormal morphology and probably electrophysiological properties which connect two zones of normal myocardium through an area of increased thickness and fibrosis produced by ischaemia.
2. Flat layers of cardiomyocytes occupying the subendocardial layers create a bidimensional anatomical substrate which may be favouring a vortex-like ventricular tachycardia showing a *torsade de pointes* pattern[21].

Inflammatory phenomena

1. We have seen previously that the transitional cells showing vacuolisation suggest an active - phenomenon. This could be associated with arrhythmogenesis, independently of the presence of myocarditis.
2. Recent data have demonstrated that activated neutrophils are able to strongly alter the electrophysiological properties of cardiomyocytes and may produce early after depolarisation[22]. This situation may play a role in the form of ARVD complicated by acute myocarditis.

Long-term prognosis of ARVD

The pure form of fibro-adipous dysplasia of the right ventricle is clinically relatively stable, and most of these patients have a long life expectancy. This may be explained by the fact that in most cases involvement of the left ventricle is quite limited, and that adjacent muscle has a normal contractile function. This also explains the observation that these patients can live a normal life and could practise sports without adverse consequences.

Differential diagnosis of ARVD

Idiopathic dilated cardiomyopathy

In practice the most frequent differential diagnosis is the idiopathic form of dilated cardiomyopathy, which could be frequently confused with dysplasia if an anatomical diagnosis is not available. Dilated cardiomyopathy with VT of right ventricular origin shows a global diffuse involvement of the right ventricle with a variable degree of involvement of the left ventricle, at least at the beginning of the disease. In this situation the right ventricle is obviously poorly contractile, frequently dilated and without segmental anomalies, and bulges both on echocardiography and angiography.

Uhl's anomaly

This is an extremely rare condition, properly called "parchment heart". It has been frequently confusing when there are translucent areas of the right ventricle in patients with ARVD. Under these circumstances the term "partial Uhl's anomaly" has been used[23]. However, it is clearly different both on clinical presentation and pathology. In Uhl's anomaly there is apposition of the epicardium against the endocardium with few interspersed adipocytes, but no myocytes. The wall is therefore extremely thin, or even transparent in some places. There are, however, some cases of ARVD where in some limited areas (a few millimetres) there is a total absence of cardiomyocytes between epicardium and endocardium, giving rise to the term a partial Uhl's anomaly". However, in this case the interstitium is occupied by a thick layer of adipous tissue.

Ischaemic lesions

Ischaemic lesions observed after myocardial infarction could extend to the right ventricle. However, in this situation the presence of adipous tissue in the right ventricle, associated with fibrosis related to ischaemic heart disease, has to be interpreted with caution. In those cases there is generally a coronary atheroma even if there are no typical signs of old myocardial infarction.

Discussion

In its typical form, arrhythmogenic right ventricular dysplasia is characterised by a specific histological structure. This consists of replacement of myocardium by fat in the right ventricular free wall extending to the adjacent area towards the septum corresponding to the crista supraventricularis[24]. In other cases the basic histological structure of ARVD extends toward the apex of the left ventricle[25].

Pathological material, including a systematic study of both right and left ventricles, suggests that this phenomenon may be more diffuse than previously realised, affecting the whole ventricular myocardium, even though the right ventricle is the most extensively involved.

The pathogenesis of the disease is only partially known. ARVD has been found in a 7.5-year-old boy who died suddenly[26]; other paediatric cases have been reported. The case of Makanda et al described in a 16-month-old child has been criticised; however, with time a clear pattern of dysplasia became evident[27]. Our own case of fetal ARVD demonstrated that the origin of the disease is probably already present in the embryo even if clinical signs are first observed later in life. An arrhythmogenic substrate requires the presence of critical electrophysiological parameters. This clinical manifestation should therefore be considered as an epiphenomenon. It is interesting to speculate that ECG signs consistent with the diagnosis of ARVD may be present prior to the onset of an arrhythmia, since the mature arrhythmogenic substrate may take longer to develop. This stresses the possibility that ECG findings may lead to an early diagnosis of RVD. In turn, this could allow preventive measures to be undertaken before the surge of cardiac arrhythmias to prevent sudden cardiac death.

However, it may be that ARVD and Uhl's anomaly are closely related entities sharing the same pathogenesis but with different patterns of evolution. James et al have suggested that these two entities are due to a process of programmed cell death called apoptosis. However in Uhl's anomaly there is rapid destruction of a large number of fibres early in life. In contrast apoptosis may cause ARVD with a slow process extending over a long period of time[24]. ARVD could encompass a wide spectrum of clinical presentation related to the extent of right and left ventricular diseases. The most severe form of ARVD is represented by a biventricular cardiomyopathy leading to irreversible cardiac insufficiency when the dysplastic phenomenon extends to the left ventricle with major replacement of left myocardial fibres by fat. In that case cardiac failure is the result of extensive loss of myocardium[28]. A second pattern is observed when the left as well as the right ventricles are involved in a process consistent with myocarditis superimposed on the genetically determined substrate of the disease. Triggering of an autoimmune phenomenon has not conclusively been demonstrated in ARVD. This phenomenon could account for the clinical picture of a small subgroup of patients who have rapid progression of the disease with a left ventricular involvement leading to a decrease in left ventricular ejection fraction below 40%[29,30].

Therefore, the cardiac arrhythmias which are frequently a marker of the disease could be an epiphenomenon triggered by an acute inflammatory episode of unknown mechanism. In ARVD the decrease of thickness of cardiomyocytes of the right ventricular free wall is partially controlled by hypertrophy of trabeculae carne and papillary muscles, which give the typical pattern of fissuring observed by contrast angiography of the right ventricle. However, even in the most diffuse form of the disease there are segmental alterations of contraction.

The concept of a superimposed myocarditis has led to the understanding of some clinical and evolutive aspects of the disease leading to impairment of both right and left ventricular function. All these forms are able to produce ventricular or supraventricular arrhythmias.

In conclusion, the term "dysplasia" is appropriate to characterise the fatty replacement of the free wall of the right ventricle due to apoptosis, probably determined genetically at the time of embryogenesis. Right ventricular dysplasia is a well-defined clinical and histological entity with multiple aspects, where the distinction from other forms of cardiomyopathies has direct implications for the prognosis and treatment of the disease. The presence of a superimposed myocarditis on the background of dysplasia may explain certain clinical situations which were previously unclear.

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Chapter 14

VENTRICULAR ARRHYTHMIAS IN HYPERTENSIVES

Dimitris A. Sideris

Hypertension is associated with increased mortality and morbidity[1,2]. The increase in mortality is partly due to increased sudden cardiac death, which is mostly attributed to malignant cardiac arrhythmias[3]. Several authors have demonstrated that hypertensive patients have more premature beats than normotensive ones[4–9]. Ventricular arrhythmias often appear in a paroxysmal-like way, although at other times they may be more or less permanent. They are thought to be caused by a paroxysmal functional factor or "trigger" acting on a suitable structure or "substrate". The substrate may be a scar, left ventricular hypertrophy, congestive heart failure, inhomogeneity of the myocardium from various causes, drugs, ionic disturbances, etc. On the other hand the paroxysmal factor may be premature beats, ischaemia, heart rate (HR), blood pressure (BP), stress, the autonomic nervous system, time itself, etc. Furthermore, arrhythmias have a tendency for self-perpetuation, as for example in paroxysmal tachycardia, fibrillation or bigeminy.

An important question is which of the conditions associated with hypertension is the cause of the ventricular arrhythmias. Left ventricular hypertrophy has been considered a major arrhythmogenic factor in hypertensives[10]. On the other hand, James and Jones[11], working on hypertensive and normotensive rats, reported that left ventricular hypertrophy actually protected the heart from developing arrhythmias in response to sudden pressure changes when electrolyte concentrations were normal; however, it led to a marked increase in the sensitivity of the myocardium to pressure changes during perfusion with low levels of potassium and magnesium. Acting on such a substrate the BP may well be the triggering factor.

By definition there may be no hypertension without raised BP. Curiously enough very little attention has been paid to the BP as a possible cause of ventricular arrhythmias in hypertension. In the following the BP–arrhythmias relationship will be discussed, as well as the possibility that a reduction in BP in hypertensive patients with cardiac arrhythmias may be associated with their amelioration.

Experimental data suggest that an acute increase in BP by any means will cause ventricular ectopy in the form of isolated ventricular ectopic beats (VEB) or bigeminy, or even ventricular tachycardia if the pressure increase is extreme[12]. In clinical cases also with a history of ventricular arrhythmias a modest increase in BP may be associated with the appearance of VEB, while in cases with preexisting ventricular ectopy, even at a BP within normal limits, an acute reduction of BP by sodium nitroprussate may eliminate or ameliorate ectopy[13]. This effect of BP on arrhythmogenicity is independent of coronary flow or sympathetic activity[14,15], presenting a

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clinical manifestation of mechanoelectrical association[16] or contraction-excitation feedback[17,18].

The exact mechanism of mechanoelectrical association is unknown. Non-specific stretch-dependent ion channels seem to exist, the opening of which may be arrhythmogenic; these channels may be inhibited by gadolinium[19]. The electrophysiological mechanism of these arrhythmias also is not clear. Mechanical load may lengthen or shorten or not affect repolarisation and refractoriness, depending on various factors[20–24]. Dispersion of refractoriness, however, may well contribute to pressure-related arrhythmias. Early afterdepolarisations with the possibility of abnormal or triggered automaticity have been repeatedly observed during overloading of the ventricular myocardium[21,22]. Other authors, however, observed early afterdepolarisations in less than 10% of aortic occlusions, and their presence was unrelated to ventricular ectopy[23]. Although increasing either pre- or or after-load may have an effect on the electrophysiological properties of the myocardium, it seems that it is an increase in systolic pressure that exerts an arrhythmogenic effect on the ventricles[24].

The pressure threshold above which ventricular arrhythmias may appear varies greatly even in the same animal or subject under various conditions. An important substrate affecting the proneness to pressure-related arrhythmias is mechanical inhomogeneity. In 45 patients with coronary artery disease intravenous metaraminol was given until either ventricular ectopy appeared or the systolic BP was raised to 200 mmHg. Isolated VEB or runs of non-sustained ventricular tachycardia appeared in 13 patients at a systolic BP of 170 ± 28 mmHg. Dyskinesia existed in 77% of these patients, hypokinesia in 15% and normal wall motion in only 8%. Corresponding values in those without induced arrhythmia, in whom the BP was raised to 201 ± 6 mmHg, were 6%, 35% and 59%, respectively ($P < 0.00001$). The history of hypertension or myocardial infarction, the number of affected vessels, the presence of myocardial ischaemia at an effort test, the use of β-blockers and the HR were not predicting factors of the pressure-related arrhythmogenicity. The overall ejection fraction was significantly lower in the cases in which arrhythmias were generated, but analysis of variance showed that this was not an independent factor[25].

As a trigger BP coexists with other potential triggers with which there may be interdependence. Of special interest is HR. Sympathetic stimulation may increase both HR and BP, manifesting e.g. as a parallel circadian variation of these two parameters[26]. On the other hand, a primary increase in BP causes bradycardia due to a baroreflex mechanism. In dogs the pressure threshold for ventricular ectopy is increased significantly by atrial pacing at a high rate[12]. Thus, whenever a parallel change in BP and HR exists, the effect on ventricular ectopy cannot be anticipated. The circadian variation of extrasystolic arrhythmia parallels that of BP and HR[26]. In patients with a history of VEB spontaneous circadian increases in BP are associated with the appearance of ventricular ectopy which, however, may persist after the reduction of BP, possibly as a result of self-perpetuation due e.g. to the "rule of bigeminy"[26].

The antihypertensive effect of an acute reduction of BP need not be shared by a chronic pressure reduction. However, the use of agents with an antihypertensive action has been variously described to exert an antiarrhythmic effect, although this effect was not always attributed to pressure lowering. Thus clonidine[27], nifedipine[28], captopril[29], enalapril[30], diltiazem and metoprolol[31] have been shown to reduce ventricular ectopy under several conditions. Apart from the direct antiarrhythmic effect of pressure lowering by these agents, they may have a direct antiarrhythmic action themselves, or they may affect left ventricular structure, thus reducing the arrhythmogenic nature of the substrate[32]. The antiarrhythmic effect of thiazide diuretics is under dispute[31]. If associated with amiloride, so that no hypokalaemia occurs, these agents may reduce the incidence of VEB if they reduce the BP[26].

During exercise both BP and HR are increased, the former exerting a proarrhythmic effect and the latter an antiarrhythmic one. The increase in BP and HR is attributed to autonomic nervous system stimulation which is expected to be arrhythmogenic. In 58 exercise tests (Bruce protocol) of 30 patients with ventricular ectopy the VEB incidence was correlated positively with BP in 16 cases, negatively in two and not significantly in 40; on the other hand, it was positively correlated with HR in four cases, negatively in 16 and not significantly in 38 ($\chi^2 = 18{,}14$; $p < 0.0001$ for two degrees of freedom). A 2-week antihypertensive treatment in 28 of these patients, using either an ACE inhibitor with a diuretic (nine cases) or hydralazine with a diuretic (19 cases), significantly reduced resting BP during exercise but not mean BP, resting HR, mean HR or overall VEB incidence. However, in those in whom VEB incidence was reduced, the fall in resting

systolic BP (–17.5 ± 19.7 mmHg), was significantly ($p < 0.02$) greater than in those in whom the VEB incidence was not reduced (–3.4 ± 14.0) unpublished observations).

In spite of strong evidence that antihypertensive treatment may reduce ventricular ectopy, definite proof is missing that this treatment in hypertensive patients will be beneficial in reducing arrhythmias and sudden cardiac death. Although an extreme pressure increase may provoke ventricular tachycardia in healthy experimental animals, ventricular fibrillation has been a very exceptional phenomenon[20]. Thus there is no clear experimental evidence that pressure-related arrhythmias are the cause of sudden cardiac deaths in hypertension. Furthermore, although the vast majority of patients treated with a thiazide-amiloride combination showed a reduction of arrhythmias on the day with the lowest pressure, there was a minority in whom the ectopy was more evident on the day with the lowest pressure[26]. The possibility of a proarrhythmic effect of pressure lowering in a minority of hypertensive patients as it may occur with antiarrhythmic agents cannot be excluded, although it does not seem very likely in view of the beneficial effect of antihypertensive treatment on longevity of such patients.

In conclusion, hypertension is associated with an increased incidence of ventricular arrhythmias. There is no hypertension without raised BP. An acute elevation of BP is associated with ventricular ectopy even without preexisting hypertension, while an acute reduction of BP is associated with elimination or amelioration of preexisting ventricular arrhythmias. There is some-evidence that a chronic reduction of BP may be associated with a reduction of ventricular ectopy. More work is needed to show if antihypertensive treatment in hypertensives may ameliorate coexisting ventricular ectopy and mortality.

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Chapter 15

The Value of Electrophysiological Testing in Diagnosis of Syncope in Post-infarction Patients, without Complex Ventricular Arrhythmias Detected in 24-hour ECG

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Introduction

The most frequent reasons for syncope in patients after myocardial infarction are complex ventricular arrhythmias (CVA)[1–4]. Ventricular arrhythmias (VA) are present in approximately 20–50% of patients after myocardial infarction[5]. On the other hand 90% of sudden cardiac death episodes are caused by VA[6]. Most patients present with VA in standard 12-lead ECG or in 24-h ECG Holter monitoring. However, in some patients after myocardial infarction, detection of VA is impossible, in spite of repetitive 24-h ECG recordings. In these patients we may observe only symptoms related to VA, such as syncope, presyncope or vertigo. These patients are thus especially in danger of sudden cardiac death because of the impossibility of arrhythmia mechanism assessment; 24-h ECG Holter monitoring is not a sufficient diagnostic tool in such cases. Improvement of suitable diagnostic procedures, for instance programmed electrical stimulation (PES), in this group of patients after myocardial infarction, is very important both for defining the very high sudden cardiac death risk patients and for sufficient antiarrhythmic treatment[7,8].

The aim of this study was to assess the value of PES in the diagnosis of syncope in patients after myocardial infarction, without complex ventricular arrhythmias in 24-h ECG.

Methods

Patient selection and evaluation

We report on 36 patients (27 male, nine female), aged 36–62 years, with syncope during the course of the post-myocardial infarction, without CVA (class IV according to the Lown scale) detected in 24-h ECG. Coronary angiography and ventriculography with left ventricle

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ejection fraction assessment were performed in all patients. The patients were divided into two groups.

Group I: 26 persons with syncope observed prior to myocardial revascularisation procedures.
Group II: 10 persons with syncope observed after myocardial revascularisation procedures, i.e. percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG).

Based on the results of coronary angiography, patients from group I were administered either pharmacological treatment or referred to elective CABG. Electrophysiological testing was performed in all patients.

Electrophysiological testing protocol

In all patients referred to electrophysiological testing potentially antiarrhythmic drugs were discontinued at least for five half-life periods before the study. Electrode catheters were inserted percutaneously and positioned in the high right atrium, across the tricuspid valve to record the His bundle electrocardiogram and in the right ventricle. Surface ECG leads I, III, V1 and V6, and intracardiac recordings from the high right atrium, His bundle and right ventricle, were displayed simultaneously by a Quinton EPLab monitoring system. Stimulation was performed with a programmable stimulator (Biotronic UHS 20) at a current strength twice the diastolic threshold and with a pulse duration of 2 ms.

The following variables were determined: atrioventricular conduction time (AH and HV intervals) and sinus node recovery time (SNRT). The ventricular stimulation protocol consists of single and double extrastimuli introduced after five beats of ventricular pacing at three basic drive cycle lengths: 550, 400 and 330 ms) and three extrastimuli introduced after five beats of ventricular pacing at two basic drive cycle lengths: 550 and 400 ms. Programmed ventricular stimulation was performed at the right ventricular apex then at the right ventricular outflow tract.

A positive electrophysiological study was defined as a study that demonstrated an electrophysiological abnormality likely to be the cause of syncope; that is, sustained monomorphic ventricular tachycardia, repetitively induced non-sustained monomorphic or polymorphic ventricular tachycardia, supraventricular tachycardia associated with a fall in systolic blood pressure to < 80 mmHg, a markedly prolonged SNRT (> 3000 ms), infranodal block during atrial pacing or a markedly prolonged HV interval (> 100 ms).

A negative electrophysiological study was defined as a study that did not demonstrate an electrophysiological abnormality likely to be related to syncope. This included an entirely normal electrophysiological study, supraventricular tachycardia without hypotension, an HV interval between 55 and 99 ms, or induced ventricular fibrillation.

Non-invasive ECG evaluation

Repetitive 24-h ECG Holter monitoring was performed twice in each patient: before admission to the coronary disease department (ambulatory monitoring) and then after admission to the department and every 3 months during a 1-year follow-up. A three-channel ECG Medilog Oxford recorder and an Excel 2 computer system were used.

High-resolution ECG was recorded in all patients using a HIPEC 200 analyser. Time domain analysis was performed. Standard criteria for late ventricular potentials (LP) were used[9]. A head-up tilt test was employed to detect vasomotoric syncope.

Results

Results of non-invasive ECG testing

Mean LVEF was 46 ± 8% in patients with syncope observed prior to invasive myocardial revascularisation (group I) and 49.2 ± 9% in patients suffering from syncope after invasive revascularisation of myocardium (group II). Twenty-four-hour ECG recordings performed prior to PES did not reveal CVA (repetitive forms such as pairs of ventricular premature complexes, non-sustained or sustained ventricular tachycardias). The tilt test was negative in all patients. The results of high-resolution ECG analysis are illustrated in Table 1.

Table 1. Results of average high-resolution ECG

High-resolution ECG parameters	Group I		Group II	
QRSf (ms)	139.8	(21.6)	137.2	(19.4)
RMS40 (μV)	10.5	(9.4)	13.5	(7.4)
LPD (ms)	51.4	(12.2)	48.3	(9.8)

Figures in parentheses are standard deviation.

Table 2. Arrhythmias induced during electrophysiological testing

Induced arrhythmia	Group I (n = 26)		Group II (n = 10)	
	Number	[Percentage]	Number	[Percentage]
Sustained VT, monomorphic	15	57.7	6	60
Repetitive non-sustained VT	4	15.4	1	10
Reciprocal narrow QRS complex tachycardia	2	7.7	0	0
Sick sinus syndrome	3	11.5	1	10
No arrhythmias induced	2	7.7	2	20

LP was observed in 22 patients (84.6%) from group I and in eight patients (80%) from group II.

Results of electrophysiological testing

Monomorphic ventricular tachycardia was induced in 62% of patients with late ventricular potentials from group I and 75% from group II. Parameters of atrioventricular conduction were normal in all patients (AH interval 95 ± 15 ms, HV interval 46 ± 8 ms). SNRT was abnormal in four patients (6520 ± 4150 ms vs 1260 ± 210 ms).

Applied antiarrhythmic treatment

PES-guided pharmacological antiarrhythmic therapy was introduced in 16 patients (group 1, 14 patients; group II, two patients). A dual-chamber pacemaker was implanted in six patients (group 1, five patients; group II, one patients); four patients because of sick sinus syndrome, two patients because of bradycardia-complicated effective antiarrhythmic treatment with class III drugs. Eleven patients were referred to non-pharmacological treatment (group 1, seven patients; group II, five patients); six patients for ICD implantation, five patients for antiarrhythmic surgery (LV aneurysmectomy with endocardiectomy).

The effectiveness of antiarrhythmic drug therapy was evaluated by 24-h ECG monitoring during a 1-year follow-up in 20 patients. Antiarrhythmic therapy was changed in three patients because of drug side-effects (hypothyreosis observed during amiodarone treatment) and in two patients with evidence of proarrhythmia (sotalol).

Discussion

Unexplained syncope in patients after myocardial infarction still remains an important problem both for diagnosis and treatment. Many previous studies report that complex ventricular arrhythmias, particularly monomorphic sustained ventricular tachycardia, are responsible for postmyocardial syncope[10–12]. It is evident that ventricular arrhythmias in patients after myocardial infarction are responsible for 90% of sudden cardiac death episodes[6]. Life-threatening arrhythmias observed after myocardial infarction are associated with the presence of arrhythmogenic substrate related to a myocardial scar[12,13]. Improvement of coronary circulation achieved by invasive myocardial revascularisation procedures (PTCA, CABG) did not decrease the frequency of ventricular arrhythmia occurrence because of persistence of arrythmogenic substrate. In about 80% of patients inducible sustained monomorphic VT still persists after coronary artery bypass grafting[14,15].

Complex ventricular arrhythmias detected in standard or 24-h ECG registration, in patients with syncope after myocardial infarction, worsen the prognosis[16]. However, risk of sudden cardiac death is easy to assess in such patients, and they may be appropriate candidates for antiarrhythmic therapy without any additional invasive testing[17,18].

Syncope in post-infarction patients without complex ventricular arrhythmias, detected by non-invasive ECG examinations, is fundamental diagnostic and therapeutic problem. Invasive electrophysiological testing seems to be an important and useful tool for evaluating the mechanism responsible for syncope in such patients[19].

In our study sustained monomorphic VT was induced in 57.7% of patients with syncope observed prior to invasive myocardial revascularisation (group I) and in 60% of patients suffering from syncope after invasive revascularisation of myocardium (group II). Sustained monomorphic VT was induced in 62% of patients with late ventricular potentials from group I and 75% from group II. Gomes et al reported similar results[18]. Sick sinus syndrome as a reason for postmyocardial infarc-

tion syncope was revealed in four patients (group 1, three patients; group II, one patient). In four patients (11%) electrophysiological testing revealed no reason for syncope. Electrophysiological testing has proved to be of significant value in the selection of antiarrhythmic drugs and non-pharmacological treatment of ventricular arrhythmias. Taking into consideration the results of electrophysiological testing we referred six patients for ICD implantation, five for antiarrhythmic surgery (left ventricle aneurysmectomy and/or endocardiectomy) and five for a dual-chamber pacemaker.

Invasive electrophysiological testing demonstrates greater" effectiveness than non-invasive electrocardiographic testing (i.e. 24-h ECG monitoring) in diagnosis, and particularly in the therapy of syncope in patients after myocardial infarction, who did not reveal complex ventricular arrhythmias in routine ECG monitoring.

Despite the ESVEM study, which showed that ECG monitoring and PES stimulation have similar diagnostic values[20], there is a group of patients, especially after invasive myocardial revascularisation, who benefit more from PES stimulation than from Holter monitoring, considering prevention of SCD pharmacological or non-pharmacological therapy.

Conclusions

1. Electrophysiological testing allows to assess the arrhythmia mechanism responsible for syncope and to evaluate antiarrhythmic therapy in postmyocardial infarction patients with syncope and without complex ventricular arrhythmias revealed in 24-h ECG.
2. Programmed electrical stimulation is very useful in the assessment of sudden cardiac death risk in post-myocardial infarction patients with syncope and without complex ventricular arrhythmias revealed in 24-h ECG.

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Chapter 16

Value of Different Mapping Strategies for Ventricular Tachycardia: Sinus Rhythm and Pace Mapping, Activation and Entrainment Mapping

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Introduction

Several electrophysiological phenomena have long been recognised to be helpful in the localisation of arrhythmogenic substrates. In the context of ventricular tachycardia, local abnormalities observed during sinus rhythm (sinus rhythm mapping), comparison of QRS morphology during tachycardia and during pacing in sinus rhythm (pace mapping), comparison of local activation time during tachycardia at different sites (activation mapping) and observations made during resetting and transient entrainment of tachycardias (entrainment mapping) are considered the most useful tools to localise the arrhythmogenic substrates.

Although the value of each of these techniques is indisputable, a question that could be asked is whether the value of each of these phenomena is comparable in order for a precise localisation (and subsequent ablation) of arrhythmogenic substrate. Furthermore, the usefulness of these techniques could vary in different patients according to specific characteristics of the arrhythmia and/or the substrate that is under study. In light of these questions, the purpose of this chapter is to analyse: (1) the influence of the arrhythmia mechanism on the value of each of these mapping strategies, and (2) the limitations of these techniques in relation to the type of substrate and how can they be overcome by the combination of mapping techniques.

Influence of arrhythmia mechanism on the value of mapping strategies

In Table 1 several mapping techniques are listed, considering their relative usefulness in localising arrhythmogenic substrates according to whether the arrhythmia mechanism is reentrant or not.

Sinus rhythm mapping can identify areas of abnormal electrograms related to abnormalities in conduction. This can be moderately useful in the identification of reentrant ventricular tachycardia[1], but it does not seem to be of interest in non-reentrant rhythms.

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Table 1. Relevance of ventricular tachycardia mechanism for mapping

	Reentrant	Non-reentrant
Sinus rhythm mapping	++	0
Activation mapping	++	+++
Earliest activity	+	+++
Isolated middiastolic activity	+++	0
Resetting/transient entrainment	+++	+*
Post-pacing interval	++	+*
Concealed entrainment	+++	0
Pace mapping	+	+++

* Not well characterised.

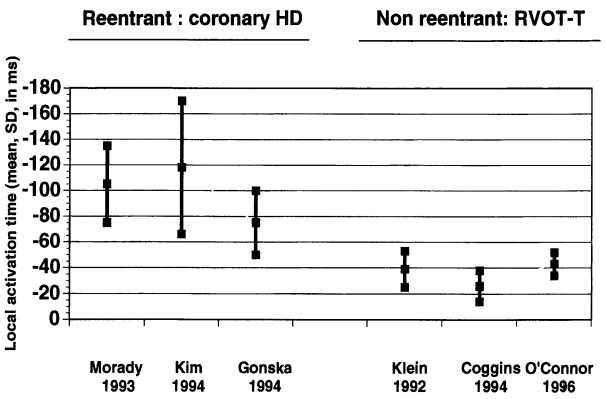

Figure 1. This figure compares the mean and standard deviation of the local activation time at successful ablation sites as reported in a variety of published series of ventricular tachycardia ablation[2–7]. The tachycardias have been divided into two groups according to their most likely mechanism, as reentrant or non-reentrant. See text for further discussion. HD: heart disease; RVOT-T: right ventricular outflow tract tachycardia.

Activation mapping may be used in two different ways: one is to search for the earliest electrical activity by comparing different ventricular sites. In this respect, it is clear that in non-reentrant rhythms there is no electrical activity at any site in the ventricle between the end of activation of each impulse and the following one. Thus, for each beat, the earliest activity will occur at the site of origin of tachycardia and, consequently, this technique should be of maximal accuracy. On the other hand, in reentrant rhythms there is activation throughout the cardiac cycle, adding difficulties to the interpretation of simple comparisons among activation times at multiple sites.

In reentrant rhythms, tissue has to be activated continuously throughout the cardiac cycle. It has been postulated that, during "electrical diastole" (i.e. between the inscription of two QRS complexes), only tissue that belongs to the circuit is being activated. Thus, identification of isolated mid-diastolic activity will be important in the mapping process. This will not be the case in non-reentrant rhythms where continuous activation is absent.

The impact of these differences can be appreciated by the analysis shown in Fig. 1. This figure compares the local activation time at successful ablation sites as reported in a variety of published series of ventricular tachycardia ablation[2–7]. The tachycardias have been divided into two groups according to their most likely mechanism, as reentrant or non-reentrant. Reentrant ventricular tachycardias were considered to be those occurring in the setting of coronary artery with previous myocardial infarction, since reentry is the generally accepted mechanism for these tachycardias[8,9]. Ventricular tachycardias arising from the right ventricular outflow tract were considered as examples of non-reentrant rhythms since the bulk of the evidence suggests that these arrhythmias are non-reentrant[7]. The value for each local activation time represents the mean and standard deviation of the local activation time of the ventricular electrogram relative to the QRS onset for the cases reported in each series. It can be noted that the degree of prematurity at successful sites is much less in non-reentrant tachycardias (in the range 20–50 ms) than in reentrant tachycardias (in the range 50–150 ms). The values for the latter group frequently correspond to mid-diastole, which is never the case in the former group. A second observation of these results is that the standard deviation of the mean is higher for reentrant than for non-reentrant tachycardias. The latter exhibit a more homogeneous behaviour. The behaviour of tachycardias in the setting of coronary artery disease is probably related to the fact that a reentrant circuit can be interrupted at several sites along its path (thus with variable degrees of prematurity).

The phenomena of resetting and entrainment in response to pacing manoeuvres are not exclusive of reentry and can be potentially observed in non-reentrant rhythms[10,11]. However, the response to these phenomena in terms of the analysis of the first post-pacing interval has not been well characterised in non-reentrant arrhythmias. In particular, the phenomenon of concealed

entrainment, as usually defined in tachycardias in the setting of coronary artery disease, i.e. with a long stimulus to QRS onset interval[12], has never been described in non-reentrant rhythms. The reverse is true for reentrant tachycardias, where both techniques are potentially useful in localising the arrhythmogenic substrate[12–14] (Table 1). In contrast, pace mapping is expected to be extremely useful in non-reentrant rhythms, but less so in reentry (Table 1). The site of origin of non-reentrant rhythms is extremely focal and, as long as it is endocardial, it is expected to be perfectly reproduced with endocardial pacing; in ventricular reentry the QRS onset is determined by the exit of the propagating wave front from an area were the amount of tissue deploarised is small (thus lacking electrocardiographic representation) to an area of nearly simultaneous depolarisation of a large amount of tissue. Such a change may be more gradual and can potentially involve a "wide" exit that could hardly be replicated by local pacing.

Figure 2 illustrates how these rather theoretical differences in the response to pacing relate to clinical observations. This figure compares the percentage of cases meeting each of the above pacing criteria in several published series[2,6,7,14–16]. Series are divided into the same two groups as in Fig. 1, according to the type of ventricular tachycardia treated. Pace mapping was good at virtually all successful sites in right ventricular outflow tract tachycardias, as expected for non-reentrant rhythms, whereas in reentrant tachycardias a good pace mapping was or was not present. Concealed entrainment was never described in non-reentrant tachycardias, but was present in a good proportion of successful sites in reentrant tachycardias. In a recent series, in which concealed entrainment was the only sign that was looked for, a high success rate was achieved[14].

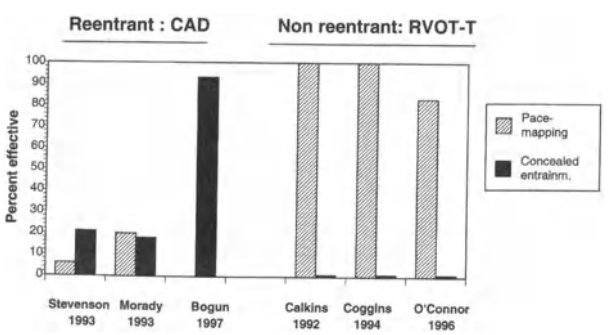

Figure 2. The height of each bar represents the percentage of cases meeting each of the pacing criteria at the successful ablation site in several published series[2,6,7 14–16]. Published studies are divided, as in Fig. 1, according to the most likely mechanism of the ventricular tachycardias treated. Abbreviations as in the previous figure.

Limitations of electrophysiological phenomena that help to localise arrhythmogenic substrates

Sinus rhythm mapping, as characterised more than 10 years ago[1], is highly sensitive, since approximately 85% of ventricular tachycardias arise at sites with abnormal electrograms during sinus rhythm. However, these abnormalities are not specific, since they can be found, in diseased ventricles, at several sites other than those where ventricular tachycardias are originated[1]. In the ablation era a recent study found that the electrograms during sinus rhythm at sites that show concealed entrainment during ventricular tachycardia, are always fractionated, and frequently late[17].

In using activation mapping for reentrant ventricular tachycardia, it is important to realise that several assumptions are made, and each of them may or may not be true in specific cases; these assumptions, as well as their limitations, are listed in Table 2.

In "vortex-like reentry" and macro-reentry the activation wave front may be continuously exiting from the circuit to the surrounding myocardium. Under these circumstances an ECG reference, i.e. the QRS, onset may be hard to find. In some other instances,

Table 2. Assumptions and limitations of activation mapping in reentry

Assumptions
1. Relatively localised exit from the circuit
2. Good identification of QRS onset
3. Depolarisation of myocardial mass divided into two general areas:
   (a) "Electrical" systole: with ECG representation
   (b) "Electrical" diastole: without ECG representation
4. All mass depolarised during electrical diastole belongs to the circuit

Limitations
1. Vortex-like and macro-reentry without localised exit: no ECG reference
2. Areas of slow conduction unrelated to the circuit may be diastolic
3. Side branches from the circuit may be diastolic
4. Areas of the circuit depolarised during systole are not identifiable

particularly in fast tachycardias, it is common experience that the QRS onset is hard to establish with precision, because of either confounding factors, such as the repolarisation of the previous beat, or intrinsically slow QRS forces. This may be a limitation since the degree of prematurity of the local electrogram at each site is established in relation to the QRS onset.

The rationale behind the consideration of presystolic or diastolic electrograms as part of the reentrant circuit postulates that the depolarisation of ventricular mass during ventricular tachycardia can be divided into two general areas (Table 2): (a) "electrical" systole, that involves the majority of the myocardial mass, is relatively synchronous, and thus has ECG representation; (b) "electrical" diastole, during which only a minority of myocardial mass is deplorised, conduction is likely to be slow to expand this phase over a long period of time and, consequently, there is no surface ECG representation. A corollary of these postulates is that during electrical diastole only myocardium belonging to the reentrant circuit is being depolarised. Therefore, identification of sites with local activation during electrical diastole would mean identification of sites that belong to the reentrant circuit.

A first, and obvious, limitation to this approach is that areas of the circuit depolarised during electrical systole, even if they are localised, are not identifiable by activation mapping.

The assumption that all diastolic electrograms belong to the reentrant circuit has two major limitations (Table 2): (a) side branches from the circuit may be diastolic; (b) areas unrelated to the circuit but having slow conduction and relative protection may also be inscribed during diastole, being in fact extremely late sites from the preceding beats. We proposed years ago that pacing at a distance from the circuit producing resetting or entrainment of ventricular tachycardia could differentiate these late sites from early sites related to the circuit[18]. As depicted in Fig. 3, the electrograms of both types of site could behave similarly during VT,

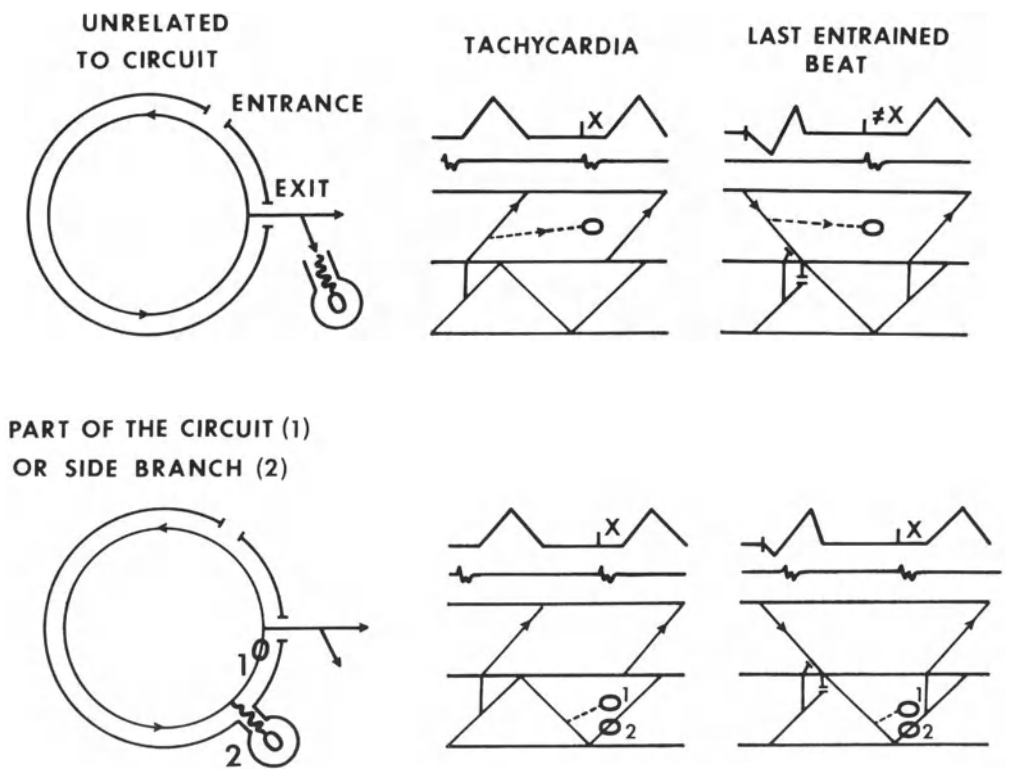

Figure 3. Schematic representation of the expected behaviour of diastolic electrograms in response to stimulation producing transient entrainment according to whether the electrogram is a component of the reentrant circuit (or a side branch from the circuit) (upper panel) or a site with slow conduction but unrelated to the tachycardia circuit (lower panel).

preceding the QRS onset by x ms. However, on the first tachycardia beat after pacing, sites that are components of the circuit (or side branches related to it) are likely to bear a similar time interval to the QRS onset as during tachycardia (x ms, Fig. 3, lower panel). However, late sites unrelated to the tachycardia (Fig. 3, upper panel) would bear a fixed relationship to the preceding paced beat during pacing and entrainment. Thus, after the last paced beat, the time interval to these late sites would be independent from the time interval to the following tachycardia beat. This phenomenon is expected to result in a different time interval between this electrogram and the QRS onset of the first tachycardia beat after pacing (Fig. 3).

Figure 4 illustrates an example of this type of phenomenon. The tracing shows the last few beats of a pacing train producing transient entrainment of a ventricular tachycardia followed by resumption of tachycardia. During tachycardia (on the right of Fig. 4) two electrogram components (named "a" and "b" in the figure) are inscribed during electrical diastole, preceding the QRS onset by 150 and 115 ms respectively. However, although both electrograms are recorded by the same bipolar signal and both are diastolic, they behave differently on the first beat after pacing. The "b" component precedes the first tachycardia QRS complex by 115 ms, exactly the same as during tachycardia. In contrast, the "a" component precedes the QRS onset by 300 ms on that beat, but by 150 ms during tachycardia, suggesting that this "a" component is in fact "late" and unrelated to the circuit.

As previously stated, pacing at a distance from the circuit may not be able to distinguish between true components of the circuit and sites located in the

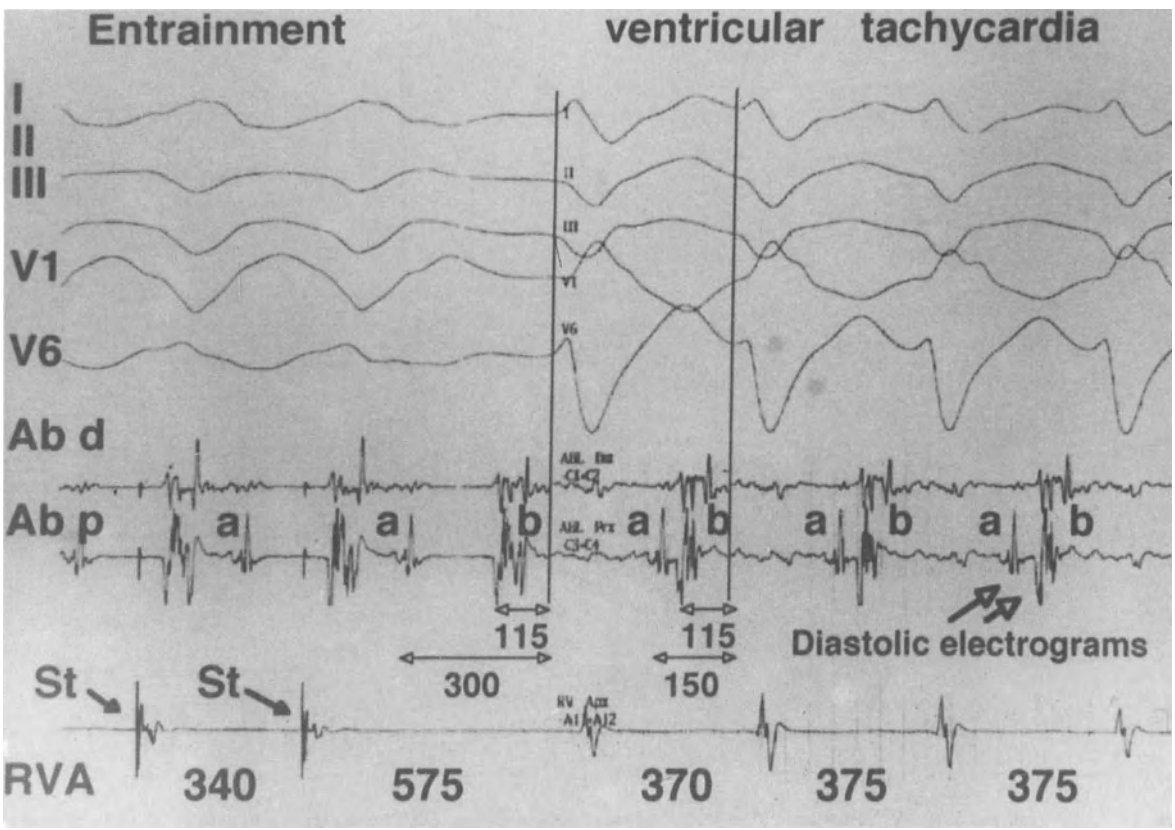

Figure 4. Tracing illustrating different behaviour of diastolic electrograms in response to pacing producing transient entrainment of ventricular tachycardia. Four surface electrocardiographic leads are shown along with intracardiac electrograms from the distal (d) and proximal (p) bipoles of the ablation catheter (Ab) located in the left ventricle and the right ventricular apex (RVA). The tracing shows the last two beats of a pacing train delivered during tachycardia followed by resumption of tachycardia. See text for further discussion.

so-called side branches of the circuit. This problem could be approached by pacing manoeuvres performed at the same site that is to be analysed. The presence of concealed entrainment, that is entrainment without surface ECG fusion (paced QRS morphology identical to tachycardia QRS morphology) and with a long stimulus to QRS interval[12] can serve as a general identification of areas that are at or close to the tachycardia circuit. A difficulty with the phenomenon of concealed entrainment is that classic criteria for entrainment are absent and it may be hard to establish that entrainment is in fact taking place. The presence of a constant first post-pacing interval in relation to pacing trains of variable number of beats at the same paced cycle length[19,20] may help to distinguish entrainment from other phenomena such as concealed perpetuation of tachycardia during pacing. Pacing at a side branch from the circuit can also produce concealed entrainment. Two additional criteria during concealed entrainment may help to distinguish side branches from true components of the circuit: the presence of a first post-pacing interval that equals the tachycardia cycle length and the presence of an interval between stimulus and QRS onset that equals the interval between the local electrogram at that site and the QRS onset during tachycardia[13,21]. The differentiation between side branches and true components of the circuit may at times be complex, as illustrated in the tracing of Fig. 5, obtained

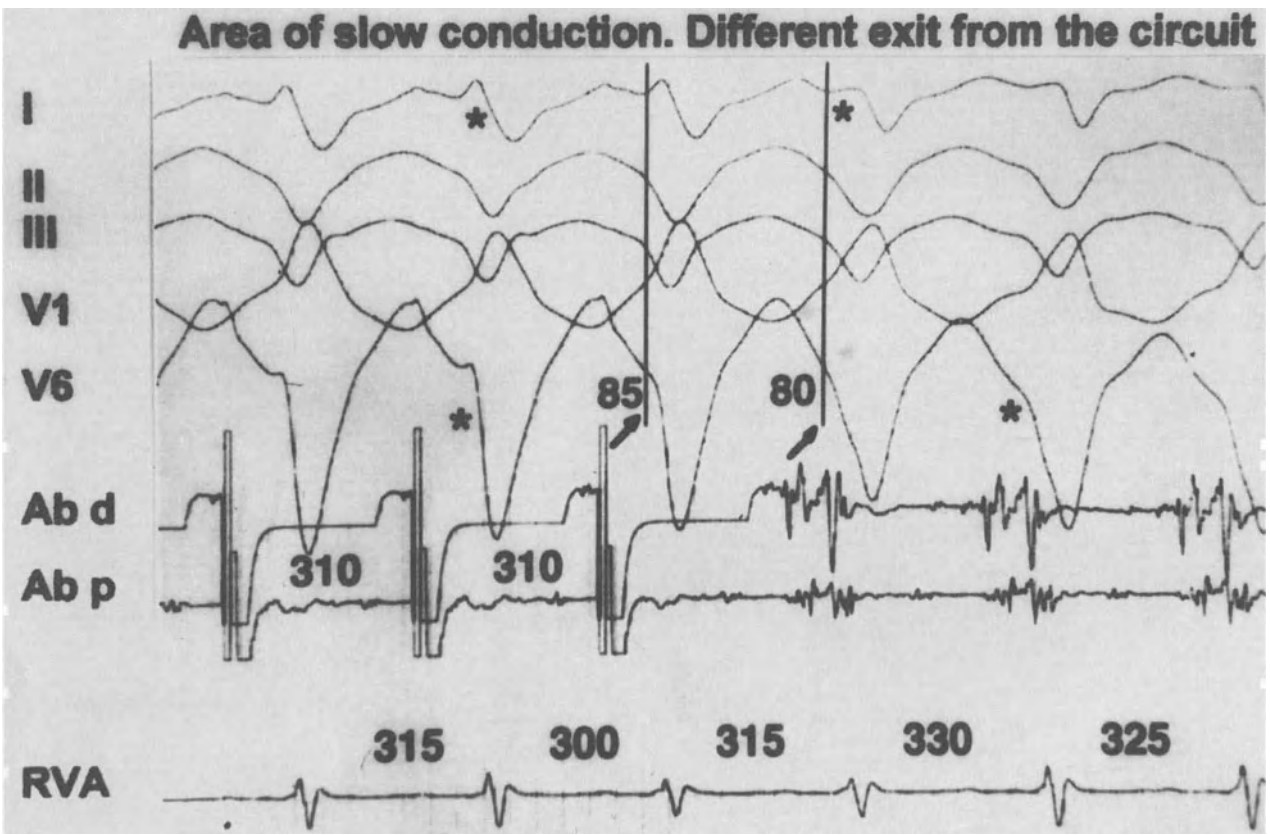

Figure 5. Tracing illustrating complexities in distinguishing true components of reentrant circuits from side branches of them. The figure is organised as Fig. 4, and shows the last three beats of a pacing train delivered during tachycardia followed by resumption of tachycardia. Although several findings such as a long stimulus to QRS interval and the similarity between the interval stimulus to QRS and electrogram to QRS during tachycardia suggest that the site belongs to the circuit, a minor difference in the QRS morphology during pacing as compared to the morphology during tachycardia provides evidence that the site is probably a side branch with a separate exit. See text for a more detailed discussion.

from an unsuccessful site. This presystolic electrogram at the ablation site preceded the QRS complex by 80 ms during tachycardia. Pacing produced entrainment with a stimulus to QRS onset that was long and of a similar value (85 ms), and a rather short first post-pacing interval. However, a careful look at the QRS morphology during pacing showed minor differences as compared to the QRS during tachycardia, suggesting that pacing is performed at a side branch of the circuit that has an exit to the surrounding myocardium that is different from the exit of the tachycardia circuit.

Despite these limitations, the value of the phenomenon of concealed entrainment to localise sites at the circuit has recently been analysed in a systematic way by delivering radiofrequency current at all sites demonstrating this phenomenon in a subset of patients with ventricular tachycardia in the setting of coronary artery disease[14]. Twenty-six tachycardias were included in 14 patients. Radiofrequency current was delivered at 46 sites with concealed entrainment. Success was achieved in 25 of 26 tachycardias (96%). The positive predictive value for the phenomenon of concealed entrainment was 54%.

Final considerations

From the presented data, it seems that the arrhythmia mechanism has a definite impact on "what to expect" from the mapping data. Thus, efforts to evaluate the underlying arrhythmogenic mechanism are of more than intellectual interest, and seem to be justified, particularly when the substrate is unusual or unclear.

All presently available mapping strategies have definite limitations, both on theoretical and practical grounds. These limitations may be overcome, to some extent, by combining techniques. The impact of technological advances in mapping techniques could be important but deserves careful evaluation.

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Chapter 17

THE MADIT TRIAL: WHAT WAS WRONG?

Philippe Coumel

The Madit trial[1] showed that implantation of a cardioverter defibrillator (ICD) in patients at risk of post-myocardial infarction ventricular tachyarrhythmias and their implicit further risk of sudden death was significantly more effective in preventing the latter than receiving "conventional" medical therapy. The problem resides in the definition of what was conventional treatment in Madit, and its potential differences with any better, if not best, medical therapy. However the main, if not the only, problem with Madit clearly is that the conventional treatment utilised in non-implanted patients was much less than optimal, whereas implanted patients benefited after all from better conditions. This may explain why the difference between the two groups became significant after a 27-month follow-up. However, this does not exclude the fact that implanted defibrillation cannot improve the performances of presently available better therapies than those used in Madit. Many problems evoked below were discussed in an excellent editorial published together with the original article[2].

The conception and design of Madit were finalised in the very late 1980s, that is, just after an active controversy on the real interest of serial drug testing in invasive electrophysiology[3], and at a time when the cardiological community was realising that type I antiarrhythmic drugs could be detrimental in patients with impaired myocardial function[4]. Experience with serial testing never contested that a patient apparently resistant to type I drugs was indeed at risk of arrhythmia recurrence, a situation that does not apply to β-blockers or amiodarone. Still, Madit selected patients especially for their resistance to procainamide, so that from the very beginning no chance was given to demonstrate the superiority of any drug, because their failure was taken as a premise. This protocol was poorly considered in Europe, taking as reference a drug not used in this continent for a decade. This situation is clearly reflected in the fact that a single European centre participated only until its end to Madit that grouped a total of 32 centres.

In order to evaluate the potential risks and benefits of any treatment in a protocol based on electro-physiological data, some important information is needed, that is missing in Madit. For instance, the proportion of patients who did not have any inducible arrhythmia at baseline is unknown. We do not know either what proportion of patients became non-inducible after procainamide. Finally we do not know what was the outcome of such groups, compared to the groups studied. The 8–10% mortality rate observed in the ICD group is far from being impressive, if one recalls that it is now commonly observed with truly beneficial medical therapy in patients at high risk.

Figure 1 summarises, from the published Madit data, what the "conventional" treatment was. This far from reflects current drug usage in the late 1990s, so that comparison of current reality with ICD is not valid. Type I drugs were given to 11% of patients in the non-ICD

P.E. Vardas (ed.), Cardiac Arrhythmias, Pacing & Electrophysiology, 121–124.

DRUGS	1 month		Last Contact	
	Drug Tx	ICD	Drug Tx	ICD
Class I agents	10	12	11	11
Sotalol	7	1	9	4
Digitalis	38	58	51	57
Beta-Blockers	8	26	5	27
Amiodarone	74	2	45	7
No Medication	8	56	23	44

Figure 1. The data (in percentages) are taken directly from the referenced publication of Madit, and have simply been rearranged. The 1-month and the last contact visits are considered. In the upper part the potentially detrimental drugs are presented, and potentially beneficial drugs are shown in the lower part. Important data are surrounded and linked for comparisons.

group at the 1-month follow-up visit, a surprisingly high incidence in patients already identified as resistant, and 2 years after the Cast study. This proportion may have been even larger during the first month, thus increasing the risk during the early phase. This may be more than a simple hypothesis, if one notes that the divergence of survival curves takes place early within the first 6-month follow-up period. It is quite acceptable that a definite advantage of ICD over drug therapy is to dissuade cardiologists from prescribing harmful drugs. Among these one must also mention digitalis, which was taken by 38% of patients at the 1-month visit, a proportion that increased to more than 50% of patients at the last follow-up visit: this drug was identified as an independent risk factor in earlier quite trustworthy studies[5]. The same applies to sotalol, that was given in close to 10% of the non-ICD patients, whereas the trial (SWORD) was interrupted, like Cast, for safety reasons. From the data available it is not possible to identify which proportion of patients actually took these potentially detrimental drugs, either alone (up to 50–70%) or in combination.

Looking now at potentially beneficial medications, the tenants of Madit argue that up to 74% of non-ICD patients were using amiodarone. In fact, only 45% of patients were indeed on amiodarone at the last contact, a proportion of "drop-outs" that is commonly observed in trials including amiodarone when arrhythmias are asymptomatic. For clinicians it is wise to admit that the beneficial effect of amiodarone is closely linked with its actual use rather than with intention-to-use. The EMIAT[6] and CAMIAT[7] trials demonstrated that a significant proportion of sudden deaths can be prevented by using this drug. It should be recognised that a definite advantage of ICD over any drug is compliance.

The most important item concerning drugs certainly is formed by β-blockers, given alone or in combination with amiodarone. The beneficial effect of β-blockers in the long-term follow-up of myocardial infarction is not contested, and the proportion of saved lives can amount to 50% in patients with depressed cardiac function. It is also fascinating to see not only that these drugs were practically not given in non-ICD patients in Madit (5% at the last follow-up visit) but that they were preferentially given to implanted patients, actually more than one-quarter of them. No explanation is proposed for such a situation, which might be usual in the US but is in sharp contrast to current European practice. Not only is the small number of non-ICD patients on β-blockers somewhat surprising, but the contrast with ICD patients suggests that β-blockers are still considered to be potentially dangerous drugs, to be given with caution only in patients benefiting from the protection of an ICD, a precaution that does not apply to type I drugs, digitalis or sotalol. Curiously, such a bias from prescription habits was also recently observed in the AVID[8] study. Finally, no information is given about the respective use in the two groups of other types of potentially beneficial drugs, and one may have some doubts about whether ACE inhibitors, aspirin, or lipid-lowering drugs were preferentially used in ICD patients, as were the β-blockers.

The question remains as to whether one can propose, if not an ideal medical treatment, at least a better treatment than the one used in Madit. Indeed the latter aim is much easier to attain than the former, and in this regard we can refer to our own experience. As early as 1986, 3-years before the results of Cast, we undertook a prospective study that systematically precluded the use of type I antiarrhythmics in the management of ventricular tachyarrhythmias in patients with an impaired left ventricular function. These patients were systematically treated with nadolol first, then the combination of amiodarone and nadolol in case of arrhythmia recurrence, which actually occurred in 50% of cases. Implanting a dual-chamber pacemaker became necessary when the

drug-induced bradycardia not only was poorly tolerated but partly responsible for arrhythmia recurrence. Finally, 25% of patients were implanted. Within the years 1986–87 45 patients were enrolled, with a history of 4 ± 3 attacks of sustained ventricular tachyccardia, and a left ventricular ejection fraction of 30 ± 8%. After a follow-up of 87 ± 11 months in the 19 patients who are still alive, the yearly mortality rate is less than 10% (Fig. 2). This number has to be compared with the 20% or 25% mortality rates of historical series, or of the non-ICD Madit patients. This may give an idea of the benefit that can be obtained from avoiding type I antiarrhythmics in such patients, and we certainly did so at a time when they were still largely being used. Finally, 12 of the 21 cardiac deaths in our patients were sudden, and they were equally distributed all over the long-term follow-up. Supposing that sudden deaths were arrhythmia-related deaths (a hypothesis which is actually not verified) one can regret that such patients were not protected with an ICD. At least some of these 12 patients might have survived for some more time thanks to an ICD, thus certainly shifting upward the survival curve of Fig. 2. From the beginning these patients were known to be sudden death candidates according to conventional risk factors. The real problem is to identify individuals more precisely. In this regard the absence of a statistical benefit when comparing the numerous series treated with drugs or with ICD does not suggest a limitation of ICD technology, but simply a limitation in our knowledge in the area of detection of sudden death candidates.

In Fig. 3 we compared survival curves observed in the two groups of Madit with the survival of our patients in the preceding study. The patients' collectives do differ, but the difference in the severity of ventricular tachyarrhythmias favours the Madit groups, in which the sustained tachycardias were non-clinical, although identified as potentially resistant, whereas in our group they were clinical and verified as resistant. The initial number of patients was less in our group, but almost identical numbers were available at the 27-month follow-up of Madit. At this date it is striking to see that the survival curves of ICD patients and our patients exactly coincide: had these patients been taken as a

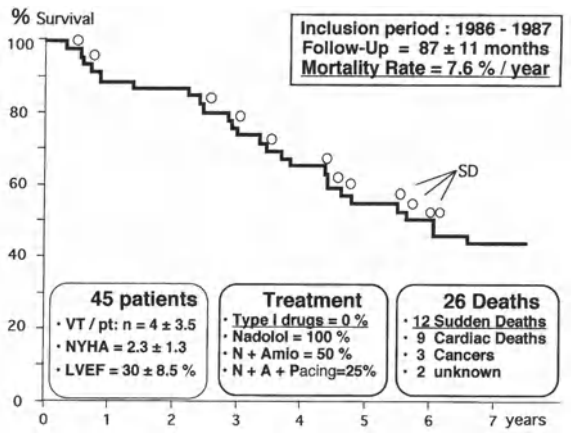

Figure 2. Medical management of tachyarrhythmias. A 7-year follow-up. A cohort of 45 patients with a history of ventricular tachycardia and an altered myocardial function was collected during a 2-year period and the complete follow-up of all patients covers some 7 years. The treatment systematically avoided type I drugs and included nadolol. It was combined with amiodarone in case of arrhythmia recurrence (50%), and a dual-chamber pacemaker was implanted in half these latter cases. The yearly mortality rate was 10% in the long term, and 12 of the 26 deaths were sudden (open circles). VT/pt = number of attacks of ventricular tachycardia per patient, NYHA = functional class, LVEF = left ventricular ejection fraction. Numerical values expressed as mean ± SD.

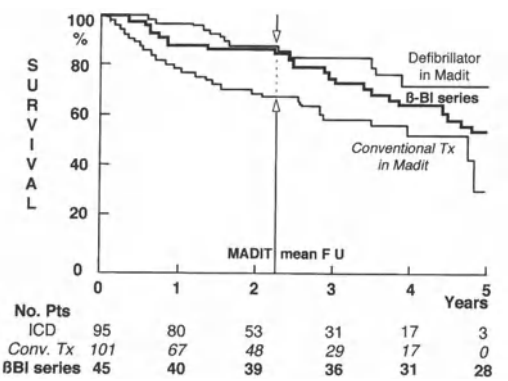

Figure 3. Comparison between Madit series and patients reported in Fig. 1. The Kaplan-Meier survival curve of the ß-blocker series is inserted in the two subgroups of the Madit trial (defibrillator and conventional treatment). At the 27-month follow-up, at which the Madit trial was interrupted because of the significantly better survival of ICD patients, survival of the ß-blocker series exactly matches ICD patient survival. Between this limit and the 5-year follow-up the apparent decrease of the ß-blocker series survival is based on a follow-up of all patients, whereas the actual number of cases in Madit decreases rapidly.

reference, clearly the Madit study would still be ongoing. Finally, the maximal 5-year follow-up period displayed in the Kaplan-Meyer actuarial curve of Madit should not make illusion, particularly when compared to ours if one refers to the number of patients: practically none in the Madit groups, compared to 28 in our group.

The reflection one can make as a conclusion is certainly not that ICD indications should not be extended to patients who are correctly treated by adequate drugs. Even well-treated patients can still die suddenly, and should benefit from ICD. Also, it may be questioned whether, in the long term, it is better to be protected by an ICD rather than amiodarone with its side-effects. On the other hand, however, ICD should not prevent the use of β-blockers, as their potential benefit is not restricted to sudden death prevention, but also extends to heart failure according to the accumulated evidence of various trials[9].

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Chapter 18

Survival Analysis and Classification of Death in Patients under Antiarrhythmic Treatment

Hugo Ector, Hein Heidbüchel and Frans Van de Werf

Introduction

The practice of medicine is becoming increasingly complex and, paradoxically, despite greater knowledge, even more uncertain[1]. Today, knowledge itself is defined on the basis of an arbitrary but accepted statistical test, performed in a randomised clinical trial[2]. What the physician thinks, suspects, believes, or has a hunch about, is assigned to the "not-knowing" category. Technical advances, expected to reduce clinical uncertainty, have not only contributed to its increase, but have even been used to obscure it[1]. Obscurity and uncertainty are also promoted by the lack of statistical expertise of the average clinician and by the sophisticated, sometimes overtly unclear, presentation of trial results.

As regards actual modern antiarrhythmic treatment, we struggle with the fact that arrhythmic death is an almost impossible definition[3,4]; so total mortality seems to be the only reliable endpoint. Total mortality is an inevitable 100% endpoint, when follow-up is long enough. In our opinion, for the study of arrhythmias, survival analysis cannot be reduced to a superficial matter of life and death[3]. This contrasts with other opinions, considering "sudden cardiac death" as a "soft surrogate endpoint"[5,6]. Total mortality as primary endpoint avoids difficult issues, but it may reduce the sensitivity of a trial below acceptable levels. Particularly in older patient populations, other causes of mortality are also likely to be recorded notably. An analysis of cause-specific mortality, rather than intention-to-treat analysis of total mortality, is to be preferred, and should be prespecified in the protocol, in line with the hypothesis under test[7].

More complications and confusion arise from the sloppy application of the "intention-to-treat" principle[7]. Clinicians and trialists also face controversies in counting and attributing events in clinical trials[8].

Classification of death

Presently accepted classifications of death do not fully describe or tabulate all significant aspects of terminal events, nor do they consider unique aspects of arrhythmia investigations[9]. Epstein et al present a new classification scheme; this uses the following categories: (i) primary organ cause (cardiac [arrhythmic, non-arrhythmic or unknown], non-cardiac or unknown); (ii) temporal course (sudden, non-sudden or unknown); (iii) documentation (witnessed, monitored [yes, no or unknown]); (iv) operative relation (preoperative, perioperative or

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postoperative); and (v) system relation (procedure-related, pulse generator-related and lead-related [yes, no or unknown]). A NASPE (North American Society of Pacing and Electrophysiology) Policy Conference recommended a set of definitions, statistical considerations, and minimal standards for reporting the outcome of ICD therapy[10]. All deaths should be classified as cardiac or non-cardiac deaths. Cardiac deaths should further be subclassified as sudden or non-sudden cardiac deaths. In addition, operative mortality, waiting period deaths and deaths related to hardware problems should be identified.

In CAST, death was judged to be due to arrhythmia if it was characterised in any of the following ways: (i) witnessed and instantaneous, without new or accelerating symptoms; (ii) witnessed and preceded or accompanied by symptoms attributable to myocardial ischaemia in the absence of shock or class IV congestive heart failure as categorised by the New York Heart Association; (iii) witnessed and preceded by symptoms attributable to cardiac arrhythmia – e.g. syncope or near-syncope; or (iv) unwitnessed but without evidence of another cause. In the presence of severe congestive heart failure, death was judged to be not to arrhythmia if death from heart failure appeared probable within 4 months of the fatal episode[11].

In the CAPS study it was suggested that, considering all the possible effects of antiarrhythmic drugs as well as the difficulty in classifying events, it may be more practical simply to evaluate total cardiac mortality in the conduct of any future randomised intervention trial[12]. The authors stress that such a classification could increase the sample size necessary to detect a difference between treatment and placebo, or could even obscure an improvement in arrhythmic mortality, if the active drug caused death by some other mechanism, such as congestive heart failure. Unless more precise measurements of the mechanism of death are developed, the combination of a time-based and aetiology-based assessment of cause of death will be necessary, since "sudden" death is not equivalent to "arrhythmic death".

A classification based on the condition of the circulation immediately before death appears to be the most relevant to studies of sudden death. In 58% of the 142 deaths[13] the subject collapsed abruptly and the pulse ceased without prior circulatory collapse (arrhythmic death); in 42% the pulse ceased only after the peripheral circulation had collapsed (deaths in circulatory failure). Ninety-three per cent of final illnesses that lasted less than 1 hour ended in arrhythmic deaths; 74% that lasted more than 1 day ended in deaths in circulatory failure. Eighty-eight per cent of deaths that occurred outside of the hospital were arrhythmic; 71% of deaths that occurred in the hospital were deaths in circulatory failure. Ninety per cent of deaths in which the primary illness was heart disease were arrhythmic; 86% of deaths in which the primary cause was other than heart disease were deaths in circulatory failure. Ninety-one per cent of deaths precipitated by an acute cardiac event were arrhythmic; 98% precipitated by acute respiratory obstruction, haemorrhage, infection, stroke or other non-cardiac events were deaths in circulatory failure. A classification of deaths as arrhythmic or circulatory failure cannot be entirely accurate unless the ECG is observed or recorded at the time of death.

In this study an estimate, based upon the proportion of cases in which the observational data were least complete or somewhat ambiguous, suggests that the number of misclassifications is not greater than 5% and, if present, primarily occurred among the unwitnessed deaths.

In clinical reports clarity competes with details. An appropriate code, together with total mortality and total cardiac mortality, is necessary for adequate reports on the natural history of life-threatening arrhythmias and on the results of modern treatment[14,15]. There are examples of coding systems in cardiology. NYHA functional class I–IV is a parameter used in nearly every clinical report[16]. The Lown grading of ventricular arrhythmias has achieved wide acceptance in the world of arrhythmias[17,18]. So a similar, concise, and descriptive code for reporting sudden death would be extremely convenient. Figure 1 represents the code $S_{1-4}D_{1-4}$. This code has been explained previously[14,15]. The code is applicable for drug-treated and for device-treated patients. We have forward put suggestions for a more complicated description of events in ICD patients[15] but, again, complexity creates a barrier, as is the case for the other quoted classification systems. If the code $S_{1-4}D_{1-4}$ limited the number of misclassifications to 5%[13], it would be a handy tool in all trials and studies on antiarrhythmic treatment.

Survival analysis and other statistics in clinical medicine

Today, for unproved treatments, it is a standard requirement to perform a properly designed randomised clinical

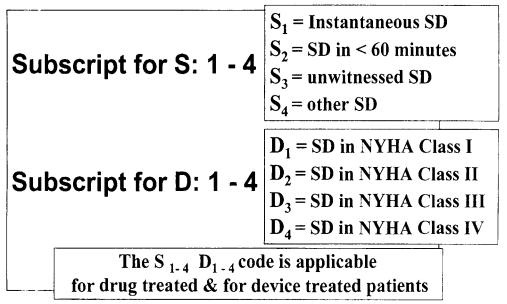

Figure 1. Classification of death in cardiac patients. SD = sudden death.

trial[19]. However, in view of the limitations of randomised trials, valuable observational studies remain necessary. We have to pay major attention to the events and observations that occur in the ordinary circumstances of clinical practice. Randomised trials are unfeasible for studying multiple therapeutic candidates, instabilities due to rapid technological improvements and long-term adverse effects[20]. In comparison to the normal, expected life expectancy of individuals included in major trials, the mean follow-up duration is very short: CAST[11]: 10 months; MADIT[21]: 27 months; CAMIAT[22]: 1.79 years; EMIAT[23]: 21 months (median); so it is obvious that, when the trial ends because of excess mortality in one treatment arm, the long-term complications and side-effects remain unknown.

The most notorious techniques for survival analysis are the Kaplan-Meier method, life-tables, log-rank statistics, Cox's proportional hazards model, multivariate logistic regression, odds ratios, relative risk calculations and, more recently, a triangular sequential design modified for two-sided alternatives. The books listed in refs 24–27 have been crucial for our understanding of survival analysis.

For the clinician it is necessary to differentiate between statistical significance and clinical relevance. Many studies refer to risk reduction, without clearly accentuating the absolute value of risks. Confidence limits and attention to the power of a study are of major interest. The statistical representation of results is too often not as simple and clear as it should and could be.

Age, gender and duration of follow-up deserve full attention. These demographic data allow the calculation of expected survival, mortality. An easy and attractive tool is the "standardized mortality ratio"[27]: the number of observed deaths divided by the number of expected deaths. Life-tables and Kaplan-Meier curves only reflect the duration of follow-up, occurrence of death, and time of censoring. There is no correction for the age at the time of inclusion in the study. The standardised mortality ratio adjusts the mortality rate to eliminate the effects of age, sex, and follow-up duration[28]; so it adds to a better comparison of outcomes in randomised and observational studies. It is a parameter to be added to the standard patient characteristics such as means and standard deviations of age and follow-up. It is a pity that standard statistical packages do not provide easy processing of the procedure.

Intention-to-treat analysis and analysis by actual treatment

The intention-to-treat analysis ("analysis as randomised") is a standard way of handling survival data for randomised studies to minimise biases resulting from exclusion of selected patients[29]. It includes all randomised patients in the groups to which they were randomly assigned, regardless of their compliance with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol[30]. It has been argued that intention-to-treat encourages sloppiness: "Whatever we do, give the treatment or not, it is OK since the analysis is by intention-to-treat!"[7]. It is very likely that the percentage of nonsense conclusions equals the percentage discontinuation of allocated treatment for reasons other than outcome events. Maximal adherence to the original treatment allocation is a must! An analysis by actual treatment, including only those patients who satisfy the entry criteria, and who adhere to the protocol subsequently, is mandatory, but requires a strict follow-up. If both analyses lead to the same conclusion the strength of that conclusion is considerably increased. When they lead to different conclusions, troubles arise[7,10,29]. A secondary analysis by actual treatment, in which data are censored at a specific time, such as in the case of ICD explant (without replacement) or cardiac transplantation, may provide useful explanatory information[10]. The intention-to-treat principle has different implications in function of the test hypothesis: comparison of an active agent with placebo, assessment of equivalence between two treatments, competing risk situation, safety analysis[7].

Modern trials and some fallacies

For the clinician it is important to be concerned about classical statistical errors[31]. Type 1 errors are false-positive errors that assign statistical benefit to a given modality, when such benefit does not exist. Type 2 errors are false-negative errors: the observed distinction is regarded as not significant (no benefit), whereas in reality a benefit exists. Type 2 errors can arise in circumstances in which the numbers of observations are too small: insufficient power of the study. Another report advocates type 3 and type 4 errors[31]. Type 3 errors are errors in which the risk of a given medical or public health approach is underestimated, undetected or not specifically sought, leading to an underestimate of the risk-benefit balance. Type 4 errors arise because the risks of a given medical intervention are overestimated, leading to under-use or abandonment of a useful intervention. It should be emphasised that type 3 errors appear to be much more frequent than type 4 errors. This stems, in part, from the failure of medicine to establish effective mechanisms for the rapid recognition and correction of errors. Most recorded medical history deals with triumphs of medicine. The disasters are usually interred along with the victim-patients. The introduction into the field of antiarrhythmic treatment, of notions as type 3 and type 4 errors, could offer interesting perspectives.

Besides these classical errors, other misunderstandings can arise from insufficient data analysis and/or presentation as there are: omission of simple absolute risks[23], omission of simple mortality data[11], conventional medical treatment without preset minimum requirements[21,32], one-sided significance tests[22], inappropriate drug selection[11,33], cumulation of results for different drugs in one group[11,21,34]. Discontinuation of antiarrhythmic drug treatment, especially when compared to ICD therapy, can be a fatal error in high-risk patient groups. In the MADIT study[21,32], only 45% of the patients with drug treatment were taking amiodarone at the time of the last follow-up visit. Study medication withdrawal in the placebo/amiodarone arm was 21.4/38.5% in EMIAT[23] and 25.5/36.4% in CAMIAT[22].

Conclusions

The most provocative challenge in cardiology for the next decade will be the attempt to delay "sudden death" as long as possible. To replace this final event by another "terminal endpoint" such as death from heart failure, carcinoma, cerebrovascular accident, is not at all attractive. The implantable cardiac defibrillators cut deaths[34] by reverting sudden arrhythmic death. Amiodarone can prevent arrhythmic death[22,23]. Length and quality of life interfere with cost/benefit considerations. In the Madit patient population the cost of ICD treatment per life-year saved was US$27 000, in the AVID study it was US$114 000[35].

Can survival and financial calculations ever offer a definite solution for individual patients in different socioeconomic and philosophical backgrounds? We believe not. We concur with Voltaire that "common sense is not so common", but the clinician hardly needs unbiased information, based on adequate and objective data analysis. The study of money is the one in which complexity is used to disguise truth or to evade truth, not to reveal it[36]. Let us hope that clinical trials and practice will not suffer from this syndrome, described by Galbraith[36].

What should the practitioner do when a new treatment is described? The most concise answer comes from Kassirer[37]. We cannot uncritically adopt the new strategy, but are obliged to use our inferential skills to answer several questions. Is my patient similar to the subjects studied? Is the magnitude of the difference between the new treatment and the existing one sufficient to justify a switch? Can the results of the study be generalised to patients in my practice and to the type and quality of care available locally? Affirmative answers to these questions will encourage a switch to the new therapy.

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Chapter 19

Quality of Life in Clinical Trials and Practice

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Introduction

Since 1948, when the World Health Organisation defined health as being not only the absence of disease and infirmity but also the presence of physical, mental, and social well-being, quality-of-life issues have become steadily more important in health-care practice and research[1]. There has been a nearly exponential increase in the use of quality-of-life evaluation as a technique of clinical research since 1973, when only five articles listed quality of life as a reference key word in the Medline database. During the subsequent 5-year periods there were 195, 273, 490, and 1252 such articles[2]. Quality of life is increasingly being incorporated into clinical trials as a complementary endpoint to the traditional outcomes of mortality and morbidity. Several factors are related to the growing interest in quality of life: advances in medical care have made available an array of therapeutic options, with quality of life being the only difference in treatment choice. Quality-of-life issues are becoming central to the treatment of chronic conditions that accompany the growth of an ageing population. Increasingly, patients expect to participate as partners in therapeutic decisions, and quality-of-life data are important in these decisions. Finally, regulatory authorities are requesting quality-of-life outcome data as a part of new drug or device approval[3]. These factors highlight the limitations of traditional mortality and morbidity endpoints and the need for a more comprehensive assessment of therapies which include a range of variables referred to as quality of life. Furthermore, the growing fields of outcome research and health-technology assessment evaluate the efficacy, cost-effectiveness, and net benefit of new therapeutic strategies to determine whether the associated increases in expenditures for health care are justified.

Although the objective dimension is important in defining a patient's degree of health, the patient's subjective perceptions and expectations translate that objective assessment into the actual quality of life experienced. It is now generally agreed that quality of life should be measured as an integral component of most trials, particularly where treatments are given with palliative or symptomatic intent[4]. Although a recent editorial has criticised the routine inclusion of quality-of-life evaluation in clinical trials even when the structure of the evaluation and its rationale appears ill-defined, the incorporation of quality-of-life measures in clinical studies is receiving a higher priority, and often provides information which would be unobtainable by

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other means[5]. It is important to distinguish the different applications of quality-of-life measures because instruments that have proved useful when applied in one context may be less appropriate elsewhere. A good research tool may be impractical for clinical uses. Generally, more attention has been given to the use of quality-of-life instruments in clinical trials than to examining their value in routine clinical care, medical audit, or resource allocation[2–8].

Definition of quality of life

The term "quality of life" misleadingly suggests an abstract and philosophical approach, but most approaches used in medical contexts do not attempt to include more general notions such as life satisfaction or living standard, and tend rather to concentrate on aspects of personal experience that might be related to health and health care[6]. The term "quality of life", as applied in the medical literature, may not have a distinctive or unique meaning. Many investigators seem to substitute quality of life for other terms intended to describe a patient's health, such as health status or functional status[9]. Although the concept of quality of life is inherently subjective, and no universal definition exists, there is an emerging consensus that quality of life can be assessed on the basis of four components: physical condition, psychological well-being, social activies and everyday activity. All of those four dimensions can be subdivided in various aspects: for instance, physical function includes mobility and self-care, whereas the social dimension includes aspects such as intimacy, social support and social contact to the family. The emotional dimension includes aspects such as anxiety and depression. Thus, quality of life can be viewed as a multidimensional concept that is best approached empirically through multiattribute measurement techniques.

Unfortunately, many trials dealing with aspects of quality of life do not assess the construct properly, or they assess only a single or limited aspect of what is a multidimensional construct. Moreover, multidimensional endpoints such as quality of life present particular problems of design, analysis and interpretation[6]. Quality-of-life assessment measures changes in physical, functional, mental, and social health in order to evaluate the human and financial costs and benefits of new programmes and interventions[2]. The rationale for a quality-of-life assessment in clinical research should be outlined in an analytical model that describes the relations among predictor variables and response variables and the time frame during which the effects on quality of life are elicited.

Constructing quality-of-life measurement scales

The measurement of quality of life should address each objective and subjective component that is important to members of the patient population and susceptible to being affected, positively or negatively, by interventions. In order to compare quality of life with other patient groups it is strongly recommended to use standardised instruments. Many new instruments reflect the multidimensionality of quality of life. There are several factors influencing the selection of appropriate instruments to assess quality of life[7]. The first and most important issue when selecting an instrument is how well it will perform in the required situation. This can be assessed from the instrument's psychometric properties.

Validity and reliability are necessary for all contexts. *Reliability* means that all instruments must produce the same results on repeated use under the same conditions. This can be examined by test-retest reliability, although in practice it may be difficult to distinguish measurement error from real changes in quality of life[6]. Reliability is often assessed by examining internal reliability – the degree of agreement of items addressing equivalent concepts. Inter-rater reliability also needs to be established for interview-based assessments. The *validity* of quality-of-life measures is more difficult to assess because instruments are measuring an inherently subjective phenomenon. An informal but essential approach is to examine face validity by asking whether instruments seem to cover the full range of relevant topics. This process may be enhanced by including people with a wide range of backgrounds in the assessment process. In addition, in-depth descriptive surveys of the relevant patient group should be consulted, as these provide invaluable evidence of the range of patients' experiences. Once validity has been shown for one purpose it cannot be assumed for all possible populations or applications. Measures of quality of life that can distinguish between patients at a point in time are not necessarily as sensitive to changes (responsiveness) in patients over time when repeated. *Responsiveness* is a measure of the association between the change in the observed score and the change in the true value of the construct. Responsiveness is a crucial requirement for

most applications, especially in clinical trials. The absence of a standard against which to assess the measurement properties of a quality-of-life instrument is a particular problem when examining instruments sensitive to change. Although a measure may be responsive to changes in the true value of the construct, graduations in the metric of the observed score may not be adequate to reflect these changes. *Sensitivity* refers to the ability of the measurement to reflect true changes or differences in the true quality-of-life value. Problems such as an inadequate range or delineation of the response can mask important and therapeutically meaningful changes in quality of life. One of the most important areas for further development is in making quantitative change scores for quality of life more clinically meaningful. To ensure that the quality-of-life measure used is the most appropriate, the health problem and likely range of impacts of the treatment being investigated need to be carefully considered. Established instruments cannot be assumed to be most appropriate. One approach to improving the appropriateness of quality-of-life measures is to use instruments that let patients select the dimensions of most concern. Quality-of-life measures that are to be used routinely should be brief and simple. Brevity may mean, however, that potentially important information about patients' experiences is missed, and the validity and responsiveness of shorter instruments need to be studied[6]. Basic requirements of quality-of-life assessments are: reliability, validity, sensitivity, responsiveness, appropriateness to use and practical utility.

Quality-of-life instruments

Quality of life is commonly measured with a complex collection of items, scales, domains, and instruments. An *item* is a single question, a *scale* contains the available categories or other mechanisms for expressing the response to the question[9]. For example, a specific question might be answered with a scale having an open-ended blank to be filled in as the patient desires, or a set of several categories, or a visual analogue line on which the patient places a quasidimensional mark. All three of the scales cited above are called global, because no specific criteria were offered to demarcate the choice of categories or other expressions. A *domain* identifies a particular focus of attention, such as digestion or functional capacity, and may comprise the response to a single item or responses to several related items. An *instrument* is the collection of items used for obtaining the desired data. The instrument may contain a single global question or multiple items that may or may not be categorised into separate domains. To measure quality of life in a particular study, investigators may employ one or more instruments. For a single instrument the output result of multiple component items or domains is typically formed in one of two ways[9]. In the first way the components are preserved and cited individually, in tandem, to form a *profile*. In the second method of forming an output the component parts are aggregated to create a single composite *score*. For some instruments the results may be reported as either a profile or a single aggregated score, or both.

The instruments and techniques used to assess quality of life vary according to the identity of the respondent, the setting of the evaluation and the type of questionnaire used (short form, self-assessment instrument, interview, clinic-based survey, telephone query, or mail-back survey), and the general approach to evaluation. Generic instruments are used in general populations to assess a wide range of domains applicable to a variety of health states, conditions, and diseases[2]. They are usually not specific to any particular disease state or susceptible population of patients, and are therefore most useful in conducting general survey research on health and making comparisons between disease states. Generic instruments have advantages and disadvantages. Many health-related dimensions remove the need to select dimensions for a particular study and allow for the detection of unexpected effects. A further benefit of generic instruments is to facilitate comparisons among different disease groups. A negative aspect is that a broad approach may reduce responsiveness to effects of health care. Disease-specific instruments focus on the domains most relevant to the disease or condition under study, and on the characteristics of patients in whom the condition is most prevalent. Disease-specific instruments are most appropriate for clinical trials in which specific therapeutic interventions are being evaluated. Disease-specific instruments have several theoretical advantages. They reduce patient burden and increase acceptability by including only relevant dimensions. Disadvantages are the lack of comparability of results with those from other disease groups and the possibility of missing effects in dimensions that are not included[7]. Batteries of scales and modular instruments combine the generic and disease-specific approaches by maintaining a core module of questions applicable to diverse disease states and patient

populations to which the questions most relevant to the disease and therapy in question are added as needed. Studies have shown that clinicians' and patients' judgements of quality of life differ substantially, and systematic assessment may improve health professionals' judgements[6]. Therefore, self administered questionnaires or questionnaires administered by interviewers should be used. Three study designs are most commonly used in quality-of-life evaluation[2].

The first is the cross-sectional or non-randomised longitudinal study, which describes predictors of quality of life (for example, specialty versus primary care). The second common design is the randomised study of a clinical intervention. In these studies the measures must reflect the nature of the disease, be responsive to perceptually meaningful changes, and be sensitive to changes within the range of function specific to the disease. The third common design is the study of cost-effectiveness and cost-benefit analysis, which estimates the incremental cost of a programme or treatment as compared with the programme's incremental effects on health, which are usually measured by adjusting a clinical outcome such as survival by the quality of life.

Quality of life in cardiovascular diseases

Quality of life has been systematically studied in many cancer trials[10]. Besides the evaluation of quality of life in cancer patients, interest has been focused on quality-of-life aspects of cardiovascular diseases. Studies on quality of life after open-heart surgery are available for the following patient groups: heart transplantation[11–14], heart valve replacement[15], and coronary angioplasty and bypass surgery[16–18]. In addition, reports have been published on quality of life in patients with severe heart failure[19], in patients with hypertension[20], and in patients with implanted antibradycardia pacemakers[21]. Recently, quality-of-life aspects have been addressed in patients with paroxysmal atrial fibrillation[22–24], in patients after radiofrequency catheterblation[25–28], and in patients with implantable cardioverter-defibrillators[29–32]. Because prospective and systematic quality-of-life studies are lacking in a large number of patients with implantable cardioverter-defibrillators and in patients with atrial fibrillation, we have undertaken systematic studies to address the impact of device therapy and atrial fibrillation on quality of life in these specific patient populations.

Quality of life in patients with implantable cardioverter-defibrillators

In 1991 a prospective and systematic evaluation of quality of life in implantable cardioverter-defibrillator recipients was started at the University of Bonn. In a pilot study the impact of an implantable cardioverter-defibrillator on quality of life, psychological profile and patient acceptance was assessed in 57 consecutive patients using a specifically designed questionnaire. The results of this pilot study demonstrated that the acceptance of the implantable cardioverter-defibrillator was remarkably high (Figs 1 and 2). Based on the encouraging results of our pilot study we started a prospective study design on quality of life, anxiety, depression and acceptance of the implantable cardioverter-defibrillator over a long-term follow-up period using standardised intruments. In our prospective study two different types of instruments are applied (Table 1): specifically designed questionnaires as well as standardised and validated instruments. The specifically designed questionnaires cover the following dimensions: socio-demographic data including age, education, occupation level, driving behaviour, return to work and sexual activity. Further dimensions address social adjustment, expectations of the device, future perspective and adaptation to the ICD. In addition, the following standardised instruments are completed by the patients: the Freiburger Personality Inventory (FPI) to assess personality structure, the State-Trait-Anxiety Inventory

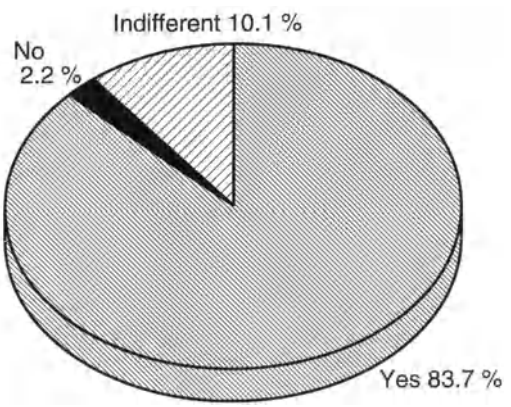

Figure 1. Was it worth having an implantable cardioverter-defibrillator implanted? Responses to the key question of a specifically designed questionnaire.

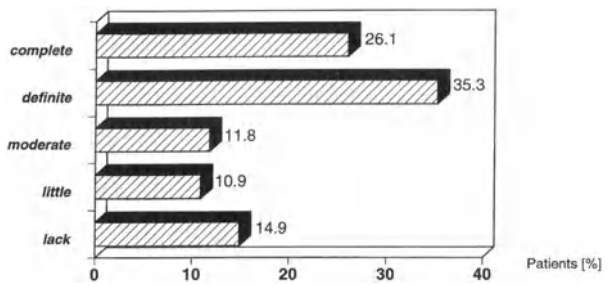

Figure 2. Quality of life 12 months after ICD implantation. After 1 year there was a complete improvement of quality of life in 26.1% of patients, a definite improvement in 35.3%, a moderate improvement in 11.8%. No change in quality of life occurred in 14.9% of patients.

(STAI) to examine anxiety, the Medical Outcomes Study Short-Form General Health Survey (MOS-SF 36) to address generic quality-of-life aspects, the Beck Depression Inventory (BDI) to assess mood disorders, the Complaint List to evaluate physical symptoms and a questionnaire to examine coping behaviour. The personality structure was evaluated only once before ICD implantation. The coping behaviour was studied before and 12 months after ICD implantation. All other questionnaires and standardised instruments were addressed before and 1, 3, 6, and 12 months after ICD implantation.

Description of test instruments (Table 1)

Freiburger personality inventory (FPI)

This test was used to examine the personality structure before ICD implantation. The inventory comprises 138 questions about personality disorders, attitudes, and behaviour. Each question is rated as yes or no.

Medical outcomes study short-form health survey (MOS-SF 36)

This instrument asks for views about health. This information will help us to know how the patient feels and how the patient is able to do usual activities. The MOS-SF 36 has been developed as a brief and simple questionnaire in order to be useful in practice. The test is a generic instrument that covers a broad range of quality-of-life dimensions in a single instrument. The test has been translated into German and has been validated in a large number of different patient populations. The short form of the MOS comprises 36 items, each rated on a four-point-scale measuring physical dimensions of quality of life. It is easy to score and can be divided into different subsets. The MOS-SF 36 addresses the following dimensions: physical, social, and role functioning; everyday life; patients' perceptions of their general health and well-being and satisfaction with treatment.

State-trait-anxiety inventory (STAI)

The STAI is a self-rating scale for evaluating two different components of anxiety. The X1 scale is designed to measure state anxiety and the X2 to measure generalised (trait) anxiety. The X1 form comprises 20 items which relate to the subject's present situation. The possible response categories are 1 (not at all), 2 (somewhat), 3 (moderately) and 4 (very much). The X2 form, which also comprises 20 items, assesses how the subject feels in general, irrespective of the given situation. The possible responses are: 1 (almost never), 2 (sometimes), 3 (often) and 4 (always). The total scores are calculated for each subject as measures of state and trait anxiety respectively. The test-retest reliability of the STAI is well documented (trait $r = 0.84$, state $r = 0.34$). Studies on construct validity in which the

Table 1. Quality of life in implantable cardioverter-defibrillator recipients: study design

	Baseline	1 Month	3 Months	6 Months	12 Months
Disease-specific questionnaires	○	○	○	○	○
Medical Outcomes Study MOS-SF36	○	○	○	○	○
State-Trait-Anxiety Inventory	○	○	○	○	○
Symptom Checklist	○	○	○	○	○
Beck Depression Inventory	○	○	○	○	○
Personality Inventory	○				
Coping Behaviour	○				○

scale was administered repeatedly on different conditions have shown point-biserial correlations of $r = 0.60$ and $r = 0.73$. The X1 scale can be used for follow-up measurements. The minimal sum for each scale is 20, the maximum sum score is 80.

Complaint list (B-L)

The Complaint List evaluates the extent of subjective impairment due to the physical and general complaints. It covers a particularly broad range of physical and mental disorders. The test is suitable for evaluating clinical course. Two parallel versions of the B-L are available (B-L, B-L′), each of which comprises 24 items. The symptoms are rated on a four-point scale as follows: 0 (not at all), 1 (scarcely), 2 (moderately) and 3 (severely). The scores of the items in each of the two versions are added together to form total raw scores, which give the overall impairment due to physical and general symptoms. Norm values are available for calculation of *t*-values and stanine-values. The parallel test reliability is between $r = 0.85$ and $r = 0.93$. The validity of the test is also well documented. The test can be used for repeated measurements. Data should not be evaluated if more than 10% are lacking.

Beck depression inventory (BDI)

The Beck Depression Inventory categorises patients as depressed or not depressed. The higher the score the greater the degree of depression. The questionnaire comprises 21 dimensions. Each dimension is rated on a four-point scale in order to measure mood disorders. The Beck Depression Inventory has been translated into German and has been validated in a large patient population. A score of 11 or less implies normality, 12–17 weak depression, 18–26 moderate depression, and 27 or more suggests severe depression. The psychometric properties are well documented and a considerable number of studies have shown the usefulness of this test in English-or German-speaking cardiac patients.

Coping behaviour

All patients complete a questionnaire before and 12 months after ICD implantation, consisting of 67 items each rated on a four-point scale to assess coping behaviour. The different coping strategies are subdivided into problem-orientated strategies aimed at alteration in environmental pressures and barriers, and emotion-orientated strategies aimed only at modifying awareness of the problem situation. Problem-orientated coping strategies include confrontative coping, self-control, efforts to achieve social support, and planned problem-solving, while distancing, flight avoidance and positive reevaluation are classified as palliative approaches. It is an excessively one-sided view to regard a patient's efforts to cope with this disorder as an adaptive process only from a viewpoint of long-term physical health. Since subjective well-being and quality of social functioning at any particular time are included in the assessment, the overall judgement may vary widely.

Multicenter study on quality of life in atrial fibrillation

Atrial fibrillation is a frequent and costly health-care problem representing the most common arrhythmia resulting in hospital admission. The overall prevalence of atrial fibrillation in the United States ranges from < 1% in young, otherwise healthy individuals up to nearly 9% in elderly patients. In addition to symptoms of palpitations, patients with atrial fibrillation have an increased risk of stroke and may also develop decreased exercise tolerance and left ventricular dysfunction. All of these problems may be reversed with restoration and maintenance of sinus rhythm. Thus, treatment of atrial fibrillation is warranted in hopes of eliminating symptoms, preventing complications, and possibly decreasing mortality associated with this commonly occurring arrhythmia. The impact of atrial fibrillation on quality of life has not been widely evaluated, and of the relatively few studies in this area few have defined quality of life in a comprehensive manner or used validated methods. Therefore, a worldwide prospective study will address the impact of atrial fibrillation on patient health-related quality of life using validated generic measures and specific conducted disease scales (Table 2). The following centres will participate in this multicenter trial: Bonn, Germany (Investigators: W. Jung, S. Herwig, B. Lüderitz); London, United Kingdom (A. Brygave, J. Waktare, A.J. Camm); Milwaukee, WI, USA (J. Sra, M. Akhtar); Toronto, Canada (M. Paquette, D. Newman, Paul Dorian); Redmond, WA, USA (K. Wood, G. Ayers, InControl).

Description of the instruments (Table 2)

A standard *demographic* component (11 items) given to patients at baseline only will be used to record the patient's age, sex, education, social contents and socio-economic status. *Predictive scales* are given to patients at baseline only in order to help identify subsets of patients who may be more or less responsive to various psychosocial interventions. The *Life Orientation Test* (LOT) (13 items), which is a measure of optimism, has been shown to have good internal consistency in past studies and it has good discriminant validity. The LOT is currently being used in the Multicentre Quality of Life in Paroxysmal Atrial Fibrillation Study. The *Barsky Somatization Scale* is a 10-item measure of somatisation and has been used in a wide variety of cardiac populations including patients with paroxysmal atrial fibrillation.

The following *outcome scales* will be given to patients at baseline, 3 months, 6 months, and one year: the *Medical Outcomes Study Short-Form Health Survey (MOS-SF 36)* is a generic health scale measuring several health domains including physical functioning, role functioning, social functioning, mental health, vitality, pain, and general health perceptions. It has been utilised and validated in a diverse spectrum of disease states, in general cardiac populations and in patients with implantable cardioverter-defibrillators. The 20-item modified Goldman *specific activity scale* (SAS) is a functional status scale for patients with cardiovascular diseases. The original version of this scale is in a "yes/no" format but the current version has been revised to increase its discriminatory power. The *symptom checklist* (16 items) quantifies both symptom frequency and severity of symptoms related to arrhythmias. Initial investigations of content validity were in an atrial fibrillation population, and it is currently being validated as part of an ongoing study (Multicenter Registry of AV Nodal Ablation and Pacing in Atrial Fibrillation – Ablate and Pace Trial). The *illness intrusiveness scale* is a 13-item scale designed for patients with chronic illness. The concept of illness intrusiveness is introduced to represent the disruptions to activities, interests, and general functioning caused by the patient's chronic illness. Often the illness will also compromise psychosocial well-being, and increase emotional distress. This scale has been validated in a number of diverse disease states including end-stage renal disease, mood disorders, and rheumatoid arthritis.

Clinical disease variables (assessed by patient and physician). A summary score will be used to classify the patient's clinical burden of atrial fibrillation as mild, moderate, or severe. *Atrial fibrillation severity scores* will be assessed by objective and subjective portions of the clinical disease burden according to patient and physician assessments. These variables will provide a matrix of clinical disease severity and a summary score.

Summary

The efficacy of a treatment is primarily based on objective criteria such as mortality and morbidity. Besides these criteria, the interest in measuring quality of life in relation to health care has increased in recent years. Although the concept of quality of life is inherently subjective, and definitions vary, it is generally agreed that quality of life is a multidimensional construct and can be assessed on a basis of four major components:

Table 2. Quality of life in atrial fibrillation: timing of questionnaire administration

Questionnaire	Baseline	3 Months	6 Months	12 Months	After	
					Shock	Atrial fibrillation
Demographic data	○					
Clinical evaluation	○	○	○	○		
Short-Form 36	○	○	○	○		
Specific Activity Scale	○	○	○	○		
Symptom Checklist	○	○	○	○		
Illness Intrusiveness Scale	○	○	○	○		
Life Orientation Test	○					
Barsky Somatisation Scale	○					
Atrial Fibrillation Severity Score	○	○	○	○		
Impact of Events Scale					○	○

physical condition, psychological well-being, social activities, and everyday activities. Basic requirements of quality-of-life assessments are: reliability, validity, sensitivity, responsiveness, appropriateness to use and practical utility. The instruments to assess quality of life can be disease-specific or generic, depending on the context. Recently, interest has been focused on quality-of-life aspects of cardiovascular diseases. However, the impact of the implantable cardioverter-defibrillator or of atrial fibrillation on quality of life has not been widely evaluated, and of the relatively few studies in this field, few have used validated methods. Therefore, a prospective and systematic evaluation of quality of life in implantable cardioverter-defibrillator recipients was started at the University of Bonn in 1991. The results of the pilot study demonstrated that the acceptance of the implantable cardioverter-defibrillator was remarkably high. Furthermore, a worldwide prospective study will address the impact of atrial fibrillation on patient health-related quality of life using validated generic measures and specific conducted disease scales.

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PART TWO

NON-INVASIVE ELECTROCARDIOLOGY

Chapter 20

Heart Rate Variability in Vasovagal Syncope

George Kochiadakis and Panos Vardas

Introduction

Heart rate variability (HRV) is considered to be a marker of autonomic nervous activity[1–3]. Today, there is substantial interest in using the analysis of HRV to evaluate a variety of medical conditions, either as a means of quantifying the severity of the disease or as a way to explore the role of the autonomic nervous system in its pathophysiology.

A small number of valuable studies have employed temporal and/or spectral analysis of HRV in order to investigate the role of the autonomic nervous system in the pathogenesis of vasovagal syncope[4–10]. Vasovagal syncope has attracted a great deal of research interest, since it occurs in a large number of patients and its pathophysiology is still unclear[11–13]. Although previous studies agree that the autonomic nervous system appears to play an important part in the pathogenesis of vasovagal syncope, its precise role is unknown[12–17]. The importance of resting autonomic tone in the aetiology of vasovagal syncope and the precise pathophysiological mechanisms of the parasympathetic response are still under investigation.

Assessment of resting autonomic tone in patients with vasovagal syncope

Previous studies have used analysis of HRV to assess whether patients with vasovagal syncope have altered baseline autonomic tone when compared with healthy individuals, but the results so far have been conflicting. Lipsitz et al[4] reported diminished HRV parameters under baseline conditions just before tilt in vasovagal patients. Abi-Samra et al[18] reported increased heart period variability in tilt-positive subjects. In contrast, Morillo et al[8] and Lippman et al[9] reported normal autonomic tone just before tilt in these patients. Sneddon et al[19] recently reported comparable cardiac autonomic inputs, assessed by 24-h HRV, in patients and control subjects.

One of our studies[20] using the analysis of HRV showed that patients with vasovagal syncope exhibit a significant day-to-day variation in vagal tone. In particular, in 35 patients with vasovagular syncope and 15 healthy volunteers, who underwent two tilting tests 1 week apart, we determined the HRV indices over the 24-h period prior to every test. Of the 35 patients, 21 also experienced syncope in the second test (group P-P), whereas the remaining 14 did not (group P-N). None of the 15 control subjects experienced syncope during either of the tilt table tests.

Statistical analysis showed that, while in healthy individuals all HRV indices showed a high degree of stability over time, in patients with vasovagal syncope the time and spectral indices of HRV which reflect parasympathetic tone (HF, rMSSD, pNN50) had a significantly higher day-to-day variation. It is important to note that, according to our results, the above

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variation in vagal tone was confined to the patients whose clinical result was not reproduced in the second tilt table test (Table 1). The positive first test in all the patients was associated with increased parasympathetic tone, as shown by the elevated spectral and time domain indices of HRV, which reflect parasympathetic activity, and by the reduced LF/HF ratio, which indicates a swing of the sympathovagal balance towards the parasympathetic. However, for the patients with a negative second test (P-N), the associated values of all HRV indices were not significantly different from those of the control group, whereas for the patients with two positive tests (P-P) the HRV indices of parasympathetic tone were consistently higher than normal on both occasions (Table 2).

The above observations strongly suggest that patients with vasovagal syncope do not enjoy the autonomic stability found in healthy individuals, but instead undergo periodic fluctuations in parasympathetic activity which, at times when their vagal tone is augmented, render them more susceptible to syncopal episodes. This variation in vagal tone could explain the conflicting results of earlier studies which investigated the importance of resting autonomic tone in the aetiology of vasovagal syncope.

Autonomic nervous system changes during tilting in patients with vasovagal syncope

Previous studies have used temporal and/or spectral analysis to investigate RR variability before and during

Table 1. Day 2-day 1 differences in time domain and spectral indices of HRV in the groups and the associated 95% confidence intervals

	NL		SP		P-P		P-N	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
	95% CI		95% CI		95% CI		95% CI	
ΔNN	−17.13	51.74	−44.29*	63.71	−9.90	33.72	−95.68*	63.99
	−45.78 to 11.52		−66.17 to −22.40		−25.25 to 5.44		−132.80 to −58.91	
ΔLF	0.06	0.41	−0.10	0.35	−0.07	0.27	−0.15	0.45
	−0.17 to 0.28		−0.22 to 0.02		−0.19 to 0.06		−0.41 to 0.11	
ΔHF	0.01	0.31	−0.26*	0.45	−0.04	0.26	−0.59*	0.48
	−0.16 to 0.18		−0.42 to −0.11		−0.16 to 0.08		−0.87 to −0.32	
ΔL/H	0.01	0.05	0.04*	0.07	−0.002	0.05	0.10*	0.06
	−0.02 to 0.04		0.02 to 0.06		−0.03 to 0.02		0.07 to 0.13	
ΔSD	−2.73	8.41	−1.43	11.43	−0.57	12.48	−2.71	9.95
	−7.39 to 9.47		−5.36 to 2.50		−6.25 to 5.11		−8.46 to 3.03	
ΔrMSSD	−1.47	3.89	−7.54*	9.47	−1.05	5.58	−17.29*	4.05
	−3.62 to 0.69		−10.80 to −4.29		−3.59 to 1.49		−19.62 to −14.95	
ΔpNN50	−1.17	2.30	−4.84*	5.37	−1.23	2.19	−10.24*	3.94
	−2.45 to 0.10		−6.68 to −2.99		−2.23 to 0.24		−12.23 to −8.24	

* $p < 5\%$ compared to NL

We would expect 95% of the mean differences to fall within that interval. Thus, tight intervals around 0 containing medically unimportant differences are a sign of a stable outcome. Significant differences in day-to-day variations among groups were revealed in mean RR and HF, LF/HF, rMSSD and pNN50.

All HRV measures in the control group displayed slight day-to-day variability in both time domain and spectral indices. In the patients with vasovagal syncope only LF and SD show comparable behaviour. The LF/HF ratio, even though the 95% confidence interval of the day2-day 1 difference was tight, did not contain 0, meaning significant change, while HF, rMSSD and pNN50 both showed greater variability in individual day2-day 1 differences and were far removed from 0, also meaning significant changes. This fluctuation was due entirely to the P-N subgroup, which differed significantly from the P-P subgroup and the controls in ΔRR, ΔHF, ΔLF/HF, ΔrMSSD and ΔpNN50. The P-P subgroup showed slight variability of all HRV measures, matching that of the controls.

Table 2. Means and standard deviations (SD) of HRV indices in NL and SP over 2 days

	NL				SP				P-P				P-N			
	Day 1		Day 2		Day 1		Day 2		Day 1		Day 2		Day 1		Day 2	
HRV index	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
NN	814.93	90.32	797.80	82.93	914.9*	107.39	870.6†	119.90	921.0*	113.61	911.1*	116.54	905.8*	100.79	810.00	100.52
LF	5.96	0.45	6.01	0.40	6.06	0.64	5.96	0.72	6.03	0.61	5.96	0.64	6.12	0.71	5.37	0.84
HF	5.24	0.36	5.24	0.34	5.68*	0.54	5.42†	0.66	5.58*	0.53	5.54	0.60	5.84*	0.52	5.25†	0.72
L/H	1.14	0.06	1.15	0.05	1.06*	0.07	1.09†	0.08	1.07*	0.07	1.07*	0.08	1.04*	0.06	1.14†	0.08
SD	60.73	21.65	58.00	18.54	59.06	16.11	57.63	21.47	58.81	17.01	58.24	22.74	59.43	15.29	56.71	20.21
rMSSD	32.27	14.33	30.80	12.88	40.23*	11.91	32.69†	13.47	37.86*	13.89	36.81*	15.26	43.79*	7.16	26.50†	6.90
pNN50	11.29	10.37	10.12	8.67	22.44*	9.45	17.60†	9.17	22.22*	8.53	20.99*	7.97	22.76*	11.01	12.52†	8.71

* $p < 5\%$ compared to NL; † $p < 5\%$ day 1 vs day 2.
NL: normal controls; SP: syncopal patients; P-P: two positive tilt table tests; P-N: first test positive, second test negative.
Frequency domain indices of HRV: LF: low (0.06–0.15 Hz) frequency components of spectral power (a measure of sympathetic activity with some influence from the parasympathetic nervous system); HF: high (0.15–0.40 Hz) frequency components of spectral power (an index of parasympathetic activity); L/H: a measure of the sympathovagal balance.
Time domain indices of HRV: SD: mean of all 5-min standard deviations of NNs; rMSSD: root mean square of difference between successive NNs; pNN50: proportion of adjacent NNs differing by more than 50 ms. (The first of these time domain indices reflect total HRV, whereas the last two provide an indication of vagal tone.)

tilt testing, mostly in normal individuals[17,21–23]. These studies tend to agree that, in normal subjects, a change in posture from lying to standing causes a decrease in vagal modulation of the RR interval and an increase in sympathetic nervous system activity. However, their findings conflict with regard to the relationship between autonomic tone and syncope[8,12–14,17,21–23].

Lipsitz et al[4], in a study of young individuals with no history of syncope but a positive tilting test, reported an increase in both sympathetic and parasympathetic activity immediately after tilt. Morillo et al[8] reported an impaired sympathetic response and failure to withdraw parasympathetic tone under orthostatic stress in 15 syncopal patients with a positive tilting test. Both these studies compared the HRV measures immediately after tilt with the baseline values.

Two other studies looked at HRV measures towards the end of tilt testing. Lippman et al[9], in a study of 17 patients with vasodepressor syncope, reported that values representing parasympathetic tone shortly before syncope were higher than the end-test values in tilt-negative patients. In contrast, Mizumaki et al[10] reported an alteration in sympathovagal balance leading to sympathetic predominance just before syncope in 13 patients.

It can be seen from the above that there is no general consensus as to the most appropriate time points for recording HRV indices. Furthermore, so far there has been no attempt to classify tilting test subjects on the basis of the type of their haemodynamic response and to relate this to changes in autonomic nervous system activity. These factors, together with the relatively small size of the patient populations investigated, may go some way towards explaining the discrepancies in the above findings.

In an attempt to clarify these matters, in a study of 44 patients and 20 control subjects we used spectral analysis of HRV to record changes in autonomic nervous system activity associated with different stages of the tilting procedure. More precisely, we compared the spectral indices of HRV for three 4-min intervals defined as follows: the last 4 min before the test, the first 4 min immediately after tilt and the 4 min just before the end of the test. Furthermore, the patients were classified into three groups, according to the type of their haemodynamic response, and each group contained sufficient patients for statistically valid comparisons to be made.

Our findings in principle confirmed previously published data, demonstrating that, in normal subjects, there is a clear activation of the sympathetic system and a withdrawal of the parasympathetic system immediately after tilt. This shift in vasovagal balance persists until the end of the test (Table 3)[17,21–23].

In syncopal patients the pattern of changes in autonomic nervous system activity during tilt testing is quite different (Fig. 1). Although these patients experience the same parasympathetic withdrawal as do control subjects immediately after tilting, the autonomic balance does not change, since there is a parallel decrease in sympathetic tone. Furthermore, syncopal patients experience a "delayed" activation of both sympathetic and parasympathetic systems just before the onset of syncope, although the increase in the LF/HF ratio indicates sympathetic predominance at that time (Table 3). Among syncopal patients the three subgroups showed the same pattern of autonomic nervous system changes during tilt, suggesting that the pathophysiological mechanism is basically the same in each case (Fig. 2).

Table 3. Low (LF) and high (HF) frequency spectral power and the LF/HF ratio for four-minute intervals before (Rest), during (Tilt) and at the end of tilt testing (End) in normal controls and syncopal patients

	Controls		Syncopal		
	Mean	SD	Mean	SD	p
LF					
Rest	4.99	0.85	4.90	1.17	n.s.
Tilt	5.63*	0.69	4.44*	1.15	0.01
End	5.59*	0.91	6.15*†	1.15	0.001
HF					
Rest	5.19	0.70	4.94	1.11	n.s.
Tilt	4.66*	0.87	4.54*	1.10	n.s.
End	4.57*	0.98	5.66*†	0.94	0.0001
LF/HF					
Rest	0.96	0.14	1.00	0.17	n.s.
Tilt	1.21*	0.24	0.99	0.19	0.001
End	1.22*	0.25	1.10*†	0.13	0.0001

Rest: the last 4 min before the test. Tilt: the first 4 min immediately after tilt. End: the 4 min just before the end of the test.
* Significantly changed compared with baseline (Rest) value.
† Significantly different from post-tilt (Tilt) values.
The p-values refer to differences between controls and syncopal patients.
It is quite clear that the LF/HF ratio, an index of autonomic balance, was unchanged by tilt in syncopal patients, while the increase which appeared just before syncope (End) did not reach the levels measured in normal subjects at the corresponding time point.

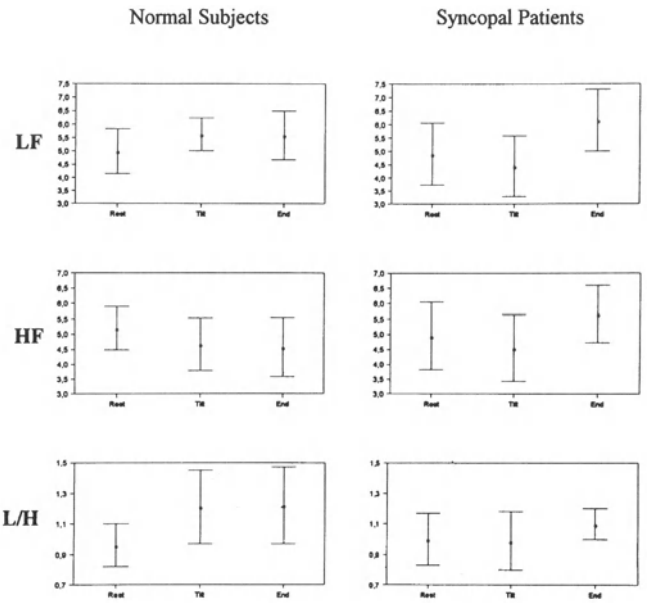

Figure 1. Means and standard deviations of heart rate variability parameters for 4-min intervals before (Rest), during (Tilt) and at the end of tilt testing (End) in normal controls and syncopal patients. There is a clear difference in the pattern of response between the two groups.

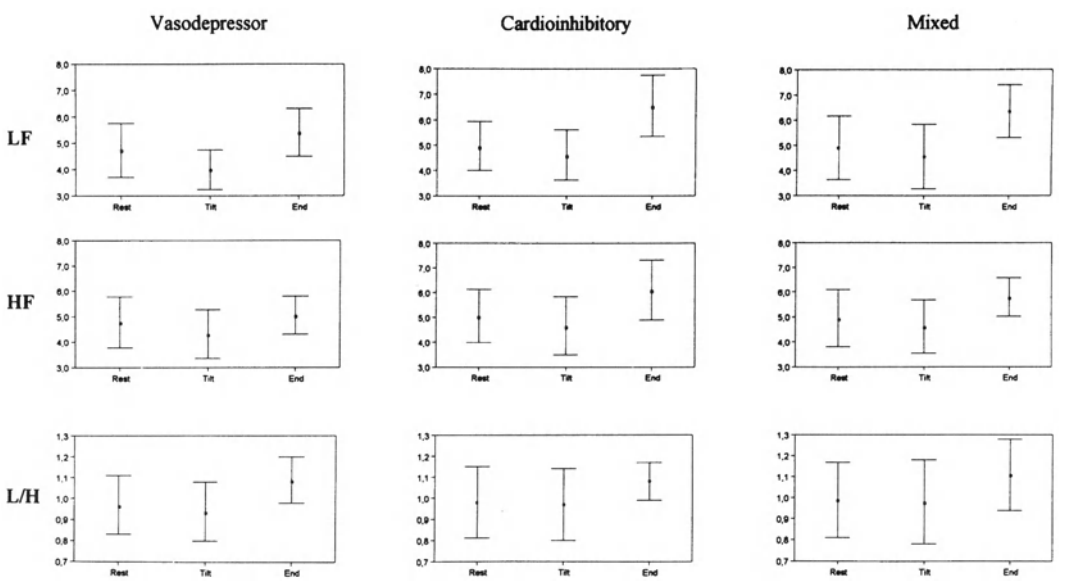

Figure 2. Means and standard deviations of heart rate variability parameters for 4-min intervals before (Rest), during (Tilt) and at the end of tilt testing (End) in three subgroups of syncopal patients. All three subgroups have a similar pattern of response.

It is clear from our results that the cycle of events leading to the final reaction begins very soon after tilting and becomes clinically evident later.

Cohen et al[24] have suggested that there is a parallel response, involving the LF/HF ratio and forearm vascular resistance, when lower body negative pressure is applied. Thus, a lack of increase in the LF/HF ratio immediately after tilt in our patients with vasovagal syncope is probably an indication of abnormalities in vascular control immediately after the assumption of an upright posture, perhaps indicating an abnormal response on the part of the cardiopulmonary and/or arterial baroreceptors. This hypothesis is consistent with our haemodynamic findings, which showed that patients with vasovagal syncope exhibited no significant increase in heart rate or in systolic or diastolic blood pressure immediately after tilt, with the result that the first two of those parameters had values significantly lower than the control values at that time (Table 4). Evidence suggesting that individual susceptibility to vasovagal syncope may be modulated by an impaired vasoconstrictor response to head-up tilt, as well as increased cardiopulmonary baroreceptor gain during lower body negative pressure, provides further support for our findings[19,25,26].

Our observation that patients with vasovagal syncope exhibit a sympathetic and parasympathetic activation with sympathetic predominance shortly before the onset of syncope, agrees with the results of previous studies which evaluated autonomic nervous system activity in terms of hormonal indexes[3,7,27,28]. Our findings are also supported by evidence which suggests that immediately preceding syncope there is a vigorous myocardial contraction and a significant decrease in left ventricular end-systolic dimension[29]. However, as is shown in the results (Table 3), the fact that the mean values of the LF/HF ratio in syncopal patients, though increasing significantly before syncope, do not reach the levels measured in normal subjects at the corresponding time point, may be an indication that the sympathetic activation just before the onset of syncope is insufficient to produce an adequate increase in peripheral vascular resistance. The significantly lower systolic and diastolic blood pressure found in syncopal patients shortly before the syncopal episode provides further support for this hypothesis (Table 4).

Table 4. Haemodynamic variables for 4-min intervals before (Rest), during (Tilt) and at the end of tilt testing (End) in normal controls and syncopal patients

	Controls		Syncopal patients	
	Mean	SD	Mean	SD
HR				
Rest	63.50	10.00	60.46	11.98
Tilt	78.10*	13.14	69.22	14.95
End	77.90	12.86	77.56*	15.80
SBP				
Rest	133.85	22.52	129.51	18.26
Tilt	142.70*	23.45	129.56†	17.09
End	133.70	20.44	94.37*†	23.37
DBP				
Rest	77.47	12.57	77.68	14.24
Tilt	84.84*	11.15	81.07	11.39
End	86.70*	9.58	64.49*†	22.08

* Significantly changed compared with baseline (Rest) value.
† Significantly different from control values.
HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Conclusions

Although the measurement of HRV parameters employed is an indirect method for the assessment of autonomic nervous system activity, and cannot be assumed to represent global events, we consider that it contributes to a fuller understanding of the pathophysiological mechanism of vasovagal syncope. First, on the basis of our findings and those of previous investigators[12,25,26], we consider that, in patients with vasovagal syncope, the cycle of events leading to the final reaction begins very soon after tilting and becomes clinically evident later. More precisely, the failure of muscle vasoconstriction could be a primary phenomenon responsible for increased susceptibility to tilt-induced syncope. Failure of adequate muscle vasoconstriction and the gradual reduction in blood pressure may explain the subsequent increase in sympathetic activity which has been reported in all relevant studies. The coexistence of increased sympathetic tone with a diminished venous return leads to vigorous ventricular contraction on a relatively empty cardiac chamber. This results in the activation of mechanoreceptors in the ventricular wall that trigger the reflex bradycardia and/or vasodilatation. However, since the pattern of changes in autonomic nervous system activity during tilt testing does not differ between the three subgroups of syncopal patients, we are forced to conclude that other factors, so

far unknown, must be involved in the pathophysiological mechanism which determines the type of haemodynamic response to syncope.

Secondly as far as the tonic autonomic tone is concerned, analysis of HRV showed that it demonstrates a considerable fluctuation in these patients in contrast with the normal subjects, and that increased vagal tone at certain times renders them more susceptible to syncopal episodes. These fluctuations could explain both the variability of the clinical outcome of tilt table testing and the sporadic nature of clinically symptomatic presentations of vasovagal syncope.

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Chapter 21

The Role of Non-invasive Diagnostic Techniques in Reducing Mortality in Postmyocardial Infarction Survivors

Ronald W.F. Campbell

Introduction

The postmyocardial infarction patient is an important and relatively easy target for clinical attention. Having survived a potentially serious event, there is a variable outlook based on a variety of mechanical and electrical criteria. High-risk and low-risk survivors of infarction can be identified. Indeed, long before sophisticated tests, clinical acumen was quite sufficient to make a reasonable separation of infarct survivors in respect of those who would do well subsequently and those who would not. A remarkable variety of non-invasive diagnostic techniques have been used to predict mortality in myocardial infarction survivors. Regrettably, in many circumstances these features are seen to be in competition. Each, however, may predict something different. This would encourage the concept of using a battery of tests, each designed to predict a variety of adverse future outcomes.

Postmyocardial infarction

The average 1-year mortality of post-infarct survivors is between 4% and 9%. With relatively simple techniques a very low-risk population (1-year mortality 3% or less) and a high-risk group (1-year mortality 20% or more) can be identified. The purpose of defining prognosis, however, is to offer therapeutic interventions which bring benefit. For these purposes the nature of the adverse event must be predicted. Postmyocardial infarction patients may die of new ischaemic events, of mechanical complications or of electrical complications.

Non-invasive predictors

Given the need to predict different types of adverse outcome for myocardial infarction survivors, it is surprising that currently available techniques perform as well as they do. Some procedures are directed at the status of myocardial perfusion. These include exercise testing[1,2] and ST analysis on Holter monitoring. Other techniques examine the extent of myocardial functional damage and in this respect ejection fraction determined by echo or by nuclear procedures is the best developed[3]. Yet other procedures examine the electrical stability of the infarct survivor's myocardium. These include: Holter monitoring for ventricular ectopic beat density[4,5]; signal-averaging to identify late potentials representing scarred myocardium and zones of slowed conduction[6–9], QT interval prolongation[3,10,11] and QT dispersion abnormalities on the surface ECG[12]; and heart rate variability changes analysed from Holter monitoring[13]. The latter

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reflects conditions of autonomic tone which have been linked with an adverse prognosis.

A practical strategy

No single non-invasive test post-infarction stands out from all others. Each type of investigation has its champion. Arguably the most important tests are those which identify modifiable circumstances. Even more important might be test results which identify adverse prognostic circumstances *and* which are beneficially modified when effective therapies are provided. Currently, there is no evidence that antiarrhythmic drugs prescribed to infarct survivors bring prognostic benefit. The value of the variety of electrical tests is rather to define a general high-risk patient for whom other prognostically beneficial interventions are indicated. Such therapies include revascularisation, aspirin, β-blockers, and ACE inhibitors. Much needs to be done to improve risk prediction post-infarction. The two newest non-invasive electrical tests, heart rate variability and QT dispersion, are worthy of development. Both are being applied to the EMIAT population[14] in an attempt to determine their value as risk predictors and to assess whether their modification by administered therapy has in itself predictive information regarding the usefulness of that therapy.

Other considerations

Postmyocardial infarction prediction is complicated by the fact that the underlying disease is dynamic. It is unrealistic to expect that defining risk at a particular moment in time will provide a secure long-lasting risk estimate for an individual patient. Very few studies have been performed examining the time-dependent variation in risk prediction. No risk prediction stategy can omit more general disease-related risk features such as cholesterol, homocysteinaemia, family history, etc. Many of these can be modified to the benefit of the patient. Clearly they work in concert with the previously described more specific risk predictors.

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Chapter 22

QT Prolongation and Proarrhythmia

Ronald W.F. Campbell

Introduction

The QT interval is a surface ECG measure of time for cardiac depolarisation and repolarisation. The component reflecting depolarisation, the QRS complex, is relatively short (typically less than 100 ms) compared with the time for repolarisation typically 300 ms or more. Since the first descriptions of the congenital long QT syndrome[1], QT interval prolongation has been feared as a harbinger of serious arrhythmias, particularly torsade de pointes[2]. This most serious of drug-related proarrhythmic forms occurs with a wide variety of drug therapies including antiarrhythmic drugs, antibiotics and antidepressants. On the other hand, amiodarone, which often produces remarkable QT prolongation, has very rarely been associated with proarrhythmia in the form of torsade de pointes. Recently, the concept of QT dispersion has been advanced to explain this anomaly[3,4]. Basically, QT dispersion is a surface ECG measure of QT interval variability that is thought to reflect dispersion of cardiac repolarisation. Conceptually, QT prolongation might reflect either homogeneous or inhomogeneous cardiac repolarisation. If the former, then proarrhythmia might not be expected; whilst if the latter, arrhythmias might be encouraged. There is growing evidence to support this notion.

Torsade de pointes

Torsade de pointes is the preeminent form of proarrhythmia which causes concern. This arrhythmia was first described in the specific context of a slow cardiac rhythm, QT prolongation and a late ectopic initiation of a self-terminating ventricular tachycardia[2]. The VT showed a cyclical axis change. Since then the term has been used much more loosely to describe many forms of polymorphic ventricular tachycardia, not all of which would meet the original criteria.

The mechanism of torsade de pointes is disputed. It is not electrophysiologically inducible by programmed stimulation and has characteristics which suggest triggered automaticity more than reentry. This might mean that a critical extent of action potential prolongation is necessary for its occurrence, in which case absolute maximum QT interval may be more relevant in the prediction of torsade de pointes than QT dispersion.

QT and proarrhythmia

A variety of drugs which prolong the QT interval are associated with torsade de pointes. The earliest reports concerned quinidine[5]. Almost all antiarrhythmic drugs have now been associated with torsade events, although very few have implicated amiodarone despite its marked

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effect on cardiac repolarisation. The β-blocker sotalol, which possesses class 3 activity, is known to provoke torsade de pointes[6]. The risk may be related to the QT interval. Torsade de pointes associated with non-antiarrhythmic drugs such as prenylamine, terodiline[7] and the antidepressants correlates well with prior QT abnormalities.

QT dispersion and torsade de pointes

Despite the suggestions that torsade de pointes may be based on triggered automaticity, with the implications that the absolute maximum QT interval should correlate with risk, QT dispersion may also be relevant. Hii et al examined 38 patients, nine of whom developed torsade de pointes on quinidine[8]. In these patients, quinidine provoked marked QT dispersion, whereas QT dispersion was uninfluenced by quinidine in the 29 patients not developing torsade de pointes. When quinidine was stopped and amiodarone substituted, QT dispersion remained normal in both groups of patients. QT dispersion has also been shown to be associated with arrhythmogenesis in respect of terodiline[7].

Conclusions

Torsade de pointes is a serious problem which may significantly limit the use of some cardioactive drugs. The problem is also seen with drugs given for non-cardiovascular disease, including antidepressant therapies, antibiotics and more recently antihistamines. QT interval prolongation is a hallmark of these situations, but it remains unclear why some patients show QT prolongation yet do not develop a pro-arrhythmic response. It may be that there are important subtleties of the QT interval, as perhaps reflected by QT dispersion, which will help explain this. Early evidence would suggest that the highest-risk situations occur in those patients with absolute QT prolongation in whom there is also significant (more than 100 ms) QT dispersion.

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Chapter 23

QT Dispersion: Its Clinical Value

A. Bayés de Luna, M. Fiol, A. Bayés-Genís, X. Viñolas, A. Cabrera and A. Martinez-Rubio

Animal studies[1–3] have shown that increased basic dispersion of repolarisation lowers the ventricular fibrillation threshold and facilitates induction of reentrant ventricular arrhythmias.

On the other hand, the QT interval has long been known[4,5] to vary, sometimes significantly, between the individual leads of the 12-lead ECG. This interlead difference may provide a measure of repolarisation inhomogeneity and consequently may represent an electrophysiological substrate for ventricular arrhythmias.

Recently Day et al[6] have considered that QT dispersion may be studied in surface ECG as the difference between the maximum and minimum QT interval duration in individual ECG leads.

Zabel et al[7] found a correlation between the QT interval duration in different ECG leads and the repolarisation durations measured by monophasic action potential recordings. These results support the hypothesis that QT dispersion is an indirect measure of the heterogeneity of ventricular repolarisation. Owing to the relative ease of measurement and the perceived need for new markers of arrhythmogeneity, the method of measuring QT dispersion in surface ECG has attracted the interest of clinical investigators.

Thus in recent years QT dispersion has been studied in different clinical situations[8] (healthy volunteers, acute myocardial infarction, postmyocardial infarction, heart failure, hypertension, ventricular arrhythmias, long QT syndrome, etc.).

The first important limitation is that we do not know which are the normal values of QT dispersion. Although the range of normal values is not completely established in the majority of studies, it is lower than 50 ms[8]. Usually values in women are significantly lower than in men. Some series have found normal values until 65 ms, but if we accept this value as the upper limit of normal values we will have many false-negative values in patients with heart disease.

It has been demonstrated[9] that in the congenital long QT syndrome the arrhythmias are secondary to increased dispersion of repolarisation. Frequently in this group of patients QT dispersion is > 100–120 ms. This assumption has been applied to other clinical conditions in which the QT dispersion is usually greater than 65 ms. Nevertheless, a critical role of dispersion of QT in the genesis of ventricular arrhythmias in other groups of patients (acute myocardial infarction, postmyocardial infarction, congestive heart failure, hypertensive cardiomyopathies, etc.) has not been completely established. The results, although more frequently positive[8–12], present some discordances[13–15].

The modification of QT dispersion in relation to antiarrhythmic drug administration allows us to suggest the positive or negative effect of different

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drugs. If QT dispersion decreases after the administration of one drug, as has happened with some class III agents, it is assumed that the risk to present malignant arrhythmias is reduced[16]. On the contrary, increased QT dispersion caused by different drugs (for example some class I agents) may be associated with their pro-arrhythmic effect[17]. Recently the European agency for the evaluation of medical products have included the study of QT disperson for the assesment of the potential of new active substances (NAS) to modify repolarisation, in order to provide reassurance concerning the safe clinical usage of these drugs. In these cases measurements of QT interval and QT dispersion should be assesed as the mean of three to five beats and an ECG with a paper speed of 50 mm/s should be used and calibrated to 2 cm/mV. According to this agency[18] the appearance after the administration of a new active substance of QTc dispersion greater than 100 ms, or a change in dispersion of more than 100%, should raise concern about the potential of NAS to induce arrhythmias, including torsades de pointes. These concerns may also be useful with drugs already on the market.

Figure 1 (taken from Surawicz[8]) summarises the average values and standard deviations of QT dispersion in different studies of normal controls (N), patients with heart diseases (HD), but without serious ventricular arrhythmias, patients at risk of serious ventricular arrhythmia (AR), and long QT syndrome (LQT). There are no clear differences between groups N and HD, but patients with potential ventricular arrhythmias, and especially long QT, clearly present longer QT dispersion.

It is probable that some errors in measurement are due to the vectorial effects that do not allow adequate measurement. Other errors are related to the difficulties of measurement itself. To avoid these errors it is advisable to follow some rules (12-lead machine, paper speed of 50 mm/s). Use of automatic measurement has also been suggested[19]. Nevertheless, these automatic methods may also present errors[20]. Various authors have tried to overcome these methodological difficulties using QTc dispersion[21] or measuring JT instead of QT[11]. It has also been postulated very recently that morphology of the spatial T wave loop to discriminate different substates of repolarisation inhomogeneity is a useful technique[22,23]. This new approach shows promise in providing additional information in the future. Due to these and other factors[24], a need for standardisation of technique is mandatory before the technique can be considered useful in clinical practice.

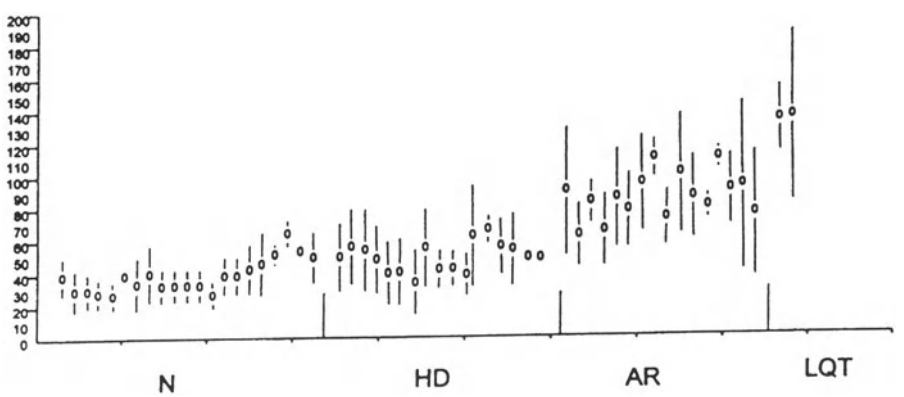

Figure 1. Average values (○) and standard deviations (vertical bars) of QT dispersion in milliseconds (ordinate) in 21 studies of normal control subjects (N); 12 studies (17 patient groups) of patients who had either heart disease or diabetes mellitus but no serious symptomatic ventricular tachyarrhythmias, or ventricular tachyarrhythmias in the presence of structurally normal heart (HD); 13 studies (16 patient groups) of patients at risk of serious ventricular tachyarrhythmias or sudden cardiac death (AR); and two groups of patients with congenital long QT syndrome (LQT). (Taken from ref. 8.)

As a conclusion we may say the following:

1. The range of normal values for QT dispersion has not been definitively established.
2. Available evidence suggests that the definitively abnormal QT dispersion is encountered predominantly in conditions associated with a high risk of serious ventricular arrhythmias, and especially in long QT syndrome.
3. Clear changes in QT dispersion after the administration of a drug raise concern about the potential of this drug to induce serious ventricular arrthythmias.
4. Nevertheless, there are some discrepancies and controversies in the results of different series for consideration of this technique, at this moment useful in clinical practice.
5. To overcome these obstacles it would be necessary to standarise the method and afterwards to demonstrate its real prognostic value in comparison with other markers of arrhythmogenicity.

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Chapter 24

New Perspective in Non-invasive Risk Factors

Yee Guan Yap and Marek Malik

Introduction

Despite tremendous strides in the diagnosis and management over recent years, coronary heart disease remains the leading cause of death in the industrialised world. In the UK about 459 people die of a heart attack every day – over 170 000 people every year[1]. One in three men and one in four women in the UK die from coronary heart disease. Death rates from coronary heart disease in the UK remain among the highest in the world[1]. In the United States nearly 1.5 million patients suffer from acute myocardial infarction annually[2]. The major cause of death is ventricular arrhythmias and sudden death.

For this reason there has been considerable effort in stratifying patients at high risk of ventricular arrhythmias and sudden death following myocardial infarction, so that appropriate preventive therapeutic interventions and risk factor modifications can be instituted. Conventional techniques using electrophysiological testing are expensive, time-consuming and involve risk to the patient, rendering this tool unsuitable for routine screening of high-risk patients postmyocardial infarction. Recent interest concentrates on the use of non-invasive parameters in identifying high-risk patients following myocardial infarction. New techniques have allowed many of these non-invasive parameters for ventricular arrhythmias and sudden death to be identified, including heart rate variability, baroreflex sensitivity, signal-averaged ECG, left ventricular ejection fraction, ventricular premature complexes, and ventricular repolarisation.

Heart rate variability (HRV)

In recent years it has been shown that impaired function of the autonomic nervous system plays an important part in the genesis of ventricular arrhythmias. Therefore, a marker of autonomic control on cardiac electrophysiological properties might provide important information in the risk stratification of patients following myocardial infarction. HRV has been investigated extensively recently in both human and animal models. It is generally accepted that HRV reflects the autonomic modulation of firing of the sinus node. The analysis of HRV is an established non-invasive method for assessment of autonomic influence on heart rate at the sinus node level[3]. The so-called high-frequency component of physiological HRV is almost exclusively mediated by vagal activity, whereas the low-frequency component of HRV is under the influence of sympathetic activity with some contribution from vagal activity[4]. In other words, HRV represents a measure of sympathovagal modulation.

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HRV can be analysed in the time or frequency domain using 24-h Holter monitoring. However, different parameters of time and frequency domain measurements of HRV have been used, most commonly being the standard deviation of RR intervals, and their mutual dependency should be considered for better comparability of clinical results[5–7]. A recent publication by the task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology has comprehensively discussed the various methods used for measuring HRV and their corresponding normal values[8].

Early animal studies showed that decreased vagal tone or increased sympathetic activity with experimental myocardial infarction predisposed to ventricular fibrillation[9]. More recent studies on human subjects confirmed a significant reduction in the parasympathetic (high-frequency) components of HRV in patients at risk of subsequent mortality after myocardial infarction[10]. Kleiger et al studied the HRV on post-infarction patients and found that HRV had the strongest univariate correlation with subsequent mortality. The relative risk of mortality was 5.3 times higher in the group with HRV (i.e. standard deviation of RR intervals) < 50 ms than the group with HRV > 100 ms. In other words, the relative risk of mortality was higher in patients with depressed HRV[11].

Work done in our department using multivariate analysis showed that while depressed HRV, low ventricular ejection fraction, ventricular ectopic beats and age were determinants of total cardiac mortality, depressed HRV was the strongest predictor of arrhythmic death after acute myocardial infarction, independent of other risk predictors such as late potentials, left ventricular dysfunction, Holter findings and Killip class[12–14]. This was especially true in younger patients aged < 60[15]. Other studies confirmed similar findings, in which depressed HRV predicted inducibility of ventricular tachycardia during programmed ventricular stimulation[16–18] and arrhythmic and/or sudden death during follow-up[19].

It is also known that in post-infarction patients there is a significantly reduced circadian variation of normalised HRV in the high-risk patient as compared to the low-risk patient experiencing malignant ventricular tachyarrhythmias[20]. The latest study by Klingenheben et al confirmed that post-infarction patients surviving ventricular tachyarrhythmias had markedly reduced high-frequency component of HRV using spectral analysis, particularly during the early-morning hours (04:00–08:00 a.m.) and showed no difference in the amount of high-frequency energy during daytime and night-time as compared to patients without arrhythmic events[21]. This evidence suggested that predominance of sympathetic tone in the early-morning hours may account for the pathophysiological mechanism for the circadian variation observed in the occurrence of sudden cardiac death, and analysis of diurnal variation of HRV may further improve its prognostic value.

There is a progressive increase in HRV over time in patients with previously decreased HRV after a myocardial infarction, implying a normalisation of impaired parasympathetic control of the heart after acute myocardial infarction[22]. Recent evidence also showed that thrombolytic therapy had no effect on HRV, which continued to retain its independent prognostic significance in post-infarction patients of all ages treated with thrombolysis[23].

The evidence so far suggests that HRV could become an important prognostic tool, particularly in post-infarction patients. A prospective multicentre study to determine the sensitivity, specificity and predictive accuracy of HRV is urgently needed. There is a recently completed large multicentre trial, ATRAMI (Autonomic Tone and Reflexes in Acute Myocardial Infarction), investigating the relative and combined predictive values and prognostic implications of HRV and baroreflex sensitivity after myocardial infarction. The trial is now completed and the anticipated findings on HRV should help clear the issue.

Baroreflex sensitivity (BRS)

While HRV is a measure of sympathovagal modulation of the autonomic nervous system, BRS assesses the ability of the autonomic nervous system to respond to a stimulus with an increase in acetycholine release (i.e. vagal reflex activation). A bolus injection of phenylephrine is a well-accepted standardised technique of proven value in assessing BRS. The slope of the regression line of the beat-to-beat variation in blood pressure plotted against the beat-to-beat change in the RR interval is taken as BRS.

Earlier studies showed that BRS was more reduced in post-infarction patients with ventricular tachycardia on Holter monitoring or during an exercise stress test compared to those without arrhythmias[24], and in the patients in whom sustained ventricular tachycardia was induced with programmed ventricular stimulation[25].

Indeed, BRS appeared to be an independent risk factor for predicting cardiac death and the risk of dying was 17 times greater for those patients who had a depressed BRS 1 month after a myocardial infarction[24].

Furthermore, a reduction in BRS appears to correlate with the severity of coronary artery disease. BRS is significantly more reduced in post-infarction patients with three-vessel disease than in those with one-vessel coronary artery disease[24]. In patients with stable coronary disease the decrease in BRS is correlated with the extent and severity of coronary narrowing[26]. Indeed, the latest evidence from the recently published ATRAMI study on BRS confirmed that the presence of an open infarct-related artery is associated with a higher BRS and lower incidence of markedly depressed BRS (< 3 ms/mmHg), therefore reducing the risk of postmyocardial infarction mortality[27]. The association between infarct-related artery patency and BRS was more evident in anterior than in inferior myocardial infarction. In the same study, multivariate regression analysis showed that the age of the patient and patency of the infarct-related artery were the major independent determinants of BRS, while left ventricular ejection fraction was weakly related to BRS. These data offer new insights into the mechanisms by which coronary artery patency may affect cardiac electrical stability and survival.

Odemuyiwa et al showed that the mean BRS at 6 weeks post-infarction was higher in patients treated with thrombolysis compared with non-treated patients, although this difference disappeared at 6 weeks and 3 months subsequently[28]. This finding has now been substantiated by the preliminary results from a separate ATRAMI report which showed that there were fewer patients with a markedly depressed BRS in patients who received thrombolytic treatment compared with those who did not[29].

Farrell et al studied the prognostic significance of BRS on 122 post-infarction patients and reported a sensitivity of 89%, a specificity of 91% and a positive predictive accuracy of 44% for predicting sudden death[30]. In the ATRAMI study, preliminary results on 1085 patients confirmed that depressed BRS was significantly related to mortality with a relative risk of 5.5 and 2.7 on univariate and multivariate analyses respectively. This demonstrated that analysis of BRS does significantly contribute to the early identification of post-infarction patients at higher risk[31].

Recently, Kautzner et al[104] described a non-invasive method of assessing BRS utilising a Valsalva manoeuvre which did not require a bolus injection of phenylephrine. In this method systolic blood pressure and heart rate were measured during phase IV of a Valsalva manouevre. The value of the BRS is then calculated by measuring the slope of the linear regression between the systolic blood pressure and the length of the subsequent RR interval during this period. Alternatively, the ratio of the difference between the maximal and minimal RR interval and the difference between the maximal and minimal systolic blood pressure, the so-called BRS index, can also be used as a surrogate value of the BRS. A direct comparison with the standard phenylephrine methodology is needed before these alternative indices can be widely accepted.

Signal-averaged ECG

In the genesis of malignant ventricular arrhythmias the role of reentry due to slow conduction is important. In regions of experimental infarction slow conduction is the result of delayed fractionated electrical activity during diastole. These potentials that occur in or after the end of the QRS complex are known as "ventricular late potentials". They are characterised by multiple low-amplitude spikes, sometimes separated by isoelectric intervals, which can be detected on signal-averaged ECG (SAECG)[32]. Areas of myocardium from which ventricular late potentials have been detected are thought to be "arrhythmogenic electrophysiological substrate" for the genesis of reentry ventricular arrhythmias.

Clinically, among survivors of acute myocardial infarction, late potentials have been shown to be a significant predictor of spontaneous ventricular arrhythmia or sudden death and induced ventricular tachycardia, independent of both ventricular function and ventricular arrhythmia on Holter monitoring[33–35]. In their substudy, Steinberg and co-workers performed a meta-analysis of all available prospective studies on the use of SAECG after myocardial infarction. They found that SAECG predicted a six-fold increase in risk of arrhythmic events independent of left ventricular function, and an eight-fold increase in risk of arrhythmic events independent of Holter results[33]. The total number of patients in the meta-analysis, however, was small. Recently, in the CAST/SAECG substudy report, signal-averaged ECG predicted serious arrhythmic events in the first year after infarction better than do clinical, ejection fraction and ventricular arrhythmia variables[36].

The majority of the trials on SAECG were performed in the pre-thrombolytic era. The significant impact that

thrombolysis has had on the natural history after acute myocardial infarction may have altered the clinical relevance of previously established risk factors. Effective thrombolytic therapy may prevent the development of an abnormal electrophysiological milieu after myocardial infarction. Thrombolytic therapy had been found to reduce the frequency of SAECG abnormality (filtered QRS duration > 120 ms) by 37% and the filtered QRS duration[37] as well as the predictive value of late potentials on the SAECG[38]. Nevertheless, McClements et al showed that signal-averaged ECG remains an independent predictor of arrhythmic events after myocardial infarction[39].

Different approaches have been used for the detection of ventricular late potentials: time- and frequency-domain analysis and spectral temporal mapping, which are a combination of time and frequency analyses. Work done in our department showed that time-domain analysis is superior to frequency-domain analysis, spectral temporal mapping and spectral turbulence analysis of the SAECG in predicting arrhythmic events after myocardial infarction[40–43] although spectral turbulence analysis is more powerful in predicting 1-year mortality. Other investigators have also confirmed the superiority of time-domain analysis[44]. It has been suggested that a combined use of time- and frequency-domain analysis of SAECG should be used to enhance the accuracy of this technique as a screening test for selecting patients for programmed electrical stimulation after myocardial infarction[45]. Although SAECG had an excellent negative predictive value of late potentials (between 96% and 99%), the positive accuracy was low (between 7% and 27%), which limits its role in risk stratification[32].

Left ventricular ejection fraction (LVEF)

Earlier studies showed that left ventricular dysfunction and the presence of frequent or repetitive ventricular premature depolarisations on ambulatory monitoring were independent risk factors for subsequent mortality among survivors of acute myocardial infarction[46–49]. Univariate analysis demonstrated a progressive increase in 1-year mortality following myocardial infarction as the ejection fraction fell below 40%[47]. Bigger et al showed that, after adjusting for other variables, the risk of dying for patients with a LVEF of less than 30% was 3.5 times that for patients with a LVEF of 30% or greater[48]. There was a high incidence of ventricular arrhythmias and sudden cardiac death in patients with poor left ventricular function following a previous myocardial infarction[48]. Among variables such as signal-averaged ECG, complex ventricular ectopic activity and left ventricular dysfunction, left ventricular dysfunction was the most powerful predictor of subsequent arrhythmic events after myocardial infarction[50]. It was also one of the most important predictors of prognosis[51].

Based on recent data from a TIMI phase II study, Zaret et al reaffirmed that LVEF remained an important prognostic index in predicting total and cardiac mortality in patients receiving thrombolytic therapy following a myocardial infarction[52]. Peak exercise ejection fraction and the change in ejection fraction from rest to exercise were also performed, but did not provide appreciable prognostic data beyond those obtained at rest. When compared with the Multicenter Postinfarction Research Group data in the pre-thrombolytic era[47], there was strong evidence of a difference in survival in the two studies. At any level of ejection fraction, mortality was lower in TIMI II patients than in patients in the prethrombolytic era. For cardiac death prediction Copie et al reported that a LVEF < 35% had a 40% sensitivity, 78% specificity and 14% positive predictive accuracy[53].

Stevenson et al estimated that the mortality for myocardial infarction survivors with LVEF less than 0.40 is 20% over 3.5 years and that half of the deaths were sudden[54]. They went on to assess the potential impact of current arrhythmia detection and management strategies on mortality in survivors of myocardial infarction with reduced left ventricular function who were managed in a contemporaneous manner. Using Holter ECG recordings, a SAECG, or an invasive electrophysiological study to select higher-risk groups among the survivors of myocardial infarction with reduced LVEF, they estimated that one life could be saved for every four to 11 patients treated. However, to achieve this benefit, additional and potentially invasive arrhythmia testing must be applied to between 28 and 47 patients for each life saved. Thus, with contemporary management of acute myocardial infarction, the risk of sudden death for survivors was sufficiently low that broad application of available antiarrhythmic therapies has limited potential for further improving survival, particularly if therapy also has significant adverse effects. Despite this, Hallstrom et al found that both ejection fraction and functional class of heart failure were powerful predictors of arrhythmia suppression and cardiac events in patients with ventricular

arrhythmia after myocardial infarction, with each providing incremental prediction[55].

Ventricular premature complexes (VPC)

A strong association between prevalence of ventricular ectopic activity and mortality risk after myocardial infarction has been documented[47,48,56,57]. VPC was identified as another independent prognostic factor for subsequent mortality among hospital survivors of acute myocardial infarction[47,48]. Results from the Multicentre Postinfarction Research Group showed that there was a progressive increase in 1-year cardiac mortality as the frequency of VPC rose above one per hour[48].

Statters et al reassessed the role of VPC in risk stratification of patients postmyocardial infarction in the thrombolytic era. They examined 680 patients, of whom 379 received early thrombolytic therapy. All patients underwent 24-h Holter monitoring in a drug-free state between 6 and 10 days after acute myocardial infarction. Patients were followed up for 1 to 8 years. Mean VPC frequency was significantly higher in patients who died of cardiac causes, in those who died suddenly, and in those with arrhythmic events during the first year of follow-up. This was also true when patients who did and did not undergo thrombolysis were considered separately. The positive predictive accuracy of VPC frequency in predicting adverse cardiac events was greater in patients who did than in those who did not undergo thrombolysis. At a sensitivity level of 40% the positive predictive accuracy for cardiac mortality and arrhythmic events for the group with thrombolysis was 19.4% and 25.8%, respectively, compared with 16% and 16% for those without thrombolysis. Moreover, the highest VPC frequency for the dichotomy of patients into high- and low-risk groups was 25 VPC/h for patients without thrombolysis. Thus, VPC frequency appears to be more highly predictive of prognosis after acute myocardial infarction in patients who have undergone thrombolysis than in those who have not, but the optimal frequency for dichotomy is higher in the former[58].

Despite the good correlation between ventricular ectopic activity and prognosis, ventricular ectopic activity has limitations as a predictor of outcome, especially in respect to the link between ventricular premature complexes and the risk of sudden death specifically. Moss et al showed that complex ventricular premature complexes were associated with a significantly increased cardiac death rate, but did not discriminate between sudden and non-sudden cardiac death[59]. Ruberman and co-workers found that complex premature complexes were the strongest influence on the risk of sudden coronary death[46]. It is important to separate sudden coronary death from total mortality. This is because sudden coronary death was most commonly attributed to ventricular arrhythmia in the absence of new myocardial infarction, whereas cardiac deaths not fulfilling this definition were overwhelmingly associated with new myocardial infarction, with a smaller number ascribable to congestive heart failure without evidence of new myocardial infarction[60,61]. Such distinction is also important with regard to the use of antiarrhythmic agents to improve the rate of sudden death.

The CAST studies had attempted to address this issue by testing whether class Ic antiarrhythmic drugs used for suppression of premature ventricular extrasystoles detected on ambulatory electrocardiographic monitoring would prevent sudden death over the long term in post-infarct survivors. The studies were stopped prematurely because of increased mortality in the active treatment groups, despite markedly suppressed premature ventricular extrasystoles[62,63]. This questioned the hypothesis that suppression of asymptomatic ventricular ectopy can reduce mortality. An explanation for the result might be the proarrhythmic effect of sodium channel blockers (class I action) due to facilitation of reentry, especially during acute ischaemia[64].

Another problem was that the Holter monitoring used to record ventricular ectopic activity had its limitation in identifying high-risk individuals. For instance, the results of data analysis in placebo patients in the BHAT Study (Beta-Blocker Heart Attack Trial) showed that a number of patients who had sudden death remained undetected (low sensitivity) whereas there were a considerable number of false-positive results in the subclass analysis[65].

Ventricular repolarisation

Ventricular repolarisation duration is an important electrophysiological parameter that is poorly investigated in conventional ECG. Ventricular repolarisation is a complex electrical phenomenon and the repolarisation forces can be recorded using precordial mapping[66]. Heterogeneity of repolarisation may be manifested in an individual beat (spatial heterogeneity) or in a sequence of beats (dynamic temporal heterogeneity). The spatial

heterogeneity of repolarisation throughout the myocardium may be expressed electrocardiographically as variability of QT interval between ECG leads (i.e. QT dispersion) computed in simultaneously recorded leads. On the other hand, the beat-to-beat changes in the repolarisation pattern (duration and/or amplitude) account for a dynamic (time-dependent) dimension of heterogeneity, seen as QT variability and T wave alternans respectively. There is emerging evidence that ventricular repolarisation characteristics, namely QT dispersion, QT variability and T wave alternans, have shown promising results as non-invasive tools for risk stratification of patients with cardiac diseases.

QT dispersion

QT dispersion is defined as the variability of QT interval between simultaneously recorded ECG leads on a surface ECG. QT dispersion has been proposed as an indirect measure of spatial heterogeneity of ventricular repolarisation[67,68]. In patients with coronary artery disease, QT dispersion is increased after an acute myocardial infarction[69] and levels are higher in patients with subsequent ventricular arrhythmias or arrhythmic cardiac death[69–71]. Glancy and co-workers found that QT dispersion measured on an ECG recorded 2–3 days after acute myocardial infarction did not predict mortality during the next 5 years[72]. However, increased QT dispersion at ≥ 4 weeks after infarct may be associated with subsequent mortality. A recent study on QT dispersion during coronary angioplasty demonstrated that QT dispersion increased significantly during both ischaemia and reperfusion, thus indicating that both ischaemia and reperfusion altered ventricular repolarisation, thereby inducing a less homogeneous ventricular recovery pattern[73].

QT dispersion is defined empirically as QT maximum minus QT minimum as measured on a 12-lead ECG[74]. The measurement of QT interval remains to be standardised[75–78]. Some methods lead to poor intra- and inter-observer reproducibility[78], which may explain the discrepancies between reports from different centres. A standardised measure of QT dispersion is currently needed. A general consensus seems to be that the processing of an electronically recorded ECG is the only realistic possibility for a non-invasive assessment of the heterogeneity of spatial ventricular repolarisation.

QT variability

QT interval, as an index of ventricular repolarisation and a critical determinant of ventricular arrhythmias and sudden death, is influenced by autonomic tone and exhibits a circadian rhythmicity[79–82]. It is suggested that beat-to-beat changes of QT interval (i.e. QT variability) as measured on Holter recording will provide more information on the dynamic heterogeneity of ventricular repolarisation and sympathovagal imbalance, and hence as a predictor of arrhythmic risk. However, direct evidence to support this is lacking and urgently needed.

Coumel et al showed that the difference between daytime and night-time QT values was reduced in patients with stable coronary artery disease, left ventricular hypertrophy with or without heart failure, and long QT syndrome, compared with normal control[83], confirming the effect of heart disease on QT dynamicity. However, the number of patients in this study was small.

The temporal variability of QT intervals is assessed using a Holter recorder to obtain a 24-h rhythm strip. There is not yet an agreed algorithmic method for calculating QT variability. The main problem is that QT interval changes are influenced by both heart rate and autonomic changes. In addition to the measurement of the rate-modulated absolute changes of the QT interval duration, the assessment of the ventricular response to the autonomic changes based on QT variability has to "filter out" the influence of HRV. Most studies have so far utilised the QT/RR relationship to examine QT variability[84–86] and/or its rate-corrected form (i.e. QTc/RR)[86]. Others investigators use power spectral analysis[87,88].

T wave alternans

T wave alternans, defined as alternating beat-to-beat changes in the amplitude, shape and polarity of the T wave during sinus rhythm without concomitant QRS changes on ECG[89], was an electrocardiographic curiosity until recently. It is now recognised as another marker of cardiac electrical instability[90] and a harbinger of sudden cardiac death[91]. It is also another dynamic dimension of heterogeneity of ventricular repolarisation. Previous reports documented the presence of visually apparent T wave alternans immediately preceding the occurrence of ventricular arrhythmia in conditions such as long Q–T syndrome[89], Prinzmetal's angina[92] and acute myocardial ischaemia[93,94]. However, visually apparent alternans is very rare. It was not until sub-

sequent studies by Adam et al[95] and Smith et al[90], who used fast Fourier transformation techniques, that the presence of microvolt-level T wave alternans and its susceptibility to ventricular arrhythmias was demonstrated.

Rosenbaum et al demonstrated a highly significant relationship between electrical alternans measured during atrial pacing with inducibility of sustained VT or VF during EPS, as well as with 20-month arrhythmia-free survival in a study of 83 patients with cardiac diseases undergoing EPS. They found that ST segment alternans and T wave alternans, but not QRS alternans at microvolt level, were predictive of inducibility and arrhythmia-free survival[96]. Others confirmed these similar findings[90,97]. Repolarisation alternans has been observed under conditions conducive to myocardial ischaemia, including myocardial infarction[94,98], angioplasty[99], and Prinzmetal's angina[100]. In Prinzmetal's angina a study by Rozanski et al showed that the occurrence of ST segment and T wave electrical alternans frequently heralded the onset of ventricular arrhythmias[100].

There are important technical limitations with the current methods of detecting T wave alternans using standard surface ECG[101]. As a result, a new technique using power spectral analysis has since been developed to measure T wave alternans at the microvolt level, and this has revealed a substantial level of alternans in tracings which was not detectable by visual inspection[90,102]. It is also recognised that T wave alternans is heart rate-dependent and that alternans demonstrates a threshold effect, as heart rate is elevated[102]. The exercise test has been used to accomplish this.

Conclusions

Evidence to date suggests that LVEF < 40, VPC > 10/h, abnormal SAECG and reduced HRV and BRS are all risk factors for subsequent cardiac mortality, particularly ventricular arrhythmias. These techniques appear to be superior to more conventional non-invasive methods such as exercise testing. However, no single variable can accurately predict arrhythmic death. Most of the studies so far suffer from low positive predictive values and low numbers in their subject population, so that their ability to impact on current medical practice has been limited. Furthermore, the endpoints for assessing prognosis after myocardial infarction are not well defined. The endpoints may include either sudden and non-sudden death or the occurrence of arrhythmic events such as sustained ventricular tachycardia or survived cardiac arrest. In many reports, both sudden death and death due to sustained ventricular tachyarrhythmias were combined together in the endpoint "arrhythmic death". Combining these endpoints into a common one is debatable and potentially misleading, since the mechanisms may be different[103]. There is a need for a universal definition and categorisation of sudden death, arrhythmic death, cardiac death, etc.

It is conceivable that a combination of several risk factors may be the only way of increasing the predictive accuracy of these non-invasive techniques as a means of risk stratification of patients postmyocardial infarction. However, an optimum set of risk factors and the corresponding dichotomy limits have not yet been established. Only when this is achieved can appropriate preventive therapeutic intervention and risk factor modification be implemented.

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Chapter 25

Spectral Analysis of Cardiovascular Variability Signals

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Introduction

It is well known that the control mechanisms of heart rate and blood pressure, as well as of many other cardiovascular parameters, manifest themselves though beat-to-beat variations in the related signals[1,2]. The quantification of these variations, both in control conditions and after provocative tests, plays a fundamental role for a better comprehension of the pathophysiological properties of such mechanisms which act through neural, mechanical, vascular, humoral and other factors.

In particular, in the past few decades, interest has mainly focused on the study of the heart rate variability signal concerning the possibility of simple and non-invasive recording of such a signal, and for its relevant information content[3]. Measures in the time domain, as well as in the frequency domain, are extensively employed in clinical practice and in pathophysiological studies. Recently, a Task Force constituted by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology developed a document aimed at defining appropriate standards on: (1) nomenclature and definitions of terms, (2) methods of measurement, (3) physiological and pathophysiological correlates, (4) currently appropriate clinical applications and (5) identifying areas for future research[4].

Thus, the quantification of heart rate variability, in time as well as in frequency domains, is becoming a diffused tool both in physiology and in clinical practice. Research is now proceeding towards more detailed and sophisticated procedures (mainly due to the improved power and diffusion of calculation tools), including analysis of transient conditions and non-stationarity in the signal, the multivariate approach and system modelling, long-term analysis and non-linear dynamic studies.

In this chapter spectral analysis techniques will be reviewed, for processing the heart rate variability signal, starting from the more traditional "batch" approach as well as time-variant parametric methods. Furthermore, spectral analysis in the long term will be approached with the introduction of suitable parameters which may significantly discriminate between normal and pathological conditions, and which seem to provide different and (in general) uncorrelated information with short-term spectral parameters. Parameters obtained in the frequency domain through the above-mentioned approaches

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are reputed to provide important and complementary information on the complex-regulating system of cardiovascular functions.

Parameters in the frequency domain

The first step in the analysis of the heart rate variability (HRV) signal is the proper extraction of such a signal from ECG recordings. Usually, the peak of the R wave on the ECG is considered a fiducial point, and the RR interval is a measure of the time duration of the cardiac cycle. The sampling rate must be chosen carefully. A low sampling rate may produce a jitter of the fiducial point, which alters the spectrum considerably, especially in reduced variability conditions: newborn studies, diabetic neuropathy, etc. The optimal range is 250–500 Hz or higher, while a lower sampling rate may behave satisfactorily only if some interpolation algorithm is used to refine the R-wave fiducial point[5,6].

After detection of the R waves on the ECG the HRV signal can be obtained in various ways. The sequence of RR time intervals may be plotted as a function of beat number, thus originating the *interval tachogram* (or simply *tachogram*); in this case the time is not measured in seconds, but in cardiac cycles. Frequently the plot of the RR series is versus time (each RR value is represented at the occurrence of the corresponding R wave), giving rise to an irregularly time-sampled signal. For subsequent analysis it is necessary to make continuous the signal in time by proper interpolation, and then to resample it using a constant sampling rate. A detailed description and comparison of the techniques usually employed in obtaining the HRV signal is contained in ref. 7.

Frequency domain analysis of the time series can be performed by various methods detailed in the literature. Power spectral density (PSD) analysis provides basic information on how each single frequency contributes to the total signal power (variance). The algorithms for the PSD calculation are classified as *non-parametric* or *parametric*. The former are based on the Fourier transform which can easily be evaluated through the FFT algorithm. The expression of the PSD as a function of frequency can be obtained directly from the time series by the periodogram expression:

$$\mathrm{PSD}(f) = \frac{1}{N\Delta t}\left|\Delta t \sum_{k=0}^{N-1} y(k) e^{-j2\pi f k \Delta t}\right|^2 = \frac{1}{N\Delta t}\left|Y(f)\right|^2$$

where Δt is the sampling period. N is the number of samples in the analysed time window, and $Y(f)$ is the discrete time Fourier transform of the time series $y(t)$. Equivalently, PSD(f) may also be obtained as the Fourier transform of the autocorrelation function (ACF) of the signal.

FFT-based methods are the best known and diffused for their easy applicability, computational speed and direct interpretation of the results. However, application on real signals, and on finite data sets, makes it necessary to introduce assumptions, sometimes non-realistic, about the data outside the recording time interval. Usually the signal is supposed to be zero outside the analysis window. This implicit rectangular windowing of the data results in a spectral leakage in the PSD, that can be reduced by means of proper windows that smoothly connect the side samples to zero. This procedure, however, introduces a reduction in the frequency resolution of the spectrum estimation. Furthermore, the PSD estimate of a signal is not statistically consistent when using the periodogram, and therefore it needs various procedures for improving their statistical performances (i.e. spectral averaging). Such procedures cause a further reduction in frequency resolution[8].

The parametric approaches assume the time series to be the output of a given mathematical model and no drastic assumptions are made on the data outside the recording window. The PSD(f) is calculated as a function of the model parameters according to appropriate expressions. A critical point is the correct choice of the model structure more suitable to represent the data sequence. The model is completely independent from the physiological, anatomical and physical characteristics of the biological system generating the time series, but simply provides the input-output relationship of the process in the so-called black-box approach[9].

Among the numerous possibilities of modelling, linear models, characterised by a rational transfer function, are able to describe a large number of different processes. In the most general case they are represented by the following linear equation that relates the input driving signal $w(k)$ and the output of an autoregressive moving average (ARMA) process:

$$y(k) = -\sum_{i=1}^{p} a_i y(k-1) + \sum_{j=1}^{q} b_j w(k-j) + w(k)$$

where $w(k)$ is the input white noise with null mean value and variance λ^2, p and q are the orders of AR and MA parts, respectively and a_i, bj are the related coefficients.

If the coefficients b_j or a_i are set to zero, the model is reformulated AR or a MA, respectively. The most diffused form is the AR for its easier identification through linear equations. The AR PSD(f) estimation is then obtained as:

$$\mathrm{PSD}(f) = \frac{\lambda^2 \Delta t}{\left| 1 + \sum_{i=1}^{p} a_i z^{-i} \right|^2_{z=\exp(j2\pi f i \Delta t)}}$$

Parametric methods are methodologically and computationally more complex than the non-parametric ones, as they require some *a-priori* choice of the structure and of the order of the model. In the literature various criteria have proposed for the choice of the optimal order, but they require identification of multiple models with order ranging between a minimum and a maximum. In addition some tests are required *a posteriori* to verify the whiteness of the prediction error in order to assess the reliability of the estimation. On the other hand, parametric methods do not require any assumption on the signal outside the analysis window, show more statistical consistency even on short segments of data, and allow automatic calculation of spectral parameters from the overall spectrum, which are directly interpretable from a physiological and clinical standpoint[10–12].

In the PSD of the HRV signal the power is concentrated in a few bands which assume physiological relevance: a LF (low-frequency) component, centred around 0.1 Hz in a range between 0.04 and 0.15 Hz, that always increases as a consequence of a sympathetic activation[3]; a HF (high-frequency) component, at the respiration frequency (from 0.15 up to 0.4 Hz) that is an expression of the respiratory sinus arrhythmia, vagally mediated[12,13]; a relevant amount of spectral power is in a VLF (very low frequency) component, below 0.04 Hz. The physiological meaning of such a component is not yet clear; it contains long-term regulation contributions, probably originating from non-linear mechanisms.

The spectral parameters that quantify the action of the autonomic nervous system in controlling heart rate are the powers and central frequencies of the LF and HF components. The spectral power is expressed in absolute units when interest is in some variation in the signal variance, such as in diabetic neuropathy[14], or in normalised units (percentage of the component power over the overall power without the VLF contribution), when interest is mainly in evaluation of the mutual interaction between the components; in this regard the LF/HF ratio is an index that significantly takes into account the sympathovagal balance[12].

As an example of the frequency analysis of the HRV signal, Fig. 1a shows an interval tachogram obtained during resting condition (nbeats = 300) and during upright position (nbeats = 350) after a transition interval (300 < nbeats < 350). The traditional frequency domain analysis can be performed on stationary segments of data during both conditions. Figures 1b and 1c represent the PSD obtained through an autoregressive model in resting (Fig. 1b) and in standing (Fig. 1c) positions. The spectral parameters that quantify the sympathovagal balance in the two different conditions are reported in the tables. In particular the LF/HF ratio, that is commonly assumed as an index of sympathovagal balance, increases from a value of 2.7 to a value of 14.5 after assuming the upright position, thus testifying to the related sympathetic activation. In refs 4 and 15 various examples are reported of clinical use of these methodologies in the diagnosis and prognosis of different pathologies.

Multivariate analysis

More complete information on the behaviour of the controlling systems of the cardiovascular system is obtained through multivariate analysis of different signals. The cardiovascular variables may be different (ECG, respiration, blood pressures, recorded at different levels and at different sites, peripheral flow, etc.) and related to one another. Each one may be considered as a function of the others through complex neural, mechanical, humoral or other mechanisms.

Figure 2a shows the ECG signal (upper panel) and the simultaneous recording of the arterial blood pressure (ABP) (middle panel). The respiration signal (lower panel) is not strictly a cardiovascular parameter; however, it strongly affects, as an external stimulus, cardiovascular and other physiological variables. Variability series, shown in Fig. 2b, can be extracted from the cardiovascular signals on a beat-to-beat basis. The *interval tachogram* (upper panel) is the sequence of the RR time intervals, in seconds, plotted as a function of heart beat number. From the ABP the sequence of systolic pressure values can be obtained, thus originating the *systogram* (middle panel). Similarly the *diastogram*, the *pulsogram*, and the *mediogram* (not shown in the figure) can be obtained as the sequences diastolic, pulse,

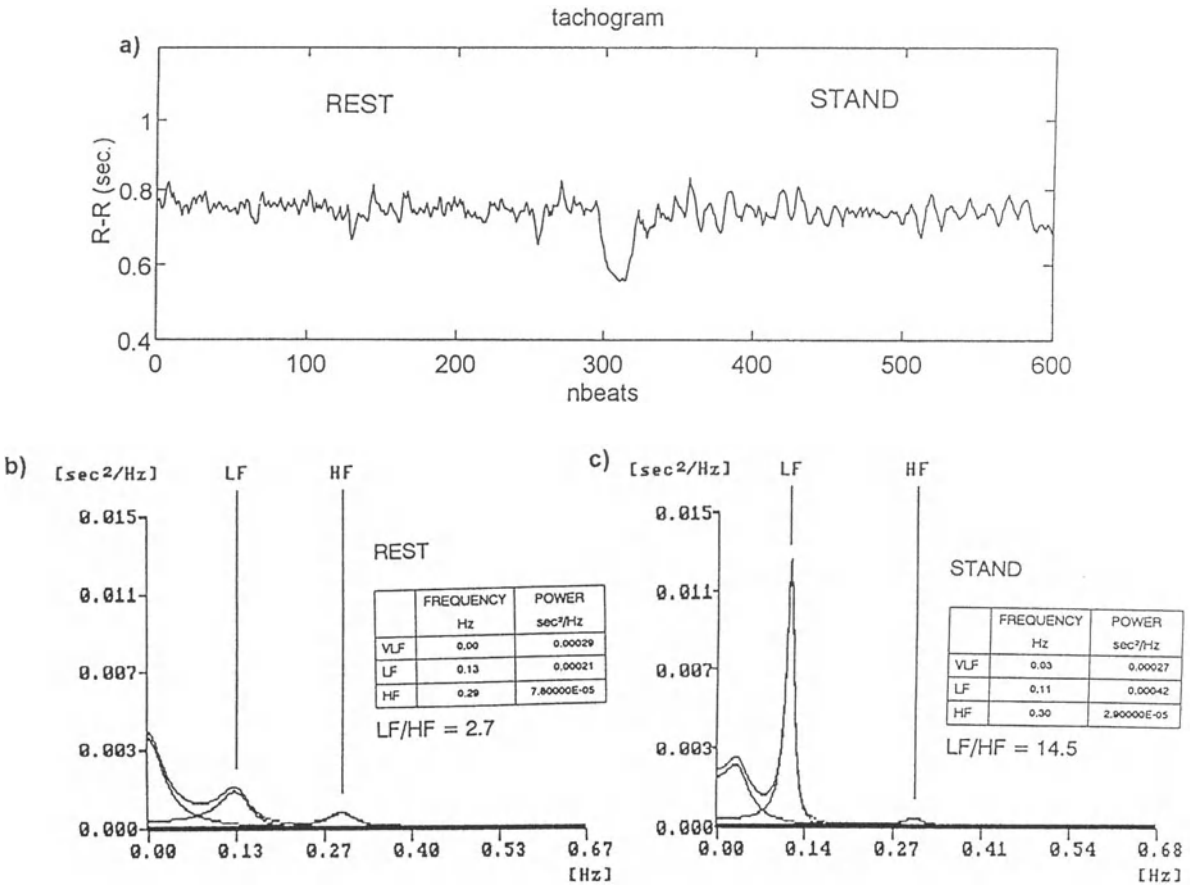

Figure 1. **(a)** RR interval tachogram of a normal subject obtained in resting and in standing position; **(b)** and **(c)** PSD of the tachogram shown in **(a)** evaluated in resting and standing position, respectively, through autoregressive modellisation. The tables show the spectral parameters that quantify sympathovagal balance.

or mean pressure values, respectively. The respiration signal is sampled in correspondence of each R wave on the ECG, thus generating the *respirogram* (lower panel) that is synchronous with the tachogram.

Frequency domain analysis of these variability signals shows common rhythms: the spectra displayed in Fig. 2c show a well-recognisable peak on the respirogram PSD (lower panel) at the respiratory frequency. The same rhythm is also present in tachogram and systogram (upper and middle panels, respectively), while both tachogram and respirogram show a common LF oscillation. In order to quantify the degree of interrelationship between signals, a bivariate or, in general, a multivariate analysis is required. This gives parameters able to measure the coherence (total or partial) between common oscillations and their phase relations[16].

Figure 3 shows the results obtained through multivariate analysis. The spectral and cross-spectral parameters are plotted in matrix form, with autospectra on the diagonal, phase relations in the upper triangular matrix and the squared coherence in the lower triagular matrix. The autospectra of both tachogram and systogram are characterised by the LF and HF peaks with a high level of coherence (> 0.5), while the VLF component, present in both spectra, does not show generally high values of coherence. This means that the VLF oscillation probably has a different origin mechanism in the two signals.

Both tachogram and systogram show very high coherence (close to 1) with respirogram in the HF range, indicating the strong respiratory influence on the cardiovascular variables. The multivariate spectral analysis of

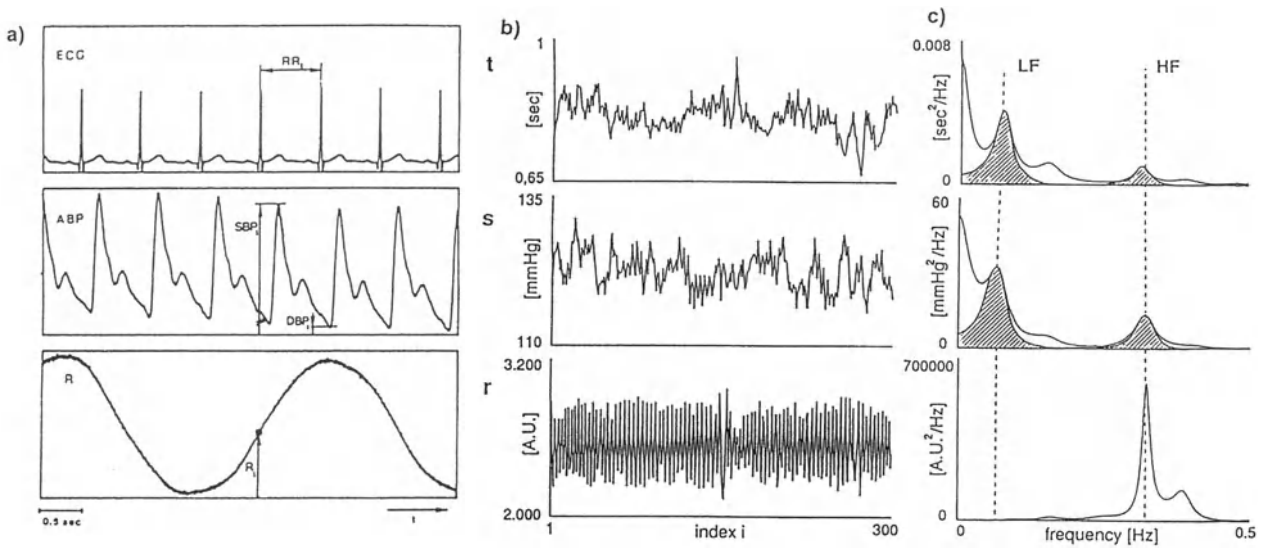

Figure 2. **(a)** Signals obtained from the cardiovascular system: ECG (upper panel), arterial blood pressure (middle panel) and respiration signal (lower panel); **(b)** corresponding variability signals: tachogram (upper panel), systogram (middle panel) and respirogram (lower panel); **(c)** PSD obtained from the variability signals shown in **(b)**.

HRV, systolic blood pressure and respiration, or other signals, has indicated several properties of exchanging powers in determined frequency bands, precise delay relationships between the signals, high coherence values in correspondence with LF and HF rhythms, and so on. All these observations have led to the formulation of models which account for the physiological results. In the literature various and different models of the cardiovascular system have been presented, which take into account different aspects and different degrees of interaction. A model is not intended to give a complete and exhaustive description of physiology, but is aimed to explain and interpret some well-defined aspects. For this reason, according to the underlying problem, the model can be a simple cause-effect relation, an open-loop model, a closed-loop model, can be linear or may account for non-linearites in the system, and so on.

Different model structures have to be employed according to the characteristics of the signal under analysis and the aim of the study[17]. The simple model shown in Fig. 4a can be successfully employed when considering the effect of respiration on the HRV (or on systolic blood pressure series). The model separates the effects of respiration, taken as an exogenous input, from different sources of sinus arrhythmia described by the autoregressive model. Thus, a quantitative evaluation of respiratory arrhythmia is possible and the PSD of the tachogram is divided into the sum of two partial spectra. The partial spectrum due to respiration is also referred to as the part of the spectrum of the tachogram that is coherent with respiration (CRP). This procedure is particularly useful when clear HF and LF rhythms are difficult to recognise; for example with a highly reduced variability consequent to diabetic neuropathy. In these cases separation into a non-coherent and a coherent part can substitute the usual decomposition into an LF and an HF component, in order to assess sympathovagal balance[14].

Considering the HRV signal and the variability signal obtained from the SBP (e.g. the systogram) the principal characteristic is in their closed-loop interaction, as represented in the model shown in Fig. 4b. Tachogram affects the systogram mainly through mechanical effects summarised in the block H_{st}, while baroreflex mechanisms perform a feedback block H_{ts}. After closed-loop identification the gain of the block H_{ts} constitutes a quantitative measure of the cardiac baroreflex response.

The model shown in Fig. 4c contains all the elements of the more simple models described above, and is specifically designed to study interactions between tachogram, systogram and respirogram. The kernel of the model is the closed-loop structure described in

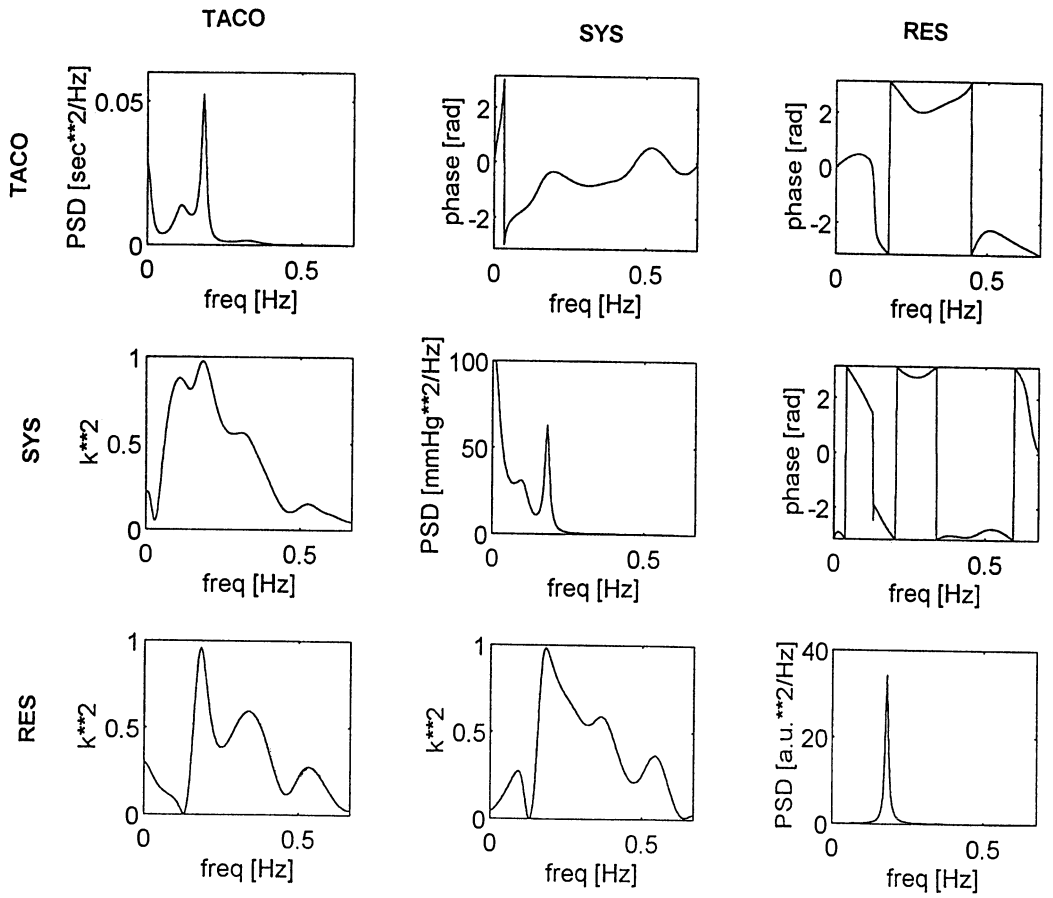

Figure 3. Results obtained from multivariate spectral analysis from tachogram (TACO), systogram (SYS) and respirogram (RES). The spectral and cross-spectral functions are plotted in matrix form. The signal autospectra are shown on the diagonal; in the upper triangular matrix the phase relations are shown, and the lower triangular matrix shows the squared coherence functions.

Fig. 3b that accounts for the mutual interactions between tachogram and systogram. The influence of respiration on both signals is described by blocks R_t and R_s according to the model shown in Fig. 3a. In addition, block H_{ss} accounts for a resonance effect of the systogram on the systogram itself, and blocks H_{ut} and H_{us} are designed to describe the external oscillations which enter the considered loops and which modulate either the tachogram or the systogram. Identification of the blocks shown in Fig. 4 allows access to parameters of pathophysiological values, such as $|H_{ts}|$ block (also called α-baroreflex mechanism gain) or H_{st} in modulus and phase, which account for the mechanical properties of RR changes induced on arterial blood pressure. For further details on model identification and interpretation see refs 18 and 19.

Time-varying analysis

The above techniques are successfully applied in the study of variability signals from the cardiovascular system when the series shows characteristics of stationarity. However, many phenomena of physiological or clinical interest are characterised by dynamic changes in autonomic control. Such dynamics may take place in a short time, thus making traditional batch spectral analysis unreliable. In the literature the problem of the time-frequency representation of a signal is extensively addressed, and in the past few years some methods have been applied in the study of transitions in the HRV signal[5,20]. The more diffused ones are the time-frequency distributions, based on the Wigner transform[21]; however autogressive modelling can also be implemented in recursive form in order to estimate a

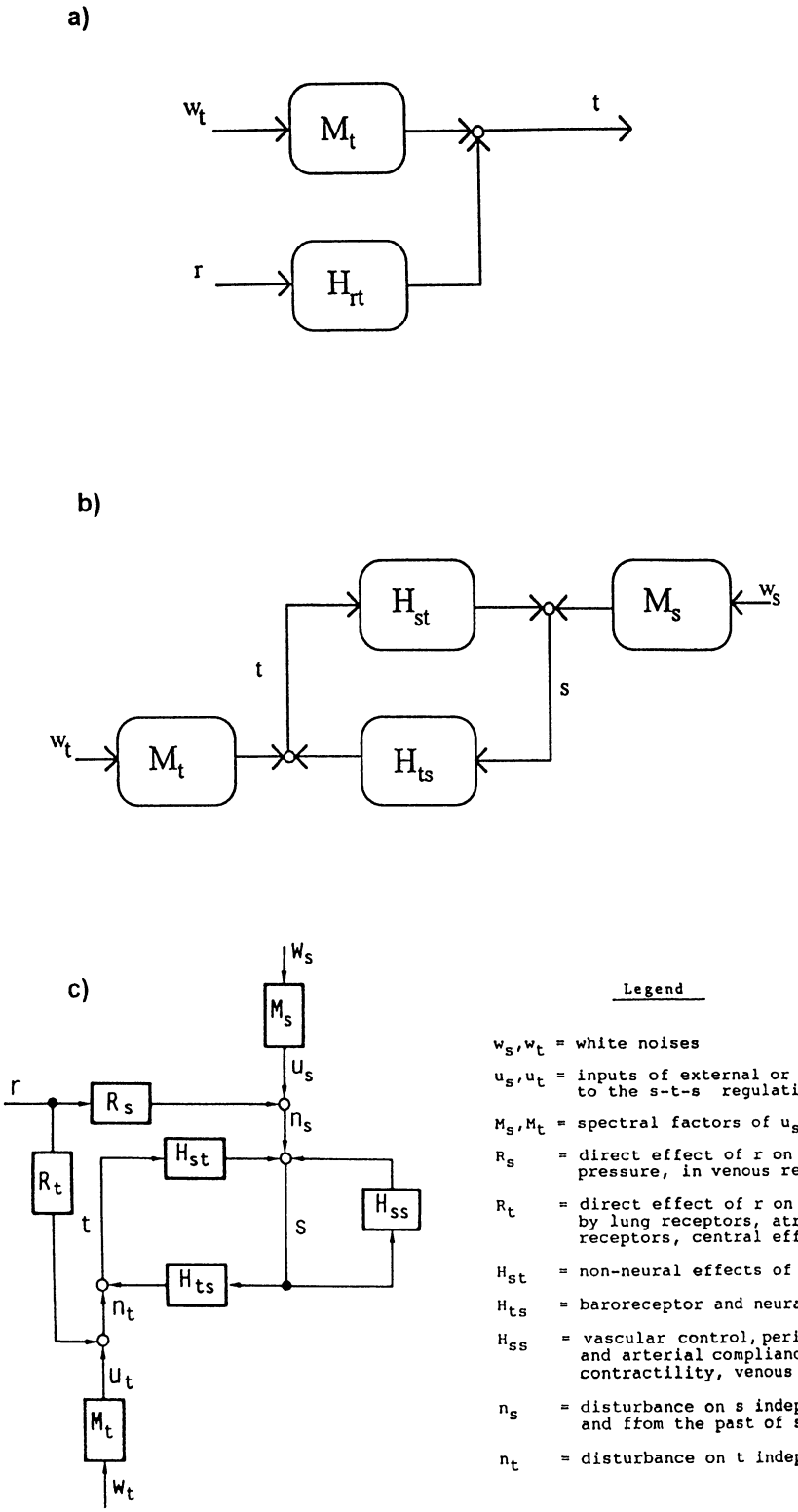

Figure 4. **(a)** Model of interaction between HRV and respiration signal; **(b)** closed-loop model that accounts for the mutual interactions between tachogram and systogram; **(c)** model of the cardiovascular system (see text for details).

PSD in correspondence of each sample in the signal[5]. The set of *ai* parameters is recursively evaluated according to the following relation:

$$\mathbf{a}(t) = \mathbf{a}(t-1) + \mathbf{K}(t)e(t)$$

which shows how the model at the present time t is obtained from the model at the preceding time instant, by summing an innovation term which is a function of the prediction error $e(t)$ and of the gain term $K(t)$. In particular, the gain formulation contains a *forgetting factor*, w, that exponentially weighs the past error terms in order to discount the oldest data and to allow the identification to track the dynamic signal variations. In correspondence of each set of spectral parameters, and thus in correspondence of each sample in the signal, a PSD is evaluated.

Figure 5 shows the variability signals obtained during vasovagal syncope induced in a young subject through passive tilting. The T marks the beginning of the tilting, and S denotes the occurrence of the syncope. In correspondence of the syncope the tachogram clearly shows a bradycardia, while in both the pressure series (systogram and diastogram) the characteristic hypotension effects recognisable. Interest is mainly focused on showing autonomic dysfunctions in the time instants before the syncope: for that reason a time-frequency approach is applied.

Figure 6a shows the tachogram during the tilting manoeuvre and the syncope, and Fig. 6b is a contour plot of the time-frequency distribution obtained through the Wigner transform. Figure 6c shows the contour plot of the time-varying spectra obtained through recursive AR identification.

Figures 7a and 7b show the sequence of the spectra in compressed spectral array (CSA) form for tachogram and systogram, respectively. The time is displayed from the top downwards and one PSD every five is plotted, for a more concise representation. A marked LF component rises after the tilting and increases with time, but becomes less sharp just before the syncope. Simultaneously, the HF component appears again, indicating a decreased sympathetic activation just before the syncope. The decrease in the LF component is earlier in the systogram. A more extensive study which also evaluates the cross-spectral parameters on a beat-to-beat basis indicates a reduced coherence between the signals in correspondence of the syncope and a marked phase shift[21]. An abnormal sympathetic response to tilting seems to cause a vagal reaction that generates the syncope. In addition the vagal reaction is earlier on the vessels, and the control mechanisms involved (on the heart and on the vessels) seem to be mismatched in correspondence to the syncope.

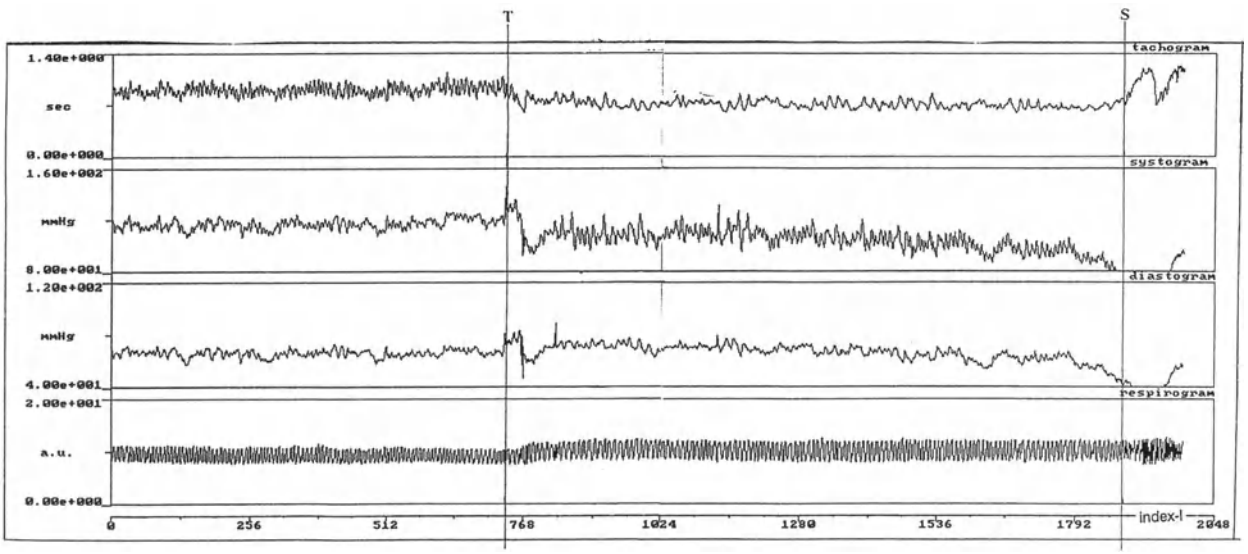

Figure 5. Variability signals obtained in correspondence of a vasovagal syncope (S) induced by a tilting (T) manoeuvre. Top to bottom: tachogram, systogram, diastogram and respirogram.

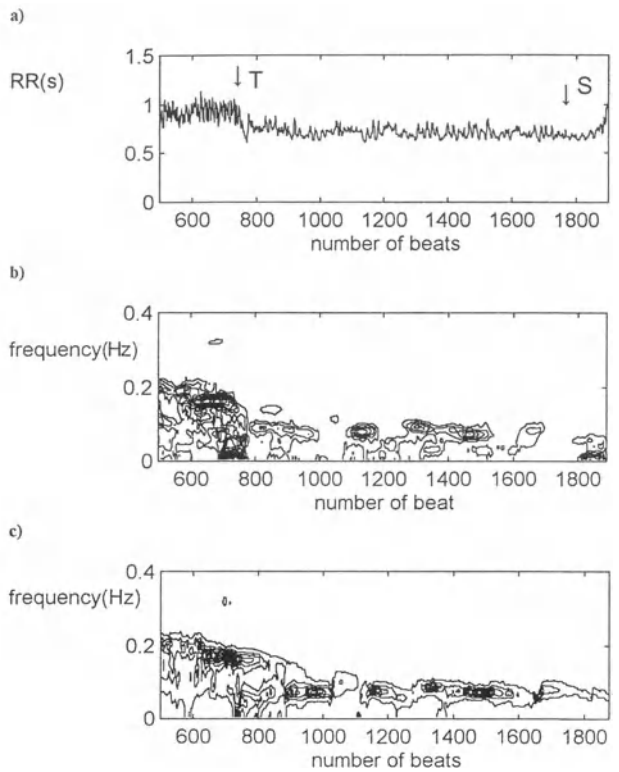

Figure 6. **(a)** RR interval signal obtained in correspondence of a vasovagal syncope (S) induced by a tilting (T); **(b)** contour plot obtained by pseudo-smoothed Wigner-Ville transform; **(c)** contour plot obtained by time-variant RLS identification.

Long term 24-hour spectral analysis

Spectral analysis of the HRV signal may also be carried out on long-term recordings (up to 24 h and over). Recent research has indicated the existence of processes characterised by non-white, time-correlated noises in a wide variety of natural environments. These non-white noises have self-similar patterns and they show Fourier spectra which are non-flat and have $1/f$ power distribution, i.e. with inverse proportionality to the frequency values. This behaviour has also been found in biological and physiological systems.

The analysis of the HRV signal spectrum in the ULF and VLF components range has evidenced a $1/f^{\alpha}$ pattern (power-law spectrum) where α is close to 1. Such behaviour has been found in a wide variety of signals in complex systems which possess a fractal-like geometry characterised by many rhythmic components which interact over different scales.

Such a complex structure requires a non-linear generating system where coefficient α plays an important role for the classification of normal and pathological cases.

Initial evidence of $1/f$ behaviour for the human HRV signal was reported in ref. 22 and then confirmed in refs 23 and 24 for arterial blood pressure in dogs.

Pathological conditions can modify the cardiovascular control parameters in the long term: this is also confirmed by the trend of short-term spectral parameters measured in sequences over 24 h[25]. Together with the mentioned LF and HF spectral contributions, a third component is generally present in the short-term spectrum, in the very low frequency range, whose behaviour is more or less erratic, not precisely harmonically defined, and not coherent with other signals[4]. This observation leads us to consider that some non-linear mechanisms of control may play a significant role, especially in long-term regulation.

Systems with periodic or quasi-periodic behaviour have spectra which show a small number of components, while broad-band spectra are generally characterised by more complex patterns, which are typical of stochastic noise or deterministic chaos. As previously mentioned, a particular broad-band spectrum has power values which scale with the frequency

$$P(f) = \frac{1}{f^{\alpha}}$$

where α is a constant. In the range $1 < \alpha < 3$ the curve has non-integer (fractal) dimension.

In pathological states, such as essential hypertension, and other cardiovascular pathological conditions[26], α increases significantly, thus indicating a shift from a "broad-band" to a "narrow-band" spectrum. $1/f^{\alpha}$ spectra have been observed in functions presenting self-similar, fractal (non-integer) characteristics. This pattern, detected in many biological series, encourages the investigation of non-linear, deterministic dynamic models, possibly chaotic, which can be at the basis of some cardiovascular control mechanisms[27]. The inverse power-law spectrum can be viewed as the resultant of many processes interacting over a myriad of interdependent scales. This property makes the system more fault-tolerant, in respect to other distributions, with regard to errors in the growth process of the organism and sensitivity to external disturbances. Physical examples of this kind of structure could be His-Purkjnie fibres of the heart, vascular and lung trees, biliary ducts and so on[27].

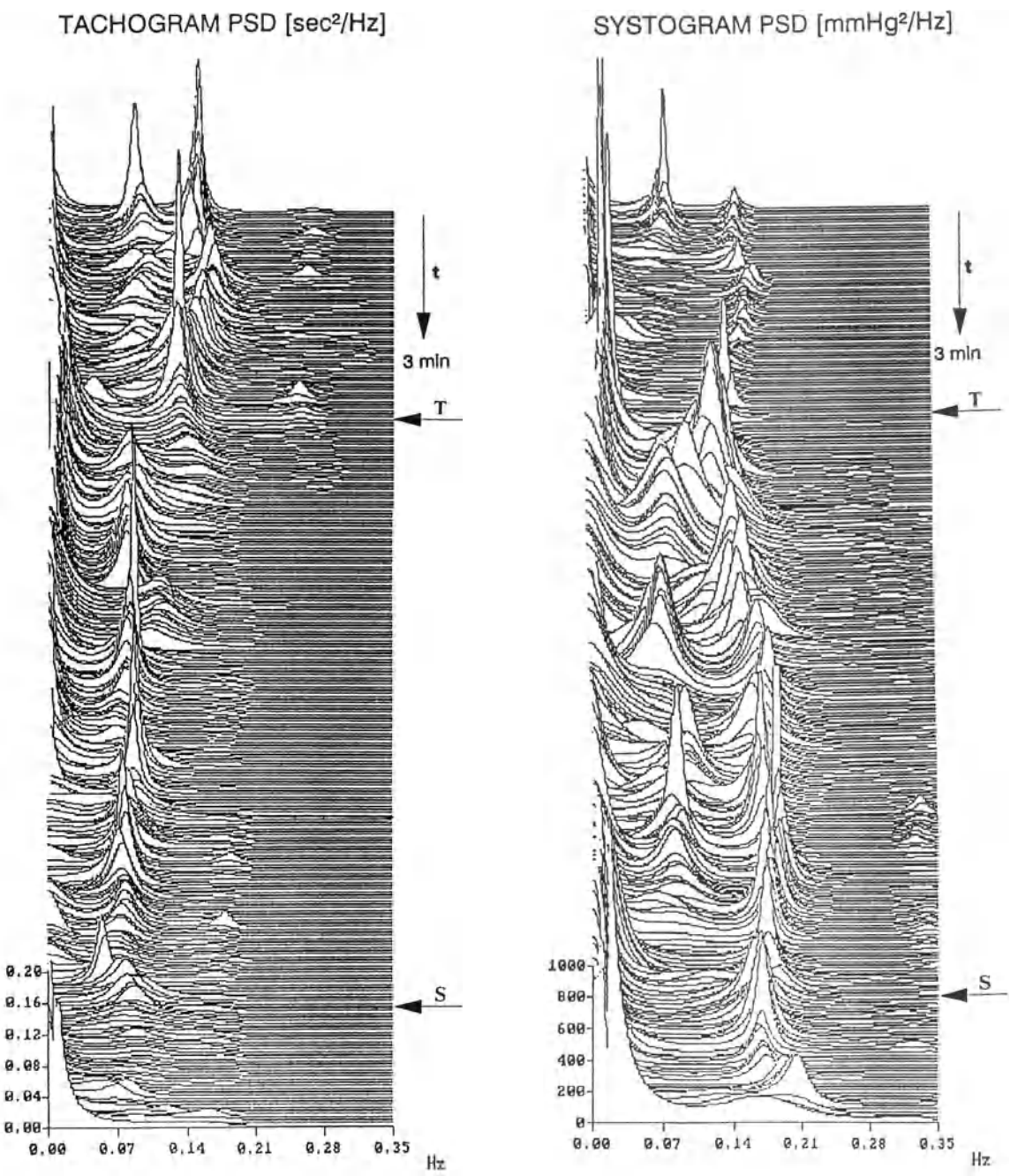

Figure 7. Compressed spectral arrays obtained from the tachogram and the systogram shown in Fig. 6. The frequency is plotted in the Horizontal axis, the power spectral density is on the left vertical axis; time is plotted from the top downwards. T and S mark the tilting and the occurrence of the syncope, respectively.

Similar considerations can be made for signals presenting fractal properties in their time evolution as HRV signal. Such geometric properties of structures can be extended in the time scale of signals. Time series can show fractal characteristics in their patterns, as well as in the temporal scales. The same time series, under

different degrees of magnification of temporal step, show patterns which possess self-similar characteristics to a large or small extent[28].

For each 24 h record a single power spectrum was calculated on the whole data by using the fast Fourier transform algorithm. Generally the discrete series constituted by the occurrence of QRS is interpolated via a sine function and the resulting curve is sampled by respecting Shannon's theorem. Due to stationarity requirements only the ULF and VLF components are generally considered. After plotting the spectrum in log-log scale, the log (power) was regressed on log (frequency) in the range between 10^{-4} and 10^{-2} Hz. The α parameter was obtained as the slope of the regression line on power spectrum on time series length exceeding 90 000 points.

No filtering procedures have been performed, maintaining the original integrity of the data. The possible presence of high-frequency artifacts, such as those induced by ectopic beats, only slightly affects the results, as the analysis is mainly concerned with the very-low frequency and ultra-low frequency (ULF) components (up to 10^{-2} Hz).

Despite the apparent simplicity of the method, which does not require any *a-priori* hypothesis, this approach has demonstrated a powerful capability in the global evaluation of time series properties.

Recent works[29,30] has assessed the capability of power law regression parameter α to classify and predict the risk of death in patients after myocardial infarction. Other methods exist for estimating the long range dependence and self-similarity in variability series[31]. Some of these are particularly suitable to show the long memory characteristics in biological processing as the behaviour of VLF and ULF components in cardiovascular time series seems to suggest. These very slow dynamic changes could reflect an autonomic perturbation that can be captured quite easily by computing the log-log regression parameter[4].

In normal conditions the index α shows values near 1, confirming the broad-band nature of the spectrum, while in the presence of pathological cardiovascular events it significantly increases.

Values of α near 1 are characteristics of a signal with long time correlation with fractal properties and scaling law. This pattern characterises the normal behaviour of the HRV signal.

Figure 8 reports the HRV 24 h spectrum of a normal subject (a) and of a heart-transplanted patient (b). Both are plotted in log-log scale. Values of the α slope, regressed over a frequency of 10^{-4} and 10^{-2}, are reported. As expected, the normal subject shows an α = 1.055, whereas the transplanted subject has α = 1.615. Differences have also been found in HRV signals in other cardiovascular pathologies. Figure 9 shows values of the α slope estimated in normal, hypertensive, severe heart failure and heart-transplanted subjects. The α index assumes values that are significantly different in normal versus heart failure and transplanted groups ($p < 0.05$). In particular, the normal population presents values of α quite close to 1 in respect to the other groups, for which α values increase. Since $1/f$ scaling characterises fractal processes with

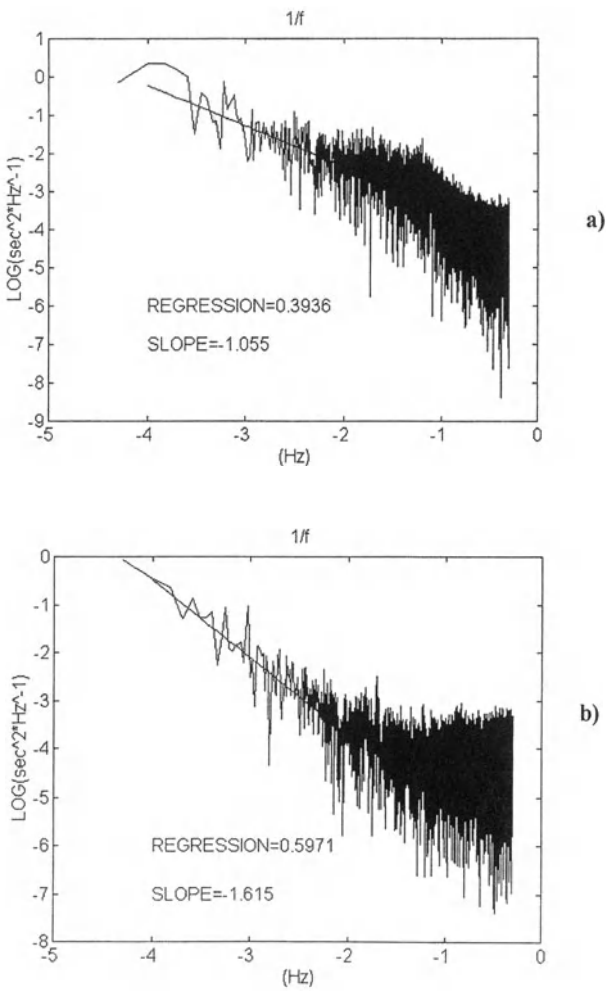

Figure 8. Log-log plot of HRV signal power spectrum density as a function of frequency for **(a)** a normal subject and **(b)** a patient after heart transplant. The α slope and regression values are indicated.

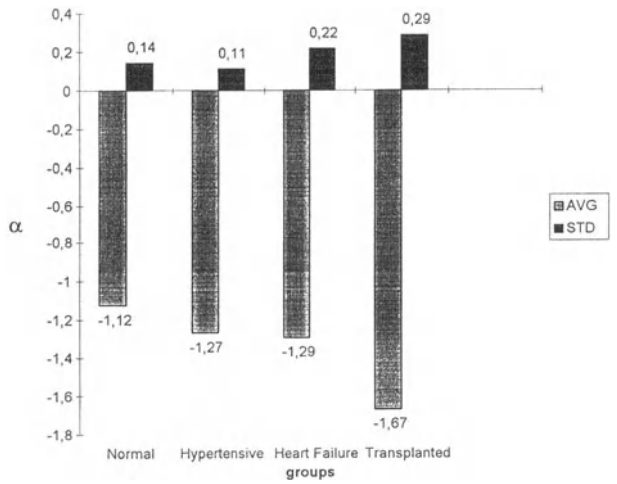

Figure 9. Values of α spectrum slope in nine normal, six hypertensive, 11 severe heart failure and seven heart-transplanted subjects. Values are shown as bar graphs reporting average and standard.

multiple geometric and time scales, this behaviour suggests that physiological HRV generation and control is associated with a higher-complexity degree of HRV signal. As further confirmation, long-term parameters were significantly different between myocardial infarction patients with normal and reduced ejection fraction. The former showed α-slope values close to 1 (almost normal values), while the latter had significantly higher values[29]. Morever, the increase of α values in patients who show reduced ejection fraction (< 40%) confirmed the prognostic value of the index for the evaluation of the death risk[30]. In this case the classical analysis in time domain, based on the calculation of the HRV signal variance, does not show significant differences between the two groups.

Long-term parameters seem to be significantly predictive of patient death even in the presence of different disorders and moderate arrhythmias during the recordings.

In conclusion, long-term spectral parameters can be usefully employed for the assessment of patient status in cardiovascular pathologies. They show significantly increased α values in many pathological conditions, in particular when the death risk is higher, as in myocardial infarction patients. Results reported in this chapter constitute further confirmation of the importance of evaluating the α value on RR 24-h spectra as a global diagnostic and prognostic index.

Conclusion

The HRV signal has considerable potential to assess the role of the autonomic nervous system in physiological conditions (normal healthy individuals) and in patients with various pathologies of cardiovascular or other origin. In addition, HRV studies should enhance the understanding of physiological phenomena, the action of medications and disease mechanisms.

In recent decades processing techniques have been developed from simple time series analysis in the time domain, to frequency domain approaches, which provide important information on the dynamics and rhythms contained in the signal.

Power spectrum analysis through the Fourier approach first indicated the rhythmic activity of the HRV signal, concentrated basically in determined frequency bands. Parametric approaches enhanced the pseudo-stochastic nature of such a signal, and allowed the separation of the wide-band noise superimposed to the well-defined LF and HF spectral components. Long-term analysis, mainly aimed at explanation of the VLF component, indicated the chaotic behaviour of the control system originating the HRV. The above information is employed in the development of models which may take into account different variables and levels of interaction among them, and help explain many physiological and pathological phenomena.

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Chapter 26

Physiological Background of the Heart Rate Variability Spectral Components

Alberto Malliani, Nicola Montano and Massimo Pagani

Introduction

The existence of physiological rhythms embedded in the beat-to-beat heart period signal has been reported in the pioneering observations by Peñaz et al[1] and Sayers and co-workers[2,3]. Subsequently, Akselrod and co-workers[4] had the merit of advancing the hypothesis that the power spectrum analysis of heart rate fluctuations could furnish a quantitative evaluation of cardiovascular control.

This challenge, from the beginning, seemed difficult to address. The traditional subtractive approach had already indicated that vagotomy, in acute experimental conditions, was capable of abolishing the respiration-related component of heart period variability[5], a finding soon confirmed by administration of atropine[4]. However, besides this unequivocal observation, there was a vast twilight zone. In fact the three spectral peaks (low-, mid- and high-frequency) identified in the short-term time series by Akselrod and co-workers[4] were respectively attributed to the parasympathetic nervous system (the high- and the mid-peak) and to the sympathetic, parasympathetic and renin-angiotensin system (the low-frequency peak). In particular, both branches of the autonomic nervous system were considered capable of increasing the amplitude of the low-frequency peak.

A subsequent study from the same laboratory[6], by analysing, in normal human subjects, two different body positions before and after the administration of atropine and/or propranolol, concluded (in this paper only two spectral components were identified) that in the supine position the low-frequency component was entirely mediated by the parasympathetic system, while in the orthostatic position it was mediated by both autonomic outflows.

On this basis the high-frequency (HF) component could be used as a marker of vagal activity while the low-frequency (LF) component, due to its mixed origin, appeared to be largely deprived of possible practical significance in order to interpret specific autonomic control mechanisms.

The sympathovagal balance

Our conceptual approach has been quite different as it was, from the beginning, linked to a definite physiological model. It is well known that, in the neural regulation of circulatory function, the activation of either sympathetic or vagal outflow is accompanied by the inhibition of the other[7,8]. In closed-loop conditions

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such a balance is likely to be influenced by at least three major factors: central neural integration, peripheral inhibitory reflex mechanisms (with negative feedback characteristics) and peripheral excitatory reflex mechanisms (with positive feedback characteristics)[9,10] (Fig. 1).

It was the core hypothesis of our approach that this balance, viewed as a reciprocal relation, could on the whole be explored in the frequency domain[11,12].

We have repetitively summarised[12–14] the data that support the assumption that: (1) the respiratory rhythm of heart period variability, defined as the HF spectral component, is a marker of vagal modulation; (2) the rhythm corresponding to vasomotor waves and present in heart period and arterial pressure variabilities, defined as the LF component, is a marker of sympathetic modulation; and (3) a reciprocal relation exists between these two rhythms that is similar to that characterising sympathovagal balance.

In this context we thus prefer to further speculate, on the basis of new experimental findings, about the crucial role of central neural structures in providing the push-pull organisation of this complex rhythmicity.

The interpretation of rhythms

LF and HF components are both simultaneously present in sympathetic and vagal efferent fibres[12]. The fact that the response time of the sinus node pacemaker activity to the parasympathetic transmission is much shorter than

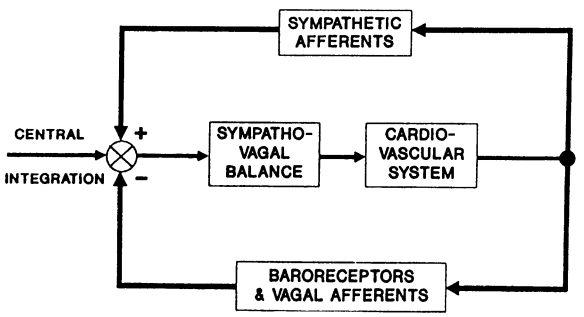

Figure 1. Sympathovagal balance can be schematically represented as the interaction of three major factor: central neural integration, peripheral inhibitory and peripheral excitatory reflex mechanisms. Baroreceptive and vagal afferents mediate negative feedback mechanisms, determining excitation of vagal outflow and inhibition of sympathetic outflow. Conversely, sympathetic afferents mediate positive feedback mechanisms, associated with excitation of sympathetic outflow and inhibition of vagal outflow. (From ref. 12 with permission from American Heart Association.)

that to the sympathetic transmission, appeared, since the early papers[4], to be an adequate reason for excluding the possible participation of sympathetic mechanisms in the modulation of HF of RR interval power spectrum. Conversely, LF was considered a fluctuation capable of conveying both autonomic influences. The finding that β-blockade was incapable of abolishing the LF component[6,15] was consistent with this view. These were the main reasons that justified, at the beginning, a great scepticism when we proposed that the LF component could be used as a convenient marker of sympathetic modulation[15]. A methodological issue was crucial to our proposal, dealing with a normalisation procedure. We had noticed that vagal predominance was associated with an increased total power (or variance), and hence with an increased absolute value of both spectral components, but with a shift of power towards HF. Conversely, a sympathetic predominance was often associated with a reduction of total power, leading to a reduction in absolute power of both spectral components, however, with a shift of power towards LF. In brief, during sympathetic activation the LF component could be reduced in absolute units but clearly increased in normalised units. Having to choose, as in music, between notes and decibels, we thought that the fractional distribution (and the normalisation procedure) of power was one of the key issues of the frequency domain.

The pragmatic reward was quite high. When normalised units were used to assess the progressive shift in sympathovagal balance induced by a graded tilt[16], the correlation coefficient was 0.78 for LF and –0.70 for HF. The LF/HF ratio, an additional index that we had proposed since the beginning[15] for evaluating sympathovagal balance, was also highly correlated ($r = 0.68$).

How can we explain the heuristic value of this sympathovagal model? If LF reflects the activity of both autonomic branches, how is it possible that its normalised value has never failed, so far, to signal changes in sympathetic modulation in multifarious models (with the exception of conditions devoid of sufficient stationarity and with too-intense transients and artifacts, as occurs in medium and strenuous physical exercise)?

On the other hand, why does a vagal afferent stimulation induce an increase only in the HF and not in the LF component[17]?

The following is our hypothesis. Both LF and HF components arise from a quite complex central and peripheral sympathetic and parasympathetic interaction.

Any reductionistic view is inappropriate: for instance, even in terms of biological good sense it is difficult to believe that the HF oscillation of sympathetic nerve activity is purposeless in view of its presumed incapability of modulating the target function at that frequency. In closed-loop conditions there is a complex synchrony between peripheral disturbances (respiration and vasomotion) and central rhythmicity: the latter is conveyed to the periphery through autonomic outflows and returns to the centres though afferent nerve activity in phase with peripheral disturbances. Which comes first is an egg/chicken problem.

It is the nub of this hypothesis that two main rhythms, one marker of excitation (LF) and linked to sympathetic activation, and one marker of quiet (HF) and linked to vagal predominance, would be organised, in physiological conditions, in a reciprocal manner. Accordingly, a state of excitation would be accompanied by the central prevalence of LF rhythm, conveyed to the periphery by the simultaneous increase in sympathetic nerve activity, while a state of quiet would be accompanied by a central prevalence of HF rhythm, conveyed to the periphery by the simultaneous increase in parasympathetic activity.

This hypothesis can be tested experimentally. In our study[18], experiments were carried out on decerebrate artificially ventilated cats in which, together with cardiovascular signals, the sympathetic activity was directly recorded from thoracic preganglionic fibres likely to participate in cardiac innervation. In control conditions both LF and HF were present in both power spectra of RR and sympathetic activity variability, with a high coherence between them. During sympathetic excitation, obtained by reducing arterial blood pressure through the inflation of a balloon in the inferior vena cava, thus decreasing baroreceptive stimulation, the control spectral profile of sympathetic discharge variability was modified towards a more marked prevalence of LF component (Fig. 2). Conversely, during sympathetic inhibition, obtained by occluding the abdominal aorta and thus increasing arterial pressure and stimulating arterial baroreceptors, the HF component became predominant

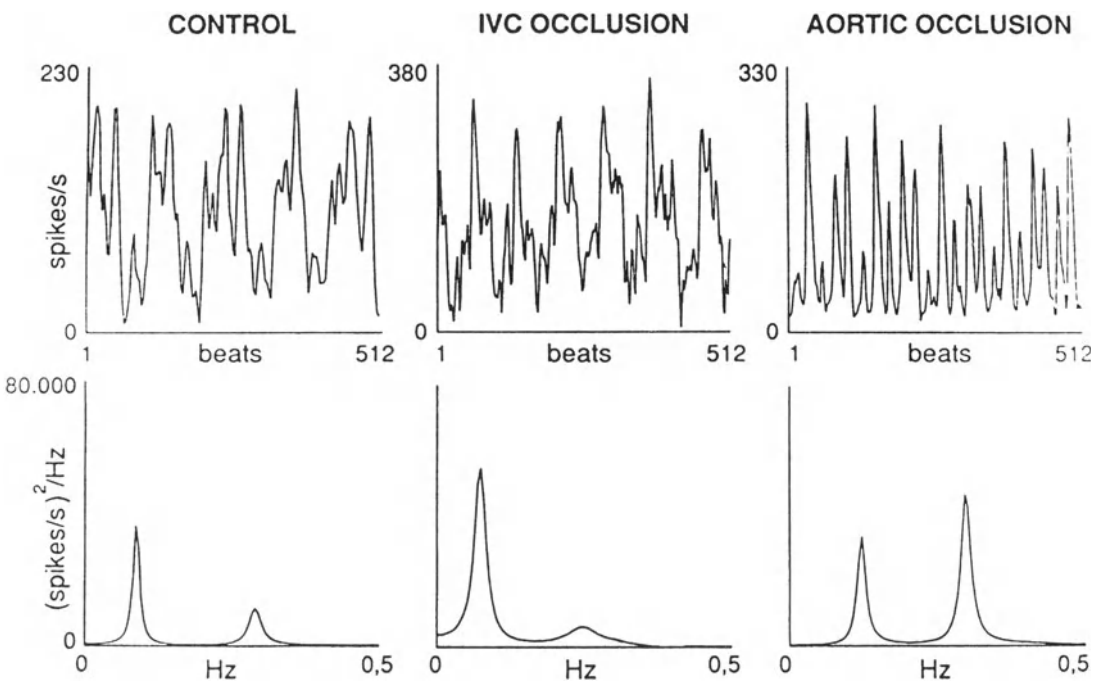

Figure 2. Time series (upper panels) and power spectra (lower panels) of cardiac sympathetic efferent discharge recorded in a decerebrate-unanaesthetised, artificially ventilated cat. Two different spectral components, LF (around 0.10 Hz) and HF (around 0.30 Hz), were detectable in control conditions. During sympathetic activation induced by inferior vena cava (IVC) occlusion, LF increased whereas HF decreased. Conversely, sympathetic inhibition induced by aortic occlusion was associated with a shift towards an HF predominance. (Reprinted from ref. 18 with kind permission of Elsevier Science – NL, Sara Burgerhartstraat 25, 1055 KV Amsterdam, The Netherlands.)

(Fig. 2). Simultaneously, similar changes occurred in the power spectrum of RR variability. These findings not only directly supported the hypothesis that the LF component of RR variability can be used as a marker of sympathetic modulation, but strongly suggested a central push/pull organisation between the two rhythms.

The limits of acute experiments, and artificial ventilation, were overcome in quite recent experiments performed in a collaborative study at the University of Iowa[19]. In normal human subjects cardiovascular signals were recorded together with muscle sympathetic nerve activity (MSNA) during graded changes in arterial pressure induced by vasoactive drugs. During sympathetic activation, induced by nitroprusside infusion, there was a predominance in the LF oscillation of power spectra of blood pressure, RR interval and sympathetic nerve activity (Fig. 3). On the contrary, during sympathetic inhibition, induced by phenylephrine administration, the HF component was proportionally increased. This relationship was best seen when power spectral components were normalised. In particular the correlation analysis using Theil regression of the relationship between LFnu of RR and LFnu of MSNA had a p value of less than 10^{-6}.

We think that only a central push/pull organisation, coupling changes in sympathovagal balance and cardiovascular oscillations, can explain these findings. In line with this hypothesis it was also found[20] that the discharge of single medullary neurons involved in the regulation of the cardiovascular system, recorded in vagotomised and sinoaortic denervated cats, was characterised by the presence of both LF and HF components. We are currently studying other populations of central neurons with the aim of exploring the dynamic characteristics of these rhythmic properties that appear to subserve a possible neural code[13].

Collateral hypotheses

The LF component has been attributed by DeBoer and co-workers[21] to the baroreflex: in their model the arterial pressure oscillations induced by respiration stimulate the baroreceptors and, through the interaction of the fast vagal response and the slower sympathetic transduction controlling arterial smooth muscle, an LF component is generated in arterial pressure as a resonance phenomenon which, in turn, stimulates baroreceptors and thereby the efferent control of RR. Sleight and co-workers[22] directly addressed this issue by mechanically stimulating at 0.1 Hz the carotid sinus region, and observed an increase in the LF component.

We obviously recognise the possibility that baroreflex mechanisms might interfere with LF amplitude, but always questioned[12] their exclusiveness in LF pattern generation. In terms of neurophysiological thinking, an increase in the rhythmicity of a neural substratum can be induced by increasing a rhythmic input to it, or by reducing some tonic inhibitory activity restraining autochthonous rhythmicity. An increased input from baroreceptors was clearly obtained by Sleight and co-workers[22] with their mechanical stimulation (but the limit of this model was, indeed, that it transformed a closed-loop system into an open input/output relation).

In usual thinking the tachycardia response, e.g. during standing or during hypotension, is attributed to a baroreflex: this attribution is obviously correct, but what seems to be forgotten is that, the baroreflex being a negative-feedback mechanism, the sympathetic excitation occurs as a release phenomenon caused by a reduction of baroreceptive restraint (for instance, when recording sympathetic efferent activity in an experimental animal the drastic reduction in baroreceptor firing obtained with bilateral carotid artery occlusion is accompanied, as a rule, by a profound change in sympathetic discharge that loses its cardiac rhythm and becomes a continuous firing). Conversely, in conditions such as mental stress or physical exercise, during which there is a simultaneous presence of tachycardia and hypertension, baroreceptor firing should increase. However, in both circumstances the LF component is increased[12]. In addition, there are conditions such as experimental regional myocardial ischaemia during which an LF increase can occur in the absence of arterial pressure changes[23]. Incidentally, in resting conscious dogs an LF component is usually present in arterial pressure variability but usually absent in RR variability[23], in spite of the high baroreflex gain. To further complicate this issue, the baroreflex gain is known to be decreased during standing, mental stress and exercise, conditions all characterised by increased sympathetic activity: should we conclude that it is a reduction of baroreflex gain or rather an increase in sympathetic activity to shift towards LF some spectral power?

For these reasons we explicitly wrote that "LF component should not be considered a specific reflection of a baroreflex compensatory response[24] but rather a general marker of sympathetic excitation, regardless of

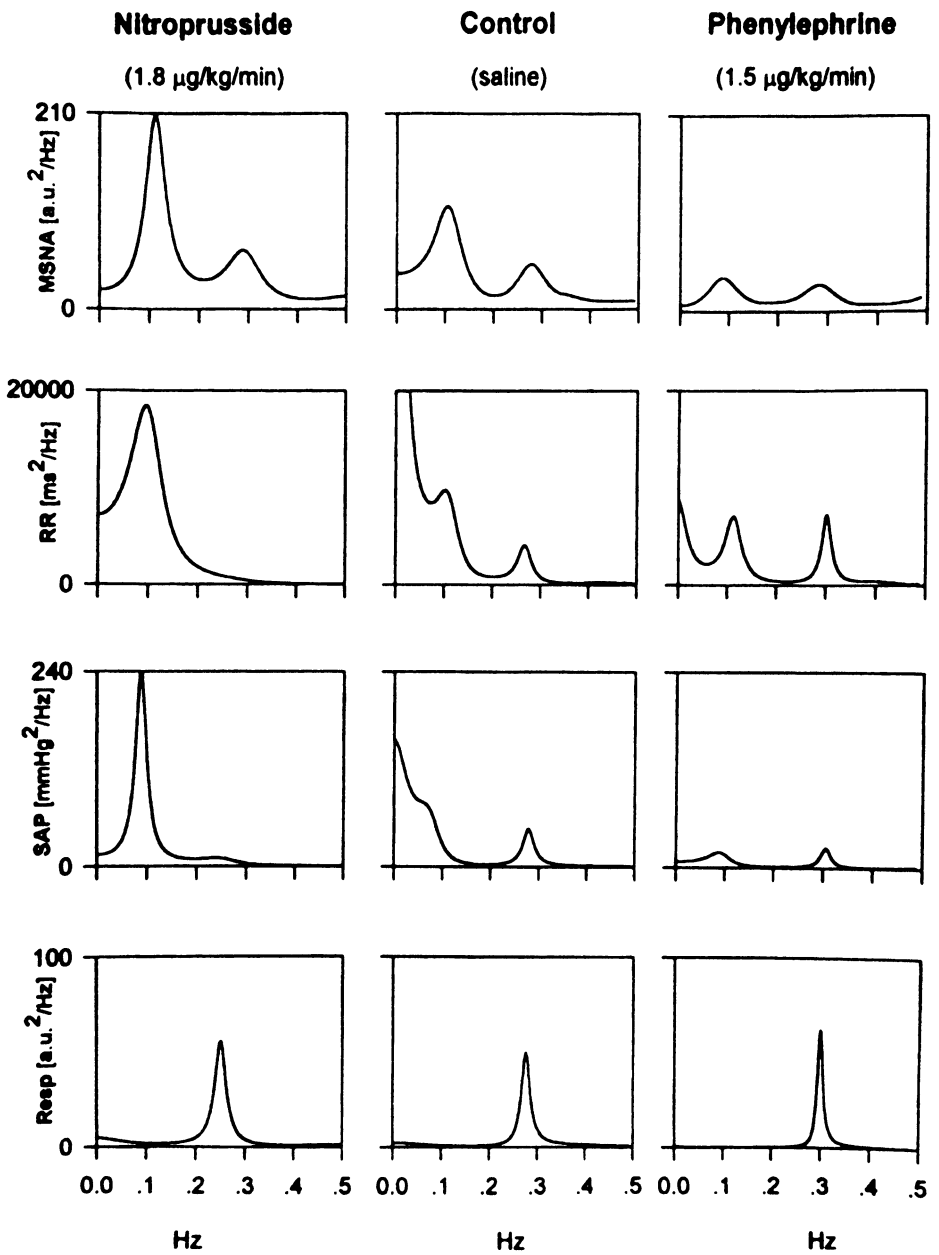

Figure 3. Power spectra of muscle sympathetic nerve activity (MSNA), RR interval, systolic arterial pressure (SAP) and respiration (Resp) variabilities during infusion of saline (Control), nitroprusside and phenylephrine in a healthy volunteer. Sympathetic activation induced by nitroprusside was associated with an increase of LF component on neural and cardiovascular signals relative to the HF component. Conversely sympathetic inhibition during phenylephrine infusion was accompanied by an increase of the HF component relative to the LF component. (From ref. 19 with permission from American Heart Association.)

its mechanism"[12]. In brief, we now think that any sympathetic excitation occurs with an LF pattern due to its complex central/peripheral organization. Moreover we also think that LF and HF patterns are intrinsically coupled.

The consequences of these different views in the interpretation of other phenomena can be quite relevant. For instance it was reported by Inoue and co-workers[25] that quadriplegic patients had no LF component in RR variability spectrum, a finding that was correctly interpreted

as the result of an interruption of the neural pathways conveying the rhythmicity from the brain to the spinal cord. However, it was subsequently demonstrated that some quadriplegic patients can have an LF component in RR and arterial pressure variabilities[26,27]. In a study by our group[26] this observation was interpreted as an emerging spinal rhythmicity influencing both sinus node pacemaker activity and the vascular bed; indeed the LF component appeared to increase with time. Incidentally, some patients presented an LF component in the RR interval, in the absence of a similar component in arterial pressure variability (a further argument against a necessary role for baroreflex mechanisms). On the other hand, in a study by Koh and co-workers[27], the LF component was interpreted as vagally mediated in response to a baroreceptor stimulation.

What is astonishing, on the whole, is how much baroreceptors are still considered as the absolute sovereigns controlling all cardiovascular reflex changes and rhythms. Incidentally, we have proven that the so-called simple baroreflex includes, in closed-loop conditions, multiple reflexes, some of which are of spinal origin[28].

To conclude on the meaning of rhythms, it is likely that the complexity of neural and cardiovascular rhythms is such that any simplistic circuit is, by definition, inadequate. For instance Introna and co-workers[29] have reported that, in patients undergoing spinal anaesthesia, when the spread of spinal block reached the highest thoracic segments (above T3) a remarkable abatement of variance and of both spectral components occurred. This observation clearly indicates how much a complex interaction of neural mechanisms is necessary in order to generate the normal variance and its rhythms.

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Chapter 27

Heart Rate Variability after Myocardial Infarction

Yee Guan Yap and Marek Malik

Introduction

The majority of deaths following an acute myocardial infarction (AMI) occur in the first year, with a mortality rate ranging between 5% and 15%[1,2]. The major cause of death in the first year after AMI is ventricular arrhythmias and sudden death[3,4]. While the definition of sudden death is still under much debate[5] it is recognised that the majority of these events, although not all, begin as a ventricular tachycardia which quickly degenerates into ventricular fibrillation, in the absence of either acute infarction or significant ischaemia[6,7].

Extensive effort has been focused on the use of non-invasive risk factors in stratifying high-risk patients from ventricular arrhythmias following AMI. All the known risk factors such as left ventricular ejection fraction, signal-averaged ECG and ventricular premature complexes are limited in their usefulness, due to the high number of false-positive results. Recently, attention has focused on heart rate variability (HRV) as a more accurate means of risk stratification in patients after myocardial infarction.

Pathophysiology of heart rate variability

The link between autonomic abnormality and sudden cardiac death following myocardial infarction (MI) has been demonstrated by a large number of clinical and experimental studies[8]. In the animal model, during myocardial ischaemia, an increase in sympathetic activity facilitates the onset of malignant arrhythmias, whereas an enhanced vagal reflex produces an increase in the ventricular fibrillation threshold, and hence an antifibrillatory effect[9].

It is generally accepted that HRV reflects the autonomic modulation of firing of the sinus node, and the analysis of HRV is an established non-invasive method for assessment of autonomic influence on heart rate at sinus-node level[10]. The so-called high-frequency component of physiological HRV is almost exclusively mediated by vagal activity, whereas the low-frequency component of HRV is under the influence of sympathetic activity with some contribution from vagal activity[11]. In other words, HRV represents a measure of sympathovagal modulation.

Methods and algorithms used to measure heart rate variability

The measurement of HRV is initially done by recording the electrocardiogram (ECG) using 24-h Holter ambulatory ECG. The periodicity in the data can then be quantified using either time domain or frequency domain measurements. There are several algorithms that can be employed for both time and frequency domains

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to assess the standard deviation, number, centre frequency, and amplitude of the oscillatory components hidden in the variability signal[12–14] (see Table 1). Some of the normal values of standard measures of HRV are summarised in Table 2. There is a need to standardise a method for measuring HRV. The most commonly used is the standard deviation of RR intervals (SDNN) of time domain analysis. The standard deviation of RR intervals has been proposed as a simple tool to evaluate overall HRV, but is limited in measuring the changes in sympathovagal balance[13]. Recently it has been recognised that the high-frequency (HF) and low-frequency (LF) components of the HRV spectrum of the frequency domain are reliable markers of vagal and sympathetic activities, respectively[13]. Both HF and LF oscillations interact in modulating target functions and determining their rhythmic properties.

Table 2. Normal values of standard measures of HRV (adopted from ref. 14)

Variable	Units	Normal values (mean ± SD)
Time domain analysis of nominal 24 hrs		
SDNN	ms	141 ± 39
SDANN	ms	127 ± 35
RMSSD	ms	27 ± 12
TI	U	37 ± 15
Spectral analysis of stationary supine 5 min recording		
Total power	ms^2	3466 ± 1018
LF	ms^2	1170 ± 416
HF	ms^2	975 ± 203
LF	nu	54 ± 4
HF	nu	29 ± 3
LF/HF ratio		1.5–2.0

Heart rate variability and risk of mortality after myocardial infarction

The predictive value of HRV was first suggested by Wolf et al, who showed a correlation between reduced sinus respiratory arrhythmia and in-hospital mortality[15]. Compelling evidence that HRV is a powerful predictor post-MI came from Kleiger and colleagues. They demonstrated that a depressed HRV was associated with a 5.3-fold increase in all-cause mortality, especially during the first 4 years after AMI[16]. Another study by Cripps et al showed that HRV was not only capable of

Table 1. Time and frequency domain parameters of HRV measurements (modified from ref. 12)

Time domain HRV	
Long-term (24 h)	
Mean	Mean of all normal RR intervals
SDNN	Standard deviation of all normal RR intervals
TINN	Width of the triangle interpolation of the RR histogram
TI	Total number of all RR intervals divided by the height of the histogram of all RR intervals
Short-term (5 min)	
SDANN	Standard deviation of the 5 min mean RR intervals
SD	Mean of the 5 min RR standard deviations
CV	Mean of the 5 min variation coefficients
Beat-to-beat	
pNN50	Percentage of subsequent RR differences greater than 50 ms
RMSSD	Root mean square of subsequent RR differences
Frequency domain HRV	
Fast Fourier transformation or autoregression (short-term, 5 min or long-term, 24 h)	
VLF	Very low frequency with frequencies centred around 0.0 Hz
LF	Low frequency with frequencies centred around 0.10 Hz
HF	High frequency with frequencies centred around 0.25 Hz
LF/HF	Ratio LF/HF

predicting total cardiac mortality after infarction but also identified patients at risk of sustained symptomatic ventricular tachycardia[17].

In a large epidemiological study the Framingham Heart Study Group showed that, in a population which was apparently free of coronary heart disease or congestive heart failure, HRV was associated with subsequent cardiac events (angina, MI, coronary heart disease death or congestive heart failure)[18]. A one-standard deviation decrement in the standard deviation of total normal RR intervals (natural log transformed) was associated with a hazard ratio of 1.47 for these new cardiac events[18]. The mechanism for such an association is as yet unknown. Interestingly, in this study, a short-term recording of 2 h of ambulatory ECG was used instead of a 24-h ECG. The predictive power of short-term HRV is still unclear. Malik et al found that arbitrary short-term recordings were not sufficient compared to a 24-h ECG, because their specificity for predicting arrhythmia risk was small[19]. In a separate epidemiological study the same Framingham Heart Study Group also demonstrated that reduced HRV predicted an increased risk for all-cause mortality[20].

Heart rate variability and location of myocardial infarction

There are conflicting results regarding the relationship between HRV and the locations of infarct. Evidence from some reports shows that patients with anterior AMI have a significantly lower HRV or pNN50 values compared with those with inferior infarcts[21–23]. On the other hand, Casolo et al found no difference in HRV parameters between patients with anterior or inferior infarction[24]. Others showed mixed results. Pipilis et al demonstrated that, in those patients with anterior AMI, the degree of HRV reduction and heart rate increase was significantly stronger than that with inferior AMI[25]. However, within a few hours after the onset of infarction the two groups were clinically similar in terms of degree of heart failure, enzyme release, and drug treatment, despite their initial discrepancy in the HRV measures. These divergent results could have been due to different recording times and their relation to the course of recovery after AMI. The suggestion that patients with inferior infarction have a higher vagal tone as judged by their HRV has yet to be established in view of this conflicting evidence.

Heart rate variability and thrombolytic treatment after myocardial infarction

Thrombolytic therapy has significantly decreased the mortality of patients with AMI. The significant impact that thrombolysis has had on the natural history of AMI may have altered the clinical relevance of previously established risk factors. Effective thrombolytic therapy may prevent the development of an abnormal electrophysiological milieu after MI.

Zuanetti and co-workers therefore set out to investigate the prognostic significance of time domain measures of HRV in post-MI patients in the thrombolytic era. They found that the time domain indices of HRV (i.e. SDNN, RMSSD, NN50+) retain their independent prognostic power in post-MI patients despite all their patients having received thrombolytic treatment. Indeed, subjects in their study with low HRV had a seven-fold increased risk of dying during the 1000 days of follow-up[26]. Similarly, Farrel et al found no effect of early thrombolysis on HRV, expressed as TINN in patients suffering from AMI. Although the incidence of death during follow-up (mean 612 days, range 1–1112 days) was significantly lower in the thrombolytic group, the incidence of subsequent arrhythmic events tends to be lower, but did not reach statistical significance[27].

Chakko et al examined the hourly spectral analysis of HRV during the first 24 h of successfully reperfused (documented on coronary angiogram) AMI patients treated with thrombolysis. They found that HRV was higher during the early phase following an AMI and decreased as hours progressed. Reperfusion caused an immediate, transient, paradoxical decrease in HRV, suggesting an abrupt reperfusion-induced decrease in parasympathetic tone[23].

Circadian variation of heart rate variability in post-infarction patients

It is also known that, in post-infarction patients, there is a significantly reduced circadian variation of normalised HRV in the high-risk patient as compared to the low-risk patient experiencing malignant ventricular tachyarrhythmias[28]. The latest study by Klingenheben et al confirms that post-infarction patients surviving ventricular tachyarrhythmias had a markedly reduced high-frequency component of HRV using spectral analysis, particularly during the early-morning hours (04:00–08:00 a.m.) and showed no difference in the amount of high-frequency energy during daytime

and night-time as compared to patients without arrhythmic events[29]. This evidence suggests that predominance of sympathetic tone in the early-morning hours may account for the pathophysiological mechanism of circadian variation observed in the occurrence of sudden cardiac death. Analysis of the diurnal variation of HRV may further improve its prognostic value.

Heart rate variability and other clinical parameters

An earlier study by Kleiger et al showed decreased HRV to be an independent predictor of mortality after MI, irrespective of demographics, New York Heart Association functional class, left ventricular ejection fraction (LVEF) and ventricular ectopic activity[16]. On the other hand, Casolo and colleagues found that HRV assessed during the acute phase of MI was significantly related to clinical and haemodynamic indices of severity, such as peak creatine kinase, LVEF, and Killip class[24].

Odemuyiwa et al investigated whether HRV, expressed as TI, was more powerful as a predictor of total cardiac mortality, of arrhythmic complication (i.e. sudden deaths and sustained symptomatic ventricular tachycardia), or sudden death alone[30]. They showed that HRV was a better predictor of sudden and symptomatic ventricular tachycardia than LVEF, whereas both HRV and LVEF performed equally well in predicting all-cause mortality in the post-infarction patients. Similarly, Hartikainen et al examined whether the HRV, signal-averaged electrocardiogram (SAECG), ventricular arrhythmias and LVEF predicted the mechanism of cardiac death after MI (i.e. arrhythmic or non-arrhythmic)[31]. They demonstrated that arrhythmic death was associated predominantly with depressed HRV and ventricular tachycardic runs, whereas non-arrhythmic death was associated with low ejection fraction, ventricular ectopic beats, and depressed HRV. These findings can be explained by our current understanding of the pathophysiology of depressed HRV following a MI[32]. The reduced LVEF reflects a liability to cardiac failure, and is therefore likely to identify patients who are at risk of non-sudden death, some of whom will develop ventricular arrhythmias and die suddenly. On the other hand, reduced HRV implies a lack of an autonomic protection against ventricular arrhythmias, and would therefore be more powerful in identifying those patients who are at high risk of sudden death or arrhythmic complications[32].

Effects of drugs on heart rate variability

As discussed above, depressed HRV after MI reflects an altered sympathovagal neurocardiac reflex regulation with either an increase in sympathetic activity, decreased parasympathetic activity or both. Such an alteration is strongly associated with both total and arrhythmic mortality. Therefore, any pharmacological manipulation of the sympathovagal balance could have a favourable effect on the mortality of post-infarction patients. Beta-blocker in patients surviving AMI has proven to be beneficial, particularly in reducing sudden death[33]. The exact mechanism is not yet understood[34]. Sandrone and co-workers examined the effects of β-blockers (atenolol or metoprolol) on HRV after MI using a spectral technique[35]. They showed that β-blocker-induced bradycardia was associated with a significant increase in the averaged 24-h value of RR variance and of the normalised power of the high-frequency component, whereas the low-frequency component was greatly reduced, especially in the daytime. In addition, a marked attenuation in the circadian variation of the low frequency was also observed. They suggested that β-blockade reduced the sympathetic activity and increases the vagal tone, which helped to explain the beneficial effect of these drugs after MI.

Recently there has been some interest in the possible therapeutic effect of scopolamine. Scopolamine, similar to atropine, exhibits opposing, dose-dependent effects. When used in high doses it blocks peripheral parasympathetic activity, whereas at low doses it exerts a paradoxical parasympathomimetic effect that is purportedly mediated by the central nervous system[36,37]. Previous studies on healthy human subjects demonstrated that low-dose transdermal delivery of scopolamine increased arterial baroreflex sensitivity and HRV[37,38]. Pedretti et al examined the effect of low-dose scopolamine on the baroreflex sensitivity and HRV in 28 survivors of MI[39]. They showed that scopolamine significantly improved baroreflex sensitivity, all time-domain and spectral measures of HRV except SDANN and SDNN. Similarly, Vibiral and colleagues examined the effect of low-dose transdermal scopolamine on the HRV of 61 male survivors of AMI[40]. They demonstrated that scopolamine significantly increased all the indices of short-term time domain measure of HRV by between 26% and 35% compared with placebo. Both studies confirmed that low-dose scopolamine increased cardiac parasympathetic activity in post-infarct patients. However,

whether such an effect is a surrogate for improvement in long-term morbidity and mortality requires a prospective, randomised, double-blind trial.

Predictive power of heart rate variability in postmyocardial infarction patients

For post-infarction risk stratification the predictive value of HRV is modest, although it appears to be better than other recognised risk factors. Differences in the timing of investigations, method of analysis and specific endpoints make comparisons of predictive accuracy between studies difficult. For instance, Kleiger et al showed that an SDNN < 50 ms had a sensitivity of 33.8% and a specificity of 87.9% for all-cause mortality[16]. On the other hand, Odemuyiwa et al demonstrated that, for a TI ≤ 30 U, the sensitivity was 75% with a specificity of 76% for the prediction of arrhythmic events[30]. Farrell et al showed that, at TINN < 20 ms, HRV had a sensitivity of 92% for arrhythmic events (sudden death or life-threatening ventricular arrhythmias) but a specificity of 77% only resulted in a large number of false-positive results and a low predictive accuracy of 17%[27].

Among all the HRV measures, time domain HRV provides better prognostic information than the rest, particularly SDNN and TI[14]. A high-risk group may be selected by the dichotomy limits of SDNN < 50 ms or TI < 15 U. It is recommended that HRV should be measured approximately 1 week after the index infarct[14].

At present, to improve the predictive value of HRV, it is necessary that HRV needs to be combined with other risk factors despite its independent risk prediction for mortality and arrhythmic complication[14]. Multivariate analysis showed that the most sensitive combination for the prediction of arrhythmic events was a reduced HRV and a positive SAECG[27]. Such combination had a sensitivity of 58%, a positive predictive accuracy of 33% and a relative risk of 18 (95% CI, 7–34) and was superior to other combinations including those incorporating LVEF, exercise ECG, ventricular ectopic beat frequency and repetitive ventricular forms.

Conclusion

The evidence so far suggests that HRV can become an important prognostic tool, particularly in post-infarction patients. A prospective multicentre study to determine the sensitivity, specificity and predictive accuracy of HRV is urgently needed. There is a recently completed large multicentre trial, ATRAMI (Autonomic Tone and Reflexes in Acute Myocardial Infarction), investigating the relative and combined predictive values and prognostic implications of HRV and baroreflex sensitivity on patients after MI. The anticipated findings on HRV should help clarify this issue.

It is hoped that, with better means of stratifying patients at high risk from ventricular arrhythmias and sudden death following MI, appropriate preventive therapeutic interventions and risk factor modification can then be instituted, and this will ultimately reduce the mortality rate.

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Chapter 28

Signal Averaging for Risk Stratification after Myocardial Infarction: Do New Technologies Improve its Predictive Value?

Gioia Turitto

Introduction

The term high-resolution (signal-averaged) electrocardiogram (ECG) encompasses any techniques that results in improvement of the ECG signal-to-noise ratio, and thus allows analysis of signals which are too small to be detected by routine measurement techniques. Among such signals are those which arise from areas of slow inhomogeneous conduction in depressed ventricular myocardium (usually called late potentials). These signals are small because the activation front is slow and fractionated and/or the mass of tissue being depolarised is small. They are important for diagnostic purposes, because they may identify an arrhythmogenic substrate. Different averaging techniques utilised in high-resolution ECG include: (1) temporal averaging – this technique is applicable only to repetitive ECG signals; the averaged signal may be analysed either in the time domain or the frequency domain, or a combination of both time and frequency display in the form of spectrotemporal maps; (2) spatial averaging – this technique may record the late potentials on a beat-to-beat basis. Time domain analysis of the signal-averaged ECG is the most commonly used technique in clinical practice. It derives data from the QRS vector magnitude (the root mean square of averaged X, Y and Z leads) that has been subjected to bandpass filters (typically between 25 and 250 Hz, or 40 and 250 Hz). This analysis mainly consists of the determination of three parameters: the filtered QRS duration, the root mean square voltage of the terminal 40 ms of the filtered QRS (RMS40), and the duration of low-amplitude signals, i.e. the time that the filtered QRS voltage remains below 40 μV[1]. The most common clinical applications of the time domain signal-averaged ECG include risk stratification for future arrhythmic events in survivors of myocardial infarction; prediction of induced sustained ventricular tachycardia in patients with organic heart disease and spontaneous nonsustained ventricular tachycardia, or unexplained syncope; assessment of the results of thrombolytic treatment in acute myocardial infarction[2]. Current techniques for time domain analysis have several limitations. First, there is lack of agreement on recording techniques, such as the optimal filter characteristics and algorithms to identify QRS onset and offset, as well as on the best numerical criteria of abnormality. A second problem is represented by the fact that, in the presence of

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intraventricular conduction defect, assessment of late potentials may be difficult. Finally, the technique has low predictive value (around 10–20%) in the post-infarction period. The attempt to develop frequency domain techniques for signal-averaged ECG analysis was based on these considerations.

Frequency domain analysis: techniques

The development of frequency domain techniques included several steps. Cain and associates pioneered the use of a fast Fourier transform (FFT) technique, after Blackman-Harris windowing, to analyse a variable length of signal-averaged ECG from orthogonal leads X,Y and Z, comprising the terminal 40 ms of QRS in addition to the ST segment[3]. Abnormalities suitable for categorising patients with or without sustained ventricular tachyarrhythmias were indicated by the presence of increased signal components in the 20–50-Hz range as measured by a variety of indices (area ratio or magnitude ratio) whose numerical definition has been somewhat modified over the course of subsequent publications[4]. Several authors have shown that Cain's techniques was not reproducible, since it appeared to be too sensitive to the position and duration of the analysed signal[5]. Because of the limitation of traditional FFT, a number of investigators have utilized "spectro-temporal" techniques[6]. The rationale for these techniques is the observation that the QRS, late potentials, and ST segment waveforms in the signal-averaged ECG have different spectral characteristics or, in other words, that the ECG signal has a time-varying spectrum. Haberl et al utilised a "normality factor" to differentiate patients with or without malignant ventricular tachyarrhythmias[6]. However, this technique was characterized by a low reproducibility, primarily because of the sensitivity of the measurement to QRS offset localization[7]. A subsequent modification of the spectro-temporal mapping technique, by Haberl et al, analysed multiple ECG segments (25 ms long) with adaptive frequency determination, an autoregressive algorithm reportedly characterised by high-frequency resolution in very short segments without the use of a window function[8].

To date, frequency domain analysis of the signal-averaged ECG with adaptive frequency determination techniques has not gained widespread clinical application. A novel approach to frequency domain analysis was published by Kelen et al[9]. This method of frequency analysis was called spectral turbulence analysis. This technique measured abnormalities throughout the entire QRS and did so without dependence on any arbitrarily defined frequency, duration or amplitude cut-offs. The hallmark of arrhythmogenic abnormality was postulated to be frequent and abrupt changes in the frequency signature of QRS wavefront velocity as it propagates throughout the ventricle around and across areas of abnormal conduction, resulting in a high degree of spectral turbulence. The technique was shown to provide an accurate marker for the anatomical/electrophysiological substrate of reentrant ventricular tachyarrhythmias[9]. Spectral turbulence analysis is characterised by a high reproducibility, significantly better than the "factor of normality", and similar to time domain analysis techniques[10,11]. At the present time spectral turbulence analysis is the most commonly used technique for frequency domain analysis, and has been utilised by our laboratory and others as a tool for risk stratifications of patients with prior myocardial infarction, and/or complex ventricular arrhythmias. Methods which have been proposed most recently for frequency domain analysis include wavelet transform analysis[12,13], as well as acceleration spectrum analysis[14]. Wavelet transform analysis was purported as a new time-scale technique that makes it possible to detect small, transient signals hidden in large waves. It utilises an automated algorithm for the detection and localisation of sharp variations of the signal, based on coherent detection of the local maxima of the wavelet transform. In contrast to short-time FFT, which used a single analysis window, the wavelet transform uses short windows at high frequencies (small scales) and long windows at low frequencies (large scales). It should thus avoid the problem of poor frequency resolution in short segments that is prevalent in Fourier analysis. The objective of acceleration spectrum analysis of the signal-averaged ECG is to enhance and extract the spectral "signature" of electrical fragmentation within 250 ms of the intra-QRS region. The Fourier transform of the second derivative signal is calculated for the three conventional orthogonal leads (X, Y, Z leads). A spectral change index is then calculated as the sum of absolute gradients in the 50–300 Hz bandwidth. An abnormality threshold was defined, based on studies on a normal population, and subsequently validated in post-infarction patients.

Frequency domain analysis: clinical applications

This section mainly refers to studies utilising spectral turbulence analysis, since this analysis has shown satisfactory reproducibility and has been widely applied. In most studies, frequency domain techniques were compared to time domain techniques, in an effort to establish if they should be used alone or in combination to improve risk stratification.

Studies in survivors of myocardial infarction

In post-infarction patients the combined use of time domain and frequency domain techniques should obviate one of the limitations of late potential analysis, namely that partial obscuring of late potentials may occur if the abnormal myocardial region is activated early during the QRS complex. This may be seen more often with anterior wall infarctions than with inferior wall infarctions, thus partially explaining the higher prevalence of false-negative recordings in patients with anterior infarctions. On the other hand, false-positive recordings may be more common in patients with inferior myocardial infarction. A prospective study from our laboratory investigated the hypothesis that combined time domain and spectral turbulence analysis of the signal-averaged ECG could improve its predictive accuracy for serious arrhythmic events in 262 post-infarction patients[15]. Seventeen of the 262 cases had arrhythmic events during a follow-up of 10.4 ± 2.4 months (13 sudden cardiac deaths and four non-fatal sustained ventricular tachycardias). The total predictive accuracy of combined time and frequency domain analysis (92%) was higher than that either time or frequency domain (respectively, 87% and 78%) (Table 1). The negative predictive accuracy of all three analyses was high (96–97%). On the other hand, the positive predictive accuracy of time domain analysis (28%) was higher than that of spectral turbulence analysis (14%). The combined analysis significantly improved the positive predictive accuracy of the test to 25% in the total group and to 40% in patients with first anterior or inferior myocardial infarction. The best results were obtained in patients with first anterior wall myocardial infarction, where the positive predictive accuracy of the combined analysis was 50%.

This study showed that the predictive accuracy of spectral turbulence analysis was generally lower than that of time domain analysis, in post-infarction patients. However, it is possible that criteria for abnormalities in spectral turbulence, which were derived from studies in patients with induced sustained ventricular tachycardia[9], may not apply for prediction of serious arrhythmic events in the post-infarction period. The latter are mainly due to fatal ventricular tachyarrhythmias rather than non-fatal sustained ventricular tachycardia. Optimising the spectral turbulence criteria in post-infarction patients, and using it in combination with the best predictive criteria of time domain analysis in this setting, may further improve the predictive accuracy of the test. This point has been emphasised in a study by Copie et al[16]. They compared the power of conventional time domain (40–250 Hz) and spectral turbulence analysis for the prediction of cardiac death, ventricular tachycardia or fibrillation, and/or sudden cardiac death in 603 post-infarction patients. This population excluded patients with intraventricular conduction defects. During 2 years of follow-up there were 40 cardiac deaths, 21 cases of ventricular tachycardia, 11 sudden arrhythmic deaths, and 29 arrhythmic events. Individual positive predictive characteristics curves, i.e. curves expressing the dependence of positive predictive accuracy on sensitivity, were computed. Based on this computation, adjusted criteria for the spectral turbulence

Table 1. Predictive accuracy of time domain and frequency domain (spectral turbulence) analysis of the signal-averaged ECG in the post-infarction period

	PPA (%)	NPA (%)	TPA (%)	Odds ratio
Total group (262 patients)				
TDA	28	97	87	12
STA	14	96	78	4
TDA + STA	35*	96	92	12
First inferior infarction (79 patients)				
TDA	15	98	85	12
STA	13	98	81	9
TDA + STA	25*	97	94*	1
First anterior infarction (74 patients)				
TDA	37	94	88	9
STA	17	94	68	3
TDA + STA	50*	94	91*	27*

NPA, negative predictive accuracy; PPA, positive predictive accuracy; STA = spectral turbulence analysis; TDA = time domain analysis; TPA, total predictive accuracy.
* $p < 0.05$.
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parameters were calculated. These new criteria were compared in terms of sensitivity, specificity, positive, negative and total predictive accuracy, with standard time domain and spectral turbulence analysis. The positive predictive accuracy of spectral turbulence analysis was significantly higher than that of time domain analysis for cardiac death at most levels of sensitivity (e.g. 26% versus 20% at 40% sensitivity, $p < 0.05$). The positive predictive accuracies of the two techniques were not statistically different for the prediction of ventricular tachycardia. For the prediction of sudden arrhythmic death and arrhythmic events the positives predictive accuracy of spectral turbulence analysis was better than time domain analysis only at the higher levels of sensitivity (9% versus 2%, $p < 0.001$ for sudden arrhythmic death at 60% sensitivity, and 14% versus 11%, $p < 0.05$ for arrhythmic events at 60% sensitivity). These authors concluded that spectral turbulence analysis based on adjusted criteria is essentially equivalent to time domain analysis for prediction of arrhythmic events after myocardial infarction. However, it performed significantly better than time domain analysis for prediction of cardiac death. These findings suggest that abnormalities detected by spectral turbulence analysis may predispose to both arrhythmic events and pump failure.

In a multicenter European Study (post-infarction late potential (PILP) study) enrolling 778 male survivors of myocardial infarction, the predictive power of late potentials in the time domain, spectral turbulence analysis and their combination was tested together with clinical variables using the Cox regression method[17]. Follow-up duration was 6 months, during which time there were 33 arrhythmic events (13 sustained monomorphic ventricular tachycardias, eight ventricular fibrillations, and 12 sudden cardiac deaths). The combination of late potentials and a spectral turbulence analysis score (one or both abnormal) had the greatest influence on the prediction of arrhythmic events. This combination reached a sensitivity of 76%, a specificity of 63%, a positive predictive value of 8%, a negative predictive value of 98%, and a total predictive value of 61%.

Conclusions

The role of frequency domain analysis of the signal-averaged ECG for risk stratification of post-infarction patients remains to be defined. Widespread clinical application of this technique may be hampered by the fact that it requires complex statistical computations and still lacks standardisation. At this time, time domain analysis remains the mainstay of signal-averaged electrocardiography. Initial results of combined time and frequency domain analyses appear to be promising; however, criteria for an abnormal frequency domain (spectral turbulence) analysis may need to be adjusted to the clinical setting, and may be more predictive of total cardiac mortality, rather than arrhythmic events, in the post-infarction period.

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Chapter 29

Artificial Neural Networks in Cardiology; A Review

Willem R.M. Dassen, Michael Egmont-Petersen and Rob G.A. Mulleneers

Introduction

In daily practice cardiologists often have to make a diagnosis based on measured or estimated data. Sometimes this is relatively simple, for example when a patient presents with: (a) typical chest pain, (b) characteristic ECG abnormalities and finally (c) a typical rise in cardiac enzymes, the diagnosis of acute myocardial infarction can be made with a high positive predictive accuracy, regardless of whether other parameters have been measured or not. Also in the interpretation of the electrocardiogram a diagnosis can sometimes be made easily, with almost 100% certainly. In a wide-QRS tachycardia with evident AV dissociation a ventricular origin is almost certain.

However, occasionally the information is not so clear and a differential diagnosis needs to be established. This requires a combination of reasoning and pattern recognition. Depending on the clinical situation the cardiologist should recognise a certain pattern. When the characteristic signs mentioned above are not so dominantly present, the relationship between these parameters and the weight of each factor used to determine a conclusion can rapidly become very complex. If a linear relationship between the parameters and the conclusion is no longer present, models based on classical statistical methods constitute only rough approximations.

A mathematical technique developed to overcome this limitation is called an artificial neural network. A major advantage of using an artificial neural network to model the relationship between the possible signs and symptoms and the diagnosis is the fact that this relationship does not have to be a linear one. Furthermore, it does not even have to be known. Based on a number of correctly classified examples, referred to as the training set, the neural network itself determines the underlying relationships.

In this chapter, after a brief definition of classification and a summary of the history and the way neural networks function, a compilation will be presented of those areas in cardiology in which the application of neural networks has been evaluated. The chapter will end with an overview of those aspects which still impede general application of this method for clinical decision support.

Classification in cardiology

Interpreting an ECG or establishing a diagnosis are classification tasks. The purpose is to draw an infer-

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ence based on available information, i.e. the signs and symptoms of the patient, medical history, etc. In pattern-recognition terminology the classification relies on so-called attributes. An attribute can, for example, be continuous, such as the temperature of the patient; or discrete, such as whether the patient has previously had an infarct. Neural networks and other classifiers require that the available information is formalised into discrete and continuous attributes. All information that may influence the classification task – e.g. whether the patient had previously suffered from atrial fibrillation – should be presented to the classifier. If relevant information is excluded the classifier may be unable to perform the best possible classification. However, in medical practice the cardiologist often has to make a decision based on incomplete information. The ideal decision aid should therefore also be able to cope with missing attribute values. The fact that a neural network cannot be computed when one or more of its attribute values are unknown, makes it vulnerable to missing data.

Clinical decision support

Since the 1970s a number of techniques have been presented that may aid medical decision making. Decisions can be perceived as classification tasks of which the purpose is to categorise an object (e.g. the patient) into one of a number of classes, e.g. healthy, infarct, ischaemia etc. Not only establishing the diagnosis but also deciding which therapy to prescribe constitutes a classification task.

A number of different classification methods – so-called classifiers – are available that can aid medical decision making; among others:

1. Statistical-inference and pattern-recognition methods: neural networks, decision trees, linear and quadratic discriminant analysis, logistic regression, and causal probabilistic networks
2. Knowledge-based systems: expert systems and hypertext systems.

The statistical-inference techniques can cope with quantitative as well as qualitative data, whereas the knowledge-based systems are suited only for dealing with qualitative data.

As can be seen, neural networks are only one among many types of classification methods. On the one hand, neural networks and decision trees are both non-parametric classifiers: the distribution of the data does not need to be known *a priori*. Classifiers based on discriminant analysis, logistic regression and causal probabilistic networks, on the other hand, are parametric: they rely on strict assumptions with respect to how the data are distributed (e.g. Gaussian).

Feed-forward back-propagating artificial neural networks

Although there are a number of different types of neural networks, we will limit ourselves to the most common one: the feed-forward back-propagating neural network.

Neural networks were first proposed during the Second World War. McCulloch and Pitts introduced a mathematical model for a typical neuron in the cerebral cortex[1]. Their artificial neuron works like a junction between "nerve" paths. Each path provides the neuron with a numerical input value. The neuron uses a weight to modify each input signal it receives. The size of the weight determines whether the input is amplified or reduced; the sign determines whether the input is exhibitory or inhibitory. The neuron produces an activation that is functionally dependent on the input signals it receives. It sends to other neurons the output 1 if its activation is positive and the output 0 otherwise. By organizing such neurons in clusters, a mapping from input (stimuli) to output (response) is performed. McCulloch and Pitts proved that when the weights have the appropriate values, a synchronously updated cluster of neurons is capable of any computation.

In 1949 Hebb introduced a theory of how learning takes place in the brain[2]. His theory was later formalised into the so-called Hebb rule, a formula for adjusting the weights in a cluster of artificial neurons. In 1986 Rumelhart et al proposed a similar learning algorithm for training networks organized in two or more layers of non-linear nodes[3]. Their training algorithm, called back-propagation or the generalized delta rule, has obtained widespread use. Artificial neural networks have developed into a promising new branch of artificial intelligence research.

The most popular neural network is the multi-layer perception with one so-called hidden layer. The number of input nodes equals the number of attributes that is provided as input to the neural network. The number of output nodes is identical to the number of different classes or decisions one wants to discriminate. The neural network takes as input vector the attribute values

of a particular case, and gives as output a vector in which each element indicates the probability that the case belongs to the associated class. When, for example, the output value that corresponds to the diagnosis "healthy" is higher than the output value associated with atrial fibrillation, the case is classified as healthy.

The layer of hidden nodes is essential to make an internal representation of the relationship between input and output. The optimal number of hidden nodes depends on the complexity of the classification task the neural network will perform, and cannot be determined *a priori*. Instead, the number of hidden nodes is chosen according to heuristic rules, or a set of neural networks each with a different number of hidden nodes are trained so as to identify the best configuration. Although the biological plausibility of artificial neural networks is still being investigated[4], the properties of artificial neural networks are mainly being explored mathematically. It has been shown that a neural network with one hidden layer may implement any decision rule[5]. The field of neural networks is developing towards mathematical statistics as still more results from this area are being used to develop new types of neural networks. Various statistical properties of neural networks have been proven.

One builds a neural network using a set of validated training cases. The information on which the classification task relies has to be formalised into attributes. For each training case (patient) the attribute values (signs and symptoms) and the correct class label (diagnosis) has to be known. It is relatively simple to train the neural network to perform the classification task using back-propagation. The neural network learns the expert's "show-how" as implicit in the training set. A well-performing network should be able to classify a large fraction of both training and test cases correctly; the latter are cases which the neural network has not previously seen.

Application of artificial intelligence techniques in cardiology

Until the end of the 1980s the application of artificial intelligence techniques in cardiology was limited to the development of expert systems.

These are computer systems in which the knowledge of a domain expert on how to solve a problem has been organised in a specific way. Based on a large number of logic inference rules the system was (sometimes) able to draw conclusions based on these rules and on the input information provided by the user.

One important advantage of these systems was the ability to explain their reasoning and to elucidate why certain questions were asked.

In practice, however, the results obtained using these expert systems were often disappointing. It turned out to be more difficult than expected to unravel the experts' reasoning process, not to mention the task of formulating it accurately. An expert can be characterised by the ability to solve complex problems, but normally not by the capability of explaining how (s)he does it it.

The introduction of the personal computer and increasing availability of software to build neural networks seemed to form an elegant bypass for this problem. The expert no longer has to be capable of explaining the reasoning process, as long as he or she provided the correct diagnoses for the training cases.

In a large number of specialties within cardiology the feasibility of neural networks for classification has been evaluated[6,7]. In some cases only one attempt was made, but in other areas an ongoing number of networks were described.

A large percentage of research published in the field of applications of neural networks in cardiology was presented at the annual conferences of Computers in Cardiology and published by the IEEE, Piscataway, NY. A compilation of these articles has been included, and forms a brief overview of which aspects of cardiology have been tackled using neural network techniques.

One of the first applications of pattern recognition in cardiology using neural networks was formed by the analysis of heart sounds[8–11].

The interpretation of the electrocardiogram not surprisingly represents an area in which the pattern-recognition qualities of neural networks have been evaluated. Apart from the resting ECG these networks have been used extensively in the analysis of cardiac arrhythmias. The detection of ventricular ectopic activity[12], and of atrial fibrillation has been studied for a number of years[13–16]. A classical topic in rhythm analysis, the differentiation of wide QRS tachycardias in supraventricular tachycardias and ventricular tachycardias, has been studied by a number of groups, and this has led to a refinement of some classical criteria[17–24]. The development of implantable devices for treatment of life-threatening arrhythmias has stimulated intracardiac rhythm classification using neural networks[22–29]. The

diagnosis of myocardial infarction and the subdivision into anterior versus inferior location was the subject of a number of studies[30–35]. Neural networks have been trained to recognize ST-T segment changes[36–38], to recognise coronary artery disease in general[39–42], to predict the number of vessels involved[43] and to identify three-vessel and mainstem disease, even at rest[44,45]. To help interpret the exercise ECG only a limited number of studies were performed[46].

The localisation of the accessory pathway in patients suffering from the Wolff-Parkinson-White syndrome using a neural network was described in one study[47].

Aspects such as classification and compression[48–53] or even recognition of electrode misplacement[54] were also described. In many fields only a few attempts were made to introduce neural network techniques, including patient monitoring[55], estimation and classification of fetal heart rate[56,57], the analysis of signal-averaged electrocardiograms[58] and cardiac angiograms[59,60], echocardiograms[61,62] and nuclear scintigrams[63,64]. Isolated studies investigated a variety of applications such as blood pressure monitoring[65,66], ventricular activation mapping[67] or improvement of prescription of anticoagulant therapy[68]. Finally the neural network approach to the classical inverse problem in electrocardiography[69], for classification of postoperative cardiac patients[70], and for substitution of ectopic beats in Holter recordings for heart rate variability analysis[71] should be mentioned.

Caveats of neural networks

Despite the wide interest in the application of neural networks there are a number of limitations that make the introduction of these tools in daily practice difficult. Using neural networks as a clinical decision aid is impeded by a number of caveats.

The neural network as a black box

First, a neural network is a complex mathematical function. It is therefore difficult to explain the user why, for example, a patient is classified as having "ventricular tachycardias" and not "supraventricular tachycardias". Different approaches to explaining the classification of a case have been suggested but, until now, none has succeeded.

Sometimes using a neural network theoretical criterion can be optimised by simulating a large number of input combinations and studying the influence on the outcome but, in general, the results obtained from such an analysis are insufficient to serve as a causal explanation.

The only way to convince the potential user is to demonstrate the superiority of a neural network in a large number of test cases.

An additional problem of the black box nature of the network is the limited possibility to influence the equilibrium between sensitivity and specificity. These networks tend to exaggerate; they are often quite certain about their answer.

Domain sensitivity

The application of neural network techniques requires a very strict definition of the domain for which it is valid. A network trained to differentiate between an anterior and inferior location in ECG of patients with a myocardial infarction will select the most likely site, even if in the test ECG there is no infarction present. Using classical criteria, the risk of making this error is much smaller, since the conditions for both sites will be evaluated independently.

In the same way a network trained to select the location of an accessory pathway in patients suffering from the Wolff-Parthinson-White syndrome will select the most likely location even in ECG of a patient without an accessory pathway.

Neural networks do not have the possibility of leaving a (possibly borderline) case unclassified.

Data representation

Some problems cannot be solved by the neural network, since it does not understand the underlying relations. If, for instance, a neural network should predict the number of cathlab procedures based on, among other information, the day in the month, it will never train if it is not told which days are weekends or holidays on which no elective cases will be performed.

In neural network development the possibility of dumping all data in the model increases the risk that data representation will sometimes not be optimal, as irrelevant information may impede a good training process.

Missing values

Furthermore, a neural network requires all input data to be computed. As already mentioned, in clinical practice many decisions have to be made based on incomplete

information. To cope with this an algorithm has been developed for estimation of incomplete data[72]. This so-called REM-algorithm is able to estimate missing attribute values in a case from the observed ones, when there is a certain correlation between them. If the missing and observed attribute values are uncorrelated, however, the REM-algorithm is unable to estimate the missing values, and the clinician has to provide more information before the case can be classified reliably.

Validation

Another problem is how to validate a trained neural network. How can one ensure that it has correctly learned the "show-how" of the clinical expert? Validation can be performed only by comparing the performance of the neural network with that of a clinician using, for example, kappa statistics. In the paper by Egmont-Petersen[72] a set of methods are presented that can support validation of neural networks. However, they have not yet been used to develop neural networks for clinical applications.

Even then, by comparing the performance of the neural network with that of the human expert, it is by definition impossible to improve this gold standard. In all cases where the human expert is wrong the neural network will be considered failing.

Conclusion

Further research to solve the mathematical obstacles will be necessary, but in the meantime both the developer and the potential user of these neural networks should evaluate the results fairly but critically.

First the trained neural network should be evaluated using an independent test set. It is often possible to train a neural network to interpret all training cases correctly, but in reality the network is simply recognising each individual case, and does not generalise the knowledge.

The need for an independent test set to evaluate criteria is also present for classical systems, but the ability to learn all cases by heart makes it even more essential for neural networks.

The most important advantage of computer systems in general, and of neural networks in particular, is that they draw consistent conclusions. Their intra-observer variability is by definition zero. Another advantage is that neural networks can be built and evaluated using a large number of cases. In the clinical setting it may take years before a young cardiologist has been confronted with sufficient cases to ensure that his/her judgement is reliable.

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PART THREE

Radiofrequency Ablation in Arrhythmias

Chapter 30

Radiofrequency Catheter Modification of Sinus Node Activity in Patients with Inappropriate Sinus Tachycardia

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Introduction

The purpose of this essay is to describe our technique and results of catheter modification of sinus node activity in humans. The sinus node is an ovoid structure that is seated in the sulcus terminalis at the junction between the superior vena cava and the right atrial appendage[1,2]. The sinus node is the dominant pacemaker of the heart, but cells with automatic activity extend along the entire length of the crista terminalis. Demonstrated shifts in origin of pacemaker activity in response to autonomic influences were first observed by Sir Thomas Lewis[3] and subsequently by Meek and Eyster[4] and Bouman et al[5].

Boineau et al[5–8] used a computerised epicardial mapping system to confirm that the dominant pacemaker extended over a wide distribution approximating the length of the crista terminalis. They clearly showed a relationship between cardiac rate and the site of impulse formation. Vagal stimulation resulted in a caudal shift of the pacemaker site, while catecholamine stimulation resulted in a more cranial shift of the pacemaker.

Initial attempts to modify sinus node activity involved wide surgical excision of the right atrium[9]. In this canine preparation the escape rhythm was localised to the caudal end of the sulcus terminalis just distal to the excised area. The area of pacemaker activity was clearly well away from the sinus node, and the histology of this region did not show evidence of specialised sinus node cells. In addition, these subsidiary atrial pacemaker cells proved to be responsive to autonomic stimulation[10,11].

More recently, several additional techniques were introduced to modify sinus node activity. Littmann et al[12] showed that epicardial laser photocoagulation of the earliest epicardial site of atrial activation could modify the sinus rate. In addition, Sanchis et al[13], in 1990 first demonstrated that radiofrequency-delivered energy to the region of the sinus node could modify sinus node activity.

In 1994, Kalman et al[14], from our laboratory, described the effects of graded application of radiofrequency energy guided by intracardiac echocardiography in the canine. We showed that changes in cardiac rate were attended by shifts of pacemaker site along the crista terminalis (Fig. 1). Infusions of phenylephrine were followed by reflex slowing of the rate and by a caudal shift of the pacemaker. In contrast, rate increases following infusion of

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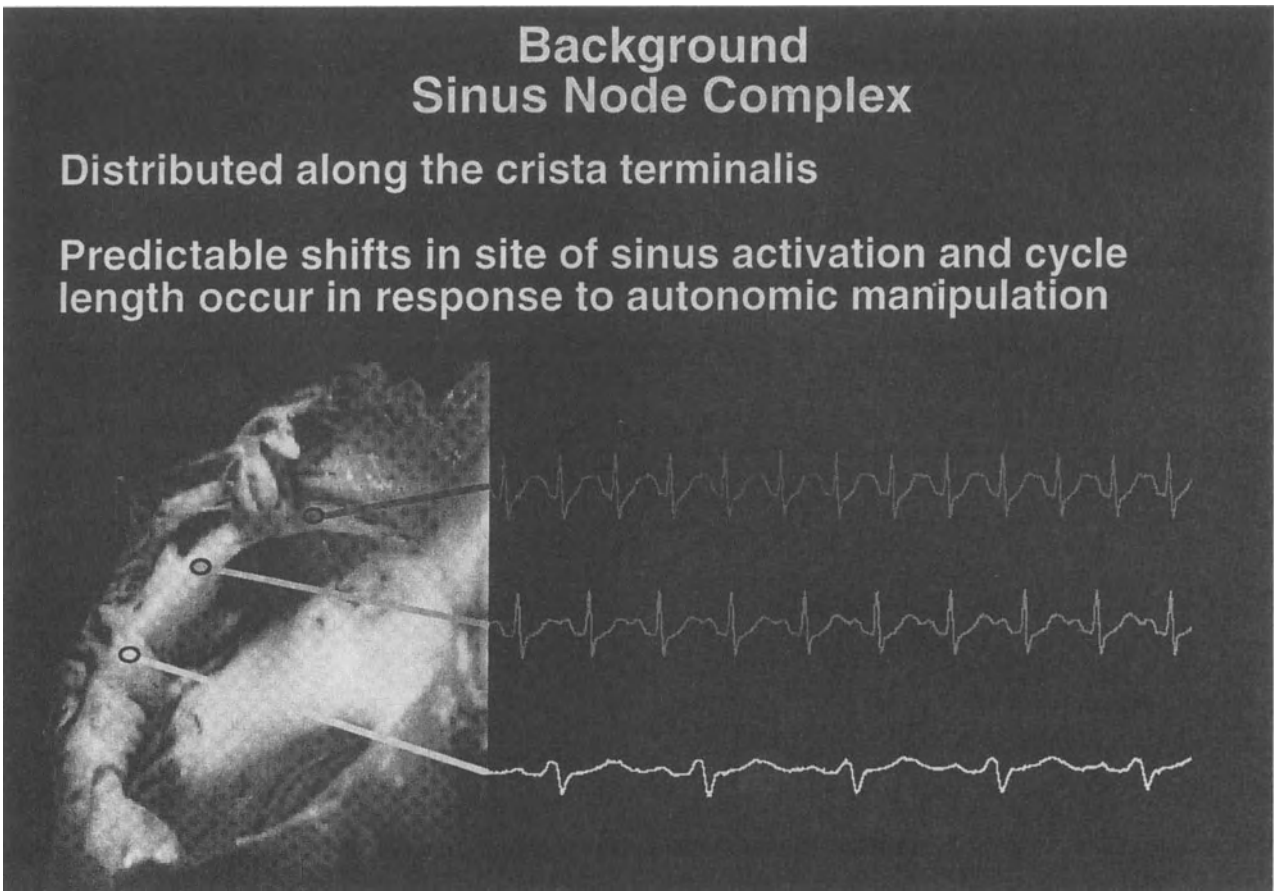

Figure 1. Schema of the posterolateral wall of the right atrium. Note that pacemaker activity from the cranial portion of the crista is associated with more rapid rates compared to foci from the caudal portion of the crista terminalis. (By permission: Fig. 1, Lee et al, Inappropriate Sinus Tachycardia/Diagnosis and Treatment. W. B. Saunders, vol. 15, no. 4, in press, November 1997).

nitroprusside (reflex) or isoproterenol (direct effects) produced a cranial shift of pacemaker activity. These experiments included application of radiofrequency energy to areas of the dominant pacemaker sites until a mean decrease in heart rate of approximately 30% was achieved. The effects of autonomic modulation were reported after ablation, and it was demonstrated that the subsidiary pacemaker was still responsive to autonomic perturbations but the responsiveness was of a lesser magnitude.

In a separate set of experiments, radiofrequency energy was applied along the entire length of the crista terminalis and a slow low atrial or junctional rhythm was produced. The latter was performed to study the effects of "total" sinus ablation. These dogs appeared to be even less responsive to autonomic modulation. Modification of the sinus node resulted in a 2–3 cm caudal shift along the crista terminalis, while "total sinus ablation" resulted in shifts of 3–4 cm essentially extending to the junction of the right atrium with the inferior vena cava.

We found interesting electrocardiographic concomitants of sinus node modification. Higher pacemaker sites were associated with a more inferior P wave axis; in contrast, progressive shift to a lower pacemaker site resulted in flattening of the P wave in the inferior leads. In contrast, dogs with so-called complete sinus node ablation showed either low atrial (inverted P wave morphology) or junctional rhythms after ablation. In these dogs a sinus complex returned within 2 weeks. These ablative techniques were subsequently applied to patients with inappropriate sinus tachycardia (see below).

Inappropriate sinus tachycardia (IST)

IST was first described by Bauernfeind et al in 1979[15]. The syndrome was described as non-paroxysmal sinus tachycardia. The arrhythmia was observed in patients without organic cardiac disease, and was thought to be related to either deficient vagal or overactive sympathetic tone. Morillo et al[16] described IST as a syndrome characterised by an abnormal resting rate and by inappropriate rise in heart rate in response to minimal activity (Fig. 2). They found that these patients had an abnormal intrinsic heart rate (which is the heart rate produced by combined sympathetic and vagal blockade), and felt that a component of this disorder was related to a primary resetting of sinus node activity. They also found normal catecholamine levels for these patients, but enhanced responsiveness to β-adrenergic stimulation and depressed cardiac vagal efferents.

Initial therapy of patients with IST involves use of β-blockers. Often the symptom may result in total disability related to either unresponsiveness to drug therapy, or inability to tolerate the large doses of drug necessary for rate control. In extreme circumstances in the past, drug-refractory patients disabled with tachycardia were managed with either subtotal right atrial excision[17] or AV nodal ablation with insertion of a permanent pacemaker[18]. In 1995[19] our group described the first attempts to modify sinus node activity in humans using radiofrequency delivery to the region of the dominant cardiac pacemaker.

Sinus node modification by radiofrequency catheter techniques

The basic technique involves placement of a multipolar electrode catheter against the crista terminalis (Fig. 3).

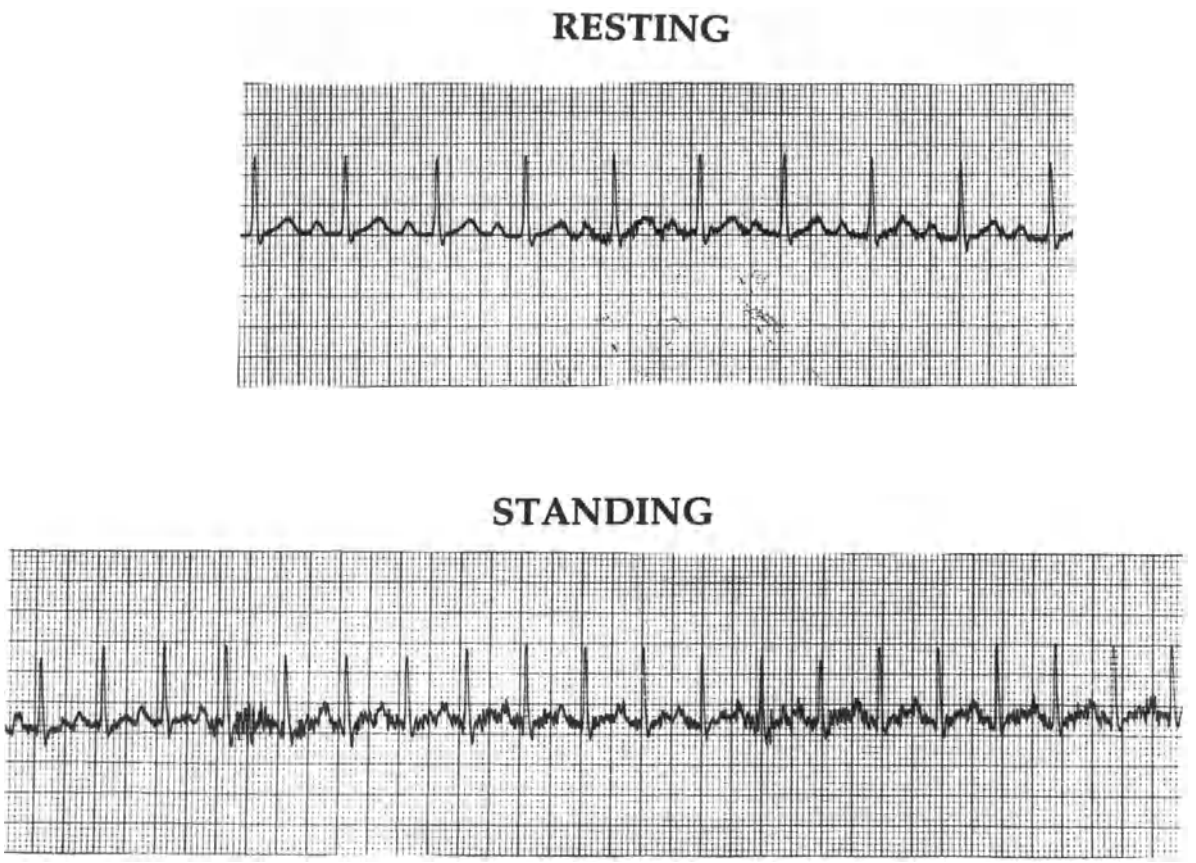

Figure 2. Dramatic rate changes in female patient with inappropriate sinus tachycardia. The resting rate was 100 beats/min and with standing increased to 150 beats/min. This change was associated with marked symptoms of palpitations and fatigue.

The latter is facilitated by use of intracardiac echo to visualise the crista, and use of a sheath to stabilise the multipolar electrode catheter along the crista. Recordings along the crista are usually characterised by a hierarchical activation pattern (craniocaudal), either in response to isoproterenol or during sinus tachycardia. A standard 4 mm thermistor catheter is used and radiofrequency energy is delivered to the site of earliest activation along the crista. In addition, before application of radiofrequency energy, the site is paced with 10 mA and a 2 ms pulse in order to exclude stimulation of the phrenic nerve. Transient phrenic nerve damage has been reported as an adverse effect of this procedure[19]. Intracardiac echocardiography (ICE) is also helpful to ensure the ablation catheter is not posterior to the crista terminalis where the phrenic nerve courses. The power is adjusted to achieve a tip-tissue interface of 55° to 70° (and energy is delivered from the distal electrode to a large surface patch). If radiofrequency application failed to achieve a charge in heart rate and a temperature setting of below 50°C within 15 s, it was decided that poor contact was the problem and the catheter was repositioned.

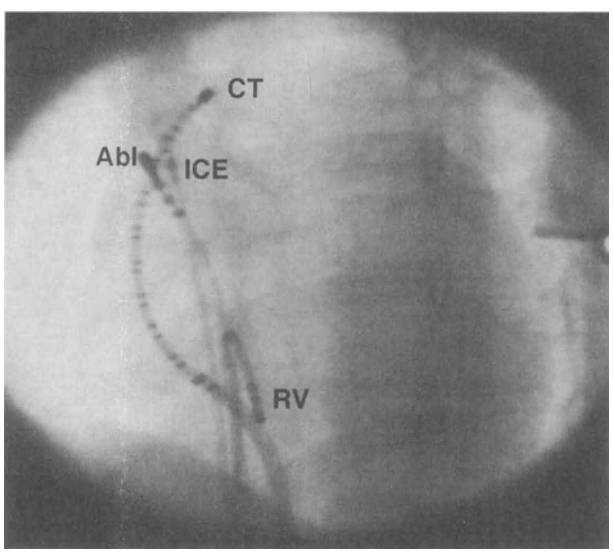

Figure 3. Technique used for radiofrequency catheter modification of the sinus node. The figure shows placement of the multipolar electrode catheter against the crista terminalis (CT). This structure is readily visualised by intracardiac echo guidance. Also shown is the position of the ablation catheter (Abl), the multipolar electrode catheter (CT) and the intracardiac echo probe (ICE). (By permission from ref. 19.)

Application of radiofrequency energy to the dominant pacemaker site generally results in transient increases in cardiac rate followed by clear-cut decreases in rate. If the decrease in rate is observed only with application of radiofrequency energy and resolves with termination of energy application, this may reflect direct vagal stimulation, or could be non-transmural heating and is not a suitable endpoint. More recently it is our practice to perform ablation under conditions of near-maximal heart rate. The latter is achieved by infusion of 5 μg/min of isoproterenol and 1 mg of atropine. The target is a 25–30% reduction of cardiac rate. In addition, there is caudal descent of the dominant pacemaker, as reflected by initial atrial activation found along the more inferiorly placed electrodes along the crista terminalis (Fig. 4).

The results of this catheter modification procedure were reported for 16 patients in 1995[19]. Of this group, the initial four patients underwent total sinus node ablation while the subsequent 12 underwent a modification procedure similar to that described in our canine model. Total sinus node ablation resulted in induction of a junctional rhythm and two of the four patients ultimately required pacemaker therapy. In the remainder, the sinus rate decreased by a mean of 25%. In addition, maximal heart rate decreased from 180 ± 36 to 133 ± 6.5 beats/min ($p < 0.001$). The 24-h ambulatory ECG recordings showed a decrease in maximal and mean heart rates after ablation, 167 ± 2.6 vs 97 ± 5.0 ($p < 0.001$) and 126 ± 5 vs 54 ± 5 ($p < 0.001$).

After a mean follow-up of 20 months, two of the four with total sinus node ablation required permanent pacemaker therapy. Patients with sinus node modification were followed for a mean of 7 ± 1.7 months and two showed tachycardia recurrence. Although rate control was achieved in the remainder, many patients remained symptomatic because of atrial or ventricular premature contractions. Two significant complications were observed in our initial study: one patient developed transient phrenic nerve paralysis while another had transient obstruction of the superior vena cava. This patient had multiple catheters crossing the superior vena cava because of multiple prior lead implants, and ICE was not used to guide ablation.

Our short-term follow-up suggested excellent results in that all but two patients had relief of symptoms without evidence of recurrent IST. A recent preliminary report from our centre documented less sanguine benefits after long-term follow-up[20].

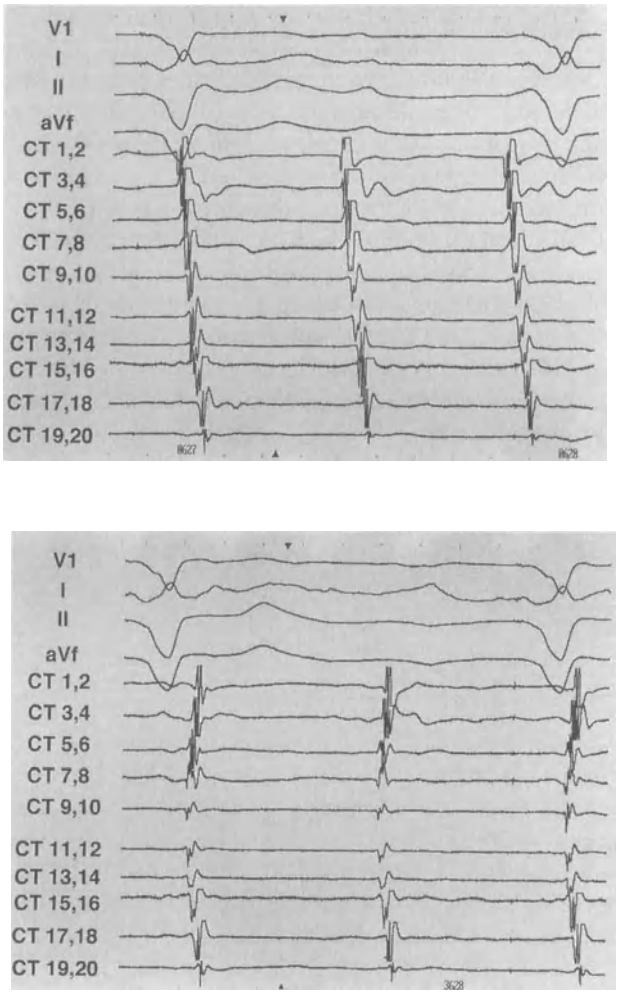

Figure 4. A: Simultaneous recordings from surface leads V_1, I, II and a Vf with recordings from the cranial portion of the crista terminalis $CT_{1,2}$ to the caudal recording sites $CT_{19,20}$ during tachycardia. The earliest atrial electrogram is recorded from bipolar electrode $CT_{1,2}$. (By permission from ref. 19.) **B**: After ablation of the sinus node, note a decrease in heart rate with caudal shift of the pacemaker to an inferior position on the crista ($CT_{7,8}$) (By permission from ref. 19.)

We reported the results of sinus node modification for 25 patients with IST[20]. For these patients the mean percentage decrease in sinus cycle length after ablation was 21%. Nine patients remained free of symptoms and heart rate was well controlled. The rest had return of symptoms either due to recurrence of IST and/or perception of palpitations due to atrial or ventricular ectopic beats. A repeat ablation was required in six patients, and success was achieved in three of six patients. In addition, permanent pacemakers were required in three patients, all of whom had multiple sinus node ablative procedures.

Similar findings were reported by Taylor et al[21]. They studied 12 patients with IST who underwent sinus node modification and were followed for a mean of 16 ± 7.3 months. Acute reduction in heart rate was achieved in all, but recurrence of IST (defined as resting rate > 90 beats/min) was observed in four, two of whom underwent repeat ablation. An additional five patients remain symptomatic despite persistent sinus rhythm or atrial premature beats. Only one patient required a permanent pacemaker.

Clinical implications of available data

The introduction of non-pharmacological, closed-chest techniques for sinus node modification has sparked renewed interest in the treatment of patients with IST. The mechanism of this disorder is still poorly understood, but appears to be related in part to resetting of the sinus node to a higher rate and hyperresponsiveness to β-adrenergic agonists. The clinical presentation is one of baseline (awake) sinus tachycardia with rate hyperresponsiveness to simple exertion (Fig. 2). The diagnosis is generally made from inspection of the 24-h ambulatory ECG. The patient will usually show an awake mean heart rate of approximately 90–110 beats/ min with normalisation during sleep. In addition, wide variations in rate will be recorded in response to routine activities. However, patients may not show this pattern at all times, and several recordings may be required to be certain of the diagnosis. A baseline exercise treadmill test will show the characteristic response, and is of importance primarily to prove efficacy of the ablative procedure. It is essential that there be a tight correlation between symptoms and increased heart rate on both Holter and stress test. It a patient manifests symptoms such as fatigue and palpitation when the heart rate is not excessively rapid, that patient is not likely to benefit from sinus node modification. It is important to emphasise that the diagnosis of IST is almost always made by simple non-invasive clinical testing. Invasive electrophysiological testing serves to exclude other diagnoses and may be performed as a prelude to the ablation.

Exclusions

In order to make the diagnosis of IST the clinician must exclude other causes of resting sinus tachycardia. The

latter include hyperthyroidism, phaeochromocytoma, anaemia, hypovolaemia, use of vagolytic drugs, patients with autonomic neuropathy (Fig. 5), etc. Most importantly, patients who are deconditioned may mimic the presentation of those with IST. This is particularly true of patients with the chronic fatigue syndrome.

In our total series we have noted a predominance of females (48 of 50 patients). In addition, 50% of these patients are employed in health-related activities. The reason for the female preponderance and the high percentage of health-care workers is not clear. It should be emphasised that a large proportion of these patients have a multitude of both cardiac and non-cardiac symptoms. Hence, unlike patients with paroxysmal supraventricular tachycardia, in patients with IST, even if rate control is achieved with drugs or ablation, other symptoms frequently come to the fore.

Treatment of patients with IST

Once the diagnosis is made, an initial trial of observation alone is justified, since I have seen this syndrome wax and wane. If symptoms persist, then a trial of β-blocker therapy (after an appropriate evaluation has excluded other causes) is indicated. No β-blocker has been shown to be more effective than another, but certainly β-blockers with intrinsic sympathomimetic activity should be avoided. The patients are treated with graded increases in drug therapy until maximally tolerated doses are achieved. It is our experience that many patients will either fail to respond to β-blockers or cannot tolerate doses required for arrhythmia control. Such patients may be considered candidates for catheter ablation, but only after appropriate psychological screening to exclude additional underlying psychological problems.

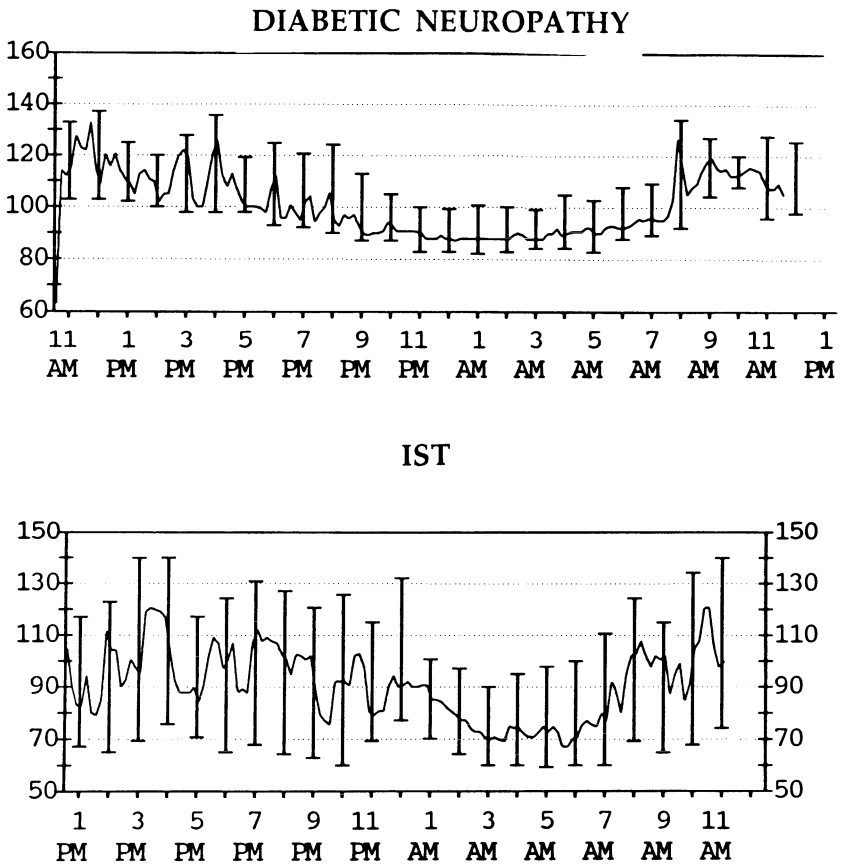

Figure 5. A 24-h ambulatory ECG for a patient with diabetic neuropathy (top panel) and a patient with inappropriate sinus tachycardia (IST) (lower panel). The patient with diabetic neuropathy shows a relatively flat heart rate response throughout the day. The patient with IST shows marked variation of heart rate during the day and much less variation during the sleeping hours.

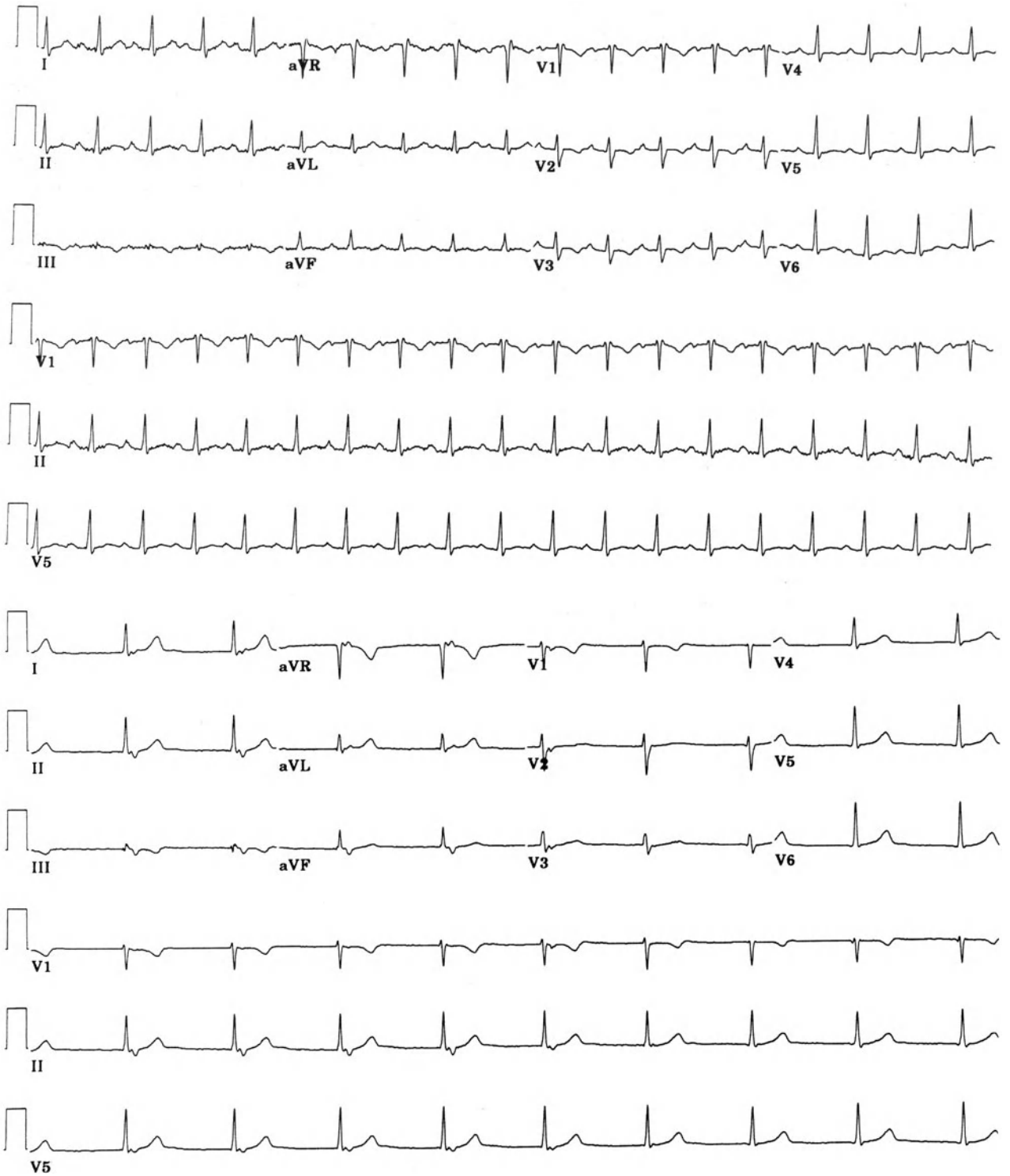

Figure 6. **A**: Resting 12-lead ECG showing sinus tachycardia (115 beats/min) in a patient with inappropriate sinus tachycardia. **B**: After ablation the 12-lead ECG shows a junctional rhythm (56 beats/min) with retrograde VA conduction.

The available data suggest that sinus node modification is associated with a high recurrence of either IST or symptoms due to atrial premature contractions or ventricular premature contractions. Therefore, this procedure should be undertaken only in patients with debilitating symptoms who are fully informed of the risks and benefits of this procedure. Atrioventricular junctional ablation and pacemaker therapy has proven not to be ideal therapy, since in most patients atrial tracking either mimics the original problem or fails to provide adequate chronotropic support. In the laboratory the earliest site of atrial activation is detected using a catheter placed along the crista terminalis. An effort to achieve maximal heart rate is executed by infusion of 5 μg/min of isoproterenol and 1 mg of atropine. Ablative lesions are applied over the crista until a 30% decrease in rate is achieved. Some patients may require total ablation for effective rate control (Figs 6A and 6B). In the latter group there is a high incidence of need for permanent cardiac pacing.

In summary, current ablative techniques have been shown to be of limited value compared to use of these techniques in patients with other mechanisms of paroxysmal supraventricular tachycardia. The optimal endpoint producing good rate control without induction of complete atrioventricular block has not been adequately defined. Our current research thrust is to aim for even greater change in heart rate (at least 30% decrease) at the time of ablation. In addition, more studies are required to allow for better understanding of the pathophysiology of this disorder. Finally, use of drugs which block the pacemaker current might eventually prove to be superior to catheter ablation.

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Chapter 31

Catheter Ablation Techniques for Elimination of Atrial Fibrillation

Demosthenes G. Katritsis

Introduction

Atrial fibrillation is the most common arrhythmia, found in 3% of asymptomatic persons over 60 years and in up to 11% in asymptomatic persons over 70 years[1]. According to the Framingham data the development of chronic atrial fibrillation is associated with a doubling of overall mortality and of mortality from cardiovascular disease[2].

Even so, atrial fibrillation still remains one of the few arrhythmias for which catheter ablation therapy cannot be offered by the cardiologist[3]. Recently, however, following clinical experience with the maze procedure and its modifications[4], several attempts have been made to provide a radical cure for atrial fibrillation in the electrophysiology laboratory. So far the techniques under clinical trial can be divided into two categories: (1) techniques aimed at eliminating arrhythmias which were the trigger for the induction of atrial fibrillation, or which were imitating the electrocardiographic pattern of atrial fibrillation; (2) attempts aimed at modifying the background for the induction and maintenance of atrial fibrillation by means of imitating, as much as possible, a simplified surgical-maze procedure.

Catheter ablation for elimination of arrhythmias triggering or imitating atrial fibrillation

It is well established that in certain clinical settings, particularly in the absence of structural heart disease, various arrhythmias can trigger the onset of atrial fibrillation; their eradication by catheter ablation can eliminate clinical atrial fibrillation. Patients with atrioventricular reentrant tachycardias due to accessory pathways[5] have a higher incidence of atrial fibrillation which can be eliminated by successful ablation of the pathway. Atrioventricular nodal reentrant tachycardia can also trigger, or even imitate, atrial fibrillation[6,7], and radiofrequency ablation of the slow pathway may prevent the paroxysms of fibrillation.

On certain occasions paroxysmal atrial fibrillation can result from degeneration of an initially rapidly firing atrial focus[8,9] or atrial flutter[10]. In these cases conventional atrial mapping can be utilised to guide successful catheter ablation. We have recently shown that patients without structural heart disease, and with a history suggestive of paroxysmal atrial fibrillation, should be investigated for evidence of common atrial

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flutter triggering the fibrillation episodes[10]. This patient group, which on electrophysiology study is identified by the recording of flutter waves from the right atrium and typical fibrillation from the left atrium, may benefit from ablation of the flutter circuit[10]. Haissaguerre's group[8,9] have reported on patients with electrocardiographic diagnosis of paroxysmal atrial fibrillation in whom the paroxysms of the arrhythmia were imitated or triggered by repetitive focal atrial activity in the form of irregular atrial tachycardia or monomorphic extrasystoles. In their recent report[9], mapping and identification of atrial foci with repetitive, irregular firing was possible in nine patients with electrocardiographic evidence of paroxysmal atrial fibrillation. Radiofrequency ablation of the foci resulted in elimination of the arrhythmia (atrial fibrillation or fibrillation-like activity) in all patients. These observations clearly demonstrate that mere recognition of the electrocardiographic pattern of atrial fibrillation is not adequate to confer a diagnosis, and underline the importance of electrophysiological assessment of these patients. More importantly, they raise the possibility of radical cure of some forms of atrial fibrillation in the cardiac catheterisation laboratory.

Catheter ablation lines for elimination of atrial fibrillation

The creation of catheter-mediated ablation lines[11–18] has also been utilised in an attempt to imitate surgical atriotomies and modify the background for the maintenance of multiple wavelets of reentry. The efficacy and long-term consequences of such an approach are not established, and several technical problems remain unresolved.

Animal studies

Elvan and colleagues[11] attempted the creation of continuous transmural lesions in five epicardial sites and in the coronary sinus wall in four mongrel dogs. Radiofrequency energy pulses were delivered around the right and left atrial appendage, from the superior vena cava to the right atrial appendage, from the lateral superior vena cava to the lateral inferior vena cava, and in the coronary sinus. The procedure markedly attenuated vagally induced shortening of effective refractory period in the left and right atria, and rendered non-inducible sustained atrial fibrillation maintained by cervical vagal stimulation or infusion of low doses of metacholine. Li et al[12], using the sterile pericarditis and rapid atrial pacing animal models of atrial fibrillation, attempted to produce conduction block of the right atrium posterolaterally by means of creating an ablation line between the superior vena cava/right atrial junction and the inferior vena cava/right atrial junction. Atrial fibrillation was no longer inducible in six out of 13 dogs. In the remaining dogs atrial fibrillation was still inducible, but with shorter duration. Histological examination of the atria in both studies showed transmural lesions of myocardial necrosis surrounded by zones of inflammation and fibroblast proliferation. Although the results of these elegant studies cannot be extrapolated to human atria, particularly in the setting of underlying cardiac pathology, they have clearly demonstrated that a catheter approach is feasible, does not result in atrial perforation and may prevent induction of atrial fibrillation.

Human studies

Swartz et al[14] and Haissaguerre et al[13], in 1994, were the first to report on the interruption of atrial fibrillation by creation of ablation lines in the human atria. Swartz et al[14] used a conventional ablation catheter to create eight discrete linear lesions (three in the right atrium, four in the left atrium and one in the septum) in a way imitating the surgical maze procedure. Atrial fibrillation was converted to rapid atrial reentrant tachycardia and, following completion of the ablation procedure, to sinus rhythm. Haissaguerre et al[13] reported on a patient with a history of previous ablation for atrial flutter and incessant episodes of atrial fibrillation. With the aid of a specially designed 14-polar catheter, three lines of ablation, one transverse and two longitudinal, were created in the anterior and posterior walls of the right atrium. The procedure achieved interruption and non-inducibility of atrial fibrillation and the patient remained arrhythmia-free at 3-month follow-up. Similar attempts followed, by the same and other groups, targeting both the right and left atrium[15,17], or the right atrium alone[13,16,18].

We have also attempted radiofrequency catheter ablation in nine patients who presented with atrial fibrillation[15]. Five patients had chronic atrial fibrillation and the remainder suffered prolonged episodes of paroxysmal atrial fibrillation. Catheters were introduced into the right atrium, the coronary sinus, and the left atrium

via a trans-septal approach. Continuous, linear radiofrequency lesions were created in the free wall and the roof of the left atrium, the left aspect of the septum, in the coronary sinus, and in the right atrium, medial and parallel to the sulcus terminalis, in the lateral wall, and in the isthmus between the tricuspid valve and the inferior vena cava. All patients with paroxysmal atrial fibrillation, and one with lone chronic atrial fibrillation, remained arrhythmia-free and in sinus rhythm at an average follow-up of approximately 8 ± 4 months, whereas the rest of the patients remained in atrial fibrillation. The success rate in chronic atrial fibrillation, therefore, was less than 25%. All procedures were uneventful and did not demand unreasonable fluoroscopy times (mean procedure time was 155 ± 46 min and mean fluoroscopy time was 41 ± 12 min).

The mechanism of prevention of atrial fibrillation by this ablation approach cannot be elucidated by the existing evidence. We do not know whether the ablation procedure modified the background of atrial fibrillation itself, or simply eliminated an important stimulus for the induction of atrial fibrillation. Radiofrequency catheter ablation in animals has been demonstrated to reduce inducibility of atrial fibrillation, probably by inducing vagal denervation of the atria[11]. Theoretically at least, the creation of ablation lesions could also modify the substrate for the creation and maintenance of the multiple wavelets which are responsible for perpetuation of atrial fibrillation. Recently, Konings et al[19] identified a subgroup of patients with atrial fibrillation in the context of Wolff-Parkinson-White syndrome, who demonstrated broad uniform fronts propagating in the right atrium, probably as part of a large reentrant circuit. This might offer a rationale for right-sided ablation only in a subset of patients.

In addition, the safety of such procedures is unknown. The potential, although relatively rare, arrhythmogenicity of the surgical maze is well established[20,21]. In their series of 33 patients with paroxysmal atrial fibrillation who were subjected to left and right atrial ablation, Jais et al[17] reported that atrial flutter circuits or arrhythmogenic foci were created or unmasked in up to 36% of the cases. Long procedure times and periprocedural strokes have been reported by Swartz et al[14]. We did not encounter such a complication in any of our patients. It remains to be seen whether this can be attributed to differences in the ablation techniques which might also translate into different clinical efficacy.

The future

The possibility of eradication of atrial fibrillation by catheter ablation in the electrophysiology laboratory is very exciting. However, even if this approach proves to be safe and effective, several problems have to be resolved before it is recommended for clinical application.

Unresolved issues

Animal studies have shown that, although a degree of transition of different types of atrial electrograms during atrial fibrillation can be observed in all areas of the atria, certain locations maintain the same type of atrial electrogram without significant temporal variation[12]. In the dog the posterior lateral right atrial wall has been shown to demonstrate predominantly disorganised atrial electrograms, whereas the right atrial appendage and the left atrium showed predominantly organised atrial electrograms[12]. It seems that the characteristics of the atrial electrogram during atrial fibrillation are mainly related to the local atrial effective refractory period, with short effective refractory periods associated with organised electrograms and long effective refractory periods associated with disorganised electrograms. Our studies in humans have also demonstrated that the anatomical distribution of the atrial electrograms during atrial fibrillation appears to be related to the anatomical location (unpublished observations). The left lateral atrial wall and the right atrial appendage, in particular, showed organised atrial electrograms regardless of the type or the duration of atrial fibrillation. However, the clinical significance, if any, of this observation, and its possible implication in the design of future ablation protocols, is unknown.

The impact of the duration of atrial fibrillation on the effectiveness of the procedure is also unclear. Atrial electrical remodelling with decrease of atrial refractoriness develops quickly, within minutes, following rapid pacing[22], and following 24 h of atrial fibrillation the possibility of a successful conversion is diminished[23]. In animals, experimentally induced fibrillation lasting more than 3 weeks usually results in chronic atrial fibrillation[23]. These observations might explain the relatively low success rate in patients with chronic atrial fibrillation, and raises the question of whether "preventive" ablation might be useful in the early stages of paroxysmal atrial fibrillation.

Technical problems

The use of conventional 4-mm tip ablation catheters clearly prolongs the procedure and fluoroscopy times necessary for the accomplishment of several linear lesions. Novel catheter designs, such as multielectrode, flexible catheters with short interelectrode gaps and bidirectional steering[24,25], are under trial. In addition, novel techniques such as ablation guidance by intracardiac ultrasound[26] or non-fluoroscopic electroanatomic mapping[27] and phased radiofrequency energy delivery[28] have also been advocated. Clinical experience with these innovations is very limited.

Conclusions

Certain clinical forms of atrial fibrillation can now be dealt with by catheter ablation. Creation of linear lesions by catheter ablation in the right and left atrium for the elimination of paroxysmal or chronic atrial fibrillation is feasible in the electrophysiology laboratory. However, its long-term safety and efficacy, particularly for permanent atrial fibrillation, are not yet established. Further work is needed in order to elucidate any potential clinical applications of such an approach for the management of patients with atrial fibrillation.

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Chapter 32

Atrioventricular Nodal Ablation and VVIR Pacing for Rate Control and Regularisation of the Ventricular Rhythm in Patients with Established Atrial Fibrillation

P.E. Vardas, E.N. Simantirakis and E.G. Manios

Introduction

Atrial fibrillation continues to be a focus of scientific interest, because of its high incidence and also because of the increased mortality and morbidity which it entails. Although the arrhythmia is usually paroxysmal in nature in its early stages, in a large number of patients it becomes progressively more frequent and eventually evolves into established atrial fibrillation. In the latter case treatment has traditionally focused on the prevention of thromboembolic episodes and on the control of the ventricular rate at rest and during exercise. It seems, however, that the continuous changes in heart rate can play a significant role in the appearance of symptoms and disturbances of left ventricular function. Thus, the past few years have seen a systematic examination of the possible benefit from the regularisation of the ventricular rhythm by means of ablation of the atrioventricular (AV) junction and the implantation of a rate-responsive pacemaker. Furthermore, this approach has been used in recent years as an alternative therapy with very good results in patients whose ventricular rate could not be controlled with drugs.

This chapter is concerned with the role of the above procedure in the treatment of patients with established atrial fibrillation, regardless of whether or not their ventricular rate can be controlled by medication.

The role of AV node ablation in patients with established atrial fibrillation and a rapid ventricular response

The detrimental consequences of supraventricular arrhythmias for left ventricular function have been recognised for a long time, while the term "tachycardia-mediated cardiomyopathy"[1] has been used to describe this phenomenon. Earlier experimental studies in animals[2–4] have shown that rapid pacing causes a deterioration of left ventricular function and dilated cardiomyopathy, while these disturbances disappear a few weeks after the cessation of pacing. Moreover, controlling the ventricular response with drugs in patients who were initially considered to have idiopathic dilated cardiomyopathy with secondary atrial fibrillation[5] led to an improvement in left ventricular function and the relief of symptoms of heart failure.

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Ablation of the AV node with direct current shocks, and later radiofrequency ablation, has been used as an alternative form of treatment in cases in which medication has failed to control the ventricular rhythm or is not tolerated by the patient. A large number of studies[6–12] have shown that this therapeutic approach results in an improvement in left ventricular function, in better exercise capacity and in an improvement in the patient's quality of life. Twidale et al[7] found that, in 14 patients with drug-refractory atrial fibrillation/flutter, the left ventricular ejection fraction increased from 42 ± 3% to 47 ± 4% ($p < 0.05$) and the exercise duration improved from 4.4 ± 0.4 min to 5.4 ± 0.4 min 6 months after AV node radiofrequency catheter ablation and permanent pacemaker implantation. Edner et al[10] used echo Doppler to examine the short and long-term effects of ablation of the AV junction on systolic and diastolic left ventricular function in 29 patients with atrial fibrillation, with and without impaired left ventricular function. In 14 patients with an ejection fraction below 50% there was an increase from 32 ± 11% to 39 ± 11% 65 days after, and to 45 ± 11% 216 days after ablation. The early filling deceleration time increased from 142 ± 46 ms to 169 ± 57 ms in 65 days and 167 ± 56 in 216 days ($p < 0.05$). In the remaining 15 patients with ejection fraction greater than 50% there was no significant change in left ventricular systolic function. The authors concluded that ablation of the AV junction for the control of the ventricular rate leads in the long term to improvement in left ventricular systolic and diastolic function in patients with left ventricular dysfunction, and that this procedure has no adverse effects on normal left ventricular function. In a recent study, Fitzpatrick et al[11] investigated the quality of life and outcomes after radiofrequency His-bundle catheter ablation and permanent pacemaker implantation in 107 patients with paroxysmal and established atrial fibrillation, with a mean follow-up of 2.3 ± 1.2 years. The 46 patients with paroxysmal atrial fibrillation showed a marked improvement in quality of life and health-care consumption but no significant change in perceived ability to perform activities of daily living. In contrast, the 54 patients with established atrial fibrillation showed a markedly significant improvement in all the above parameters. More specifically, in the latter group the quality of life score increased after treatment from 1.8 ± 1.14 to 3.5 ± 1.1 ($p < 0.0001$). The frequency of intermittent symptoms index significantly improved, from 2.45 ± 0.63 to 1.26 ± 0.52 ($p < 0.0001$). The patients' specific activities of daily living became significantly easier. The pooled score of all activities increased from 1.9 ± 0.6 to 2.39 ± 0.5 ($p < 0.001$). Hospital admissions declined from 3.3 ± 8.2 to 0.13 ± 0.49 ($p < 0.03$). Congestive heart failure episodes decreased from 12 to four after treatment. In another recent study by Buys et al[12] it was found that the exercise capacity, as measured by cardiopulmonary stress testing, of patients who underwent His-bundle ablation and VVIR pacing remained unchanged or improved during a mean follow-up of 7 months. In conclusion, radiofrequency catheter ablation of the AV junction followed by permanent pacing is an effective treatment for rate control in patients with established atrial fibrillation, improving systolic and diastolic left ventricular function, exercise capacity, quality of life, the impact of symptoms and the consumption of health care. The above data suggest that this procedure is the treatment of choice for medically refractory atrial fibrillation.

The role of AV node ablation in patients with chronic atrial fibrillation and a normal left ventricular response

Apart from the rapid ventricular rate, another factor, the continuous variation in cardiac cycle length, also appears to have an independent detrimental effect on left ventricular function. Although the negative effect of an irregular ventricular rhythm on cardiac performance was proved long ago, mainly by experimental animal studies[13] but also by clinical studies in humans[14,15], only recently has there been any investigation into the effects of regularisation of the ventricular rhythm on ventricular function and the patient's quality of life. In 1993 Naito et al[13] reported their findings concerning the effects of an abnormal ventricular rhythm on cardiac output in dogs with complete AV block. They found that ventricular pacing which caused an abnormal ventricular rhythm led to a 9% reduction in cardiac output, compared with ventricular pacing at the same rate but with equal RR intervals. Moreover, they demonstrated angiographically that mitral regurgitation appeared during pacing with the irregular rhythm but disappeared during pacing with regular beat-to-beat intervals. Daoud et al[16] were the first to examine the haemodynamic effects of regular and irregular ventricular pacing at identical average heart rates in patients with atrial fibrillation and complete AV block. They studied 11 patients with atrial fibrillation and mean

ejection fraction 0.46 ± 0.11. After radiofrequency ablation of the AV junction they measured the cardiac output (Fick method), pulmonary artery pressure and wedge pressure during regular and irregular ventricular pacing from the right ventricular apex with the same mean pacing rate. They found that at mean cycle lengths of both 750 ms (80 bpm) and 500 ms (120 bpm) irregular pacing caused a 12% reduction in cardiac output. The results of this study suggest that an irregular ventricular rhythm, independently of rate, has deleterious effects on myocardial function. Natale et al[17], in a recent prospective study, examined the impact on ventricular function and quality of life of AV nodal ablation in chronic atrial fibrillation with a normal ventricular response. The study involved 14 patients with an average heart rate per hour > 60 and < 100 bpm on a 24-h Holter recording. Ten of the 14 patients had structural heart disease (nine ischaemic cardiomyopathy, one dilated cardiomyopathy) and none was taking antiarrhythmic medications. The ejection fraction and fractional shortening were measured echocardiographically before the ablation and pacemaker implantation, and again 1 month and 12 months afterwards. At the same times the patients' physical functional capacity was evaluated, based on a self-administered customised questionnaire. The authors found that the mean ejection fraction increased significantly after ablation, from a mean value of 30 ± 11% before the procedure to 38.7 ± 10.8% at 1 month ($p < 0.001$). This improvement remained stable after 12 months of follow-up, with a mean value of 39 ± 12%. The fractional shortening also increased significantly, from 24 ± 7% before ablation to 29 ± 7% at 1 month ($p < 0.001$) and the change again remained stable after 12 months (28 ± 7%). There was also a significant improvement in most of the symptoms and quality of life scores after ablation and at 12-month follow up. NYHA class decreased from 2.6 ± 0.8 to 1.6 ± 0.4 at 1 month ($p < 0.001$) and remained stable over time. The authors concluded that a chronic irregular heart rhythm alone could produce an overall reduction in cardiac function that can be reversed by AV nodal ablation and pacemaker implantation. This procedure could represent a more appropriate therapeutic modality over treatments targeting rate control, particularly in patients with left ventricular dysfunction. In a recent presentation by Natale et al at the 1997 ACC meeting[18] the authors reported that, in patients with chronic atrial fibrillation, discontinuation of "effective" therapy for rate control (β-blockers, Ca^{2+} antagonists, digoxin) followed by AV nodal ablation and pacing seems to improve the quality of life and symptom severity, as well as left ventricular function. In this study the authors did not find any difference between the exercise duration and V_{O_2} max before and after ablation. The results from a recent study (still in progress) in our own department confirm the findings of the above investigators, while also establishing the importance of the restoration of the patients' chronotropy during exercise. This study so far involves 14 patients, aged 72 ± 6 years, with NYHA class II or III heart failure and chronic atrial fibrillation with resting heart rate between 60 and 100 bpm. The patients were taking no antiarrhythmic medication apart from digitalis. All patients underwent radiofrequency catheter ablation of the AV junction and implantation of a permanent VVIR pacemaker. One day before, and 1 and 6 months after the ablation, ejection fraction was measured echocardiographically and a symptom-limited exercise test (Naughton) with breath-by-breath gas exchange analysis was carried out to determine oxygen consumption at peak exercise and at the anaerobic threshold. The importance of the procedure to the patients' quality of life was evaluated using a special questionnaire. We found that ejection fraction increased significantly, from 34 ± 8% before to 41 ± 9% 6 months after the procedure ($p < 0.01$). The ergospirometric parameters also improved after the AV junctional ablation. Oxygen consumption showed a trend to increase from 15.4 ± 0.8 to 17.8 ± 0.6 ml/kg per minute ($p = 0.06$) at peak exercise and from 12.1 ± 0.6 to 14.8 ± 1 ml/kg per minute ($p = 0.06$) at the aerobic threshold. According to the questionnaires there was a significant improvement in quality of life and a decrease in the severity of symptoms.

It should be noted that our findings regarding the improvement in the patients' exercise performance differ from those of Natale et al. However, it is not clear whether the patient populations in the two studies are comparable: further studies with larger numbers of patients are needed to clarify this matter.

Although the precise underlying mechanism for the reduction in cardiac output associated with an irregular rhythm has not been well established, the following mechanisms have been implicated:

1. During irregular rhythm ventricular filling varies on a beat-to-beat basis. This variation influences

the intensity of cardiac systole via the Frank-Starling mechanism and the interval-force relation[19]. It is therefore likely that the reduction in ejection fraction which is observed in very short cardiac cycles (short RR intervals) is not sufficiently compensated for by the increase in ejection fraction during the long cardiac cycles (long R-R intervals) which follow.

2. The irregularity may cause a reduction in cardiac output via neurohormonal and vasculokinetic changes[20]. An irregular rhythm probably entails increased levels of natriuretic peptide compared with a normal rhythm, because of greater variation and higher peaks in atrial pressure. The increased secretion of natriuretic peptide, in its turn, causes venous and arterial dilatation and vagally mediated inhibition of cardiac sympathetic input. However, other mechanisms, such as the stimulation of atrial vasoinhibitory reflexes or an increase in parasympathetic tone, may also be responsible for the reduction in cardiac output during the irregular rhythm.
3. Another mechanism through which an irregular ventricular rhythm might cause a reduction in cardiac output is inefficient ventricular mechanics[15]. It is probable that abrupt changes in cycle length have a direct effect on myocardial contractility. Also, short RR intervals may result in incomplete ventricular mechanical restitution, wasted ventricular energy during inadequate ventricular filling and a reduction in diastolic filling time, which leads to reduced coronary flow.
4. Mitral regurgitation as a consequence of irregular rhythm may contribute to the adverse haemodynamics[13].

At this point it should be noted that a high percentage of patients with chronic atrial fibrillation show disturbances of chronotropy during exercise[21]. Ablation of the AV node and the implantation of a rate-responsive pacemaker with suitable programming of the sensor parameters leads to an improvement in chronotropy in these patients, and is thus likely also to improve exercise capacity. However, it is not known whether the increase in exercise capacity we observed after AV junction ablation and implantation of a VVIR pacemaker is due mainly to the improvement in cardiac output or to an improvement in the previously pathological chronotropy in these patients.

Conclusions

Although it is still too early to know whether radiofrequency ablation of the AV junction, combined with permanent pacing, affects the very long-term prognosis and the mortality of patients with established atrial fibrillation, the findings from the studies so far suggest that this procedure may be the treatment of choice in patients with an uncontrolled ventricular rate. Furthermore, it appears that, even in those with a normal ventricular rate, regularisation of the ventricular rhythm may lead to an additional improvement in cardiac performance. Possible alternative pacing methods, such as ventricular septal pacing, and improvements in sensor technology may further increase the efficacy of the procedure.

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Chapter 33

Ablation for Ventricular Tachycardia Related to Coronary Artery Disease

John D. Fisher

Introduction and background

Catheter ablation, particularly radiofrequency (RF) catheter ablation, has become the primary therapy for a wide range of arrhythmias, including several of the idiopathic ventricular tachycardias (VT). Successful ablation of VT related to coronary artery disease (CAD) is now well-documented[1–18], but it is far from being considered a curative therapy for most such arrhythmias[19,20]. The present status of catheter ablation in CAD-related VT will be reviewed by addressing some of the major questions and issues that exist: (1) Where is the VT? (2) How many VT are there? (3) Should some VT be ignored? (4) How to ablate effectively? (5) Can the ablation be trusted?

Where is the VT?

The answers to this question depend on an understanding of the physiology of VT in the setting of coronary artery disease.

"Site of origin" and activation mapping

Years ago it was recognised that the QRS onset during VT represented the emergence of a wave front into a mass of (near)-normal myocardium sufficient to generate a QRS complex. It was assumed that during diastole the wave front existed in an area of diseased and slowly conducting muscle, and that the location of such wave fronts would be difficult to identify, and perhaps not relevant to successful ablation. Surgical ablation procedures such as endocardial resection would remove a substantial mass of tissue surrounding the "site of origin" as identified by activation mapping. For patients who survived the operation, long-term outcomes were often quite good from an arrhythmia point of view. The majority of patients enjoyed freedom from VT recurrence for many years, typically without the need for additional antiarrhythmic drugs or other therapy.

With DC shock ablation the area or volume of tissue affected by the procedure was considerably less than with surgical approaches. Success rates declined compared to surgery, and the importance of mapping approaches other than "site of origin" became appreciated.

Pace mapping

Pacing from the right ventricular apex, outflow tract, and other sites in the right and left ventricles produce QRS complexes that are characteristic for each of these sites. It was assumed that exactly matching the paced QRS configuration with the VT configuration would localise the site of origin more precisely than activation mapping alone. Investigators were disappointed, however, to find

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that pacing over an area of several square centimetres could produce comparable QRS morphologies, and that some of the "perfect matches" could be undone by raising or lowering the stimulation amplitude. The precision of such mapping was therefore adequate for surgical ablation, but not for DC shock ablation, and certainly not for the much more limited ablation volumes associated with radiofrequency catheter ablation (Fig. 1). With further refinements in the understanding of physiology, special variations on activation mapping and pace mapping have become the key to tachycardia localisation[6,7,12,21–32].

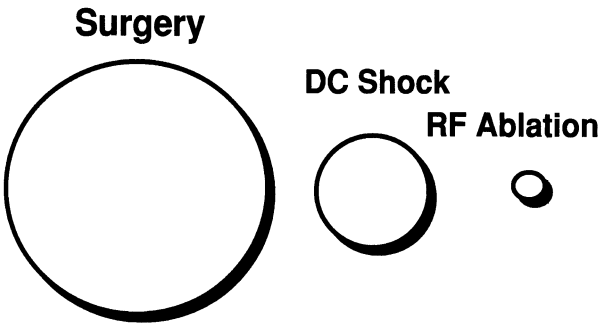

Figure 1. Relative areas ablated with surgery, DC shock, and radiofrequency (RF) ablation. Much more accurate knowledge of physiology and the arrhythmia circuit is required for successful ablation with the smaller lesions produced by RF.

The arrhythmogenic substrate

In CAD-related VT there is often no small precise target site such as exists in some idiopathic VT, Wolff-Parkinson-White (WPW), or arteriovenous (AV) node reentry tachycardia. Often there is a broad potential target area of interest, with multiple and often changing active circuits that may not always use anatomically fixed pathways. Most current clinical models assume that an array of potential tachycardia circuits exists, somewhat like an electronic circuit diagram. However, animal models of ischaemic VT are often characterised by regions of functional block, with constantly changing circuits that are more akin to a writhing snake pit.

Lessons from (concealed) entrainment

Entrainment (first emphasised by Waldo and Henthorn[31]) is the continuous resetting of a reentry circuit by stimulation in the excitable gap[24,31]. If the stimulation is delivered within the zone of slow conduction known as the isthmus (Fig. 2)[33] the stimulated wave front will eventually exit into the "good" myocardium, generating the typical VT QRS morphology. Unlike classical pace mapping, in which the stimulus is immediately followed by a QRS, stimulation in the slowly conducting isthmus region results in a substantial stimulus to QRS (S-QRS) interval[6,7,12,21–32]. Initially it was thought that perhaps this was all that was needed for targeting a precision ablation delivery. However, it soon became clear that there are blind alleys, bystander pathways, "inner loops", and a veritable archipelago of scar islands in the midst of the slowly conducting region. Among many active investigators, William Stevenson and his group have been at the forefront of characterising this arrhythmogenic substrate[21–24]. Some of the important lessons from studies of concealed entrainment are summarised in Table 1.

Table 1. Some lessons from concealed entrainment[6,7,12,21–32]

1.	*Postpacing interval* If postpacing interval = VT CL, this indicates that stimulation is in the circuit. Longer = outside.
2.	*QRS configuration during entrainment* If the same as VT, without progressive fusion, this indicates stimulation with concealed entrainment in the slow zone at or proximal to exit, *but not necessarily in the circuit* (could be a bystander).
3.	*S-QRS during concealed entrainment*[24]: S-QRS = Egm-QRS indicates stimulation in the circuit S-QRS > Egm-QRS implies stimulation in a bystander Long S-QRS = Egm-QRS may indicate inner loop site, often broader and harder to ablate.

S = stimulus; Egm = local electrogram.

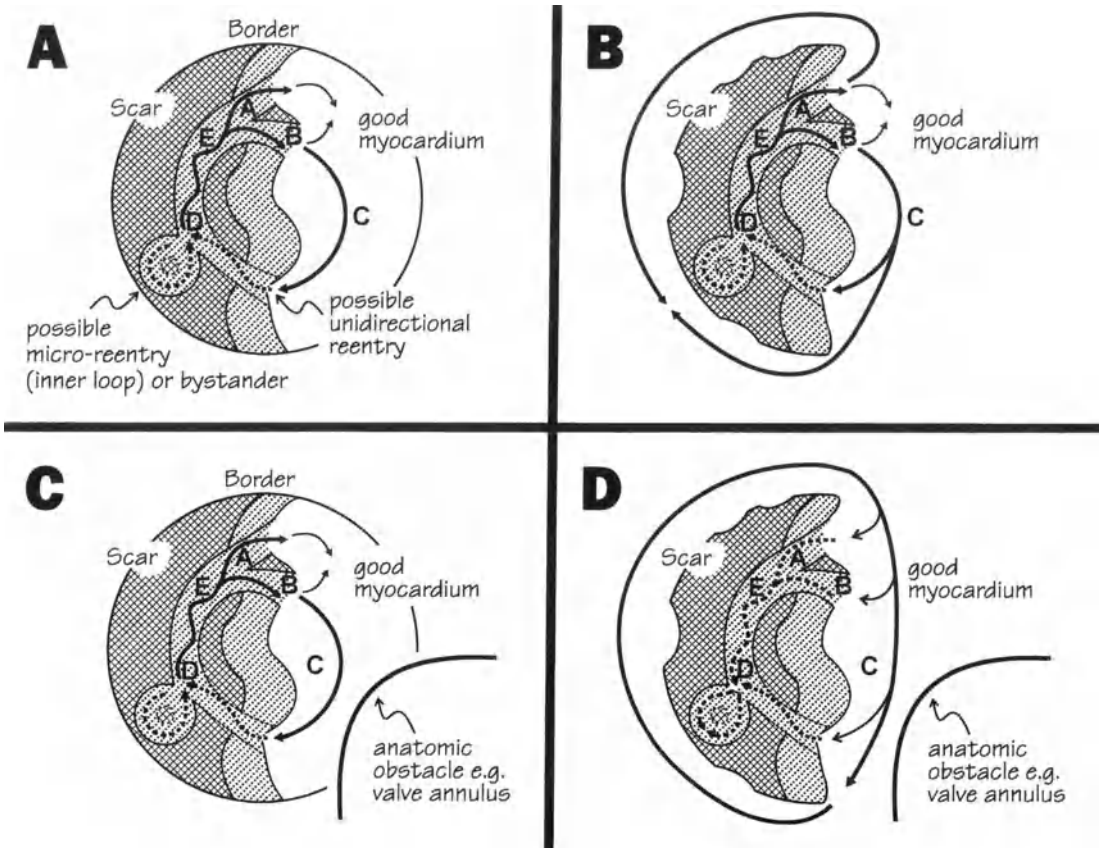

Figure 2. VT mechanisms and ablation in CAD-related VT. *Panel A*: VT circuit showing earliest activation of normal or "good" myocardium at sites A and B, with conduction through the normal myocardium (C), and then slow conduction through the abnormal zone (stippled, with sites D and E). If only site A or B effectively exits into the good myocardium, pacing at this point would produce a pace map match of the VT configuration. It is likely, however, that ablation would fail because the wave front could exit through other portions of the stippled area. If both A and B are active exit sites, then a pace map match will not exist at this point. However, entrainment could occur with stimulation at areas A, B, or C (see text). Stimulation at D or E would result in a pace map match after a delay between the stimulus and the QRS (concealed entrainment). Ablation at D or E might terminate and/or ablate the VT. Stimulation in the inner loop or bystander area could cause a pace map match, but, in contrast to stimulation at D or E, the post-pacing interval would be longer than the VT cycle length, indicating that this site is outside of the main circuit. Ablation in the bystander area would also be likely to fail. (Updated from a figure in ref. 7.) *Panel B*: In this case the scar and diseased area occupy a "patch" within a larger area of good myocardium. The true circuit is the same as shown in panel A, but because the wave front encircles the scar, the activation map could prove more complex or confusing. This is a somewhat lopsided version of the "figure of 8" type circuit. *Panel C*: The true circuit is again similar to that shown in panel A. In this case there is a nearby anatomical obstacle, e.g. the valve annulus. In such a case ablation could also be successful with the lesion placed between the annulus, across region C, and into the scar. As in each of the other panels it is possible, however, that other circuits could occur, e.g. at the inner loop area, or around the island formed at exit sites A and B. *Panel D*: In this case the true circuit revolves the patch of scar. The stippled diseased area does not play a role in this circuit. Careful attention to the details of activation mapping and stimulation with observation of entrainment is important to distinguish this from the situation in panel B. In this case ablation would be successful only between the valve annulus and the stippled area and scar near site C, whereas in panel C, ablation at sites D and E might also be successful. (Concepts based in part on many references, particularly ref. 24; from ref. 33 with permission.)

How many VT are there?[21–32,34]

The preceding section indicates that the arrhythmogenic substrate often has multiple potential VT circuits. Further, for each of the clockwise-moving circuits shown in Fig. 2, counterclockwise counterparts may also exist. Very different-appearing VT may therefore utilise the same circuit in opposite directions. Other VT may share some, or none, of any given circuit. One of the earliest lessons from electrophysiological studies in patients with CAD-related VT was that it is often possible to induce many VT beyond those which had been previously documented. For a time these were termed "non-clinical". Follow-up of patients with various types of therapy makes it clear that the term "previously undocumented" is preferable to "nonclinical", since many such VT are observed during follow-up. At present, induction of a sustained monomorphic VT is considered to be of potential clinical importance, and is not considered to be a "non-specific" finding.

Should some VT be ignored?

Previously known or inducible but unablated VT tend to recur during follow-up[9,15–19,20,25,28,32,34,35]. It is therefore important to consider the purpose or objective of the ablation procedure as follows:

1. *Clinical cure*: if the purpose is to cure VT in the same way that one attempts to cure WPW syndrome, then all relevant pathways need to be ablated. Therefore all inducible sustained monomorphic VT would need to be ablated.
2. *Stop incessant VT*: this is an important indication for ablation, and can often salvage a patient's life. Many such patients are desperately ill, and elimination of incessant VT is a valid objective. Such VT are more likely than others to recur however[20], and such patients almost always need backup therapy with drugs or an implantable cardioverter defribillator (ICD).
3. *Eliminate the most frequent VT*: this is a worthwhile objective in patients with frequently recurring VT, and the most common configuration should be the one first targeted. But why stop there?
4. *Reduce the number of ICD shocks*: although patients are extremely thankful for the security offered by an ICD, they dislike receiving shocks. Ablation to reduce the number of such shocks is in keeping with the objectives in the previous paragraphs.

How to ablate effectively?

Better and better knowledge of VT physiology and the arrhythmogenic substrate are important to the achievement of effective ablation.

Enhanced ablation tools are equally important to effective ablation. Such tools fall broadly in two major categories: (1) mapping tool enhancements[36–49] (Table 2); and enhancements to the actual ablation methodologies[35,50–57] (Table 3).

It is likely that the next few years will see brisk competition and an ultimate "shaking out" of these methods. At the present time electro-anatomical approaches[41] and basket catheters[36,37] seem to offer more intuitively plausible mapping systems than some of the others; initial comparative studies are now being reported[36]. Radiofrequency with saline irrigation/cooling[35,50] is presently receiving the most attention as a method of increasing the volume or area of ablation.

Can CAD-VT ablation be trusted?

Most published studies show a 20–40% VT recurrence rate during follow-up[9,10,15–18,20,25,28,32,34,35]. Incessant VT are most likely to recur[20]. The literature at present is somewhat amorphous. Follow-up times vary markedly. Some studies report only the immediate results or pre-discharge results as successes or failures. Some count

Table 2. Mapping tool enhancements

1.	Basket catheters[36,37]
2.	Non-contact multielectrode arrays[36,38,39]
3.	Orthagonal mapping (e.g. LocaLisa®)[40]
4.	Electroanatomical (e.g. CARTO® – Biosense-Cordis-Webster)[41]
5.	Coronary veins (or arteries)[42]
6.	Intrapericardial probes for epicardial maps
7.	Intracardiac echo (ICE, ICUS)[43]
8.	Echo-transponder catheter[44]
9.	Cryoprobe "ice mapping"[45]
10.	Trans-septal approach to left ventricle[46]
11.	Sinus mapping (redux)[47]
12.	Mapping with induced ischaemia[48]
13.	Miscellaneous: body surface potentials[49]; magnetocardiography; phase RNV; optical mapping; potential distribution mapping; etc.

Table 3. Ablation enhancements

1.	*Site testing without destruction*
	Cooling; heating
	Subthreshold pacing
2.	*Increase the volume/area of ablation*
	Saline irrigation[35,50]
	Microwave[51]
	Ethanol or other intracoronary infusion[52]
	Selective coronary occlusion[53]
	Ultrasound[54]
	Thermal balloon[55]
	Cryoablation catheters[56]
	DC shock variations (redux)
	Laser[57]

any recurrent VT; others count only if the *targeted* VT recurs; and others only if the targeted *and* initially "cured" VT recur.

The distinction between termination of VT and actual ablation of the VT is important. The most comprehensive and detailed report of ablation based on entrainment mapping in CAD-related VT is illustrative[24]. A total of 398 sites were subjected to radiofrequency delivery, *terminating* 12% of VT. The best results were from the isthmus area, with a 29% overall likelihood of termination, higher near the exit sites than others. It was surprising to the authors that as many as 3% of applications at a remote bystander site resulted in termination. These 398 applications were delivered in only 37 patients, and the authors make it clear that termination of the episode, rather than ablation of the circuit, was accomplished[24]. The following points summarise the author's answer to the question of whether ablation can be trusted in CAD-VT patients at the present time.

1. Ablation may stop incessant VT, but recurrences are frequent.
2. Ablation may reduce the number of VT recurrences and reduce ICD shocks or the amount of anti-arrhythmic drugs needed.
3. "Non-clinical" or "non targeted" VT tend to occur during follow-up; in addition to some of those targeted and thought to be ablated.
4. Current wisdom: VT ablation in coronary artery disease patients can be helpful, but *don't bet their lives on it!*

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PART FOUR

ATRIAL AND VENTRICULAR DEFIBRILLATION

Chapter 34

Historical Perspectives on Cardioversion and Defibrillation

Berndt Lüderitz

Introduction

The diagnosis and treatment of cardiac arrhythmias, including cardioversion and defibrillation, has a long and fascinating history. From earliest times no clinical symptom impressed the patient (and the physician) more than an irregular heart beat. In fact, Ludwig van Beethoven (born in Bonn, Germany, 17 December 1770) set his own cardiac rhythm disturbance to music (piano sonata opus 81a "Les adieux") long before Einthoven graphically documented the electrical expression of regular and irregular cardiac activity in the form of an electrocardiogram.

Although ancient Chinese pulse theory laid the foundation for the study of arrhythmias in the fifth century BC, the most significant breakthrough in the identification and treatment of cardiac arrhythmias first occurred in this century. In recent decades our knowledge of pharmacology and electrophysiology has increased exponentially. The enormous clinical significance of cardiac rhythm disturbances has favoured these advances. On the one hand, patients live longer and thus are more likely to experience arrhythmias. On the other hand, circulatory problems of the cardiac vessels have increased enormously, and this has been identified as the primary cause of cardiac rhythm disorders. Coronary heart disease has become not just the most significant disease of the heart, it has become the most significant disease of all, based on the statistics for cause of death in Western industrialised nations. Arrhythmias are the main complication of ischaemic heart disease, and they have been directly linked to the frequently arrhythmogenic sudden-death syndrome, which is now presumed to be an avoidable "electrical accident" of the heart.

Like any other field of medicine, the study of arrhythmias has a distinctive past. Our current level of knowledge is not the result of a straight, linear progression any more than there is a static, established, monolithic body of thought dominating this field. Instead, our knowledge of arrhythmias today is the result of many competitive, sometimes serendipitous, scientific realisations, of which a few proved useful enough to pursue, and eventually led to real advancements.

A retrospective look – often charming in its own right – may not only make it easier to sort through the copious details of this field, and so become oriented in this universe of important and less important facts; it may also assist the observer in a chronological vantage point of the subject. The study of arrhythmias is no dry compendium of facts and figures, but rather a dynamic field of study evolving out of the competition between various theories[1].

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Table 1. Chronological overview of the discovery of the cardiac conduction system

1845	JE Purkinje[2]	Purkinje fibres
1865/1893	G Paladino, AFS Kent[3]	Bundle of Kent
1893	W His, Jr[4]	Bundle of His
1906	L Aschoff, S Tawara[5]	AV node
1906/1907	KF Wenckebach[6]	Wenckebach bundle
1907	AB Keith, MW Flack[7]	Sinus node
1916	JG Bachmann[8]	Bachmann bundle
1932	J Mahaim[9]	Mahaim fibres
1961	TN James[10]	Bundle of James

The discovery of the cardiac conduction system is a cornerstone of pathophysiologically based antiarrhythmic therapy. In Table 1 the most important scientists and their contributions are listed chronologically.

In the majority of cases the diagnosis of cardiac rhythm disorders relies on non-invasive examinations in addition to the clinical analysis of symptoms. Vague or broadly defined symptoms may require invasive diagnostic techniques.

Electrocardiography, including resting ECG, exercise ECG, oesophageal ECG, and Holter monitoring, must be considered one of the main non-invasive examination techniques. For bradycardias, provocative testing may also be used (carotid sinus massage, atropine)[11].

Electrocardiography, the basic tool for non-invasive arrhythmia diagnosis and prerequisite of antiarrhythmic therapy, translates each cardiac action into a potential variation over time. The developments of electrocardiographic recording are depicted in Table 2.

In the beginning, there is not simply the anatomy and physiology of the heart, but also analysis of the pulse, which indicates the activity of the heart (Fig. 1). The analysis of the (peripheral) pulse as a mechanical expression of heart activity goes back several millennia.

Figure 1. Physician treating a young women (oil painting by J. Steen, 1626–1679).

In China, in the year 280, Wang Shu Ho wrote a classic treatise about the pulse. The Greeks called the pulse "sphygmos", and sphygmology thus deals with the theory of this natural occurrence. In Roman times Galen interpreted the various types of pulse according to the widespread presumption of the time, that each organ in each disease has its own form of pulse.

Therapy for cardiac rhythm disturbances – both clinically and in practice – may be divided into causative therapy general measures (such as bed rest, sedation possibly vagal stimulation, etc.); pharmacological therapy; electrotherapy, especially cardioversion and

Table 2. Chronology of Electrocardiography

1903	Surface leads ECG	W Einthoven[12]
1906	Oesophageal ECG	M Cremer[13]
1933	Unipolar chest wall leads	FN Wilson[14]
1936	Vector electrocardiography	F Schellong[15]
1938	Small triangle "F" (RA, LA, RL)	W Nehb[16]
1942	Unipolar amplified (augmented) extremity leads	E Goldberger[17]
1956	Corrected orthogonal lead systems	E Frank[18]
1960	Intracardial leads	G Giraud, P Puech[19]
1969	His bundle ECG	BJ Scherlag[20]

defibrillation; and, in some cases, even antiarrhythmic surgical interventions.

By definition a causative therapy must work on the cause of the condition; for instance, therapy of coronary heart disease, treatment of myocarditis, elimination of glycoside toxicity or electrolyte imbalance, normalisation of hyperthyroidism or replacement of a defective pacemaker. Yet in cases of dangerous arrhythmias it is often necessary for acute (i.e. symptomatic) treatment to eliminate the arrhythmia first; in such instances pharmacological treatment or, sometimes, electrical devices including the implantable cardioverter/ defibrillator, must be considered. The history of electrotherapy is shown in Table 3.

Antitachycardia pacing/cardioversion

In treating tachyarrhythmias (such as tachycardias caused by premature contractions, atrial flutter, supraventricular or ventricular tachycardia), temporary or permanent antitachycardia pacing is especially used once it has been determined that the rhythm disorder is drug refractory.

In the 1970s and 1980s our working group and other authors reported various pacing methods to terminate tachycardia: overdrive pacing, dual-chamber pacing[54], high-rate pacing, programmed (competitive) stimulation with or without extrastimuli[54,55] as well as scanning stimulation[21,56]. Currently, overdrive pacing, programmed stimulation, and high-rate pacing are used most often.

Overdrive pacing, which prevents as well as terminates tachyarrhythmias, is defined as supraventricular or ventricular pacing in which the pacemaker elevates the heart rate over the intrinsic rhythm. This suppresses ectopic tachyarrhythmias. Programmed stimulation, used mainly to terminate supraventricular or ventricular reentry tachycardias, involves delivering one or more output pulses to the heart at precisely timed points in the cardiac cycle. This depolarises the myocardium prematurely and, in so doing, interrupts the circus movement[57]. High-rate pacing is used to terminate supraventricular tachycardia. For atrial flutter induced by digitalis toxicity, atrial high-rate pacing is the therapy of choice. Sinus rhythm is usually restored via induction of atrial fibrillation.

Catheter ablation

Non-invasive catheter ablation of the bundle of His, atrioventricular (AV) node or accessory pathways has become an available method for treating symptomatic, drug-resistant supraventricular tachycardias.

His bundle ablation

In 1981 Gonzales et al[58] reported the first AV block induced by an electrode catheter. A patient was undergoing an electrophysiological study following defibrillation when the defibrillating electrode accidentally came into contact with an electrode catheter in the bundle of His. This accidental experiment was refined in 1982 by Gallagher et al[44], as well as Scheinman et al[45,59], in patients with drug-refractory supraventricular tachycardia. In these patients a non-invasive percutaneous excision and coagulation of the bundle of His was performed using direct current shock via a catheter. This method employs an initial electrophysiological study for diagnostic purposes, then uses an electrode catheter inserted in the bundle of His. An electrical shock is delivered from an external defibrillator. Generally, this leads to coagulation necrosis in the area around the bundle of His. Throughout this procedure an external pacemaker provides ventricular pacing support[60].

Percutaneous His bundle ablation represents a new and very promising method of treating drug-resistant supraventricular tachycardia.

Accessory pathways

In 1983 Weber and Schmitz[61] reported the first treatment of a patient with type B Wolff-Parkinson-White syndrome using catheter ablation. The accessory pathway was interrupted by positioning a tripolar electrode in the right atrium. Based on the studies by Kuck et al[51] and Jackman et al[50], (invasive, but not operative) catheter ablation is the therapy of choice for symptomatic pre-excitation syndromes[62].

In contrast to the above-described technique of high-frequency catheter ablation[50,63–66], another technique known as laser photo ablation[67,68] uses a more controllable energy to remove accessory AV pathways and, with them, the source of ventricular tachycardia. However, laser photo ablation is not routine therapy at this time.

High-frequency energy was first used in catheter ablation to interrupt an AV by-pass tract in 1986 by Borggrefe et al[48]. This group also performed the first high-frequency ablation of a ventricular tachycardia in a human being that same year. In these early procedures

Table 3. Historical perspectives on electrotherapy of cardiac arrhythmias: the history of electrotherapy from the sixteenth to the twentieth century[21]

1580	Mercuriale G (1530–1606): Ubi pulsus sit rarus semper expectanda est syncope[22]
1717	Gerbezius M (1658–1718): Constitutio Anni 1717 a.A.D. Marco Gerbezio Labaco 10. Decem. descripta. Miscellanea-Emphemerides Academiae Naturae Curiosorum. Cent. VII, VIII. 1718: in Appendice[23]
1761	Morgagni GB (1682–1771): De sedibus et causis morborum per anatomen indagatis[24]
1791	Galvani L (1737–1798): De viribus electricitatis in motu musculari commentarius[25]
1800	Bichat MFX (1771–1802): Recherches physiologiques sur la vie et la mort[26] [Physiological sudy on life and death]
1804	Aldini G (1762–1834): Essai theorique et experimental sur le galvanisme, avec une serie d'experiences faites en presence des commissaires de l'institut national de France, et en divers amphitheatres de Londres[27] [Theoretical and experimental essay on galvanism with a series of experiments conducted in the presence of representatives of the National Institute of France at various amphitheatres in London]
1827/1846	Adams R (1791–1875); Stokes, W (1804–1878): Cases of diseases of the heart accompanied with pathological observations: Observations of some cases of permanently slow pulse[28,29]
1872	Duchenne de Bologne GBA (1806–1875): De l'ectrisation localisée et de son application à la pathologie et à la thérapeutique par courants induits et par courants galvaniques interrompus et continues[30] [On localized electrical stimulation and its pathological and therapeutic application by induced or galvanised current, both interrupted and continuous]
1882	von Ziemssen H (1829–1902): Studien über die Bewegungsvorgänge am menschlichen Herzen sowie über die mechanische und elektrische Erregbarkeit des Herzens und des Nervus phrenicus, angestellt an dem freiliegenden Herzen der Catharina Serafin[31] [Studies on the motion of the human heart as well as the mechanical and electrical excitability of the heart and phrenic nerve, observed in the case of the exposed heart of Catharina Serafin]
1890	Huchard H: La maladie de Adams-Stokes [Adams Stokes syndrome]
1932	Hyman AS: Resuscitation of the stopped heart by intracardial therapy. II. Experimental use of an artificial pacemaker[32]
1952	Zoll PM: Resuscitation of heart in ventricular standstill by external electrical stimulation[33]
1958	Elmquist R, Senning A: An implantable pacemaker for the heart[34]
1958	Furman S, Robinson G: The use of an intracardiac pacemaker in the correction of total heart block[35]
1961	Bouvrain Y, Zacouto F: L'entrainement électrosystolique du coeur[36] [Electrical capture of the heart]
1962	Lown B *et al*: New methods for terminating cardiac arrhythmias[37]
1962	Nathan DA *et al*: An implantable synchronous pacemaker for the long-term correction of complete heart block[38]
1969	Berkovits BV *et al*: Bifocal demand pacing[39]
1969	Scherlag BJ *et al*: Catheter technique for recording His bundle activity in man[20]
1972	Wellens HJJ *et al*: Electrical stimulation of the heart in patients with ventricular tachycardia[40]
1975	Zipes DP *et al*: Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium[41]
1978	Josephson ME *et al*: Recurrent sustained ventricular tachycardia[42]
1980	Mirowski M *et al*: Termination of malignant ventricular arrhythmias with an implanted automatic defibrillation in human beings[43]
1982	Gallagher JJ *et al*: Catheter technique for closed-chest ablation of the atrioventricular conduction system: A therapeutic alternative for the treatment of refractory supraventricular tachycardia[44]
1982	Scheinman MM *et al*: Transvenous catheter technique for induction of damage to the atrioventricular junction in man[45]
1982	Lüderitz B *et al*: Therapeutic pacing in tachyarrhythmias by implanted pacemakers[46]
1985	Manz M *et al*: Antitachycardia pacemaker (Tachylog) and automatic implantable defibrillator (AID): combined use in ventricular tachyarrhythmias[47]
1987	Borggrefe M *et al*: High frequency alternating current ablation of an accessory pathway in humans[48]

Table 3. *(continued)*

1988	Saksena S, Parsonnet V: Implantation of a cardioverter-defibrillator without thoracotomy using a triple electrode system[49]
1991	Jackman WM *et al*: Catheter ablation of accessory atrioventricular pathways (Wolff–Parkinson–White syndrome) by radiofrequency current[50]
1991	Kuck KH *et al*: Radiofrequency current catheter ablation of accessory atrioventricular pathways[51]
1995	Camm AJ *et al*: Implantable atrial defibrillator[52]
1997	Jung W *et al*: First implantation of an arrhythmia management system[53]

the energy discharged (up to 50 W) was applied in similar fashion to direct-current ablation; in other words, using a unipolar electrode catheter and a large-surfaced reference electrode placed on the chest. However, unlike direct current ablation, in this case energy was applied for a longer period of time (10–90 s). Tissue lesions caused by thermal effects are localised. Because the energy applied can be so precisely controlled, high-energy catheter ablation carries with it less risk of complications than direct current ablation[69].

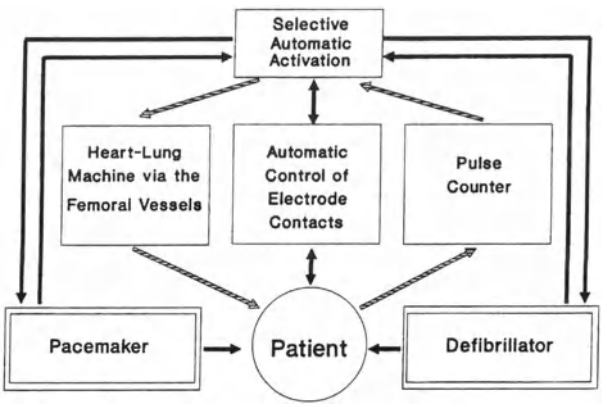

Figure 2. Schematic arrangement of the heart "resuscitation device". The patient (bottom centre) is connected to the heart monitor (top centre) by electrodes. The monitor searches for circulatory arrest and automatically activates the pacemaker (bottom left) in the case of ventricular arrest, or the defibrillator (bottom right) in the case of ventricular fibrillation. There are haemodynamic controls (middle right) which evaluate the effectiveness of the steps taken. If those steps are insufficient to bring the heart back to normal rhythm, the device provides either permanent pacing via intracardial leads or haemodynamic circulatory support via a heart-lung machine, or both.

Implantable cardioverter defibrillator

After many years of animal experiments treating haemodynamic collapse induced by ventricular arrest or fibrillation, Bouvrain and Zacouto[36] published a report in 1961 that described a combination of devices they called a "resuscitation device", consisting of a heart monitor, a defibrillator, and a pacemaker (Fig. 2). This was the first time individual pieces of equipment had been combined to work together automatically in the case of haemodynamic collapse.

Although implantable pacemakers have been available since the late 1950s, it took two more decades before implantable defibrillators were routinely used (milestones in the development of the implanted cardioverter/defibrillator are listed in Table 4).

Essentially developed by Mirowski[70–72], the AID/AICD system consists of the abdominally implanted device itself with a lead system for arrhythmia detection and delivery of defibrillatory or cardioverting shocks. An implantable cardioverter/defibrillator is indicated in patients in danger of life-threatening conditions in whom drug-refractory ventricular tachycardia or ventricular fibrillation has been documented, and for whom an antiarrhythmic cardiological surgical intervention is not suitable or appropriate.

Another important step in the development of electrotherapy for tachyarrhythmia is the combined application of antitachycardia pacemakers and automatic cardioverter/defibrillators described by our working group in 1985[47] (Fig. 3). Their use in treating ventricular tachycardia has been well documented[21,47,73,74]. Modern implantable cardioverter/defibrillator systems now combine bradycardia pacing, antitachycardia pacing, and defibrillatory options in a single device.

In conclusion, the emergence of implantable cardioverter/ defibrillators (ICD) must be seen as important progress in treating patients with life-threatening ventricular tachycardias[73,75].

Table 4. Milestones in the development of the implantable cardioverter defibrillator (ICD)

1966	Conception
1969	First experimental model
1969	First transvenous defibrillation
1975	First animal implant (Mirowski)
1980	First human implant
1982	Addition of cardioverting capability
1985	FDA approval
1988	First programmable device implanted (Ventak P)
1989	First multiprogrammable device implanted (PCD)
1993	Pectoral implantation (PCD Jewel) inactive
1994	Pectoral implantation ("Active can")
1995	First dual-chamber ICD implanted (Defender)
1996	First implantation of a stand-alone atrial defibrillator
1997	First implant of a combined atrial-ventricular defibrillation system

An automatic, implantable pharmacological defibrillator is currently being tested by Cammilli et al[76,77] (Fig. 4). This device combines electrical therapy with pharmacological treatment. It represents an alternative course in the treatment of refractory ventricular tachycardias, providing it can be refined and tested to the point that it finds clinical application.

International cardiac pacing and electrophysiology society

The World Symposia on Cardiac Pacing and Electrophysiology, which is to be called the World Congress after 1999 (Table 5) was instrumental in the many recent advances in cardiac pacing and electrophysiology. The first and second symposia had been organised under the "auspices of the New York Academy of Sciences" in New York City. The International Cardiac Pacing Society (ICPS), founded in 1973, took over the organisation of the symposium in 1976. In 1987 the ICPS was renamed the International Cardiac Pacing and Electrophysiology Society (ICPES).

Implantable atrial defibrillators

The implantable atrial defibrillator is the logical extension of intra-atrial defibrillation for treating symptomatic atrial fibrillation. This new form of electrical therapy is currently under clinical evaluation[78]. Considered candidates for an implantable atrial defibrillator are patients with intermittent, drug-refractory atrial fibrillation that occurs at a frequency of from once a week to once every 3 months. In predischarge testing the physician activates the implanted atrial defibrillator system while the patient is still in the hospital, in order to precisely document its function, efficacy, and reliability. After sufficient experience, when atrial fibrillation occurs, the patient can activate the implantable atrial defibrillator with a magnet, or the device may respond automatically. In order to function automatically, the defibrillator system regularly monitors the patient's heart for signs of atrial fibrillation. To identify atrial fibrillation the system uses a variety of algorithms with a high specificity to atrial fibrillation. Once the defibrillator system has detected and confirmed atrial fibrillation, the defibrillator's capacitors charge and a low-energy shock at a programmed energy level is delivered to terminate the atrial fibrillation. The clinical utility of the implantable atrial defibrillator remains to be seen, as there are still some open issues with respect to this innovative new electrical therapy; for instance, the potential risk of inducing a life-threatening cardiac rhythm disorder, as well as patient acceptance of a device that delivers repeated shocks. Furthermore, it has not yet been determined whether an anticoagulant is needed in conjunction with this device, to prevent thromboembolism.

The first implantable atrial defibrillation system in Germany was successfully implanted on 3 April 1996 at the University Hospital in Bonn (Metrix 3000, InControl) in a 64-year-old female patient with symptomatic, drug-refractory atrial fibrillation. The Metrix 3000 (Fig. 5) defibrillation system consists of a 79-g and 53-cm^3 generator and a right atrial screw-in lead, a

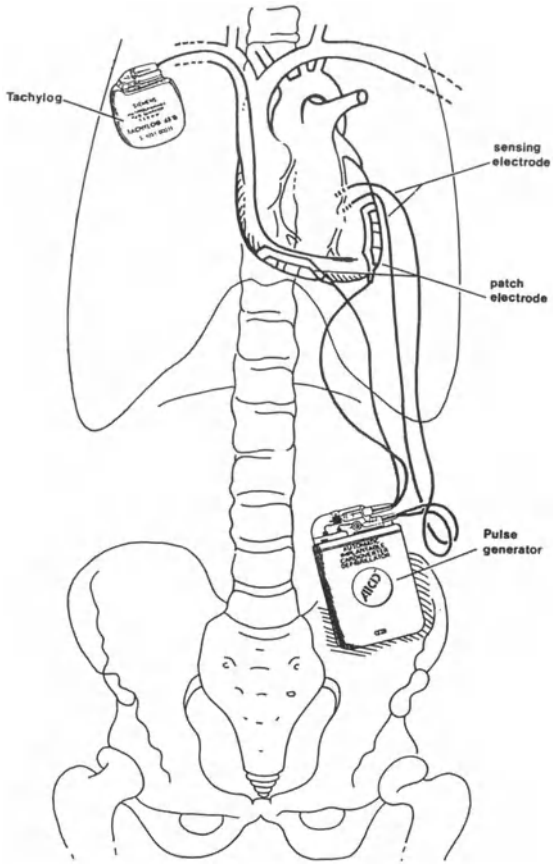

Figure 3. Implantation of a combination of antitachycardia devices: antitachycardia pacemaker (Tachylog) with transvenous, intracardiac, right ventricular leads, plus an automatic, implantable cardioverter/defibrillator with two patch leads and a bipolar control lead.

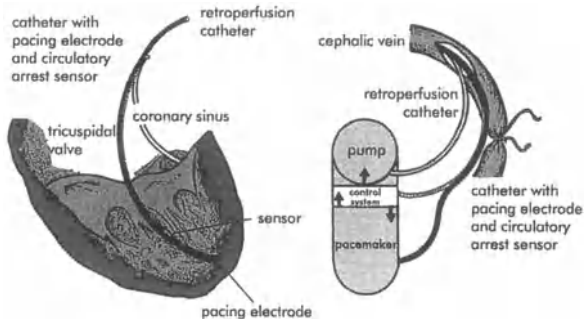

Figure 4. Automatic implantable pharmacological defibrillator (AIPhD).

coronary sinus lead and a conventional bipolar lead to trigger the R-wave. It was implanted pectorally in the patient. On 4 June 1996 another patient with symptomatic, drug-refractory atrial fibrillation received the second implantable atrial defibrillator. The next-generation atrial defibrillator (Metrix 3020) defibrillates the heart with greater energy (6 Joules) than the Metrix 3000 system (3 Joules). As of 15 January 1998, 115 atrial defibrillators have been implanted in patients around the world.

A recent innovation in the electrical management of cardiac rhythm disorders is the implantable atrioventricular defibrillator (model 7250, Medtronic Inc.) The first such device to be implanted in the world was implanted successfully, also at the University Hospital in Bonn, on 10 January 1997 in a 61-year-old female patient. The decisive advance represented by this new electrical shock system is that it combines two

Table 5. World symposia on cardiac pacing and electrophysiology

Meeting	Dates	Location	Organizer/Program Chair
1	27–28 Sept., 1963	New York, NY, USA	William WL Glenn, USA
2	17–19 Nov., 1968	New York, NY, USA	Seymour Furman, USA
3	16–18 Sept., 1970	Monte Carlo, Monaco	Bernard Dodinot, France
4	17–19 April, 1973	Groningen, The Netherlands	Hilbert J Th Thalen, Netherlands
5	14–18 March, 1976	Tokyo, Japan	Motokazu Hori, Japan
6	2–5 Oct., 1979	Montreal, Quebec, Canada	Claude Meere, Canada
7	1–5 May, 1983	Vienna, Austria	Konrad Steinbach, Austria
8	7–11 June, 1987	Jerusalem, Israel	Shlomo Feldman, Israel
9	28–31 May, 1991	Washington DC, USA	Jerry C Griffin, USA
10	22–26 Oct., 1995	Buenos Aires, Argentina	Oscar Oseroff, Argentina
11	27–30 June, 1999	Berlin, Germany	Eckhard Alt, Germany

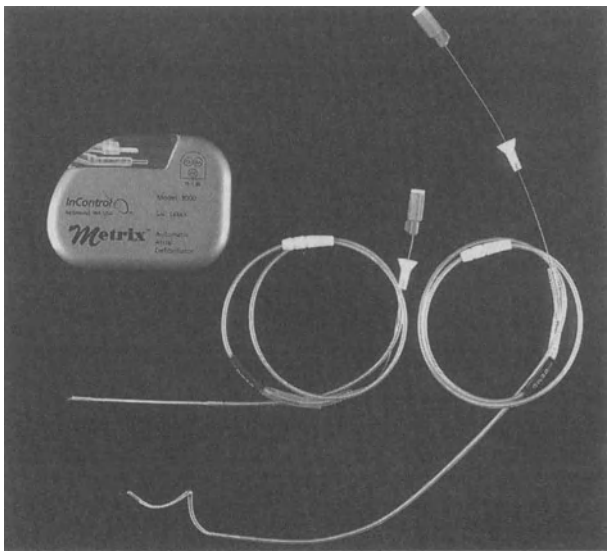

Figure 5. Implantable atrial defibrillation system Metrix 3000, consisting of a 79 g, 53 cm^3 generator and two defibrillation leads. The defibrillation lead for the right atrium (Perimeter 7205) is a screw-in lead with a 6-cm long shock coil and a total surface area of 5.2 cm^2. The defibrillation lead for the coronary sinus is a passive-fixation lead which takes on a corkscrew shape when the stylet is removed. This lead likewise has a 6-cm long shock coil and a total surface area of 4.6 cm^2.

therapeutic principles in one device, in that it automatically detects atrial and ventricular signals and delivers electrical therapy in the appropriate chamber to terminate the arrhythmia[17,18] (Fig. 6). Thus, patients with both supraventricular and ventricular tachycardias may represent potential candidates for the new arrhythmia management device (AMD).

Implantable ventricular cardioverter/defibrillators

With respect to the electrical management and prophylactic treatment of ventricular tachyarrhythmias using ICD systems, the recent MADIT study has been of particular importance.

Multicenter automatic defibrillator implantation trial (MADIT). While the implantable cardioverter/defibrillator had established a permanent place as a secondary line of defence in patients with malignant ventricular tachyarrhythmias, there were at first no proven results to recommend the use of a defibrillator as the primary prophylaxis in patients at increased

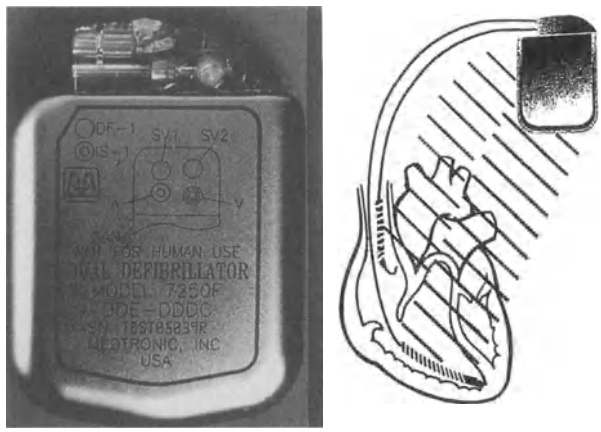

Figure 6. Multiprogrammable dual-chamber implantable defibrillator (model 7250, Arrhythmia Management Device, AMD, Medtronic Inc., Minneapolis, MN, USA). Weight 93 g, volume 55 ml. Left side: the device; right side: schematic drawing showing the pectorally implanted device connected with transvenous defibrillation leads placed in the apex of the right ventricle and in the appendage of the right atrium.

risk for sudden cardiac death. The MADIT study is the first published prophylactic evaluation in which 196 patients were randomised and treated with either a defibrillator or a conventional drug therapy regimen[79].

The study came to the conclusion that, for patients with a previous myocardial infarction and increased risk for ventricular tachyarrhythmia, there was a better survival rate with an implanted defibrillator than with conventional drug therapy (Fig. 7). Although the MADIT results showed a clear advantage for the defibrillator arm of the study, the published data should be analysed very carefully before a general recommendation for prophylactic defibrillator implantation can be made for this patient population[80].

Antiarrhythmics versus implantable defibrillators (AVID) trial Preliminary results of the AVID study were released on 14 April 1997, when the study's sponsor, the US National Heart Lung and Blood Institute, announced the trial was to be halted 18 months early because the defibrillator treatment was clearly superior; i.e. implantable cardiac defibrillators are significantly better at preventing death from ventricular arrhythmias than are antiarrhythmic drugs (amiodarone, sotalol), according to the multicentre AVID trial conducted in the USA. This trial was the first large randomised trial to show that implantable defibrillators

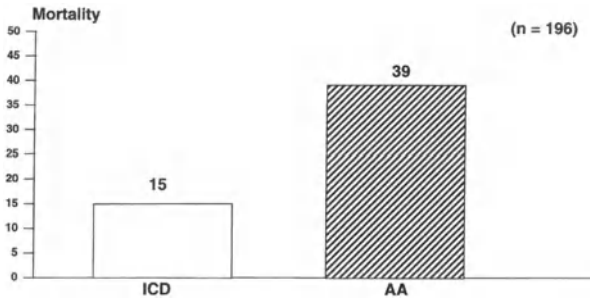

Figure 7. MADIT (Multicentre Automatic Defibrillator Implantation Trial). Defibrillation (ICD) versus conventional therapy (AA) in patients with unsustained ventricular tachycardia and left ventricular dysfunction after myocardial infarction. Mortality according to assigned treatment. The difference between the two treatment groups was significant (p = 0.009). (Moss et al[79], with permission).

actually improve survival (Table 6). The study results were formally presented at the 18th Annual Scientific Sessions of the North American Society of Pacing and Electrophysiology in New Orleans, LA, USA, 8 May 1997.

The findings of the AVID trial do not mean that drugs are no longer useful. Drugs will remain an important part of the treatment, but the principal treatment in patients who have ventricular fibrillation or ventricular tachycardias could be in the future the implantable cardioverter/defibrillator[81,82].

Summary

The history of the electrotherapy of cardiac arrhythmia is long and fascinating. In the beginning there is not simply the anatomy and physiology of the heart, but also analysis of the pulse, which indicates the activity of the heart. The Greeks called the pulse "sphygmos", and sphygmology thus deals with the theory of this natural occurrence. In Roman times Galen interpreted the various types of pulse according to the widespread presumption of the time, that each organ in each disease has its own form of pulse.

The growing clinical importance of electric cardiac stimulation has been recognised and renewed, as Zoll in 1952 described a successful resuscitation in cardiac standstill by external stimulation. The concept of a fully automatic implantable cardioverter/defibrillator system for recognition and treatment of ventricular flutter/fibrillation was first suggested in 1970. The first implantation of the device in a human being was performed in February 1980. By early 1997, 17 years after the first human implantation, more than 100 000 ICD systems had been implanted worldwide. Further developments concern atrial defibrillators, radiofrequency ablation, laser therapy and the implantable (dual)-atrioventricular defibrillator and perhaps the automatic implantable pharmacological defibrillator. The advances in the field of therapeutic application of pharmacological and electrical tools, as well as alternative methods, will continue as rapidly as before in order to give us further significant aid in taking care of the patient.

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Table 6. Antiarrhythmics Versus Implantable Defibrillators (AVID) Trial

The study	Randomised multicentre study. Compared antiarrhythmic drugs (amiodarone, sotalol) to ICD. Three-year follow-up
The patients	1016 patients (average age 65 years) with VF or VT
Preliminary results	In the defibrillator arm nearly 38% reduction in deaths after 1 year; 25% fewer deaths after 2 and 3 years

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Chapter 35

New Concepts in Electrical Defibrillation

Werner Irnich

Introduction

Since the very fist implantation of an implantable cardioverter/defibrillator (ICD) in a human in 1980, ICD technology has developed furiously, leading from large volume (160 cm^3) and heavy weight (290 g) combined with a simple pattern recognition algorithm to relatively small and light devices with highly sophisticated electronics and software capabilities. If one asks which new concepts could further improve efficacy of implantable defibrillators, the answer is surprising: we have to solve problems of which we have been aware since defibrillation investigations began:

1. What is the correct truncation of an exponential defibrillation pulse?
2. What is the influence of the time constant of the defibrillation pulse on efficacy?
3. How can the critical mass for defibrillation be reached with suitable electrodes?

The first two questions were posed decades ago in connection with electrostimulation. It was in 1902 that Georges Weiss[1] published his epoch-making paper on the possibility of making comparable appliances serving for electrical excitation, in which he discussed the Hoorweg results[2] and compared them with his own findings. In electrostimulation, regardless of whether the pulse duration or time constant of a capacitor discharge is investigated, there is always a distinct minimum in energy as a function of pulse duration or time constant.

In the following we will try to answer the questions of what the theoretical knowledge of defibrillation is and which new concepts can be derived from it.

Theory

The "fundamental law" of Weiss, completed by the terms introduced by Lapicque[3], teaches that the voltage or current which is necessary to reach stimulation threshold is a hyperbolic function characterised by the lowest threshold possible for long durations, called a "rheobase", and a type of time constant, called a "chronaxie", which determines the steepness of the ascending branch of the curve (see Fig. 1) and, still more important, where the stimulation energy has its minimum. The energy minimum is situated exactly at the chronaxie for rectangular voltages and currents; it is to the right of the chronaxie for all other pulse shapes.

We now postulate that defibrillation follows the same fundamental law as stimulation[4], which means that the defibrillating electric field produced by the electrodes is similarly governed by a hyperbola with its characteristics of rheobase and chronaxie. Is this hypothesis supported by experimental findings? The answer is clearly yes. As early as 1975 Koning and colleagues[5] reported that defibrillation thresholds for current, energy and

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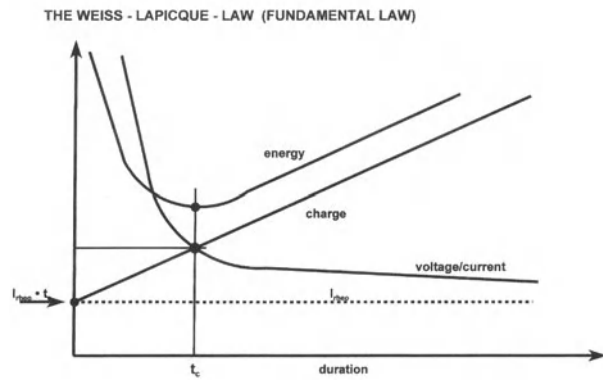

Figure 1. Threshold curves for rectangular pulses for voltage (or current), charge and energy. The energy is lowest at chronaxie.

charge with rectangular pulses applied are qualitatively identical to those for electrostimulation. Their curves were confirmed by Tacker and Geddes in 1980[6]. In 1996 Hahn and colleagues reported on trials with biphasic exponential defibrillation pulses[7]. They were surprised to discover that the energy minimum was not, as predicted, around the membrane time constant t_m but was reduced to $0.68t_m$ (see Fig. 2). Those experienced in the field of theoretical electrostimulation are familiar with the fact that the chronaxie t_c expressed in an exponential strength duration curve is:

$$t_c = t_m \cdot \ln 2 = 0.69 t_m \qquad (1)$$

Thus, Hahn and colleagues not only confirm an energy minimum, but also confirm that it is situated around the chronaxie.

The simplest way to check defibrillation trials, whether they are in accordance with the fundamental law of electrostimulation or not, is to calculate regression lines for the current-time product (which is charge) or the voltage-time product. If the correlation coefficient is higher than 0.95 one can be sure that the linear Weiss Law is fulfilled. In a recent poster presentation by Gill and colleagues[8] the rectangular current pulses of 4, 8, 16 and 32 ms proved to represent a linear defibrillation charge curve with correlation coefficients of better than 0.99.

It is interesting to note that another defibrillation hypothesis claiming constant energy for all pulse durations should have a relationship between charge Q and pulse duration t of the form:

$$Q(t) = \text{const} / \sqrt{t} \quad \text{(constant energy hypothesis[9])} \qquad (2)$$

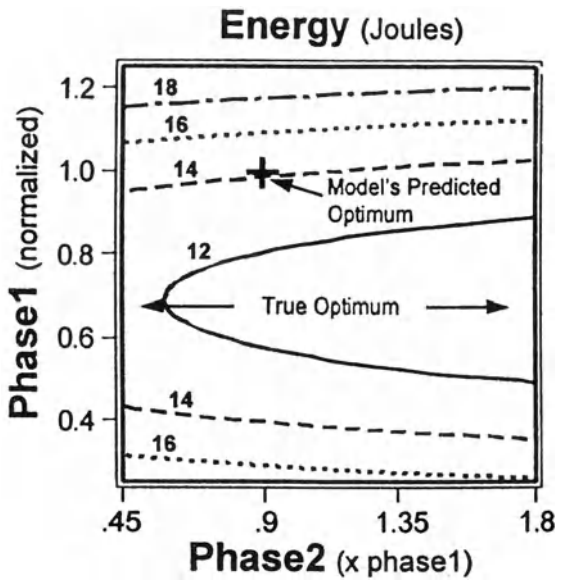

Figure 2. Investigation of Hahn and colleagues[7] proving that there is an energy minimum at about 68% of the membrane time constant, a time which is practically identical with the chronaxie.

which can easily be identified not to be in accordance with experimental results, either in stimulation or in defibrillation.

The straight line of the Weiss Law allows for another important insight into stimulation or defibrillation with untruncated exponential pulses. What is their useful duration or "dureé utile", as discussed by Lapicque[10] and Blair[11]. The charge, delivered by an exponential pulse, starts at zero and then increases to reach asymptotically its full charge given by the voltage-capacity product. As shown in Fig. 3, threshold is reached if the discharge curve just touches the Weiss straight line. Any charge beyond that touching point is without relevance, so that we can truncate the discharge process precisely at the time of contact.

For different discharge time constants, as depicted in Fig. 4, the point of contact is specific for each curve. However, for all touching discharge curves it is true that they all have the same slope at contact; namely that of the Weiss line, which is:

$$Q(t) = I_{rh} \cdot t_c (1 + t/t_c) \qquad (3)$$

$$\frac{dQ}{dt} = I_{rh}$$

where I_{rh} = rheobase current.

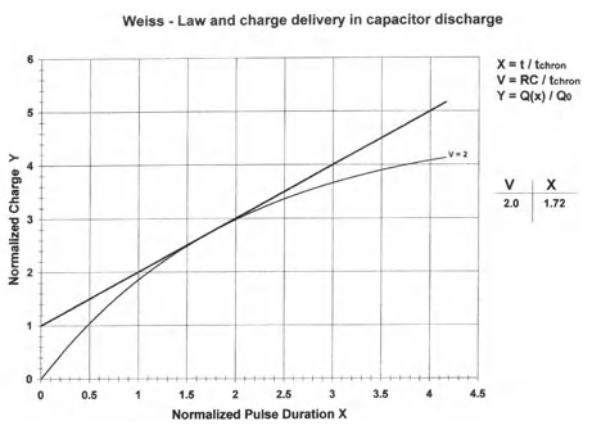

Figure 3. The useful duration (dureé utile) can be determined by using the Weiss' charge threshold line and the charge curve of a capacitor discharge. If the latter just touches the Weiss line, threshold is reached, simultaneously demonstrating that a further discharge is of no influence on stimulation. The point of contact limits the useful duration. The V–X relation is taken from ref. 9.

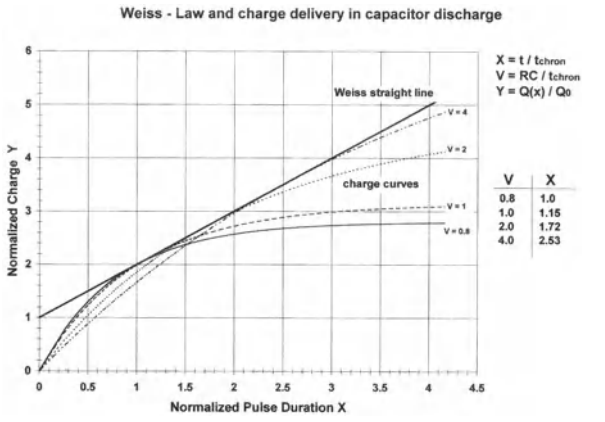

Figure 4. Weiss line and four curves with different normalised time constants: V is defined as the ratio RC over chronaxie. With a chronaxie of 2 ms assumed, V = 1 means RC = 2 ms. The V–X relations are taken from ref. 9.

We can conclude from this deliberation that a capacitor discharge pulse can be truncated if the current I has reached the rheobase value I_{rh}. Beyond this there is no stimulating or defibrillating effect, but there may be a refibrillating consequence due to "overstimulation" of the near-field region[12].

We can now generalise the Weiss-Lapicque Law in that we formulate for the electric field E:

$$\int^{t} E(T)\mathrm{d}T = E_{\mathrm{rheo}} \cdot t_c\,(1 + t/t_c) \qquad (4)$$

and

$$\frac{1}{t}\int^{t} E(T)\mathrm{d}T = \overline{E} = E_{\mathrm{rheo}}(1 + t_c / t)$$

with the boundary condition of: $E(t) = E_{\mathrm{rheo}}$ and $E(t)$ = electric field at the end of the impulse (trailing edge).

For exponentially decaying pulses the integral in equation (4) can be replaced by the term RCE_o $(1 - e^{-t/RC})$ yielding, in combination with the boundary condition:

$$E_{\mathrm{rheo}} \cdot RC \cdot (e^{t/RC} - 1) = E_{\mathrm{rhec}} \cdot t_c\,(1 + t/tc) \qquad (5)$$

Introducing the normalised variables:

$$X = t/t_c \quad \text{and} \quad V = RC/t_c \qquad (6)$$

equation (5) can be simplified to:

$$e^{X/V} - 1 = 1/V + X/V \qquad (7)$$

Equation (7) represents a transcendental function that can be solved point by point numerically in that V and X are chosen such that

$$e^{X/V} - X/V - 1/V - 1 = Z \qquad (8)$$

and Z is lower than a predetermined value (for instance 10^{-8}). The accurate derivation, approximation functions and diagrams derived from the above theory are given elsewhere[9]. It is worthwhile stating that the long-lasting discussion on the "durée utile" (useful duration) of an exponential stimulation pulse, which was opened in 1901 by Weiss and continued by Lapicque[10] and Blair[11], has found its solution using our theory. The essential message is that there is no constant ratio between the useful duration of an exponential pulse and its time constant. This is of practical relevance, as will be shown later.

Consequences from theory

If the ratio of the useful duration to time constant is dependent on time constant, the exponential term $e^{-t/RC}$ is also dependent on time constant and thus the tilt, defined as

$$\mathrm{Tilt} = 1 - e^{-t/RC}, \qquad (9)$$

must also vary. Figure 5 demonstrates our results. The tilt is shown as a function of the normalised time constant V which is the ratio RC/t_c (t_c = chronaxie).

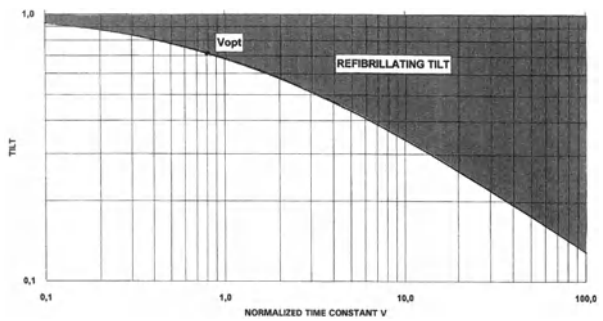

Figure 5. The tilt as a function of the normalised time constant. With a chronaxie of 2 ms assumed, $V = 1$ corresponds to $RC = 2$ ms.

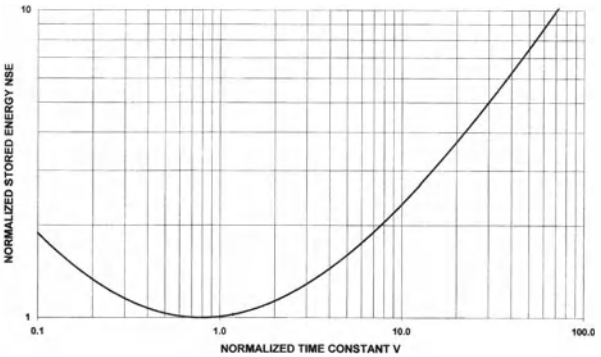

Figure 6. The normalised stored threshold energy of the output capacitor of an ICD as a function of the normalised time constant V.

With increasing time constant the tilt decreases significantly. This has consequences for the efficacy of the defibrillation process.

As demonstrated in Fig. 6 the stored energy rises remarkably right to its minimum, mainly due to the fact that the reduced tilt forces charge, and thereby energy, to remain unused on the output capacitor. The stored energy is minimum for $V = 0.8$, which means that the time constant RC is equal to 80% of the chronaxie. This raises the question of which chronaxie durations are observed in defibrillation. So far this really important parameter has not been investigated systematically. We believe, derived from several calculations, that the chronaxie for implantable ICD with transvenous leads is in the vicinity of 2 ms[4,12]. The corresponding membrane time constant, according to equation (1), is 2.9 or 3 ms, a value which is often used in literature[7,13–15]. With this parameter determined we can draw remarkable consequences from our theory:

1. Lowest stored energy is given for a chronaxie of 2 ms at a time constant of 1.6 ms, according to Fig. 6 and equation (6). With a lead impedance of approximately 50 Ω assumed the capacitor must have a capacitance of 32 μF. Such a low value was not yet installed in ICD.
2. For lowest stored energy the tilt should be 71.5%, a value which seems to be close to present-day tilts. However, for output capacitors of 120 μF or even 300 μF, the tilt must be reduced to about 51.3% or 37.8% (with 50 Ω load and 2 ms chronaxie assumed).
3. All tilts higher than indicated by our curve in Fig. 5 have no positive influence on defibrillation, but could be detrimental by reinitiating fibrillation[12]. The reason for this is mainly the strong inhomogeneity of the electrical field.
4. To indicate defibrillation threshold in energy alone is inadequate. As Fig. 6 demonstrates, one energy level (for instance 2 in Fig. 6) can be 100% above minimum threshold, but below threshold with normalised time constants of 8 and more. This corresponds to time constants of 16 ms or more with a chronaxie of 2 ms assumed. Correct description of threshold conditions should therefore indicate the time constant with which threshold measurements were made.
5. If a present-day ICD with a time constant of 7 ms possesses a maximum energy of 30 J, then this energy is less effective than administered with a time constant of 3.5 ms. Or, on the contrary, the maximum available energy can be smaller, the smaller the time constant is. The possible reduction between 7 ms and 3.5 ms is approximately one-third of the 7 ms energy, or 20 J for 3.5 ms corresponds to 30 J for 7 ms.
6. The most important parameter in optimising a defibrillation system is no doubt the chronaxie. This parameter may be dependent on the lead system, which means it cannot be determined in animal experiments with arbitrary lead systems but must be approximated individually as long as there is insufficient available knowledge about the chronaxie. It is surprising that no-one has seen the necessity to determine alternatively the stimulation thresholds with the defibrillation lead system and calculating the chronaxie from the results, as we suggested earlier[4].

Discussion

There is a strong tendency today to reduce ICD size, to simplify implantation and to reduce the discomfort of large devices for the patient. Another factor is that an active defibrillator can improve the electric field conditions in the lateral side of the left ventricle. The largest components within an ICD are the battery and the output capacitor(s). Improved efficacy, as proposed in our suggestions, could reduce battery size. On the other hand, output voltages, necessary with reduced time constants, must increase, which yields larger capacitors because of higher dielectric strength. A compromise is needed between electrophysiological and technical requirements. One statement must be made in this context: if industry propagates smaller devices with increased output capacitors, they are probably not aware of the disadvantageous consequence from the electrophysiological view: defibrillating efficacy is diminished. Clinicians should clearly see this discrepancy.

So far, one clinical group[16] has investigated the effect of varying the tilt on defibrillation threshold. They found (and this is induced in our tilt curve in Fig. 7) that a reduction in tilt can reduce the threshold to a certain degree; going further will increase it again. Output capacitance was 120 μF and mean impedance 67 Ω, yielding a time constant of 8 ms. The 50% tilt energy was 6.3 J, whereas 40% tilt was 7.8 J (23% more) and 65% tilt was 9.0 J (43% more). According to our calculations a tilt of 46.9% would be optimal.

In another article Block and colleagues[17] found that a more than 70% tilt with a system of 4 or 5 ms time constants needs more threshold energy than a 15 or 19 ms system with tilts of 46%. Their favourable results for larger time constants are mainly due to the fact that the tilt of the large time constant system was closer to our optimal tilt line and, therefore, reduced energy requirements. We believe that such comparisons with very arbitrary tilts are without any value, as such comparisons may yield results in all (desired?) directions. Our suggestion is that energy requirement for different output capacitance must be made with optimised tilts to exclude reasons other than those investigated.

Normally, supporters of the large capacitance idea imply that a reduction in output voltage, combined with the increase of the capacitance, would offer the additional advantage of reducing post-shock arrhythmias. This view is physically not justified, as it is the field strength-time product which is responsible for post-shock arrhythmias[18]. Investigating the data of Jones and Jones[18], for 4 s post-shock arrest, revealed that the field-time product, necessary for it, increases linearly with time according to equation (10):

$$\frac{E \cdot t}{V\,\mathrm{s/m}} = 4.5\,\mathrm{kV/m} \cdot 3.8\,\mathrm{ms}\,(1 + t/3.8\,\mathrm{ms}) \qquad (10)$$

where E = electric field strength for 4 s post-shock arrest; and, t = duration of the electric field.

If we form a safety factor, corresponding to a proposal of Jones and Jones[19], between equation (10) and the field-time product for defibrillation (see equation (11) derived from Table 1):

$$\frac{E_{\mathrm{def}} \cdot t}{\mathrm{V\,s/m}} = 0.25\,\mathrm{kV/m} \cdot 2\,\mathrm{ms}\,(1 + t/2\,\mathrm{ms}) \qquad (11)$$

where: E_{def} = electric field strength for defibrillation, 0.25 kV/m = rheobase field strength, 2 ms = chronaxie, we obtain as ratio:

$$SF = 34.2 \cdot \frac{1 + t/3.8\,\mathrm{ms}}{1 + t/2\,\mathrm{ms}} \qquad (12)$$

As the chronaxie for defibrillation (2 ms in the demoniator) is probably smaller than the corresponding time value in the nominator (3.8 ms), the safety factor decreases with increasing pulse duration. We can generalise the problem in calculating:

$$SF = \frac{E_{\mathrm{shock}}(t + t_{\mathrm{shock}})}{E_{\mathrm{defi}}(t + t_{\mathrm{chron}})} \qquad (13)$$

and:

$$\frac{\mathrm{d}SF}{\mathrm{d}t} = \frac{E_{\mathrm{shock}}}{E_{\mathrm{defi}}} \cdot \frac{(t_{\mathrm{chron}} - t_{\mathrm{shock}})}{(t + t_{\mathrm{chron}})^2} \qquad (14)$$

Table 1. A 4 s post-shock arrest for square-wave rectangular pulses in a myocardial cell culture, derived from Figure 1 in ref. 18.

t (ms)	E (kV/m)	$E \cdot t$/(Vs/m)
0.5	14	7.0
1	12.3	12.3
5	9	45
10	7.4	74
20	6	120
40	4.7	186

Et/Vs/m = 4.5 kV/m · 3.8 ms (1 + t/3.8 ms) (r = 0.985)

The safety factor *SF* with changing pulse duration is decreasing if the shock time t_{shock} is greater than the chronaxie, as was extracted from the Jones data[18]. Increasing voltage with simultaneous decrease in pulse duration is not, as usually stated, maleficent, but can even be beneficient. Therefore, a long-lasting defibrillation pulse can have higher post-shock arrhythmias than a short-lasting pulse with higher amplitude. This is, by the way, another consideration to reduce pulse duration to its absolute necessary value according to Fig. 5 or 7.

Which measures can be taken according to our suggestions? The first and simplest would be to follow the guidelines of optimal tilts[12]. Three values must be known or estimated: output impedance, output capacitance and chronaxie. A fourth parameter must be programmable with sufficient accuracy: either tilt or pulse duration. The necessary programmation, then, is a simple application of what we suggested earlier[12]. In any case we deem it an absolute necessity to have tilt or pulse duration programmable. The constant-tilt version of ICD has no electrophysiological justification.

Final remarks

It seems that there is a gap between the knowledge of more theoretically oriented scientists and practically working clinicians. In theory many thoughts are thinkable which, nevertheless, may never find practical application. On the other hand, as defibrillation pulses are physically characterised by amplitude, shape, duration, direction (polarity), and variation of direction (monophasic, biphasic, ambiphasic), it appears that practical researchers are faced by the "trial-and-error" method with a hopeless search for the needle in the haystack. We believe that any theory serving as a guideline is of inestimable value for practical procedures, especially in a field such as defibrillation, where experiments are difficult, time-consuming, and occasionally non-reproducible. Theoretical considerations will further help to create a picture out of the many mosaic pieces found experimentally and in practice, to date.

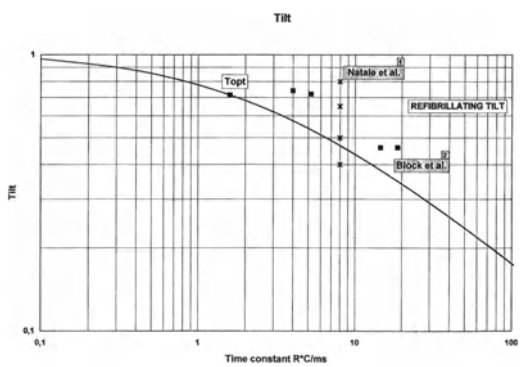

Figure 7. The tilt as a function of the time constant *RC* as derived from Fig. 5 with a chronaxie of 2 ms assumed. The data of Natale et al[16] and Block et al[17] are entered into the figure, demonstrating the correctness of our theory.

There is a tendency in defibrillator technology to reduce the size by all means possible. One of these means is augmentation of output capacitance, which would reduce the peak voltage necessary, thereby reducing capacitor size. For all those people trusting in the Nernst law of constant energy this poses no problems at all. However, as defibrillation is governed by rules of electrophysiology, to which other rules (for instance that of cell dysfunction due to overstimulation[12]) must be added, this tendency should be looked at critically. Especially in patients prone to arrhythmias, such smaller but less effective devices may pose risks. Animal experiments, with mostly healthy animal hearts, are not always good models for investigating new technologies such as augmentation of output capacitance.

We said earlier that there is a gap between practical handling and theoretical knowledge of defibrillation. It is possible that mathematical equations form insurmountable hurdles to clinicians. On the other hand, is it correct to deny theories and to proceed as if they would not exist if one is incapable of understanding the mathematics involved in the theories? Collaboration between clinicians and theorists is needed for the benefit of the patient. This elaboration is thought to help bridge the existing gap.

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Chapter 36

Role of Implantable Atrial Defibrillators in the Treatment of Atrial Fibrillation

Luc J. Jordaens

Introduction

Atrial fibrillation (AF) is an important epidemiological problem, and is a major supraventricular arrhythmia[1,2]. Its consequences are mainly the development of heart failure, and an established relationship with stroke. Apart from preventing these complications, treatment is aimed at slowing ventricular rate, converting the arrhythmia to sinus rhythm, and to maintaining sinus rhythm after conversion. Conversion can be performed with drugs or by electrical means. Drugs are moderately effective, except when AF is of recent onset[3,4]. When AF is sustained, or has existing for a longer period of time, pharmacological conversion becomes more difficult. Some hope exists that newer class III drugs will become effective for this indication, but it has to be accepted that, with the proarrhythmia as observed in recent trials, conversion remains an in-hospital procedure[5]. Furthermore, dofetilide terminated AF only 31% of the patients, comparable to the efficacy reported for ibutilide[5,6]. Torsades de pointes were the main adverse events, but regular wide QRS tachycardia, probably with aberrancy, was also reported[5–7].

In contrast, direct current transthoracic electrical shocks are highly effective in restoring sinus rhythm but, in general, it can be anticipated that recurrences appear in at least 60% of patients over a period of 2 years[8,9]. A large subgroup shows a recurrence within the first 24 h[8]. This often makes repeated cardioversion necessary. Until now no randomised trials have shown that cardioversion is superior with respect to survival, in comparison to controlling the ventricular rate. However, evidence was presented that patients in whom sinus rhythm is maintained over 2 years do not deteriorate with respect to cardiac function, while those who relapse face a diminished exercise performance[10]. Furthermore, a computer model, using all randomised studies in this field, showed that the only way of keeping patients in good quality of life in sinus rhythm, is to cardiovert, and to prescribe antiarrhythmic drugs[11]. Preventing stroke is another important issue. Anticoagulating drugs are the best choice in this respect, but the efficacy of the policy of repeated cardioversion seemed comparable in this computer model. However, antiarrhythmic drugs are sometimes feared, because of their potential of provoking or aggravating ventricular arrhythmias, or of facilitating atrioventricular conduction. Quinidine has been associated with an excess mortality, but is still the most widely prescribed antiarrhythmic drug after cardioversion[12].

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Nevertheless, it is clear that we need antiarrhythmic drugs to improve the outcome of electrical cardioversion.

Therefore, it can be understood that non-pharmacological means are used, and intensively investigated. One of these tools is an implantable cardioverter (or "defibrillator") designed specifically for the fibrillating atria. Such a device is currently undergoing clinical investigation, after extensive animal and human investigations with a transvenous, external set-up[13]. This chapter is an attempt to outline the potential place for an atrial defibrillator, among different approaches.

Invasive techniques for the management of atrial fibrillation, and their limitations

Preventive pacing (standard methods)

Whether atrial pacing as it is now used can prevent atrial arrhythmias in patients with paroxysmal atrial fibrillation is not known. However, in patients with sinus node disease, atrial (AAI) or dual-chamber (DDD) pacing clearly reduce the incidence of AF over time when compared to ventricular (VVI) pacing[14]. This might be related to the unwanted effects of VVI, rather than to the effects of atrial stimulation. Furthermore, AF is not equal to sinus node disease, which is associated with bradycardia, and pauses. These pauses in a diseased atrium can be prevented by pacing. This avoids reentry, reduces heterogeneity of refractoriness and makes intra-atrial conduction delay less likely. Whether pacing prevents AF in a similar way in real paroxysmal AF is now addressed in several prospective studies[15]. Comparisons between DDD and DDDR (dual-chamber rate responsive) pacing showed a reduction in paroxysms in patients with chronotropic incompetence, and underlying brady-tachysyndrome[16].

Preventive pacing (investigational methods)

Intelligent pacing algorithms were developed in order to prevent the onset of arrhythmias, both at the ventricular and at the atrial level[17]. One option is to prevent post-extrasystolic pauses by a single extrastimulus after atrial premature beats (APB). Modulation of heart rate by atrial pacing has recently been investigated, and was effective in some, but not in all patients at preventing AF episodes[18]. After termination of (sinus or supraventricular) tachycardia, "flywheel" or rate smoothing algorithms can play a role in preventing unwanted bradycardia. It is general clinical experience that many patients develop AF after, rather than during, exercise.

"Multi-site" pacing (with pacing catheters in the right atrium and the coronary sinus, triggering pacing in the other atrium when atrial activity is sensed) to resynchronise the atria was very effective in patients with intra-atrial conduction delay and forms of atrial flutter[19]. This method is used to equalise the refractory periods in the atrium, and has a place in the concept of future sophisticated devices aimed to treat atrial fibrillation. Recurrences were also prevented in 80% of 15 patients over a follow-up of 13 months, by another method, using real dual-site pacing in the high right atrium and at the os of the coronary sinus[20]. In this study, pacing was at a high rate to suppress spontaneous activity. This can also be achieved with simple drugs (e.g. β-blockers) in combination with pacing, or with some forms of rate-responsive pacing to ensure that the spontaneous rate is lower than the paced rate, or to suppress APB[21]. It was observed that recurrences of AF that have to be shocked were mainly observed in the perioperative period and not during later months, suggesting that reverse electrical remodelling takes place. However, electrical cardioversion was necessary in 30% of the patients[22]. Limitations for multi-site pacing remain the difficulties with actually available electrodes for the coronary sinus. The complexity of the connecting system (i.e. the hardware, and the software designed to integrate all information and deliver the appropriate response) makes the daily practice of this kind of pacing, and its integration in an atrial defibrilator, a futuristic perspective.

Ablation

His bundle ablation should be considered as a technique of last resort, in spite of the fact that patients often improve with respect to symptoms[23–25]. Pacemaker dependency is not attractive for younger persons, and the risk for embolism is not addressed by such intervention. Furthermore, sudden death occurred not only after DC shock ablation, but also when RF energy was used[26]. However, symptoms usually improve, and some improvement of ventricular function is often observed[23,24]. Modulation of AV conduction (to control ventricular rate, without complete heart block) is possible, but a subset of patients will require a pacemaker. Furthermore, it can be anticipated that irregularity as such is also a source of palpitations[27]. Surgical ablation (the Maze operation)

was designed to prevent reentry through surgical incisions in both atria, creating compartments, and limiting conduction of the wavelets. The technique is possible only in centres with a well-developed surgical programme, and procedures (at least in the beginning) resulted in a considerable proportion of patients having a pacemaker as well[28]. Catheter ablation is now investigated in a few centres, which were able to show an improvement in clinical status after applying limited linear lesions in the atria. Only focal sources of AF have been successfully targeted with catheter ablation[29]. Also promising is the idea of targeting APBs as they trigger AF. Thromboembolism remains a matter of concern in cases of left-sided ablation, and also for surgical interventions. Nevertheless, it can be hoped that such interventions, even with their limitations, can become a part of the strategy to avoid frequent, and very symptomatic, episodes.

What can be expected from an atrial defibrillator?

Crucial in the design of such a device is the degree with which proarrhythmia is avoided (i.e. provocation of ventricular arrhythmias by a shock). The initial phase of the clinical investigation focused on this feature. At this moment sufficient experience with temporary shock electrodes has been collected to know that biphasic shocks, which are R-wave synchronised, and delivered after long RR intervals, are safe with respect to proarrhythmia[30,31]. As the concept proves to be safe, as expected from these preliminary experiments, it is evident that we now have a tool for cardioversion that can be used with more confidence in an ambulatory environment than effective, but potentially dangerous, drugs (Table 1). From the point of view of efficacy, much has to be learned. Shocks are effective in more than 80% of patients when biphasic waveforms with 3 ms for each phase are used[32]. The configuration which uses leads in the right atrium and in the coronary sinus has been used for the design of the Metrix 3000 (InControl, Redmond, USA). A more recent generation uses biphasic shocks with 6 ms duration for both phases (Metrix 3020). This seems to be more effective than the first generation[33]. The shock wave morphology, the endocavitary lead position, the geometry of the atria, the presence of cardiac disease, the duration of the fibrillation, the aspect of the fibrillation (flutter, "fibrilloflutter", coarse waves, some preserved regularity, etc.) will be very important to determine the outcome with respect to conversion[33]. This outcome does not equal persistence of sinus rhythm after the direct effect of the shock, and this aspect needs to be addressed in future research. Patient tolerance, which is another question, is acceptable[30]. From recent research it seems that most patients accept a single shock, but are reluctant to have several consecutive shocks[33].

Possible indications

Internal cardioversion with an external device

It is worthwhile to consider shocks with atrial electrodes when a patient prefers a procedure without anaesthesia rather than a conventional cardioversion. The risks of the catheterisation (haematoma, pericardiac effusion, etc), however, have to be weighed against the risks of the anaesthesia (hypotension, etc.)[34]. The fact that patients are anticoagulated should be taken into account when considering catheterisation. Another possibility in considering cardioversion with shock electrodes is when atrial fibrillation occurs during an electrophysiological procedure, e.g. when an attempt to terminate atrial flutter produces atrial fibrillation. When it is impossible to catheterise the coronary sinus the left pulmonary artery is an acceptable alternative site[35]. Patients who typically pose problems during external cardioversion include obese persons, and those with obstructive

Table 1. Arrhythmias during cardioversion attempts

Intervention	Incidence	Arrhythmia	Reference
Digoxin (intravenously)	2/19 (10%)	Bradycardia	3
Flecainide	1/34 (3%)	Wenckebach block	4
Dofetilide	2/62 (3.2%)	Torsades de pointes	5
Ibutilide	5/81 (6.2%)	Runs	7
Metrix	0/131 (0%)	–	45

pulmonary disease. It could be that these are also preferential candidates for an implanted device.

Cardioversion with implantable devices

"Stand-alone" atrial cardioverters or "atrioverters". Stand-alone devices could become of interest for patients with several forms of atrial fibrillation, and without a background for ventricular arrhythmias. This population, in which the main aetiology will probably be idiopathic, is huge[1]. However, more important are the characteristics of the AF that has to be treated. In our limited experience until now, the best indication seems to be that form of AF that becomes "persistent", i.e. that does not convert spontaneously even with drug therapy[36]. Electrical conversion prevents chronicity in this form, and avoids functional deterioration[10]. A second group of indications (when we consider the time course of the "disease") is so-called "paroxysmal" atrial fibrillation. With respect to duration, paroxysms can be self-terminating in a reasonable time (within minutes or hours), but they can also last for several days. At what point a device should intervene is not clear. The ideal profile in relation to the recurrence rate is another problem. As shocks are not painless, attacks should not be too frequent. An important point is, of course, that longer-lasting attacks can be associated with emboli, and that when paroxysmal fibrillation becomes chronic, the incidence of emboli increases[37]. Therefore, the hypothetical advantage of an atrioverter is that a prompt cardioversion can be performed, with less "stunning" of the atria, which is probably related to the duration of AF before the conversion. Hence, the risk for embolism should decrease, as stroke typically occurs in the hours after cardioversion. Whether oral anticoagulation is therefore no longer required, should be addressed in prospective trials.

It was demonstrated that many patients with a pacemaker have asymptomatic episodes of AF[38]. Atrial cardioversion could therefore become important for patients with a DDD(R) pacemaker. The most common response from current pacemakers when AF occurs is mode switching[39]. This is acceptable from a symptomatic point of view, but not from a haemodynamic standpoint. Therefore, if future AAI or DDD pacemakers have a defibrillating back-up (limited to the atrium), this will have additional value on a long-term basis. Other considerations (apart from the arrhythmia type and the underlying disease) are symptoms during AF. If a patient develops pulmonary oedema when AF becomes present, this can be used as another argument to become "aggressive", and to consider a defibrillator. Syncope is probably another indicator of severity, but is not so common in the population with AF as we have studied it. It will not be prevented by a device that has to wake up to confirm the presence of AF with a certain delay. Angina in the setting of coronary artery disease is another issue; the safety of a cardioverter needs to be addressed in a study. Previous therapy is also important. When one fears or experiences proarrhythmia, or side-effects from drugs, the decision to use a defibrillator is probably easier for a physician, and for the patient.

Dual-chamber cardioverters. One could consider implantation of a double-level defibrillator for patients with an indication for a ventricular implantable cardioverter/defibrillator (ICD) alone, or with AF alone. The combination of atrial and ventricular arrhythmias also exists, and is a perfect indication.

One might expect that atrial defibrillation will become an important adjuvant for the ventricular defibrillator. AF develops in more than 3% of all individuals above 74 years of age[1]. In patients with heart disease, AF is more frequently observed. In 33% of our last 100 patients before implantation of an ICD we observed different kinds of atrial arrhythmias, but mainly AF. After implantation at least 7% suffered from inappropriate shocks because of interfering AF episodes, but also because of atrial flutter[40]. Options to managing these problems can vary from reprogramming the detection rate, to more sophisticated programmable features such as QRS width criteria. However, the only studied algorithm is rate stability, which should prevent spurious shocks in a large majority of patients[41]. Newer configurations which use atrial leads are promising, as they recognise AF in a better way[42]. Some ICDs inhibit discharges and antitachycardia pacing if the atrial rhythm is fast and the ventricular rate is unstable[43]. These "early"-generation devices will probably develop into reliable double-chamber systems, which can pace in the atrium and will include sophisticated pacing algorithms for the prevention of events[44]. The hybrid configuration that has to shock both chambers when needed will be complex. The idea of downloading specific software, using universal hardware, is very attractive, and will be a way to cope with future developments, and hopefully with all the requirements we have to deal with, for the

treatment of the arrhythmias of our patients. One of the problems is that "simple" solutions will probably not always include a shock lead in the coronary sinus[44]. This implies that shocks will require more energy to convert the atria, than with a specific designed electrode configuration.

When no indication for a ventricular defibrillator exists, some might argue it best to implant a dual-chamber device to treat ventricular arrhythmias occurring as a complication after atrial defibrillation. As pointed out earlier, the presence of a background for ventricular arrhythmias is sufficient to provide a back-up at the ventricular level. However, it has not been demonstrated that this is necessary when no history of previous arrhythmias is present. Furthermore, the preliminary data with the Metrix are reassuring, and the therapy as it was used in this study seems to be safer than quinidine therapy[45].

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Chapter 37

Management of Atrial Fibrillation by Implantable Devices: from Electrophysiological Studies to Clinical Application

Sanjeev Saksena and Philippe Delfaut

Introduction

The management of atrial fibrillation (AF) on a long-term basis with implantable device therapy is gradually becoming a clinical reality. In this development process there has been increasingly effective use of information derived from a variety of physical, technical, basic and clinical science sources[1–4]. It is the purpose of this brief commentary to highlight some recent contributions from the clinical electrophysiology laboratory that are relevant to the further development of device therapy both as a stand-alone therapy and as a hybrid therapy with other pharmacological and non-pharmacological approaches. We will also briefly review the clinical experience with pilot clinical studies of device therapy to date.

Clinical electrophysiology of atrial fibrillation

The clinical electrophysiology of AF has been problematic to study in recent years due to difficulties in defining an appropriate laboratory model and methods for its evaluation and study. Electrophysiological abnormalities such as atrial conduction delays, seen globally and in specific left atrial locations, as well as an abbreviation of atrial effective refractory period, have been noted in patients with this arrhythmia[1–3]. Recently we have developed a clinical model of induced AF in patients with spontaneous atrial flutter and fibrillation using a programmed atrial stimulation protocol with good sensitivity and acceptable specificity for clinical use[4]. The clinical protocol utilises two or more right atrial sites and up to three atrial extrastimuli. We have performed catheter endocardial mapping of AF at its onset, during its sustenance and at its termination[5,6]. Repeated initiation of AF has been attempted, to establish reproducibility and stability of the atrial activation patterns.

Our observations in these studies have provided important new insights. It is now clear that induced AF is generally associated with discrete, often regular, atrial electrograms[5]. This is seen at multiple right and left atrial regions during simultaneous catheter endocardial mapping, and assumes a surface ECG morphology of coarse AF. Fine AF on the surface ECG is usually associated with discrete atrial electrograms, but one or more atrial regions show chaotic or fragmented

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atrial electrogram activity with few if any isoelectric periods[5,6].

Initiation of AF has also not been widely studied in the electrophysiology laboratory. Remarkably, a single high right atrial extrastimulus encounters maximal conduction delay at the coronary sinus ostium, His bundle region or interatrial septum in this population. However, at the time of AF initiation by high right atrial premature beats, the earliest site of repetitive atrial activity is typically seen at the crista terminalis or interatrial septum or His bundle region for the first AF cycle. This cycle shows an inverse relationship with progressive prolongation of the return cycle length with increasing prematurity of the initiating extrastimulus. Premature beats from other right atrial sites have also shown a predilection for septal initiation with occasional patients demonstrating this in the coronary sinus ostial region. Finally, the atrial activation pattern remains stable in approximately 70–90% of patients and is reproducible during repeated reinduction of AF. These findings strongly support a reentrant rather than triggered mechanism of the induced arrhythmia. Preceding the termination of this arrhythmia we note a progressive organisation and disappearance of fragmented or chaotic atrial activity with reappearance of coarse AF on surface ECG[7]. This is then followed by progressive slowing of electrogram cycle length at one and then all atrial regions, followed by arrhythmia termination.

The evolving role of the induced AF model

The usefulness of the induced AF model lies in evaluating the efficacy of interventions. Induced AF has been used to evaluate antegrade conduction in bypass tracts, atrial defibrillation thresholds, drug therapy and, most recently, pacing therapies. The shortest RR interval during induced AF in patients with antegradely conducting bypass tracts has been long demonstrated to reflect the antegrade effective refractory period of the bypass tract and parallel spontaneous rates during AF. Serial drug testing was first performed in AF with the Wolff-Parkinson-White syndrome. Bauernfeind et al demonstrated that antiarrhythmic agents that suppressed AF induction at electrophysiological study had excellent efficacy during follow-up in prevention of spontaneous AF[8]. We have recently applied this approach to serial drug testing in AF with normal AV conduction[9].

Prevention of AF

More recently we have applied this model to test the ability of pacing therapy to suppress inducible AF and then predict the occurrence of spontaneous AF during single and multisite atrial pacing[10]. We recently demonstrated that reproducibly inducible AF or atrial flutter elicited using the extrastimulus technique can no longer be elicited after dual-site right atrial pacing at the high right atrium and coronary sinus ostium in 56% of patients. Figure 1 shows the recurrence rates of AF during single- and dual-site right atrial pacing in patients who had programmed atrial stimulation with or without inducible AF during subsequent high right atrial pacing. Patients without inducible AF during programmed stimulation had no recurrent AF. Patients with inducible AF who became non-inducible during dual-site pacing had the same high frequency of AF as those who had persistently inducible AF. Figure 2 shows the recurrence rates of AF in patients who had similar electrophysiological testing during subsequent dual-site right atrial pacing. Patients who had no inducible AF also had a good outcome with no recurrent AF in dual-site pacing. Patients who were inducible at baseline but rendered non-inducible by dual-site pacing had a more

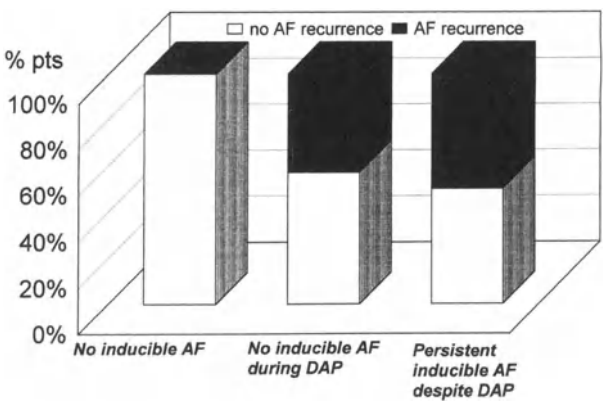

Figure 1. Correlation of the outcome of programmed atrial stimulation in patients with spontaneous AF or atrial flutter with subsequent AF recurrence during chronic single-site RA pacing from the high right atrium or coronary sinus ostium. AF recurrences were absent in patients without inducible AF with the stimulation protocol. Patients who had AF induced were at high risk of AF recurrence during single-site pacing regardless of the ability of dual-site atrial pacing to suppress the arrhythmia acutely in the laboratory. AF = atrial fibrillation; DAP = dual-site atrial pacing; pts = patients; RA = right atrial.

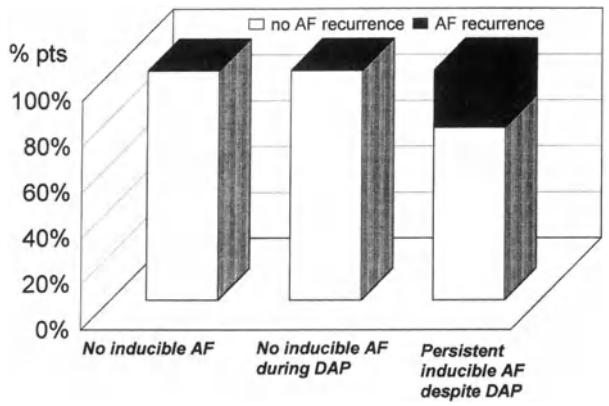

Figure 2. Correlation of the outcome of programmed atrial stimulation in patients with spontaneous AF or atrial flutter with subsequent AF recurrence during chronic dual-site RA pacing from the high right atrium and coronary sinus ostium. Recurrent AF was not observed either in patients without inducible AF or in patients with inducible AF acutely suppressed by dual-site packing. It was observed only in a modest percentage of patients with persistently inducible AF despite dual-site right atrial pacing. Abbreviations as in Fig. 1.

favourable outcome with dual-site rather than single-site pacing. Persistently inducible AF in patients predicted recurrences in this analysis. There are some limitations to these pilot data. Dual-site preventative pacing was not tested in several of the patients in the inducible group, thus overestimating the incidence of inducible patients. Secondly, drug therapy was not constant during acute testing and chronic follow-up. Nevertheless, these data open up the possible use of electrophysiological testing for assessing pacing therapies acutely and chronically.

Termination of AF

Defibrillation thresholds have been measured during induced AF. Recently, information on spontaneous AF termination by shocks programmed based on defibrillation thresholds determined with induced AF has become available[11]. In the clinical trial for the Metrix system most patients could be cardioverted by the first programmed shock, but a significant proportion required a second shock[12]. We have recently evaluated the use of high-frequency pacing in AF and atrial flutter termination[13]. In a prospective randomised study of induced AF and atypical atrial flutter, which is conventionally unresponsive to rapid atrial pacing, four high-frequency atrial pacing modes were examined. High-frequency pacing was effective in termination of 60% of episodes classified as atypical atrial flutter, but was uniformly ineffective in AF. This mode has been now included in an implantable device, and was successful in arrhythmia termination in the first implanted patient programmed to this therapy[14].

Challenges in the induced AF model

It is increasingly clear that AF is a heterogenous group of arrhythmias with varying levels of organisation. The ability of the laboratory model to mimic these different arrhythmias and in varying substrates is yet to be established. Further studies with different triggers such as left atrial extrastimuli, autonomic or adrenergic stimulation and rigid drug testing protocols are clearly needed.

Implantable atrial device therapy

We are now entering the era of implantable atrial devices for AF management. Two different approaches have been undertaken: the first, stand-alone defibrillators, requires patients with relatively low defibrillation energies and very infrequent AF who operate the implanted device under supervision. Initial experience suggests that this approach may be feasible for highly selected patients. Proarrhythmia is rare but may not be non-existent. In contrast to drug proarrhythmia which may be inapparent at onset of therapy, device proarrhythmia is concordant with shock delivery and is likely to be less well accepted. Shocks remain painful and undesirable therapy. Painless therapy in the form of high-frequency pacing may be of value in patients with atypical atrial flutter, but of limited value in AF in its present form.

In most patients with AF, high-density arrhythmia is prevalent and negates the use of such a stand-alone defibrillation device. Prevention of the high-density arrhythmia is the preferred route of management. We have recently been evaluating a preventative approach using multi-site pacing[15]. Using a continuous overdrive pacing algorithm in conjunction with previously ineffective drugs, we have demonstrated effective maintenance of rhythm control in up to 90% of patients with drug-refractory AF[16]. These patients had an average of one AF episode per week, 80% of whom had required atrial defibrillation in the year preceding pacemaker implant[15,17]. Antiarrhythmic drug therapy was needed in combination with pacing in 73%, but these drugs had

been previously ineffective in AF prevention in the same patients. They were, however, important in achieving a high level of continuous pacing, with a preferred target of > 90% paced rhythm[15]. During a follow-up period ranging from 12 to 40 months, 73% of patients became totally free of recurrent AF, with an additional 13% showing a marked decrease in AF events, most of which were spontaneously terminating. This resulted in a marked and progressive decrease in the need for atrial defibrillation shock therapy which was estimated at 3% after 1 year of follow-up. Only 10% of patients progressed to chronic AF. A hybrid therapy approach has been used in patients with incessant (defined as one or more daily episodes) AF. In our initial experience with 13 patients, limited right atrial ablation was combined with drug and pacing therapy[18]. Twelve of 13 patients could have their incessant AF suppressed by this approach.

Implantable device therapy which may be relevant to the majority of AF patients will require a device with a variety of antiarrhythmic capabilities; these are shown in Table 1. These devices will be complex and require significant new scientific understanding of the arrhythmias classified as AF and their intervention with electrical therapies.

Conclusions

The clinical electrophysiology laboratory provides important models for study of electrical therapies in AF. Further effort in defining clinical relevant models of AF and their interaction with interventional electrical therapies is needed for progress in the field.

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Table 1. Preferred features of a pacemaker-atrial defibrillator

	AF prevention	AF detection	AF therapy		
			First treatment: rapid atrial pacing	Second treatment: HFP	Third treatment: defibrillation
Method	Dual site right atrial pacing	Single site bipolar atrial sensing	Single or dual site pacing	High frequency single or dual site pacing	Low energy shock
Configuration	HRA + CSos	HRA	HRA/CS	HRA/CS	Programmable number of pathways: Dual leads: SVC/RV, RA/can, RV/can, RA/CS Triple leads: SVC + can/RV or SVC + CS/can or RV to can/SVC
Polarity	Bipolar (btw 2 leads)	Bipolar (tip to ring 1 lead)	Uni/bipolar	Uni/bipolar	Biphasic shock
Algorithm	Continuous overdrive (80–90 bpm) + rate response	> 170–180 bpm	Adaptable pacing rate 200–300 bpm	Sequences of bursts at increasing rate	Shocks alone or high energy pacing + shock × 2–3
Initial programming	2–3 pacing threshold	< AF EGM amplitude	High energy output	High energy output	1.5–2 × DFT
Memory	Percentage of atrial pacing. Holter functions, rate histograms	EGM of all high rate events	EGM, markers, time of onset and duration of all treated sustained high rate events + preceding and succeeding rhythms		

System components: 1 generator active can; 2 bipolar or tripolar atrial leads.
at HRA: bipolar pacing and sensing ± SVC defibrillation
at CS: CSos pacing + CS defibrillation
Tripolar ventricular lead
at RVA: bipolar pacing + RV defibrillation
btw: between; can: left prepectoral shell electrode; EGM: atrial electrogram; HRA: high right atrium, CSos: coronary sinus ostium, CS: coronary sinus, SVC: superior vena cava, RV: right ventricle, RVA: right ventricular apex, RA: right atrium, EGM: electrogram, DFT: defibrillation threshold

Chapter 38

Design Concepts for Implantable Atrial Defibrillators

Carolyn K. Wiemers and Gregory M. Ayers

Introduction

Atrial fibrillation is an arrhythmia characterised by disorganised atrial depolarisations resulting in uncoordinated atrial activity, a reduction in cardiac output, and a number of other significant health risks. There are three possible therapeutic goals to consider for patients with atrial fibrillation: control of ventricular rate, maintenance of sinus rhythm, and prevention of thromboembolism[1]. Present treatments for atrial fibrillation include drug therapy, ablation and pacing, and external cardioversion. All of these treatments vary in their method, invasiveness, and therapeutic goal. Recent studies have shown that a new technique of low-energy internal cardioversion with temporary leads is a feasible and effective method for restoring sinus rhythm[2–4]. Given the recurrent nature of atrial fibrillation, the promising results with low-energy internal cardioversion, and the present state of implantable device technology and application, the possibility has been raised for the development of an implantable atrial defibrillator. Levy and Camm discussed the basic requirements for an implantable atrial defibrillator in an editorial examining the feasibility of such a device[5]. The authors concluded that safety, efficacy, and tolerability were the main concerns in developing a device to terminate atrial fibrillation. Design concepts should, therefore, incorporate these concerns. This chapter will specifically address these criteria in the context of the present status of basic research and clinical experience.

Background

Atrial fibrillation is an arrhythmia characterised by disorganised atrial depolarisations resulting in uncoordinated atrial activity, a reduction in cardiac output, and a number of other significant health risks. Atrial fibrillation also accounts for more hospital admissions than any other cardiac disorder, and thus is very costly[6]. According to the Framingham Study on the development of cardiovascular disease, the prevalence of atrial fibrillation in the general population is approximately 2%, with incidence increasing with advancing age. In populations over age 60 the occurrence of atrial fibrillation reaches 4%[7]. The presence of atrial fibrillation can be unassociated with other cardiovascular conditions ("lone" atrial fibrillation), but is often concomitant with other underlying heart disease, such as congestive heart failure, rheumatic heart disease, hypertensive cardiovascular disease, and myocardial infarction[8]. The increased risk of thromboembolism, particularly stroke, is also a highly problematic complication of atrial fibrillation[8].

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There are three possible therapeutic goals to consider for patients with atrial fibrillation: control of ventricular rate, maintenance of sinus rhythm, and prevention of thromboembolism[1]. Present treatments for atrial fibrillation include drug therapy, ablation and pacing, surgery, and external cardioversion. All of these treatments vary in their method, invasiveness, and therapeutic goal.

Pharmacological treatment of atrial fibrillation is historically the most popular therapeutic modality; it can potentially address all three therapeutic goals, but can do so only with a combination of drugs. However, multiple drug interactions, contraindications, and treatment of other underlying heart disease can limit the extent of therapy. In addition, antiarrhythmics may have adverse side-effects, including an increased risk of cardiac mortality, from 2.5% per year in untreated patients to 5%, mainly due to an increased risk of ventricular proarrhythmia[9].

Ablation of the atrioventricular conduction system accompanied by pacemaker implantation allows for control of ventricular rate, but may not diminish a patient's stroke risk, or completely eliminate the compromised haemodynamic status. Other surgical treatments, such as the "maze" and "corridor" procedures, are highly invasive and involve incisions to the atria to eliminate reentrant pathways while maintaining atrial activity[10]. Although early success has been reported, the intrusiveness of the procedure, as well as the costs, risks, and morbidity, most likely hinder its widespread application.

External direct current cardioversion is an acceptable treatment option for restoration of sinus rhythm. This is a method in which shocks are delivered transthoracically in an attempt to completely defibrillate the atria. Lown et al first examined the technique of external cardioversion as an alternative to conventional pharmacological treatment for atrial fibrillation[11]. This method has been successful in restoring sinus rhythm, but is not as effective when compared to newer techniques of internal cardioversion.

In a comparison of the two methods, Levy et al randomly assigned 112 patients to undergo either internal or external cardioversion[12]. Those undergoing internal cardioversion received a 200 J shock followed by a 300 J shock, if necessary, from a catheter placed in the right atrium and a back-plate on the left posterior chest. Those undergoing external cardioversion received one 300 J synchronised shock followed by a 360 J shock if sinus rhythm was not restored. If atrial fibrillation was still present following the 360 J shock, cardioversion was then attempted internally. Acute efficacy was evaluated based on the presence of sinus rhythm 10 min following cardioversion. Long-term efficacy was similarly evaluated at 1, 3, 6, 9, and 12 months post-cardioversion. The results revealed that, acutely, internal cardioversion was significantly more effective in restoring sinus rhythm than the external method (84% vs 64% respectively). In addition, among the 19 patients who failed to convert with the external method, 12 were restored to sinus rhythm with internal treatment. Recurrence rates of atrial fibrillation after 1 year, however, showed no significant difference with regard to method of cardioversion. Therefore, in addition to being acutely more efficacious, internal cardioversion can also convert patients who have failed external cardioversion.

Recent studies have shown that low-energy internal cardioversion with temporary leads is a feasible and effective method for restoring sinus rhythm[2–4]. However, even with lower-energy internal cardioversion, recurrence of atrial fibrillation still occurs at equivalent rates to external defibrillation[13]. Given the recurrent nature of atrial fibrillation, the promising results with low-energy internal cardioversion, and the present state of implantable device technology and application, the possibility has been raised for the development of an implantable atrial defibrillator. The nature of atrial fibrillation, however, necessitates different device criteria from the ventricular cardioverter defibrillator. Because atrial fibrillation is not an immediately life-threatening or emergent disorder, an implantable atrial defibrillator can be programmed such that therapy is delivered only when the device has determined with certainty that atrial fibrillation is present and that it is safe to deliver shocks. Levy and Camm discussed the basic requirements for an implantable atrial defibrillator in an editorial examining the feasibility of such a device[5]. The authors concluded that safety, efficacy, and tolerability were the main concerns in developing a device to terminate atrial fibrillation. Design concepts should, therefore, incorporate these concerns. This chapter will specifically address these criteria in the context of the present status of basic research and clinical experience.

Safety

As with other pharmacological antiarrhythmic interventions for atrial fibrillation, ventricular proarrhythmia

(ventricular tachycardia or ventricular fibrillation) and cardiac bradyarrhythmia are potential risks associated with atrial defibrillation. The strategy for reducing these risks in an implantable device for atrial fibrillation has been threefold: correct sensing of ventricular events to allow for precise shock synchronisation, timing atrial shocks to coincide with intrinsic ventricular depolarisation to decrease the chance of delivering a shock during the ventricular vulnerable period, and supportive pacing after shock delivery to address the issue of bradycardia. In addition to these safety considerations, attention should also be paid to the detection of atrial fibrillation.

Lown et al recognised the need for accurate shock synchronisation as a safety factor for external defibrillation when the technique was still in its initial phases of practice[11]. A study conducted by Dunbar et al on intracavitary cardioversion of atrial tachyarrhythmias in dogs further illustrated the need for accurate shock synchronisation for therapeutic shocks[14]. In that study, shocks were not synchronised to ventricular depolarisation and, as a result, ventricular fibrillation was inadvertently induced in nine of 372 cardioversion attempts.

Ventricular vulnerability is directly related to the relative refractory period of the myocardium, and occurs at a time at which the ventricles are particularly susceptible to significantly strong stimuli. The period near the apex of the T wave corresponds to the ventricles' vulnerable period; therefore, shocks that are delivered close to or on the QRS complex are more likely to avoid the T wave. Several studies have documented the safety of delivering atrial defibrillation shocks when synchronised to ventricular depolarisation. Animal studies have demonstrated that synchronised atrial defibrillation shocks are safe and do not produce ventricular proarrhythmia[15,16]. In addition, worldwide clinical data reported by Murgatroyd et al revealed that, of 1212 shocks reported, 97% were R-wave synchronised and none produced ventricular proarrhythmia in any of the 86 patients[17]. More recent data also showed that 3400 R-wave synchronised shocks delivered in humans have produced no ventricular proarrhythmia[18]. The need for synchronised shocks for treatment of atrial fibrillation, therefore, is widely accepted and understood as a necessary safety precaution.

In addition to synchronising shocks to ventricular depolarisation, monitoring of the RR interval provides an additional method by which to avoid the ventricular vulnerable period, thus lowering the risk of inducing ventricular proarrhythmia. During atrial fibrillation the heart rate is irregularly irregular, making shock delivery particularly difficult; ventricular cycle lengths are highly variable, predominantly short, and are an ideal setting for intraventricular reentry. A thorough study by Ayers et al, to determine the effects of cycle length on ventricular proarrhythmia, found that all episodes of ventricular fibrillation were induced with preceding cycle lengths of $\leq$ 300 ms[19]. All shocks were synchronised to ventricular depolarisation, although shock delay did vary. Ventricular fibrillation was induced when pacing stimuli either modelled rapid cycle lengths followed by a premature ventricular contraction or modelled a long cycle length followed by a short cycle. In both situations, fibrillation was induced when the R wave fell on the ventricular vulnerable period.

In addition to Ayers' report, a study examining the effects of complete left or right bundle branch block and wide QRS complexes concluded that a minimum RR interval of 350 ms was needed to avoid shock-induced ventricular fibrillation[20]. Li et al also examined the risks of inducing ventricular fibrillation when shocks were coupled with premature ventricular contractions, and found the longest normal QRS-PVC shock interval that induced ventricular fibrillation to be 186 $\pm$ 33 ms[21]. Other studies lend support to the RR interval criteria for avoiding shock induced proarrhythmia; most studies use a minimum RR interval of 600 ms as a default safety setting[17,22]. Adams et al were able to demonstrate that a device employing this method is feasible and can reduce the risk of inducing proarrhythmia[16]; therefore, a minimum RR interval requirement is a crucial device specification so that shocks are delivered only when the ventricle has recovered.

When delivering shocks to fibrillating atria, the nature of the therapy, as well as the heart's altered state, may produce conditions under which the defibrillated heart has a delayed recovery to normal sinus rhythm and is transiently bradycardic. Because the sinus node suffers from constant bombardment during fibrillation, it may not immediately begin intrinsically pacing once the heart has been defibrillated. In addition, shocking the heart may cause transient atrioventricular (AV) block, resulting in bradycardia. The need for supportive pacing is well recognised as a necessary safety element since sinus bradycardia and transient AV block have been observed in clinical studies[11,17,23]. The occurrence of post-shock bradyarrhythmias, therefore, necessitates the need for pacing capability in any implantable automatic shocking device.

Detection of atrial fibrillation is an important safety consideration, because the goal of effective and safe therapy is to deliver shocks only when absolutely necessary. Reducing unnecessary shocks will not only decrease the risk of inducing ventricular proarrhythmia, but also prolong the life of the device and minimise patient intrusion. In order to minimise the number of inappropriate shocks, a good detection algorithm is needed that has the ability to specifically detect and discern atrial fibrillation from normal sinus rhythm. Since most patients are in sinus rhythm a majority of the time, a highly sensitive method for detecting sinus rhythm should be employed. An additional detection step is also recommended to more accurately detect atrial fibrillation once normal sinus rhythm does not appear to be present. The development of computer algorithms for atrial fibrillation detection has been vital to the evolution of a device which can automatically detect and treat atrial fibrillation.

The Metrix™ atrial defibrillation system utilises the Mirror Image Algorithm™, which includes quiet interval and baseline crossing analysis, to identify the presence of atrial fibrillation (Fig. 1). Quiet interval analysis is highly specific for sinus rhythm, and is defined as an interval during which the atrial electrogram voltage is continuously at baseline (Fig. 2). A percentage quiet time can be calculated over an 8-s electrogram recording, and if the percentage quiet time exceeds a threshold value the rhythm is classified as sinus rhythm. However, if the percentage quite time is less than the programmed value, the rhythm is classified as non-sinus rhythm, and baseline crossing analysis is instigated. In baseline crossing analysis the device examines a portion of the RR interval from an electrogram where atrial activity is normally absent in rhythms other than atrial fibrillation. This part of the algorithm looks for the number of times the electrogram crosses the voltage threshold level (Fig. 3). Its purpose is to confirm the presence of atrial fibrillation. Sra et al conducted a study using the Metrix™ atrial defibrillation system to examine the specificity and sensitivity of the atrial fibrillation detection algorithms, and found that all the rhythms encountered were detected appropriately in all patients[24]. In addition, Tse et al found the Metrix™ system to be 94% sensitive and 100% specific in detecting atrial fibrillation[25].

Efficacy

In order for a device to have clinical utility, it must be efficacious in terminating atrial fibrillation. Device design should therefore address the waveform and shock vector used in this method of treatment as they have a significant role in the effectiveness of treatment. Many investigators have already examined these issues, and provide some guidelines for development of a device.

The type of waveform, whether monophasic or biphasic, appears to play a part in the effectiveness of shock treatment. In a study on waveforms to treat ventricular fibrillation, Winkle et al found biphasic waveforms to be more effective than monophasic waveforms ($p < 0.006$)[26]. In addition, biphasic waveforms offered the greatest advantage at voltages less than 300 V. Troup et al reported that biphasic shocks with terminally negative components significantly reduced energy and average current for internal defibrillation of 10 patients undergoing ventricular cardioverter defibrillator implant with two patch lead systems[27]. These findings have direct significance in the development of an implantable atrial defibrillator because the voltage and energy requirements for therapy delivery are much lower than for ventricular defibrillation; often less than 300 V. A biphasic waveform is also appealing for a device because the energy left on the capacitor at the end of a monophasic waveform can easily be inverted to generate a negative trailing waveform without increasing the capacitor.

The advantages of biphasic waveforms seem to carry over when dealing specifically with internal atrial defibrillation. A 3/3 ms biphasic waveform proved to be

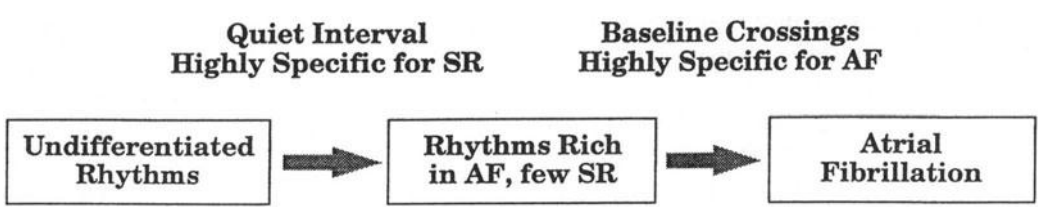

Figure 1. Detection: the "mirror-image" algorithm.

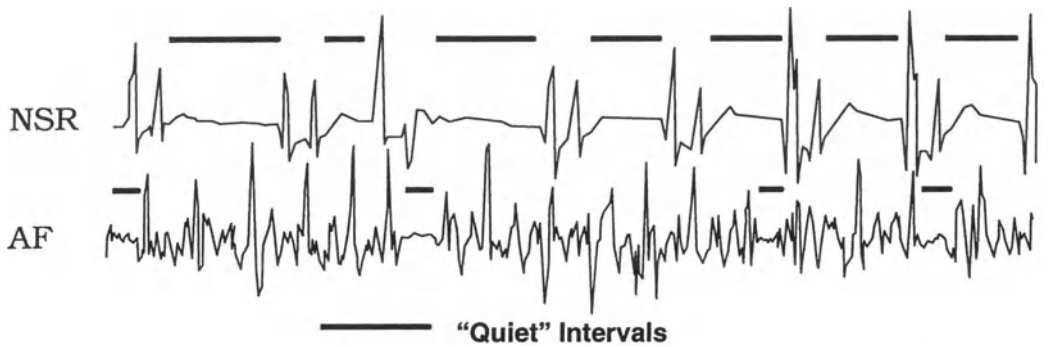

Figure 2. Detection: first stage algorithm: quiet intervals.

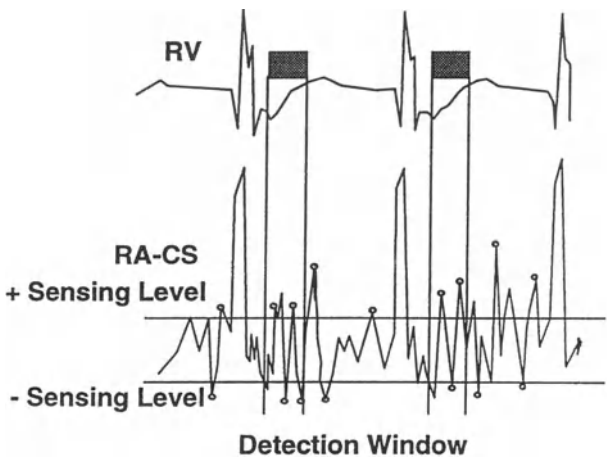

Figure 3. Detection: second stage algorithm: baseline crossings.

more effective in cardioversion than a monophasic waveform of the same duration[28]. In a more detailed examination of internal cardioversion of atrial fibrillation, Cooper et al tested the efficacy of monophasic and biphasic waveforms of several different durations. In all parts of the study the 3/3 ms biphasic waveform had lower defibrillation voltage requirements than all monophasic waveforms as well as 1.5/1.5, 4.5/4.5, and 6/6 ms biphasic waveforms[15]. In a separate study on biphasic waveforms, Cooper et al concluded that biphasic waveforms with a first phase duration greater than or equal to the second phase (5/5 ms or 7.5/2.5 ms) are more effective than simple monophasic waveforms of the same duration (10 ms) or biphasic waveforms with the second phase duration greater than the first (2.5/7.5 ms)[29]. The decrease in voltage and energy requirements for successful defibrillation afforded by biphasic waveforms may increase the efficacy and lifetime of a device, and may also increase patients' tolerance of therapy.

Electrode placement is also a critical factor in the efficacy of electrical therapy because it delineates the shocking vector. However, because the electrodes are placed internally with transvenous leads there are limitations as to where the electrodes can be secured, thus limiting possible shock vectors. According to the critical mass hypothesis, the most effective electrode system would be one that is able to encompass the most fibrillating tissue between the electrodes. Consequently, Cooper et al found a right to left electrode system (right atrium-coronary sinus) to have lower defibrillation requirements than any totally right-sided electrode configuration[15]. Left to right sided electrode systems, however, have a number of possible configurations including differing positions in the right atria, coronary sinus, as well as electrode placement in the left pulmonary artery. Further studies have attempted to more precisely define optimal electrode positioning, thereby decreasing defibrillation thresholds. Left-sided electrode positioning has mainly concentrated on the coronary sinus as opposed to the left pulmonary artery because of the difficulty in lead placement and the concern of valvular stenosis with a left pulmonary artery lead position. Further, two separate studies have concluded that an anodal electrode positioned in the pulmonary artery has significantly higher thresholds when compared to an identical electrode positioned in the coronary sinus[12,30]. A comprehensive study of electrode positioning in the coronary sinus/great cardiac vein found the optimal electrode position to be in the

anterior descending vein or under the left atrial appendage at the junction of the coronary sinus and great cardiac vein[31]. Several studies have also examined the optimal electrode position for the right atrial electrode. In general, results from these studies have shown the right atrial appendage or the lateral right atrium to be the most efficacious positions[15,32,33].

A number of investigators have demonstrated in clinical studies the feasibility and efficacy of internal electrical cardioversion at reasonable voltages and energies using a right atrium to coronary sinus lead system[18,23,33]. Two studies are of special note; in one study with 16 patients, 10 of whom had concomitant heart disease, 12 (75%) were successfully cardioverted with a mean charge of 240 ± 55 V and 2.2 ± 1 J. At a follow-up period ranging from 1.5–8.2 months, eight of the 12 patients cardioverted (67%), including one patient with chronic atrial fibrillation, who had no recurrence while also on antiarrhythmic therapy[34]. Another study conducted to illustrate the efficacy of internal shock therapy in relation to patients with differing atrial fibrillation classifications also yielded valuable information. Cardioversion was successful in 35/39 patients (90%) with paroxysmal atrial fibrillation at a mean conversion voltage of 240 V (2.09 J), 15/16 patients (94%) with intermediate atrial fibrillation at 257 V (2.5 J), 20/25 patients (80%) with induced atrial fibrillation at 216 V (1.85 J), and 30/40 patients (75%) with chronic atrial fibrillation at 313 V (3.5 J)[35]. Similar results were reported just recently in another multicentre study[2].

Another important factor in defibrillation efficacy is the time to therapy. Investigators have found that conversion voltage increases with increasing left atrial size and duration of atrial fibrillation[35,36]. Furthermore, repeated internal cardioversion requires less energy than primary internal cardioversion of chronic atrial fibrillation, given that the second episode is of shorter duration than the first[37]. If atrial fibrillation can be quickly detected and treated, patients will be at lower risk for a thromboembolic event[38] and can be cardioverted with fewer shocks and at lower voltages; an internal automatic device is ideal for this situation.

Much of the data gathered about electrode placement and defibrillation thresholds thus far has been in the short term, and little data is available about the effect of lead maturation on long-term efficacy. Nevertheless, lead system stability is an important factor in evaluating the efficacy of a device of this type. Two animal studies conducted by Ayers et al do offer some data on long-term efficacy of implanted leads. In a 3-month study done in adult sheep, no significant difference in atrial defibrillation threshold (ADFT) voltage or energy was observed[39]. Similarly, no change was observed in ADFT voltage or energy over a 6-month period in leads implanted in adult sheep, although changes in atrial wave amplitudes did vary over the study's duration[40].

These findings help establish the efficacy of internal electrical cardioversion as a therapeutic modality, and present the plausibility of the development of a device which could mediate this type of therapy. As device-mediated internal electrical cardioversion becomes a more recognised therapy for treatment of atrial fibrillation, more information will become available about electrode positioning in enhancing the efficacy of defibrillation shocks.

Tolerability

Unlike ventricular tachycardia or fibrillation, syncope is uncommon with atrial fibrillation; therefore, patient tolerance of therapy is an integral component in device design. The discomfort experienced by patient following defibrillation shocks may reduce patient acceptance of an implantable device to treat atrial fibrillation. Clinical studies have enabled investigators to gather data from patients regarding shock perception while undergoing internal atrial defibrillation. Patient perception of internal shocks includes transient pain and discomfort in the central chest area, skeletal muscle contraction, musculoskeletal pain, and direct nerve stimulation[41].

When compared to external cardioversion the decreased voltage and energy requirements for successful cardioversion with internal therapy may have several benefits which can increase patient tolerability; general anaesthesia may not be needed, and thus therapy can be delivered more easily and with fewer complications[4,15]. Hospital visits-to-treat episodes may be avoided altogether. The ultimate endpoint for device design is to identify the most tolerable situation under which a patient would receive safe and effective treatment for atrial fibrillation. This may be achieved by making modifications to shock waveforms, and defibrillation electrode design and location[4,42]. This section on tolerability will specifically discuss current research on device aspects that may reduce energy and voltage requirements while maintaining efficacy, as well as aspects that may decrease patient discomfort.

Waveform rounding, the number of shocks delivered during the course of treatment, and patient control options are a few of the issues that device design should address. Because the previous section on efficacy discussed optimal electrode characteristics, those issues will not be reiterated here.

As with optimal electrode placement, waveforms that can decrease energy requirements for defibrillation will improve patient tolerance of therapy. The studies mentioned earlier support the use of biphasic waveforms over monophasic waveforms[15,27,29]. Waveform rounding is yet another modification that can improve patient tolerability. Characteristics of defibrillation waveforms are also proving to be central in patient perception of shocks. Earlier studies on shock perception focused on shock energy; however, it seems that, while energy determines the success of a defibrillation shock, it is the voltage which determines the pain perceived by the patient[42,43]. Rounded waveforms are able to decrease the peak voltage delivered, thus potentially making shocks more tolerable. Gonzalez et al found that rounded waveforms significantly reduced defibrillation voltages without effecting energy[44]. In contrast, two separate studies by Harbinson et al, however, have found that waveform rounding reduces not only peak voltage, but also current and energy, but does not affect defibrillation efficacy[45,46]. Consequently, when compared to standard waveforms, rounded shocks also result in higher discomfort thresholds, as well as a patient's ability to tolerate both higher energy shocks and an increased number of shocks[41].

Lok et al found that, with a moderate starting voltage, most patients can tolerate shocks $\leq$ 250 V without sedation[47]. Although Lok et al's study also included three patients who were able to tolerate seven shocks of up to 400 V without sedation, Murgatroyd et al found that unsedated patients will tolerate three or four shocks, regardless of starting voltage[4]. This is yet another example of the contiguousness of the efficacy and tolerability issues. To be clinically efficacious, patients should be able to tolerate therapy, and these studies suggest that fewer shocks may be better. Therefore, the patient would be able to endure therapy if it is delivered in a brief manner.

Design features that allow patients to control the device would enhance patient acceptance; this can be accomplished by incorporating a warning signal into the course of treatment, as well as a method for the patient to activate or inactivate the device. The addition of a warning signal to the device's therapy sequence may allow a patient to prepare for the delivery of shocks and, if properly timed, may allow a patient to take short-acting sedatives and/or analgesics before shock delivery. In addition to a warning signal, patients may also have the ability to control the delivery of therapy. A method to allow the patient to initiate or interrupt therapy at any time, either by activating the device or reverting it to an inactive state, would be beneficial. Psychological conditioning, surrounding factors, and patient posture may also affect shock perception; however, there is little information available on this subject. Patient control is an important aspect of acceptance of an invasive therapeutic device; patients need to feel that the device acts in their best interests, but that they ultimately have the ability to control the course of therapy.

Many patients are currently able to tolerate the technique of internal cardioversion. Technological advancements and device modifications in the future will serve only to increase the tolerability in those patients who do not presently tolerate this type of therapy. Clearly, the possibility of incorporating rounded waveforms into device parameters is worth further investigation. Further study is needed to more specifically determine the most beneficial parameters for combined defibrillation efficacy and patient tolerability.

Conclusion

An implantable atrial defibrillator can provide alternative treatment for patients with atrial fibrillation who have not had success with other therapeutic methods. Initial experiences with a device of this type have had promising results. Device design has been able to accommodate the necessary requirements for safe, effective, and tolerable delivery of therapy. However, since atrial fibrillation is neither a single entity nor the result of a single disease process, a single appropriate treatment for all forms of atrial fibrillation is unlikely[48]. Patient selection, therefore, is an important process in choosing for implant those for whom the device is the best fit. Patients with recurrent attacks of atrial fibrillation and resistance to antiarrhythmic therapy are potential candidates, as are patients with infrequent, poorly tolerated (syncope, chest pain, or heart failure), or long-lasting attacks requiring medical intervention[49]. Clinical experience has also revealed lower atrial defibrillation

thresholds in patient populations without heart disease, higher left ventricular ejection fractions, and smaller left ventricular end-diastolic diameters[23]. Patient evaluation and identification of the most suitable course of treatment(s) will most likely result in beneficial patient outcomes. The addition of an implantable atrial defibrillator to treatment options for atrial fibrillation represents both a technological advancement in medical applications as well as an expansion of alternatives for the treatment of what has proven to be an obstinate cardiac arrhythmia.

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Chapter 39

Criteria for Selection of Patients for Internal Atrial Defibrillator Implantations

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Introduction

The prevalence of atrial fibrillation (AF) has been found to be up to 9% in elderly patients[1]. More than 179 000 patients were hospitalised for AF at 678 hospitals in the United States in 1990[2]. This represents more than one-third of all admissions for arrhythmias and is accomplished with a high cost to the health-care system.

Main concerns about traditional pharmacological therapy

There are today several accepted concepts: (1) antiarrhythmic drugs (AAD) to prevent AF recurrences are generally not curative but palliative agents, since overall recurrence rates are 50% or more after 6 months follow-up despite different class AAD[3–5]. (2) Conventional AAD may also have life-threatening toxicity[6,7]. (3) A high and irregular ventricular rate can cause progressive heart failure due to left ventricular dysfunction – so-called reversible tachycardia-induced cardiomyopathy[8,9]. (4) Among the several unwanted effects the risk of thromboembolic events is particularly high in patients with AF, especially when organic heart disease is present[10]. As AF persists, anticoagulation must be pursued in most cases, which may be a cause of complications[3]. It has been shown from large-scale studies with warfarin that the rate of major bleeding ranges from 0.8 to 2.5% per year[11]. Thus any option to avoid the use of anticoagulants is highly desirable. (5) Independently from any risk AF remains a poorly tolerated disorder

Table 1. Main problems related to conventional pharmacological therapy of atrial fibrillation

1. Antiarrhythmic treatment to prevent AF recurrences not more effective than 50% at 6 months.
2. Conventional antiarrhythmic treatment may have life-threatening toxicity.
3. High and irregular ventricular rate can cause progressive heart failure (tachycardiomyopathy).
4. High risk of thromboembolic events.
5. AF as a poorly tolerated disorder.
6. Electrical remodelling: early termination of AF may lead to prophylaxis of its recurrence.

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resulting in palpitations, dyspnoea, fatigue, heart pain, polyuria and limited exercise capacity. The majority of these complaints are related to difficulty in controlling the ventricular rate during AF[12]. It has been shown[13] from Holter recordings and exercise testing that, in many cases, the drug effect in controlling heart rate is unsatisfactory, allowing episodes of high ventricular rate to emerge during normal activity or exercise. Furthermore, despite rate control, patients may remain symptomatic. This leads to the suggestion of the main role of cardiac irregularity in the genesis of symptoms.

Electrical remodelling

Another concept is emerging from the observation that AF has a tendency to become more persistent over time. A large percentage of patients with paroxysmal fibrillation may develop chronic AF, even in the absence of an underlying cardiovascular disease[14]. Pharmacological cardioversion by intravenously or acute orally administered AAD is less effective if AF has lasted for > 24–72 h[15–17]. The success rate of electrical cardioversion and subsequent maintenance of sinus rhythm is also related to the duration of the arrhythmia[18,19].

The explanation of these observations can be related to a single progression of the underlying disease, or, as suggested in previous experimental studies introducing the concept of electrical remodelling of the atrium, could be conditioned by the prolonged high rate of activation[20].

Thus the prolonged tachycardia could influence not only mechanical contractility but also electrical behaviour, with the two variables not necessarily strictly related to one other.

Although the concept of electrical remodelling has still to be considered experimental, and thus not applicable directly to the human heart, if confirmed it will lead to the immediate consequence that the shorter is the AF length, the less is the chance of recurrence. In this respect, to halt the arrhythmia very soon after its onset could probably mean preventing its further recurrence. This theory, if proven, could open the frontiers in the non-pharmacological therapy of AF, with special emphasis on internal atrial defibrillation (IAD).

Indications to IAD implantations

The internal atrial defibrillation implanted so far in more than 100 patients throughout the world is capable of recognising and terminating the arrhythmia, in a semi-automatic mode, in order to reduce the possibility of a ventricular proarrhythmic effect. The patients implanted had no underlying heart disease. Preliminary speculations about the possible indications to this device have confirmed its employment in patients with hypertrophic[21] cardiomyopathy, who depend heavily on the atrial combination to ventricular filling and who have a propensity to recurrent atrial fibrillation with acute haemodynamic deterioration.

The major concerns related to the extensive employment of IAD are its tolerability (painful shocks especially at high energies), cost, persistent efficacy in the long run, and safety[13,22].

When discussing IAD indications we have thus to outline the present indications (Table 2) and possible expansions to future indications. The main current indication derived from clinical trials is: recurring, symptomatic, drug-refractory AF in patients without ischaemia, VT/VF and without congestive heart failure. The clinical studies performed so far only with this

Table 2. Indications to IAD

1. *Current clinical indications*
   Recurring symptomatic, drug refractory AF in patients without ischemia, bradycardia, VT/VF and CHF.
2. *Future indications (not already proven)*
   (a) Recurring symptomatic AF (less than one or two episodes a month): mild-moderate CHF aggravated by AF; previous CHF episodes due to high rate AF in normal heart; HCMP (eventually + ICD); recurrent AF has been shown to be decreased by shorter AF length
   (b) Recurring asymptomatic AF: High embolic risk, unable to be anticoagulated; first symptoms of AF are CHF, syncope or angina
   (c) Chronic AF: After partially successful ablation; after several CV when SR persistence is clinically mandatory

CHF, congestive heart failure; CV, cardioversion; HCMP, hyperthrophic cardiomyopathy; IAD, internal atrial defibrillator; ICD, internal cardioverter defibrillator; SR, sinus rhythm; VF, ventricular fibrillation; VT, ventricular tachycardia.

patient population. However, according to the above-mentioned observations, and ongoing studies, it is easy to predict future indications such as:

1. Recurring symptomatic AF (less than one or two episodes a month):
   (a) with mild-moderate congestive heart failure aggravated by AF.
   (b) with previous episodes of heart failure due to high-rate AF.
   (c) with hypertrophic cardiomyopathy (eventually together with an ICD).
   (d) Patients in whom recurrence of AF has been shown to be reduced by decreasing AF duration.
2. Recurring asymptomatic AF:
   (a) High embolic risk, unable to be anticoagulated.
   (b) When first symptoms of AF are congestive heart failure, syncope or angina.
3. Chronic AF:
   (a) After partially successful ablation.
   (b) After serial cutaneous/transcutaneous cardioversion.
   (c) When persistence of sinus rhythm is clinically mandatory.

For the time being, however, we consider the following contraindications: (a) an implanted energy-delivered device; (b) AF due to reversible causes; (c) Long QT syndrome; (d) history of acute myocardial infarction or coronary bypass graft procedure within 6 months; (e) angina pectoris or active ischaemia; (f) evidence of left atrial thrombus; (g) recurrent congestive heart failure symptoms or NYHA class III or IV; (h) left ventricular ejection fraction less than 40%.

Although the efficacy of IAD has already been documented in humans in several studies[22] there is still constant research on new algorithms, electrode configurations and size, and new shock waveforms in order to decrease the amount of energy necessary to treat patients with consequent abolition of the pain sensation. This goal, once reached, will contribute greatly to further usage of this device therapy.

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Chapter 40

Survival Benefits of Implantable Cardioverter/Defibrillators in Different Groups of Patients

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Introduction

Implanted cardioverter/defibrillators (ICD) used as a the non-pharmacological treatment modality in life-threatening cardiac arrhythmias have substantially improved patients' prognosis. This is reflected by the lower rate of sudden cardiac deaths shown in numerous pertinent studies[1]. However, overall mortality is not significantly lower in patients undergoing ICD implantation than in those treated with other modalities[2,3]. This has prompted a search for criteria to identify those patients who are likely to derive a survival benefit from ICD therapy. In this chapter, factors determining the effect of ICD therapy on prognosis are reviewed; diagnostic problems are discussed; and recommendations are made for future directions in research.

The factors which play a role for the survival benefit of ICD therapy are well known. They include: arrhythmia type, patient age, psychological status, underlying heart disease, left ventricular function, extracardiac disease, need for concomitant drug treatment, rehospitalisation for complications.

Type of arrhythmia

ICD implantation is the treatment of first choice in patients with ventricular tachycardias causing haemodynamic complications or degenerating to ventricular fibrillation. In these types of arrhythmias this treatment is definitely superior to drug treatment both in terms of morbidity and mortality[3,4]. However, it is by no means the best treatment option for patients with frequent arrhythmogenic events, because the discharges are usually experienced as annoying, and because the implanted devices have a relatively short life on account of the high energy consumption. Patients with frequent arrhythmogenic events, therefore, either need lifelong antiarrhythmic drug treatment (see next paragraph) or they are candidates for ablation[5].

Patient age

In patients of greater age, particularly those with associated cardiac or extracardiac diseases, ICD implantation offers no survival or quality-of-life benefits. In addition, it has no effect on the rate of sudden cardiac deaths beyond the age of 75 years[6,7].

Psychological status

The preoperative diagnostic work-up, the implantation of the device, the inevitable postoperative tests for titrating the defibrillation threshold and the function of the system, as well as spontaneous discharges,

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make major psychological demands on patients. As a result, ICD therapy does not improve the quality of life of patients who lack the requisite emotional stability. In the worst case some of them request that the device be removed. As the legal implications of implant removal are still poorly understood, the patient's emotional stress tolerance should be assessed before ICD implantation, and an expert opinion should be obtained in doubtful cases. Tests predicting potential psychological problems with adequate precision are, however, not available[8].

Underlying heart disease

Underlying heart disease is a major determinant of survival[9]. Particularly in patients with coronary heart disease or aortic valve stenosis the potential benefits of coronary artery surgery or valve replacement should be evaluated, to establish whether ICD implantation can be avoided altogether, or perhaps combined with them in a one-stage or two-stage procedure.

Left ventricular function

Left ventricular function is the most important factor to be considered in assessing the patient's life expectancy and the potential benefits of ICD implantation[10]. In patients with severely compromised left ventricular function ICD therapy, unless done as a bridge to transplant, does not prolong life[11]. These patients are candidates for drug treatment, although there is no hard evidence from pertinent studies documenting that this improves the outcome.

Extracardiac disease

Patients with extracardiac diseases limiting survival and quality of life, such as neoplasms or multiple strokes, do not benefit from ICD implantation, and should therefore not be considered candidates for it.

Need for concomitant drug therapy

Roughly 50% of all ICD patients need drug treatment to reduce the frequency of events and to lower the heart rate so that antitachycardic pacing is possible. In fact, antiarrhythmic drugs increase the benefit, because the termination of arrhythmogenic events by antitachycardic pacing is much more convenient for patients, and often not even noticed[12,13].

Rehospitalisation for complications

ICD therapy is associated with a fairly high complication rate. Complications are attributable to the generator/electrode system (high DFT, electrode dislocation or breakage), to the underlying heart disease, and to extracardiac diseases. Of the authors' patients 50% had to be rehospitalised[14]. No doubt, rehospitalization – no matter whether prompted by the generator/electrode system or by patient-related factors – limits the benefits of ICD implantation.

Criteria for evaluating ICD benefits

Variables to be considered in evaluating the effects of ICD therapy on the patients' prognosis include overall mortality, sudden cardiac deaths, symptoms, side effects, quality of life, and cost. While the effect of ICD therapy on survival (overall mortality, sudden cardiac deaths) is the main factor to be considered when evaluating patient benefit, quality of life also plays an important role. The effects of ICD on quality of life should be assessed in terms of the expected improvement of physical activity and psychological status. For evaluating the expected psychological impact an attempt should be made to assess whether the patient's reduced fear of yet another arrhythmogenic event outweighs the inconvenience of shock delivery, or whether the psychological stress associated with shock delivery outweighs the real chance of terminating a life-threatening arrhythmogenic event. Quality of life is also determined by the side-effects of concomitant drug treatment which most patients need, and by the underlying disease.

Last, but not least, current worldwide economic constraints necessitate a cost–benefit analysis of ICD therapy. Particularly in patients with a short life expectancy ICD implantation is not cost-effective, because the inevitable preoperative diagnostic studies, as well as the technical equipment, are expensive, and because a much more comprehensive follow-up programme is needed than for other treatment modalities[15].

Ideal patients for ICD

Patients who will definitely benefit from ICD therapy in terms of reduced morbidity and mortality are characterized by: sustained ventricular tachycardia not suited for ablation/surgery, primary ventricular fibrillation, young age, normal or nearly normal left ventricular function, infrequent arrhythmogenic events (one per month or

less), ventricular tachycardia terminated by antitachycardic pacing, and no need for concomitant drug therapy.

Patients who are not likely to benefit much from ICD therapy are characterised by: frequent events (one per week or more), ventricular tachycardia terminated only by shock, severely compromised left ventricular function, need for concomitant drug therapy, and psychological instability. In these patients ICD therapy should be considered only as a bridge to transplant.

ICD therapy versus alternative treatment strategies

The benefits of ICD implantation should be balanced against those of alternative treatment strategies, both medically and economically[16]. Ablation should be preferred to ICD implantation both because it cures ventricular tachycardia and because it is more economical. Antiarrhythmic surgery is a useful alternative medically and economically, if it is combined with coronary artery surgery. Coronary artery revascularisation by coronary artery bypass growth (CABG) or percutaneous transluminal coronary angioplasty is curative for patients with ventricular fibrillation by eliminating myocardial ischaemia[17]. In light of their greater benefits, alternative treatment strategies should therefore be preferred to ICD implantation in these patients.

So far there is no evidence showing that drug treatment is equal or superior to ICD implantation in improving the prognosis of patients with malignant ventricular arrhythmias[13]. Neither for the primary nor for the secondary prevention of arrhythmogenic events has its equality or superiority been established. However, the MADIT study, which was stopped before the scheduled time about 12 months ago, showed ICD implantation to be superior for primary prevention, just as the AVID study, stopped 6 weeks ago, showed its superiority in secondary prevention[12,13]. Both of these studies were, however, criticised because the validity of the results was questioned on account of methodological problems[17,18]. The preliminary results of the CABG patch trial to establish the effects of preventive ICD implantation on the prognosis of high-risk patients did not show it to be superior[19].

Studies to answer the right questions

All studies performed to date, whether concluded or ongoing, were designed to shed light on the superiority of ICD implantation versus other treatment strategies. Critics repeatedly urged that, instead of concentrating on this issue, it would be more important to identify subsets of patients who might best benefit from ICD treatment[19,20]. To use ICD therapy to its best advantage patient selection should be improved. A subset of patients should be defined for which the prevention of sudden cardiac death by ICD implantation ensures prolonged overall survival. To achieve these objectives the variables to be tested in a study with a prospective randomised design should include: patient age, gender, underlying heart disease, exercise testing, signal averaging, 24-h ambulatory ECG, echocardiography, coronary angiography, programmed electrical stimulation. In view of all these variables such a trial would require a large number of patients, so that it would have to be performed on a multicentric basis. For reasons of economy it would have to be based on a different design: instead of clinical utility, cost utility should be the prime point of interest (Fig. 1).

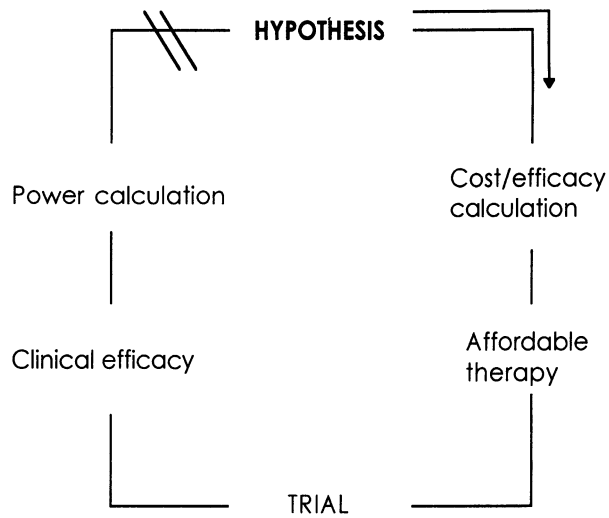

Figure 1. Scheme for planning studies calculating cost/benefit of ICD treatment.

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Chapter 41

Continuing Evolution of Implantable Cardioverter/Defibrillators: Smaller Size, Longer Life, Improved Cost-effectiveness

Seah Nisam

Introduction

In less than two decades since Michel Mirowski introduced the implantable cardioverter/defibrillator (ICD) into clinical practice, it has been acknowledged as *the* most effective therapy for protecting patients against sudden arrhythmic death, due to ventricular tachycardia or fibrillation (VT/VF)[1–3]. Many factors have contributed to elevating ICD therapy from a treatment "of last resort" to the primary intervention for such patients. Certainly, the growing evidence that no antiarrhythmic drugs have been able to improve survival has played a major role. However, without the improvements in ICD technology, resulting in implantation procedures similar to cardiac pacing, it is unlikely that ICD would have attained the current high degree of acceptance – by physicians and patients. The most obvious aspects of this technological evolution are major improvements in size, transvenous implantation, device reliability and longevity, and ease-of-use. At the same time, continued pressure on health expenditures has brought great focus on proving ICD cost-effectiveness, so that health authorities would grant reimbursement for this sophisticated technology. The questions on ICD therapy which we will address in this chapter concern in particular the balance between cost-effectiveness and rapid technological improvements.

ICD size

Figure 1 depicts the tremendous reduction in pulse generator size (volume, weight) in the short time (17 years) since Mirowski's first device implanted in 1980. In essence, device size has been reduced by about 80%, and ICDs in the near future will be below the 50 cc/80 g barrier. Coupled with high-performance ICD leads[4,5], capable of multiple, demanding functions (high-energy voltage conduction, detection of VT and of extremely fine VF, telemetry and intracardiac electrograms), ICD system implantation is already now similar in approach, implant time and minimum morbidity to that for cardiac pacemakers. The specific technological improvements which have made these achievements possible are related primarily to improved waveforms, "packaging" of components, and possibly most importantly, to the high-performance ICD lead systems, enabling reliable defibrillation and adequate "safety

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margins" with lower energies. We will not cover the details of these improvements, as they have been elaborately reported previously[4–7]. The most important fact is that device size has for some years posed no major obstacle to implantation, and the situation will only improve in the coming years.

Device longevity

Also in this respect, technology has made great strides. Whereas the original "automatic implantable cardioverter/defibrillators" (AICD) usually required replacement within 30 months, the lifetime of current ICD pulse generators is approximately double that. Even more than with pacemakers, the use of the ICD determines how long it will last: the number of high-energy shocks and percentage of time VVI pacing is required. Figure 2 shows the expected lifetime of a typical modern ICD, varying from a maximum of over 8 years with minimal shocks and pacing to about 5 years with 100% pacing and frequent high-energy shocks. Considering that patient longevity is < 5 years for about 50% of ICD recipients, the first device should last the lifetime of over half the patients[8].

Costs: an industrial perspective

As a preface to discussing cost-effectiveness, it may prove enlightening to examine the factors contributing to the current costs for ICD systems. Figure 3 provides insights into comparing ICDs to pacemakers, on an industrial basis. Important in this respect is that pacemakers have existed for four decades, thereby permitting amortisation of research and development investments made over these many years; in contrast, ICDs are in their first decade of true clinical acceptance, and much of the technology is new with each succeeding generation of systems: ICD pulse generators, programmers, leads, and accessories. Further contributing to the high development and manufacturing costs of ICD systems is that their volume of use is still very low, compared to pacemakers: 5% worldwide, and only 2% in Europe. The extremely short life cycles of ICD accentuates the problem of return on research and development investment. This situation is shown clearly in Fig. 4: in this example no less than eight (!) new models of ICDs from a single manufacturer were developed and introduced to the market in the space of just 7 years. In parallel, there were four new programmers and three families of ICD leads. Typically, the former model becomes

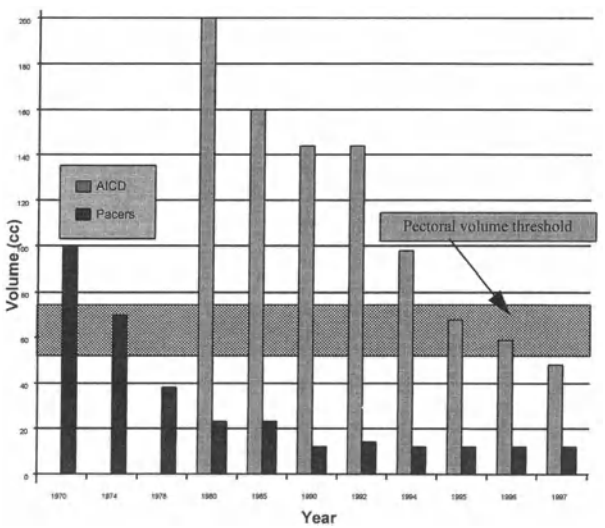

Figure 1. Evolution in volume and weight of ICD pulse generators, compared to cardiac pacemakers over the same time frame. Sizes below the "pectoral volume threshold" indicate devices acceptable for implantation in the pectoral region for the great majority of patients.

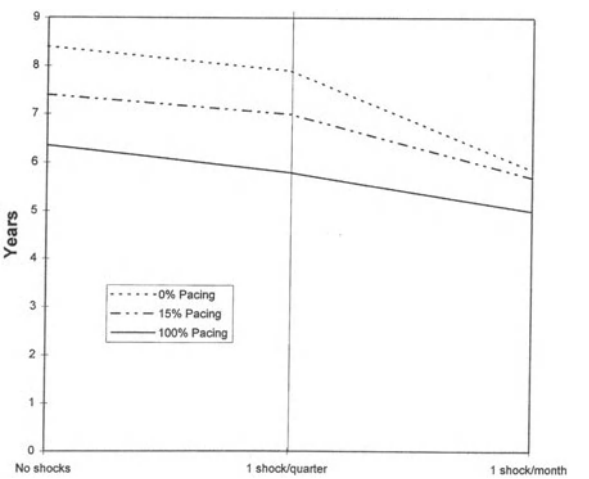

Figure 2. Expected pulse generator longevity (Ventak MINI+, CPI), calculated for different rates of device utilisation ranging from 100% VVI pacing/one maximum energy shock/month to 0% VVI pacing/no shocks. (Note: the MINI+ is the "long-life" model with larger capacity battery; normal, somewhat smaller models with smaller batteries should achieve about 80% of these life expectancies under similar usage conditions.)

obsolete within a few months of the introduction of the succeeding model. For example, the Ventak MINI, introduced in the Fall of 1995, was superseded by the MINI II just 7 months later! The development time for the DDD device (Ventak AV) was 6 years, yet the time it will be "in the market" before being replaced by the next generation will be less than a year. Another major contributor to the cost structure for ICDs is the technical support needed, both during the clinical trials, and even after the market introduction of these products. The degree of sophistication, programming possibilities, and troubleshooting requirements makes this support much more personnel-intensive than for pacemakers, heart valves, interventional devices, or any other currently used technology.

Cost-effectiveness of ICD therapy

Since, as seen above, most of the technical improvements have been, and are continuing to be, achieved, the primary remaining question concerning the balance between technology and cost comes down to the cost-effectiveness of ICD therapy. It is important to put these costs into perspective, with regard to other currently accepted medical interventions (Table 1). From this table it is clear that, while the initial costs for ICD implantation appear high, the cost of this therapy in terms of "life-years-saved" is equal to, or better than, many therapies well accepted by society and reimbursement authorities[2,9–11].

Specific to treatment options for patients with malignant ventricular tachyarrhythmias, the effectiveness of the various alternatives has begun to receive a lot of attention. With the exception of β-blockers, *no currently available antiarrhythmic agent has demonstrated prolongation of life*[12–19]. The Electrophysiologic Study versus Electrocardiographic Monitoring (ESVEM) study, reported sotalol as preferable to class I agents, but nevertheless associated with high rates of VT recurrences: 20% at 1 year, 50% VT and sudden death by 4 years[12]. Two studies with *d*,l-sotalol concluded with results inferior in the first study to placebo, and in comparison with ICD in the second[13,14]. Amiodarone, long considered the "best" antiarrhythmic drug, has been shown in multiple studies to be associated with approximately 20–25% sudden death at 5 years[15–17]. Probably the most powerful confirmation of amiodarone's limitations comes from recently completed large randomised, prospective trials in coronary patients with poor left ventricular function, indicating that amiodarone resulted in no reduction in mortality compared to placebo[18,19]. In stark contrast, with regard to the effectiveness side of the equation, ICD therapy has been shown in head-to-head comparisons (Table 2) to reduce sudden death and all-cause mortality *far* more effectively than anti-

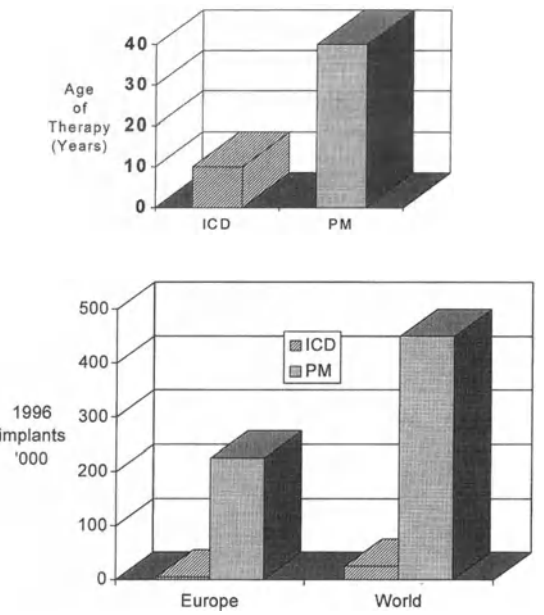

Figure 3. Industrial comparison of pacemakers (PM) vs ICD. Top graph: relative "age" of the two industries, showing pacemakers in use for four decades and ICD over one. Lower graph: number of pacemaker and ICD implantations during 1996, showing the relative numbers in Europe and the USA.

Table 1. ICD cost-effectiveness: comparison to other common therapies

Therapy	$/year-life saved
ICD – thoracotomy	12 000–30 000
Treatment of hypertension	23 200
Heart transplantation	26 900
Oestrogen replacement	32 900
Neonatal intensive care	5500–38 800
Coronary artery bypass	7200–44 200
Renal dialysis	58 000
ICD – transvenous/pectoral/longevity ↑	7500

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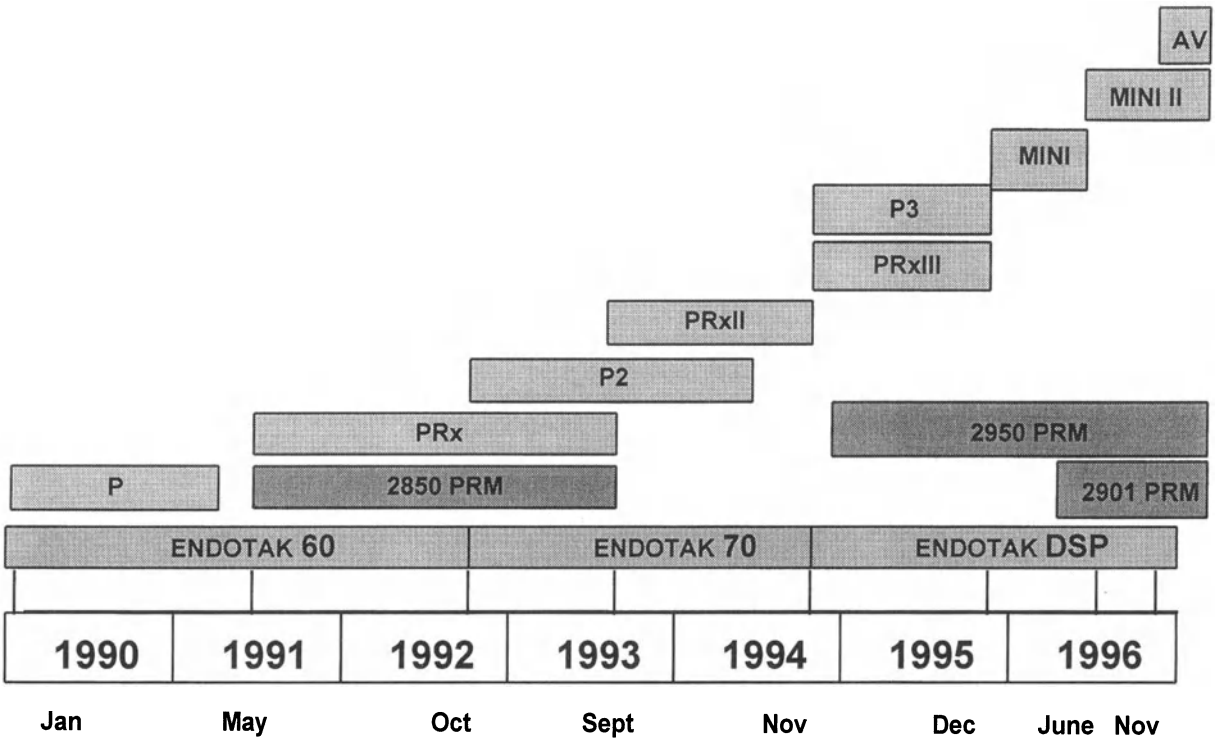

Figure 4. ICD product life cycles), 1990–1997 (CPI/Guidant). Pulse generators (top blocks), programmers (middle), and lead systems (lower blocks). The left edge of each block coincides with clinical introduction of a specific model, the right edge shows the time when the model begins to be superseded by a succeeding model.

Table 2. Total mortality, ICD versus antiarrhythmic drugs

Study	Patients	Drugs used	Mortality antiarrhythmic treatment (%)	Mortality ICD (%)	Reduction due to ICD (%)
Wever et al[20] (R) (*n* = 60)	CAD, resuscitated from VT/VF	Class 1 (EP-guided)	35	13	61
MADIT[21]* (R) (*n* = 196)	CAD, LVEF ⩽ 0.35, NSVT, inducible	Amiodarone/ sotalol/class 1a (74%/7%/10%)	38.6	15.8	59
AVID[22] (R) (*n* = 1001)	Resuscitated from VT/VF + Symptomatic VT	Amiodarone/sotalol (90%/10%)	22.9	15.9	31
Newman[23] et al (MC) (*n* = 180)	Resuscitated from VT/VF	amiodarone	51†	35†	31†
Böcker et al[14] (MC) (*n* = 100)	Resuscitated from VT/VF	*d*-1 sotalol	25†	15†	40†

CAD = coronary artery disease; LVEF = left ventricular ejection fraction; VT/VF = ventricular tachycardia; ventricular fibrillation; NSVT = non-sustained VT; EP = electrophysiological; R = randomised, prospective trial; MC = matched case controls.

* No past history of VT/VF.

† Actuarial survival at 3 years.

(Table 2 reprinted, with permission, from ref. 24.)

arrhythmic drugs[14,20–23]. It is anticipated that, as ICD therapy matures and gains even greater acceptance, the greater volumes (and, longer life cycles) will permit significant price reductions. However, as seen from Table 1, it is already now a cost-effective therapy, and becoming more so, with longer-life devices and shorter hospitalisation procedures. In light of the current results with antiarrhythmic drugs, one cannot get away from one stark reality: alternatives (to ICD therapy) which do not succeed in prolonging patients' lives may be *too expensive at any price*!

Summary

The size of modern ICDs has decreased to below the "threshold" permitting transvenous, pectoral implantation, and further size/weight reductions are imminent. The circuit efficiencies have improved to the extent that, under normal usage (15% VVI pacing, four high-energy shocks/year), pulse generators should last about 5 years, thus exceeding life expectancies for about half of the recipients. With regard to cost issues, ICD prices largely reflect the youth of the ICD industry: small volumes, short product life cycles, personnel-intensive technical support. Nevertheless, compared to other well-accepted high-technology therapies, ICDs are already now highly cost-effective, in terms of "life-years saved", particularly as pharmaceutical alternatives have to date shown no prolongation of life.

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Chapter 42

Prophylactic Implantation of the Implantable Defibrillator in Asymptomatic Patients

Poul Erik Bloch Thomsen

Introduction

Patients who have suffered a recent acute myocardial infarction (AMI) have a high risk of subsequent death despite advances in treatment. A large recent Danish study (TRACE) has demonstrated an overall mortality of 23% during the first year for patients admitted alive with an infarction[1].

Roughly half of the mortality appears to be sudden death defined as death occurring within 1 h of new symptoms, both overall and in important subgroups[2,3]. Most of this mortality is assumed to be caused by ventricular tachyarrhythmias, but firm evidence is not available. The Seattle studies of out-of-hospital cardiac resuscitation demonstrate that a large proportion of people experiencing sudden cardiac arrest can be resuscitated, if promptly treated with defibrillation[4].

Mortality of patients with an infarction is not evenly distributed, and it is possible by several methods to select patients with a high risk of overall mortality as well as a high risk of sudden death.

First, reduced left ventricular systolic function following an infarction is a well-established marker for increased mortality, and it has been demonstrated that echocardiography and estimation of the wall motion index (WMI) can be used in a multicentre setting to select patients with an overall mortality exceeding 30% within 2 years following the index infarction[2].

Other known risk factors for sudden cardiac death are heart rate variability, non-sustained ventricular tachycardia (VT), atrial fibrillation and increased QT dispersion (H. Elming, personal communication)[2,5,6].

Table 1 shows preventive measures to reduce occurrence sudden cardiac death in survivors of AMI. Among these, β-blocking agents have shown a convincingly positive effect on sudden cardiac death and mortality after AMI, whereas antiarrhythmic drugs, especially class 1C drugs, have showed a harmful effect on survival, and class 3 drugs have shown a decrease in sudden cardiac death but no effect on total mortality.

The implantable cardioverter/defibrillator (ICD) has been used in clinical practice for more than 16 years[7]. During that period the ability of the ICD to detect

Table 1. Preventive measures of cardiac death in survivors of acute myocardial infarction

Beta-blockade	Anticoagulation
Calcium antagonists	Antiarrhythmics
Thrombolysis	Statins
ACE inhibition	Revascularisation
Acetylsalicylic acid	Prophylactic ICD

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and convert sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) has been documented intensively[8–10]. Furthermore, the ICD has proven efficacious in preventing sudden cardiac death in a high-risk population[7,8]. Until recently, however, ICD therapy has been limited to patients who have already experienced a life-threatening arrhythmia.

Potentially there are several groups of patients who might benefit from prophylactic ICD implantation, and this has been documented within the past year in the MADIT study[11].

In the following a prophylactic ICD study in high-risk patients with an AMI is presented. The study is planned to be conducted in four of the five Nordic countries, starting in 1998. The present status of the pilot phase of the study is also discussed.

NORDIC: Nordic study of the implantable cardioverter defibrillator in high-risk patients with *AMI*

The hypothesis: Implantation of a cardioverter/defibrillator will prevent sudden cardiac death and thereby prolong life in patients with reduced left ventricular function, and at least one additional risk factor of arrhythmic death – i.e.: (a) reduced heart rate variability, (b) non-sustained VT, (c) atrial fibrillation, or (d) increased QT dispersion.

Inclusion criteria for screening

Patients admitted alive with an enzyme-confirmed AMI.

Inclusion criteria for ICD implantation

0.3 (EF = 0.10) < wall motion index (WMI) ≤ 1.2 (EF = 0.36) and at least one of the following: (a) reduced heart rate variability < 70 ms SDNN, (b) non-sustained VT on Holter (≥ 3 beats, frequency > 120 bpm), (c) atrial fibrillation, (d) QT dispersion > 110 ms.

Exclusion criteria

Advanced age > 75 years; NYHA class IV; ICD implantation mandatory or previously implanted; patients likely to die from other causes during the trial; patients on urgent transplantation list; patients planned for coronary bypass operation in near future; patients with coagulation defects; patients unable to cooperate, or from whom consent is not obtained; severe cases of abuse of drugs/alcohol, dementia and other conditions, where the patients cannot be expected to understand the nature of the treatment/trial or cannot be expected to participate in follow-up procedures.

Screening

Screening will take place in 10 Nordic centres capable of ICD implantation during a 2-year period, and is performed by full-time-employed nurses or doctors (Table 2). Patients are randomised after evaluation of WMI and heart rate variability locally. Videotaped echocardiography of all patients and the Holter tapes are sent to core laboratories for quality control. Nurses, technicians or doctors will be trained in echocardiography prior to study start, in order to obtain high-quality images, and doctors experienced in this technique will estimate WMI.

Randomisation

This will take place on days 8–14; 200 patients will have an ICD implanted on days 8–21, and 200 controls will receive best medical treatment. Follow-up is at least 2 years, with control 1 month after implantation and then every 2–3 months (all patients).

Primary and secondary endpoints and sample size are as follows:

1. Primary endpoint: all-cause mortality.
2. Secondary endpoints: cardiovascular mortality, sudden cardiac death, quality of life.

Sample size

A total of 150 deaths, of which 100 are expected to be sudden. With a procedure-related risk of less than 1%

Table 2. Screening

5000	consecutive patients with AMI below 75 years of age. Echocardiography obtained day 2–6 after AMI, separating patients according to WMI.
1500	patients (30%) with 0.3 < WMI ≤ 1.2. Holter recording (24 h) day 5–8 analysed for non-sustained ventricular tachycardia and heart rate variability. ECG evaluation of QT dispersion and atrial fibrillation.
600	patients (40%) with one or more of the above-listed ECG abnormalities; target population.
400	patients (67%) randomised day 8–11.

(death), an expected drop-out rate of less than 5% and a relative risk reduction of 33% the study will have a power of 90% of detecting a significant difference at the 5% level (two-sided). If mortality is below that expected the follow-up time of at least 2 years can be prolonged.

The pilot study

The pilot study started on 1 November 1996 in five centres in four Nordic countries. Principal investigators were: H. Huikuri, Oulu University Hospital, Finland; O.J. Ohm, Haukeland Hospital, Bergen, Norway; M. Rosenquist, Karolinska Sjukhuset, Sweden; J. Rokkedal, Glostrup University Hospital, Denmark; and P.E. Bloch Thomsen, Gentofte University Hospital, Denmark. The present status of the pilot study, on 1 June 1997, is shown in Table 3. In the pilot study all patients fulfilling criteria for randomisation are given an ICD. The size of the pilot study is not powered to detect a possible significant difference in endpoints. Table 4 shows implantation parameters with complications and follow-up results.

Conclusions

1. Prophylactic medical treatment is able to prolong life.
2. Prophylactic medical antiarrhythmic treatment is often harmful and at best neutral in prolonging life.
3. Prophylactic implantation of the ICD prolongs life in a selected group of patients with reduced left ventricular function after myocardial infarction and asymptomatic non-sustained ventricular tachycardia.
4. Prophylactic implantation of the ICD may be indicated in non-selected patients with acute myocardial infarction and reduced left ventricular function and electrical instability.

Table 3. Present status of the Nordic prophylactic ICD pilot study

No. of patients admitted with AMI	388
No. of patients with 0.3 < WMI ⩽ 1.2	120
No. of patients with HRV < 70 ms SDNN, NSVT, AFib, QT dispersion > 110 ms	36
No. of patients implanted	23

Table 4. Nordic prophylactic ICD study

Implantation parameters	
No. of patients	23
CPI mini/Medtronic Jewel	12/11
R wave amplitude/mV	13.4 (3.8–20)
Racing threshold/V	0.46 (0.2–0.8)
Shock impedance/ohm	52 (33–64)
Safety margin satisfactory	23
Complications	
Erosion of ICD	1
Follow-up (mean 4 months)	
No. of deaths	0 patient
No. of shocks (VT > 180/min)	1
Non-sust./sust. (VT > 140/min)	9 patients
Afib/Sinus tachycardia	2/1

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Chapter 43

Prophylactic Implantation of Implantable Cardioverter/ Defibrillators in Post-Myocardial Infarction Patients

Antonio Raviele, Aldo Bonso, Gianni Gasparini and Sakis Themistoclakis

Introduction

It has been demonstrated that total and sudden-death mortality after an acute myocardial infarction (MI) has significantly decreased in the past decade (to values of 2.8–7.1% and 1.9–3.0% at 1 year, respectively)[1,2], mainly as a result of the beneficial effects of modern therapy with thrombolytic agents[1,3], aspirin[4], β-blockers[5], angiotensin converting enzyme (ACE) inhibitors[6], statins[7,8] and revascularisation procedures[9].

Nevertheless, there is still a subgroup of patients with recent MI who are at high risk of life-threatening ventricular arrhythmias and sudden death after hospital discharge. These are patients with depressed (≤ 40%) left ventricular ejection fraction[2,3,10] and one or more of the following additional risk factors: frequent (≥ 10/h) ventricular premature beats and/or runs of non-sustained ventricular tachycardia[10–13], presence of late ventricular potentials on signal-averaged ECG[14–16], decreased heart rate variability (SDNN < 70 ms)[17–20], and/or decreased baroreflex sensitivity (≤ 3 ms/mmHg)[18,21].

Approximately 12–28% of survivors of an acute MI present with these features[19]. The risk of dying at 2 years for any cause or suddenly in these subjects is > 25% and > 12.5%, respectively[10,11,13,18–20]. Moreover, when a programmed ventricular stimulation is performed in these patients, a specific response (i.e. the induction of a monomorphic sustained ventricular tachycardia < 270 beats/min)[21] is elicited in about 40% of cases[22]. Patients with such a response at electrophysiological testing after MI have a significant incidence of serious arrhythmic events and sudden death during follow-up (35% at 6–30 months)[22,23]. The incidence is particularly high (50% at 2 years) when the induced arrhythmias are not suppressible by drugs[24].

Thus at the present time it is possible to identify, by means of appropriate screening, a small but significant proportion of patients with recent MI (about 5–10% of all post-MI patients) whose risk of sudden death remains high despite aggressive treatment with thrombolytic and other agents, and in whom preventive measures are surely justified.

The use of class I and, more recently, of class III antiarrhythmic drugs (amiodarone and *d-l* sotalol) in these high-risk (post-MI) patients has been shown to

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have a deleterious effect, or at best no effect, on total survival[25–31]. The only antiarrhythmic drugs proven to be effective in reducing all-cause mortality (including sudden death) after a recent MI are β-blockers[5], but physicians are reluctant to prescribe these agents, or to use them at the high doses employed in the large multicentre trials, especially in the presence of severe left ventricular dysfunction[32].

The implantable cardioverter/defibrillator (ICD) is an alternative measure for the prevention of sudden death in the post-infarction period. Many randomised trials were started in the USA in the early 1990s in an attempt to establish the real value of the prophylactic implantation of ICD in patients with previous MI[33–35]. The results of one of these trials (MADIT trial) have recently been published in the *New England Journal of Medicine*[36], and those of another trial (the coronary artery bypass graft (CABG) patch trial) were presented in preliminary form at the last NASPE meeting in New Orleans[37]. The third trial (MUSTT) concluded enrolment (700 patients) in November 1996 and is now in the follow-up period.

The aim of this chapter is to review the usefulness of ICD treatment in preventing sudden death and prolonging survival in high-risk post-MI patients.

Multicentre automatic defibrillator implantation trial (MADIT)

Design of the study and results

The MADIT trial started in December 1990 to test the hypothesis of whether prophylactic implantation of ICD in patients with low (≤ 35%) left ventricular ejection fraction, asymptomatic non-sustained (≥ 3, ≤ 30 consecutive beats) ventricular tachycardia and inducible/non-suppressible (after intravenous procainamide loading) ventricular tachyarrhythmias, reduces all-cause mortality compared to conventional medical management[33,36]. Previous studies had shown that these patients have a high incidence of total death and sudden death: 30% and 50% at 2 years, respectively[10,24]. Exclusion criteria from the study included acute MI ≤ 3 weeks before, active myocardial ischaemia, CABG ≤ 2 months prior, percutaneous transluminal coronary angioplasty (PTCA) ≤ 3 months prior, history of sustained ventricular tachycardia/ventricular fibrillation (VT/VF), NYHA class IV and significant comorbidity. Eligible patients were randomised to ICD or conventional therapy. Conventional therapy comprised medical treatment as decided by the investigator. Analyses of results were made on an "intention-to-treat" basis. The trial was stopped on 24 March 1996 due to significantly superior survival for the ICD group vs conventionally managed patients. A total of 196 patients (180 men, 16 women, mean age 63 years) were enrolled during the 5-year duration of the study. Ninety-five patients were assigned to ICD therapy and 101 to "conventional" therapy. No significant differences in demographics or clinical characteristics were observed between the two MADIT patient groups. Twenty-five per cent of the MADIT patients were randomised "early", within 6 months of an acute MI. The remaining 75% of patients were enrolled > 6 months after an acute episode of MI. The patients exhibited poor cardiac function: the left ventricular ejection fraction was 27% in the ICD group and 25% in the "conventional therapy" group. More than 50% of the patients had been previously treated for heart failure. In the ICD arm, 1 month after enrolment, 2% of the patients were taking amiodarone, 26% β-blockers and 12% class I antiarrhythmic drugs, compared to 74%, 8% and 10% respectively in the "conventional therapy" arm.

The ICD patient group had 54% fewer deaths. The 1-, 2- and 3-year actuarial mortality rate was 3%, 13% and 17% in the ICD limb and 23%, 32% and 46% in the conventional therapy limb. Arrhythmic deaths were considerably less frequent in the ICD-treated group than in the conventionally treated group (3% vs 13%). Unexpectedly, the same was also observed for non-arrhythmic deaths (13% vs 26%). Eighty-five per cent of the ICD group received at least one shock during the MADIT study, 60% within 2 years of enrolment. We do not know if all these shocks were appropriate.

On the basis of these results, MADIT investigators conclude that ICD, compared to conventional medical therapy, in particular amiodarone, significantly prolongs survival in high-risk post-MI patients. However, these conclusions must be taken with caution. Indeed, MADIT results apply only to a very small and selected subgroup of patients with previous MI that represent not more than 1% of all post-MI patients, and thus cannot be extrapolated to other high-risk patient populations. Moreover, the MADIT trial has some methodological biases and limitations that have been well stressed by Friedman and Stevenson in their editorial in the *New England Journal of Medicine*[38].

MADIT limitations

The first limitation of the study is the lack of information on the patients screened by attending physicians to identify those who were eligible, as well as on the eligible patients who did not qualify on the basis of the electrophysiological study (patients with non-inducible arrhythmias during baseline programmed ventricular stimulation or in whom arrhythmias became non-inducible after procainamide administration) and on patients who qualified but declined enrolment. Indeed it is surprising that, during the 5-year duration of the study, only a very few subjects (196) were enrolled by the 32 participating centres, with the majority of centres enrolling only one or two patients. This has raised the suspicion that a selection bias may have occurred during enrolment. However, recently, MADIT investigators have reported the 2-year mortality rate of all eligible patients (retrospectively determined). The mortality was 8% for patients non-inducible at baseline electrophysiological study, 20% for patients inducible and suppressible, and 25% for eligible patients who refused enrolment[39]. These data seem to validate the MADIT screening and enrolment process.

The second important limitation of the MADIT trial is the absence of a control group with the possibility that the difference in mortality found between the two study groups is mainly due to the harmful, proarrhythmic effect of class I antiarrhythmic drugs prescribed to 10% of the conventionally treated patients rather than to a survival benefit of therapy with ICD. However, in a recent review of the clinical data of the patients who died of a cardiac cause, MADIT investigators have reported that only six out of the 27 patients who died for this reason in the conventional therapy limb were taking class IA or B antiarrhythmic agents at the time death occurred (and only three of these died suddenly), and no-one was taking class IC antiarrhythmic drugs; 12 patients were taking amiodarone, two sotalol and seven no antiarrhythmic drugs at all[40].

A third limitation of the MADIT trial is an imbalance in β-blocker therapy between the study groups. Indeed, β-blockers were used much more frequently in the ICD group than in the conventional therapy group (26% vs 8%). Taking into account the beneficial effects of β-blockers on post-MI patient mortality, this imbalance might, at least partially explain the better survival of ICD patients. However, it must be emphasised that at separate Cox regression analysis no evidence was found of a meaningful influence of β-blocker therapy on the ICD : conventional therapy hazard ratio ($p > 0.2$)[36].

Another limitation is the lack of information on the proportion of patients receiving amiodarone treatment at different stages of follow-up, as well as on the loading and maintenance doses of amiodarone. The MADIT investigators only report that at 1-month follow-up visit 74% of patients in the conventional therapy limb were taking amiodarone, while at the last follow-up visit only 45% of the patients were still on this drug[36]. So it is likely that more than half of the patients did not receive amiodarone treatment at any time during follow-up. This may account for the higher mortality rate of the conventionally treated group. However, it should be noted that in the conventional therapy group the overall mortality was slightly higher among patients who were taking amiodarone at 1 month than among patients who were not taking the drug (36% vs 26%)[36]. This suggests a harmful effect of amiodarone instead of a beneficial one.

The last limitation reported for the MADIT trial is the inability of establishing the cause and appropriateness of the device interventions during follow-up due to the absence of stored electrogram capability in the majority of ICD models utilised in the trial. Although we do not know the exact proportion of MADIT patients who received an appropriate shock, it is likely that many of the device interventions were triggered by sustained ventricular tachyarrhythmias. Nevertheless, this argument should not be viewed as evidence that ICD saves lives.

Economic and technological issues

Apart from the above-mentioned methodological biases and limitations the MADIT trial has raised economic and technological concerns regarding the prophylactic implantation of ICD in high-risk post-MI patients. According to the American Heart Association[41] every year about 1 500 000 Americans suffer an acute MI. The equivalent number in Italy is estimated to be 150 000 persons[42]. Of these patients probably 1% meet the MADIT eligibility criteria[38]; this means 16 000 people in the USA and 1500 in Italy. Friedman and Stevenson[38] have calculated that the cost in the USA of identifying, evaluating and implanting ICD in the 16 000 post-MI patients who match the MADIT profile would be over $1 billion annually, excluding the cost of follow-up evaluation. In Italy the cost of ICD implant

only in the 1500 post-MI patients with MADIT characteristics would be £52 500 million, based on the current DRG payment system.

Very recently Mushilin and associates[43] have made a cost-effectiveness analysis of the prophylactic implantation of ICD for the patients included in the MADIT study. Considering only the patients who received a transvenous ICD lead system, they have reported a cost of £22 000 per life-year saved. The same estimation has been made by Saksena and others[44–46] for patients who currently receive pectoral ICD implantation for life-threatening ventricular tachyarrhythmias. They have found that the cost-effectiveness of such a therapy is $10 000–15 000 per life-year saved. These cost-effectiveness ratios are acceptable and lie well below numerous other widely used medical and cardiovascular therapies such as treatment of mild hypertension, statin cholesterol-lowering therapy, PTCA and CABG for single-vessel disease, heart transplantation and haemodialysis[44–46].

The development of a "shock-only" device, in an attempt to reduce the cost of prophylactic implantation of ICD in high-risk post-MI patients, has been proposed. However, device manufacturers state that elimination from the device of many currently available diagnostic and therapeutic features will probably not result in a considerably less expensive unit[47]. Moreover, from the patient's prospective, the possibility of avoiding a certain number of inappropriate shocks by means of an antitachycardia pacing system is not completely insignificant[46].

CABG patch trial

The CABG patch trial started in September 1990 as a pilot study; in January 1992 it became a full-scale study and 1 year later became a cooperative study with NHLBI/NIB. The hypothesis tested in the CABG patch trail is whether the prophylactic insertion of an ICD in patients with coronary artery disease, left ventricular ejection fraction < 36% and positive signal-averaged ECG who undergo elective CABG surgery will reduce the risk of death from all causes[34]. Patients with these characteristics are expected to have an overall mortality rate of 24–50% at 3 years postoperatively, presumed to be sudden in 25–50% of cases[48]. The sample size calculated by CABG patch trial investigators to detect a 26% difference in all-cause mortality (primary endpoint over 40 months) between the two study groups was 900 patients. Randomisation was terminated in February 1996; of the 900 patients randomised, 446 were assigned to ICD implantation and 454 to no therapy. In April 1997 the CABG patch trial investigators reviewed the status of the trial and decided to announce the results of the fourth interim analysis at the last NASPE meeting in New Orleans, in May 1997. Dr Bigger, the main investigator, reported that no difference in primary endpoint event was found between the two study groups (patients treated and those not treated with ICD)[37]. Thus, on the basis of this preliminary announcement, the prophylactic insertion of an ICD in high-risk CABG surgery patients does not appear able to reduce all-cause mortality. This finding is in contrast with that observed in the MADIT trial. This discrepancy probably lies in the fact that the study design of the CABG patch trial, and the risk screening process used in this trial, have led to the selection of a patient population at considerably lower risk of arrhythmic death compared to the MADIT population. Indeed, only 30% of CABG patch trial patients had documented non-sustained ventricular tachycardia, and inducibility at electrophysiological testing was not assessed; the risk of sudden death was judged only on the basis of the combined presence of a low left ventricular ejection fraction and late ventricular potentials. As an obvious corollary of this, it seems that spontaneous and induced ventricular arrhythmias are powerful predictors of arrhythmic risk in coronary artery disease patients, while an abnormal signal-averaged ECG is probably not so useful in this population. Moreover, surgical myocardial revascularisation appears to provide protection against sudden death.

Multicentre unsustained tachycardia trial (MUSTT)

The MUSTT[35] started in October 1991 and enrolled coronary heart patients with prior MI, left ventricular ejection fraction ≤ 40%, and asymptomatic or minimally symptomatic unsustained ventricular tachycardia (three complexes to 30 s). Patients who qualified underwent programmed ventricular stimulation, and those who were inducible into sustained ventricular arrhythmias were randomised to antiarrhythmic treatment guided by serial electrophysiological studies, or to no antiarrhythmic treatment. Patients in whom arrhythmias were inducible first tested antiarrhythmic drugs (class IA/C-acebutolol-amiodarone), and if the arrhythmias were not suppressible by drugs they received ICD implantation.

The major hypothesis of MUSTT is that treating high-risk patients with antiarrhythmic therapy guided by an electrophysiological study will reduce the rate of resuscitated cardiac arrests and sudden death (primary endpoint). Thus, MUSTT was designed to examine the value of electrophysiological studies, not whether an ICD is better than antiarrhythmic drugs in the treatment of coronary artery disease patients with low left ventricular ejection fraction and unsustained ventricular tachycardia. The MUSTT study terminated enrolment in November 1996 after 704 patients had been randomised, and is now in the follow-up period, which is expected to last 1–2 years. The Data/Safety Monitoring Board has reviewed the endpoint data of the MUSTT trial and has decided not to discontinue the trial[39].

Conclusions

In conclusion, the results of the MADIT trial have clearly demonstrated that ICD is useful and cost-effective in a very selected and small subgroup of patients with previous MI at high risk of arrhythmic death. However, the discordant results of the CABG patch trial suggest caution, and we must await the results of other ongoing and future randomised trials before extending MADIT conclusions to other different and larger post-MI patient populations.

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Chapter 44

Muscle-sparing Subpectoral Defibrillator Implantation

Gijs Geskes

Introduction

Surgical techniques for the implantation of implantable cardioverter/defibrillators (ICD) do not receive much attention in the literature. A few authors have described their implantation techniques, but these are methods for the implantation of epicardial systems or transvenous systems with abdominal implantation of the device[1,2]. Although, currently, almost-all new ICD systems are transvenous systems with pectoral implantation of the ICD, the surgical technique of this procedure has not been described in detail.

This chapter will describe an easy and practical technique for the subpectoral implantation of an ICD, and report the surgical and functional results of this technique.

Technique of subpectoral ICD implantation

The usual approach of the subpectoral ICD implantation has been *through* the musculus pectoralis major[3,4]. After making a horizontal or slightly oblique skin incision below the middle part of the clavicle, the clavicular head of the pectoralis major muscle is separated from the sternal portion and the space between the pectoralis minor and major muscles is reached by blunt dissection. This dissection carries the risk of damage to the thoraco-acromial neurovascular bundle which is located under the pectoralis major muscle (Fig. 1). This dissection can also lead to bleeding when small vessels in the muscle are torn.

In order to avoid the possible complications of a transmuscular approach we developed a technique in which the subpectoral region is reached by going *around* the pectoral muscle[5,6]. This region is reached by dissecting between the deltoid muscle and the pectoralis major muscle and around the lateral border of the clavicular

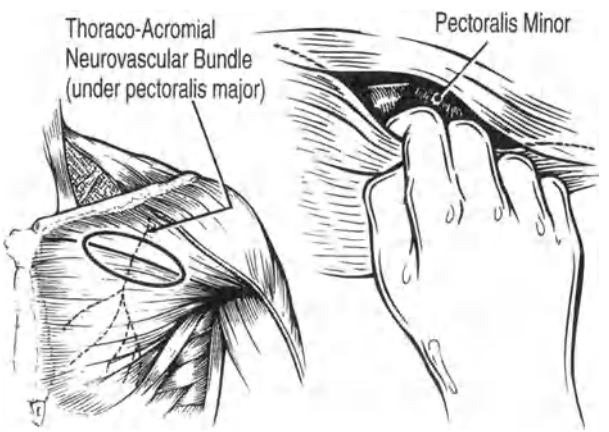

Figure 1. Skin incision for the transmuscular approach of the subpectoral region and the course of the thoraco-acromial nerve bundle.

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head of the pectoral muscle. We call this the "muscle-sparing subpectoral ICD implantation technique". A detailed description of this technique, which we have used in almost 100 consecutive patients, follows.

The muscle-sparing subpectoral ICD-implantation technique

All implantations in our hospital are performed by a team, including a cardiac surgeon and a cardiologist. The procedure takes place in the operating room, with the patient under general anaesthesia. In all patients a radial artery catheter for blood pressure monitoring is inserted by the anaesthesiologist. Antibiotics (intravenous cephalosporins) are administered prophylactically. Fluoroscopy is provided by mobile X-ray equipment.

The skin incision is made in the deltopectoral groove (usually the left), starting about 1 cm below the clavicle (Fig. 2). The length of the incision is determined by the size of the ICD; the usual length is 8–10 cm. The dissection of the subcutaneous tissue is done with the diathermic knife, which provides optimal haemostasis and maintains a clear operating field. This dissection is continued until the cephalic vein, which is located in the fat between the deltoid and pectoral muscle, comes into view. To prevent spasm of the cephalic vein, further dissection is carried out with scissors. Only a few centimetres of this vein need to be dissected free to be able to introduce an ICD lead into this vessel.

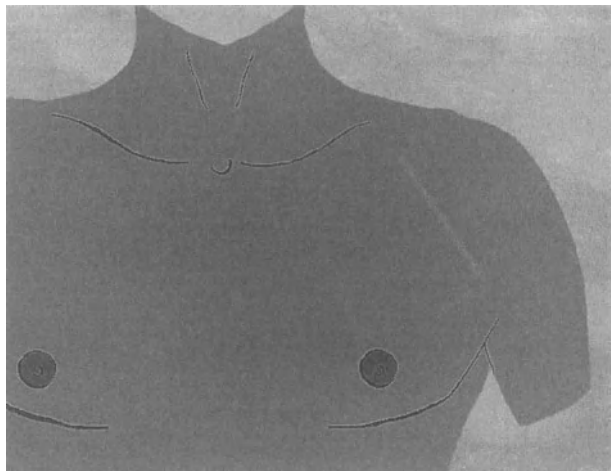

Figure 2. Skin incision for the muscle-sparing subpectoral ICD implantation.

After identification of the lateral border of the pectoralis major muscle the cephalic vein plus the medial border of the deltoid muscle are gently retracted laterally. The border of the pectoralis major muscle is freed from the surrounding tissue until the pectoralis minor muscle is reached (Fig. 3).

The subpectoral pocket is then created by blunt dissection with the index fingers of both hands (Fig. 4). As there is a natural plane between the pectoralis major and the pectoralis minor muscle, this dissection is very easy and does not cause any bleeding. The use of scissors and cautery is not necessary.

Figure 3. After the dissection of the lateral border of the pectoralis major muscle (the head of the patient is to the right). Between this border (below the ring hook) and the cephalic vein the pectoralis minor muscle is visible.

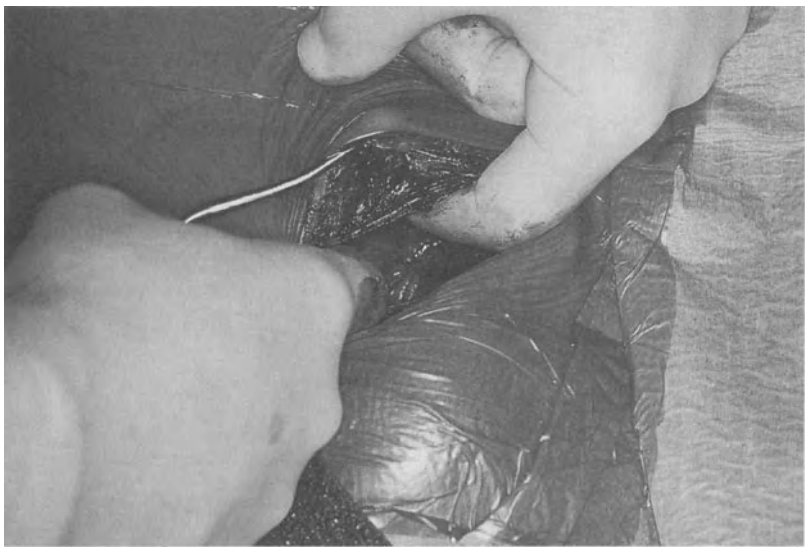

Figure 4. Creation of the subpectoral pocket by blunt dissection with two fingers.

The cephalic vein can be used to introduce the right ventricular lead in the standard fashion. When the cephalic vein cannot be used (too small in diameter, impossibility to advance the lead into the subclavian vein) or two leads must be introduced (separate superior caval vein lead and/or right atrial lead for DDD-pacing) a subclavian vein puncture can be performed by advancing the needle from the top end of the incision into this vein (Fig. 5). In order to avoid damaging the insulation of the RV lead by the needle we first perform the puncture of the subclavian vein and leave a guidewire in place, and then introduce the lead via the cephalic vein.

The leads are fixed by suturing the anchoring sleeve to the surrounding tissue with non-resorbable suture material.

After connecting the leads to the ICD, the device is placed in the pocket (Fig. 6). Sharp bends in the leads close to the connector should be avoided to prevent excessive lead stress due to movement of the ICD behind the pectoralis major muscle. Fixation of the ICD to the surrounding tissue is not necessary.

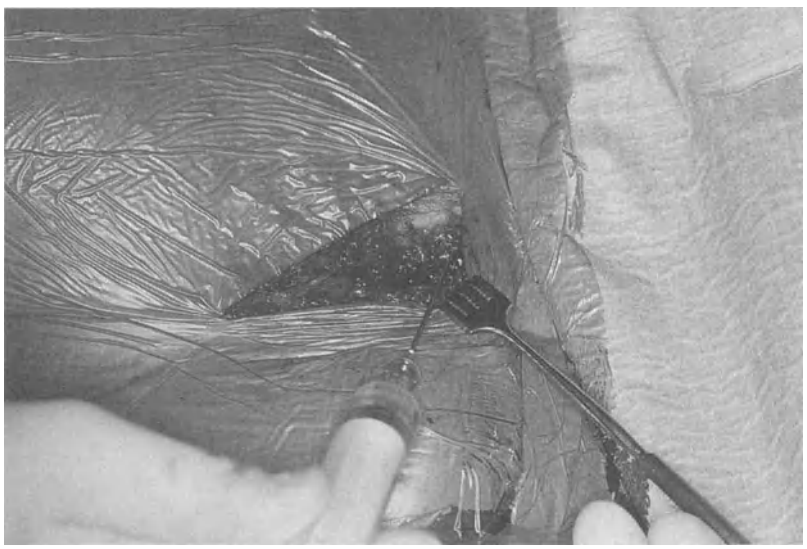

Figure 5. Subclavian vein puncture.

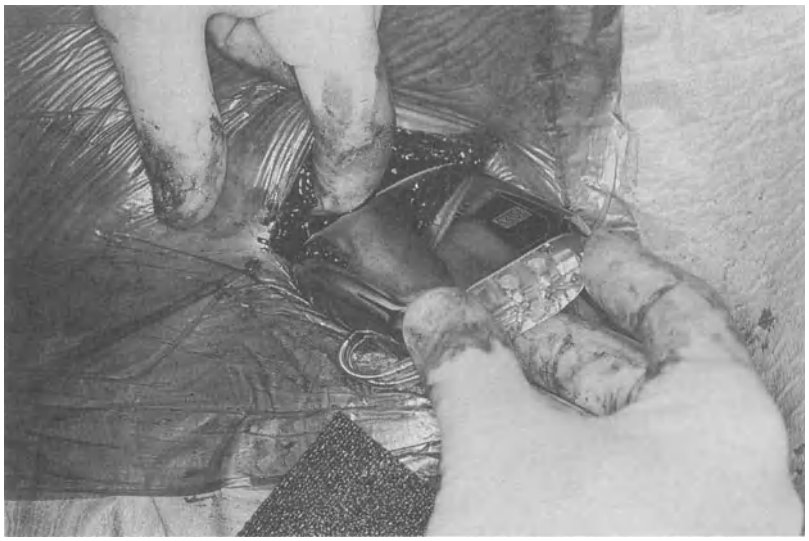

Figure 6. Placement of the ICD in the subpectoral pocket.

To obtain good covering of the device and the leads the borders of the pectoralis major and deltoid muscles are approximated with a resorbable suture (Ethicon Vicryl 2–0). The subcutaneous tissue is approximated with the same suture. We prefer to close the skin incision with a subcuticular, resorbable suture (Ethicon PDS 4–0). The cosmetic result of this type of suture is much better compared to wound closure with interrupted non-resorbable sutures. Finally the wound is covered with a simple plaster for about 4 days.

Results

We used this technique in a consecutive series of 82 patients from September 1994 to April 1997. The technique has not been modified in any way since the first implantation. There were 83 implantations in 82 patients (one patient had a second implantation after an infection of the ICD system).

The group consisted of 62 male and 20 female patients, aged 22–76 years (mean 55).

The implanted devices were:

RV lead only:	67
DDD with RA and RV lead:	9
RV and SVC lead:	7

All implants were on the left side except three (one because of a wound infection, one because of patient preference and one because of a superficial skin infection in the region of the left shoulder). The mean implantation time was 83 min (40–160); the implantation time tended to increase over time because of the introduction of the DDD-ICD, for which an additional right atrial lead has to be placed.

The surgical complications are summarised in Table 1. Early complications which required any type of treatment were: wound infection (removal of the system), pneumothorax (drainage), pneumonia (antibiotics) and early RV-lead dislocation (repositioning of the lead). Late complications which required treatment were: painful shoulder (revision of the subpectoral pocket), decreasing electrogram (repositioning of RV lead) and thrombosis of the subclavian vein (heparinisation).

Mortality during the implantation procedure was zero. Only one patient died during the first 30 days postoperatively, of a myocardial infarction.

There were six reinterventions (7.3%): two related to the implant procedure itself (wound infection, painful irritation of shoulder) and four not related to the procedure (three early lead dislocations, one decreased electrogram). In three other patients the ICD was removed temporarily during later coronary artery bypass surgery.

Discussion

There is some controversy concerning the pectoral implantation of ICDs: where should the implantation be performed (operating room (OR) or catheterisation laboratory); who should do the implantation (cardiac surgeon or cardiologist); what type of anaesthesia (general or local) and what should be the localisation of the ICD (prepectoral/subcutaneous or subpectoral)? Few

data to answer these questions are available. In most hospitals the way in which ICD implantations are performed has been determined by local circumstances (for instance the availability of an OR) and by the experience of the implanting team.

Our preference is to do all the implantations in the OR. Advantages of performing implantation in the OR are the better surgical environment (better lighting, availability of all surgical equipment including suture materials, higher degree of sterility compared to a catheterisation laboratory, better monitoring of the patient by the anaesthesiologist). A possible advantage of using the catheterisation laboratory is the higher quality of the X-ray equipment, but in general a mobile X-ray unit in the OR is sufficient for ICD implantations.

The role of the surgeon in the implantation of ICDs has become a relatively minor one since the introduction of transvenous systems, and especially since ICDs for pectoral implantation have become available. Before that, an implantation was a extensive surgical procedure involving placement of patches around the heart via median sternotomy, lateral thoracotomy or a subcostal incision. These implantations – by necessity – were performed by a (cardiac) surgeon, in the OR and with general anaesthesia. Nowadays the implantation is only as difficult as the implantation of a big pacemaker, and extensive experience in cardiothoracic surgery is not absolutely necessary.

In our hospital the implantation team includes a cardiac surgeon and a cardiologist, both with extensive experience in ICD implantation. Other members of the team are an anaesthesiologist (as all patients are under general anaesthesia) and a ICD technician. The surgeon makes the skin incision, dissects the cephalic vein and/or performs a subclavian vein puncture, creates the subpectoral pocket and finally closes the wound. The cardiologist places the leads and supervises the testing of the system.

For anaesthesia one can choose between general anaesthesia and local anaesthesia plus extra sedation during testing. When the implantation takes place in the OR general anaesthesia is preferable. Even when general anaesthesia is used, the patients can be extubated at the end of the procedure and can be fully ambulatory a few hours later. Local anaesthesia requires injection of a considerable amount of anaesthetic, and the use of intravenous sedatives during testing. This procedure also requires careful monitoring of the patient by an anaesthesiologist or anaesthesiology nurse.

Finally, regarding the localisation of the pocket for the ICD. We have a very strong preference for subpectoral placement, for the following reasons. Experience with the old pacemakers has shown that these devices, due to their weight, tended to migrate easily when placed in a subcutaneous pocket. Another serious problem was erosion of the skin, because these devices were bulky. It seems reasonable to assume that ICDs, which are even heavier and bigger than the old pacemakers, will also be prone to these problems. The risk

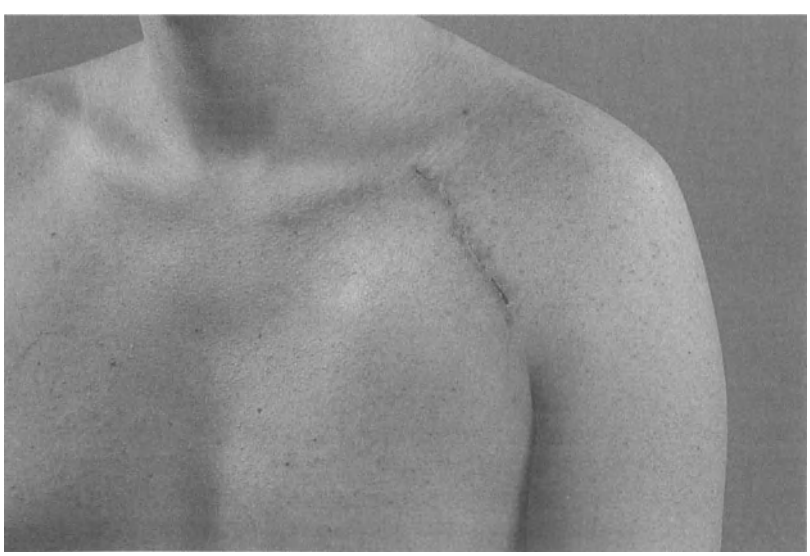

Figure 7. Aspect of the wound 6 days after implantation.

of skin erosion, which will manifest itself only in the long run, can be avoided by placing the ICD behind the pectoral muscle. Migration of an ICD may cause traction on the lead(s), with possible dislocation. Especially in older people, who have less firm subcutaneous tissue, migration of a heavy ICD will almost certainly occur. Migration of an ICD may cause traction on the lead(s), with possible dislocation. An ICD in a subpectoral pocket cannot migrate downwards easily, as the attachment of the pectoralis major muscle to the thoracic wall prevents this.

The cosmetic aspect of a subcutaneously placed ICD is not very favourable. It has been described as "wearing a packet of cigarettes under the skin". Since many patients who receive an ICD are in the younger age group the cosmetic aspect is very important. In contrast, a subpectorally placed ICD is barely visible (Fig. 7).

An argument against subpectoral placement is that creating a subcutaneous, prepectoral pocket is supposedly easier and should therefore lead to fewer complications (bleeding) than subpectoral placement. In our experience subpectoral implantation with the muscle-sparing technique is as easy as, and probably even easier than, subcutaneous placement, the reason being that there is a clearly defined, avascular plane behind the pectoralis major muscle.

Another argument is that replacement of a subcutaneous ICD will be easier than replacement of a subpectoral ICD. Our experience with five late re-interventions shows that a subpectoral ICD can be reached easily via the original approach and removed from its pocket without difficulty.

In conclusion, the muscle-sparing technique for subpectoral implantation of an ICD is very simple and has excellent surgical and functional results. In our opinion this technique is as simple as, and perhaps even simpler than, subcutaneous, prepectoral implantation, and it does not have any of the disadvantages of the subcutaneous technique. This technique can also be used when implanting a pacemaker, especially in very old patients and young children.

Table 1. Surgical complications

Early complications	
Major haematoma	1
Pain and swelling of arm for < 1 week	3
Pain for > 1 week	4
Paraesthesias for > 1 week	1
Wound infection	1
Pneumothorax	4
Pneumonia	1
Early lead dislocation	3
Late complications	
Painful irritation of shoulder joint	1
Seroma	2
Decreasing electrogram	1
Thrombosis of subclavian vein	1

Acknowledgements

The author gratefully acknowledges the help of Dr Karel den Dulk in the preparation of this chapter.

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Chapter 45

Follow-up Techniques in Patients with Implantable Cardioverter/ Defibrillators

Michael Block, Barbara Lamp, Max Weber and Günter Breithardt

Introduction

Patients with implantable cardioverter/defibrillators (ICD) suffer frequent and various complications during follow-up[1]. Within a recent multicenter study including 820 patients with a third-generation ICD, 280 patients (34%) experienced adverse events within a follow-up of only 5 ± 5 months[2]. Thus, a close follow-up of these patients by a physician aware of typical complications should be warranted. The most common adverse event is inappropriate arrhythmia detection typically resolved by programming or drug changes[3]. Other adverse events which might be resolved by reprogramming are syncopes despite ICD therapy[4], ventricular tachycardias below the programmed detection rate[5], and painful cardioversion shocks delivered during haemodynamically tolerated ventricular tachycardias[6]. Further complications, such as infection of the ICD, lead dislodgements, insulation failures, lead perforation, and emboli from thrombi attached to the leads which might be detected during follow-up, frequently require surgical intervention[1].

The first defibrillators implanted in the early 1980s by Mirowski et al were designed as automatic devices which did not allow any kind of programming of detection and therapy[7]. The only task of follow-up had been to ensure system integrity and rule out battery depletion[8]. The latter had to be done every 2 months by checking the time needed to charge the capacitors of the device. Sensing could also be checked non-invasively during sinus rhythm by a beep-o-gram, an audible tone transmitted by the device after application of a magnet for every detected ventricular signal[9]. However, this was only qualitative information which did not allow the user to foresee a problem of detection of ventricular fibrillation in the case of a poor but still detectable signal during sinus rhythm. Lead integrity could be checked additionally by X-ray which, however, is insensitive to many lead problems, e.g. insulation failures. Thus, system integrity could be ensured only by invasive induction of ventricular tachyarrhythmias, done usually before hospital discharge, some months after implantation, or in the case of any clinical problem.

In 1988 the first programmable ICD was introduced, which allowed changing the rate at which the ICD should detect ventricular tachyarrhythmias, and optionally only assumed a ventricular tachyarrhythmia in case of a broad ventricular signal derived from the defibrillation leads (probability density function)[10]. Both programming

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options were developed due to the problem that, in many patients, a rate overlap between ventricular tachyarrhythmias and sinus tachycardias, fast-conducted atrial fibrillation, or supraventricular tachycardias existed. This overlap caused inappropriate painful shocks once the detection rate was chosen too low. Additionally, two ways to influence the time interval needed from the start of the tachycardia to shock delivery were available in this first programmable ICD: the detection delay and the energy delivered by the first shock. Decreasing the time interval was an option to avoid syncope despite proper termination of the ventricular tachyarrhythmias, while by increasing the time interval, unnecessary shocks for unsustained tachyarrhythmias could be avoided.

Starting in 1989, fast development of ICD functions and stored information on detected episodes occurred[11]. Several new therapeutic options have been introduced: antibradycardia pacing (VVI, DDD), antitachycardia pacing (for supraventricular and ventricular tachycardias, for prophylaxis and termination of tachycardias), cardioversion in the atrium, and different waveforms for shocks. Several new detection options have also been introduced: stability, onset, and width criteria; multizone and dual-chamber detection; non-committed detection, redetection. Stored information on detected tachycardias now usually includes date and time of detection, shows which detection criteria were fulfilled, consecutive RR intervals and electrograms of the detected episode. Additionally detection markers and electrograms are available via telemetry. Size and duration of the signals and impedances for pacing and defibrillation leads can be determined; for example the Medtronic Arrhythmia Management Device Model 7250, introduced in 1997, offers 135 programmable parameters and stores 128 Kbytes of information. Models from different companies differ significantly in their detection algorithms, therapy options and stored information. The turnover cycles for models have become less than a year with some manufacturers. Thus, today an ICD still acts automatically, but the way it is acting can be changed by the physician in hundreds of ways, for the benefit or disbenefit of the patient. Additionally, as long as the important information from the huge amount of stored information is not highlighted by the retrieving program, the physician might overlook this information; e.g. a short-circuit of the defibrillation leads indicated by the impedance value.

COUNTER DATA REPORT ---------- Page 2 of

VF THERAPY	Rx1	Rx2	Rx3	Rx4	Rx5	Rx6
INITIATED:	1	0	0	0	0	0
SUCCESSFUL:	1	0	0	0	0	0
ABORTED:	0	0	0	0	0	0
INEFFECTIVE:	0	0	0	0	0	0
CONVERTED TO VT:	0	0	0	0	0	0
UNDETERMINED:	0	0	0	0	0	0

VT THERAPY	Rx1	Rx2	Rx3	Rx4	Rx5	Rx6
INITIATED:	16	1	1	0	0	0
SUCCESSFUL:	15	0	0	0	0	0
ABORTED:	0	0	0	0	0	0
INEFFECTIVE:	1	0	0	0	0	0
CONVERTED TO VF:	0	0	0	0	0	0
VT ACCELERATED:	0	0	0	0	0	0
UNDETERMINED:	0	1	1	0	0	0

Figure 1. Interrogation of therapy history of an ICD (Medtronic AMD™ model 7250). Detection and success rates for the VT- and VF-therapy zones are summarised for each step of therapy (Rx1, Rx2, ..., Rx6).

Follow-up techniques for ICD

The follow-up techniques described are confined to those which are related to the ICD. Pacemaker follow-up techniques required for other than VVI-antibradycardia pacemaker functions are not described here. In contrast to many pacemaker patients, most ICD patients have an underlying structural cardiac disease, and often a poor left ventricular function. ICD follow-up also gives a chance to detect and treat symptoms of progression of the underlying cardiac disease at an early stage, and should not be down graded a solely technical follow-up.

History of symptoms

Patients should be asked for symptoms of tachycardias (e.g. palpitations, dizziness, syncope), symptoms of ICD therapy (e.g. palpitations due to antitachycardia pacing, pain due to shocks, contractions of skeletal muscles adjacent to the ICD), and symptoms of infection of the ICD (e.g. secretion, reddening, pain or heating of the skin overlying the device or the lead(s), fever, chills)[12]. Additionally, patients should be evaluated for emotional stress due to ICD therapy or recurrent tachycardias.

Physical examination of the pulse-generator site

The skin overlying the device and the lead(s) should be examined for erythema, secretion, pain and heat. Especially in patients with subcutaneously implanted devices, signs of erosion and migration should be sought[13]. With abdominal devices, perforation into the peritoneal space, causing an acute abdomen, have been described[14].

Interrogation of ICD for detected tachycardia episodes

ICD store detailed information on detected tachycardia episodes. The types of information and their presentation differ between different manufacturers and models. Occasionally, hundreds of episodes might have occurred since the last interrogation of the ICD, confronting the physician with a mass of information. A standardised approach is advisable to analyse this information. First, a summary of detections and therapies which have occurred since the last interrogation should allow the physician to realise how often antitachycardia pacing and shocks have occurred, how often antitachycardia pacing was not successful or accelerated the tachycardia and how often the ICD needed more than one shock to terminate the tachycardia, or did not terminate the tachycardia at all (Fig. 1). In case of frequent tachycardias, one should assess whether a cluster of tachycardias has occurred (Fig. 2). Once a cluster has been detected, the patient should be asked about special circumstances which might have caused the cluster (use of diuretics, decreased use of potassium, changes of antiarrhythmic drugs, diarrhoea, fever, stress, heart failure, etc.). The cluster should be analysed with more detailed temporal resolution to detect episodes of incessant ventricular tachycardia which run the risk of exhausting all therapies (Fig. 3).

The individual episode has to be analysed regarding its appropriate detection and therapy. Appropriate detection of ventricular tachycardias can be assumed based on several factors (Table 1)[3]. The most diagnostic ones are a change in morphology of the electrogram com-

Episodenkalender

	August 1996	September 1996	Oktober 1996	November 1996	Dezember 1996
1 2 3 4 5					1 8 1
6 7 8 9 10					
11 12 13 14 15					
16 17 18 19 20				1 13	
21 22 23 24 25					
26 27 28 29 30 31				7	

Figure 2. Interrogation of therapy history of an ICD (Biotronik Phylax 06™). Episodes of tachycardias are summarised on a day-to-day basis using a calendar. A cluster of episodes occurred on 20 and 30 November and on 2 December.

ID	DATUM	ZEIT	TYP	DS.ZYKLUS	LZTE.Rx	ERFOLG	DAUER
63	Nov 06	11:53:21	VT	360 ms	VT Rx 1	Ja	6 Sek
62	Nov 06	11:52:13	VT	350 ms	VT Rx 1	Ja	5 Sek
61	Nov 06	11:51:04	VT	350 ms	VT Rx 1	Ja	5 Sek
60	Nov 06	11:49:05	VT	350 ms	VT Rx 1	Ja	6 Sek
59	Nov 06	11:43:40	VT	370 ms	VT Rx 1	Ja	6 Sek
58	Nov 06	11:38:45	VT	370 ms	VT Rx 1	Ja	5 Sek
57	Nov 06	11:37:11	VT	370 ms	VT Rx 1	Ja	5 Sek
56	Nov 06	11:36:57	VT	360 ms	VT Rx 1	Ja	5 Sek
55	Nov 06	11:36:04	VT	360 ms	VT Rx 1	Ja	5 Sek
54	Nov 06	11:35:28	VT	360 ms	VT Rx 1	Ja	5 Sek
53	Nov 06	11:33:02	VT	370 ms	VT Rx 1	Ja	6 Sek
52	Nov 06	11:30:23	VT	370 ms	VT Rx 1	Ja	6 Sek
51	Nov 06	11:28:14	VT	370 ms	VT Rx 1	Ja	5 Sek
50	Nov 06	11:26:32	VT	370 ms	VT Rx 1	Ja	6 Sek
49	Nov 06	11:24:35	VT	370 ms	VT Rx 1	Ja	5 Sek
48	Nov 06	11:20:42	VT	370 ms	VT Rx 1	Ja	5 Sek
47	Nov 06	11:18:42	VT	370 ms	VT Rx 1	Ja	5 Sek
46	Nov 06	11:17:27	VT	370 ms	VT Rx 1	Ja	6 Sek
45	Nov 06	11:16:37	VT	370 ms	VT Rx 1	Ja	6 Sek
44	Nov 06	11:14:21	VT	370 ms	VT Rx 1	Ja	6 Sek

Figure 3. Interrogation of therapy history of an ICD (Medtronic Jewel™). Therapies are listed in chronological order showing many detections within a very short period of time and only short intervals between two episodes, indicating the temporary situation of an incessant ventricular tachycardia. Number (ID), date (Datum), starting time (Zeit) and duration (Dauer) of episode, zone of detection (Typ), cycle length of tachycardia (Ds. Zyklus), last delivered therapy (Lzte.Rx) and its result (Erfolg) are listed.

pared to the one during normal rhythm, and termination of the tachycardia by the ICD[15,16]. However, specific diagnostic parameters are available only with dual-chamber ICD (lower atrial than ventricular rate or start of the tachycardia in the ventricles in case of 1 : 1 relation of atria and ventricles) (Fig. 4)[17]. In some cases, with an electrogram derived from the defibrillation leads, P-waves are also prominent during tachycardia, and allow one to diagnose clearly a ventricular tachycardia, e.g. based on a capture beat. To facilitate diagnosis based on the ventricular electrogram, it is useful to have collected the patients' electrograms for comparison during sinus rhythm and/or atrial fibrillation, as well as during induced ventricular tachycardias.

Myopotentials detected due to insulation failures as a cause of inappropriate ICD therapies can be diagnosed directly from electrograms derived from the sensing leads or by comparison of the stored RR intervals with the stored electrograms from the defibrillation leads (Fig. 5)[3,18,19]. The latter also allows identification of double-sensing due to additional sensing of P-waves, T-waves or pacing stimuli or double-sensing of ventricular signals (Fig. 6)[18]. Onset, stability and the relationship of the detected tachycardia to the programmed detection intervals can be better appreciated from the RR intervals stored from the sensing leads than from stored electrograms (Fig. 7).

Under-detection of ventricular tachycardias can be prevented by programming a lower detection rate once a ventricular tachycardia has been detected near the programmed detection rate[5]. Information on stability, onset and width of the ventricular signals for ventricular and non-ventricular tachycardias with a rate overlap allow optimisation of additional detection criteria to facilitate a fairly specific detection of ventricular tachycardias without significantly decreasing sensitivity[20,21].

Information on success rates of appropriate therapies allow identification of those antitachycardia pacing modes, shock energies or waveforms which individually nearly always have been successful and those which

Table 1. Discrimination between ventricular and non-ventricular tachycardias

	VT	SiTa	AFib	SVT
Rate				
Ventricular > 240 bpm	+++	–	–*	–*
Atrial < ventricular†	+++	–	–	–
Atrial = ventricular†	±††	++	–	+
RR intervals				
Stable	+	++	±	+
Sudden onset	++§	–	±	++
First in the ventricle†	+++	–	–	–
Slowly crossing detection interval	±¶	++	–	±¶
Endocardial electrogram				
Polymorphic	+++	–	–*	–
Broad during tachycardia	++††	±	±	±
Different during tachycardia	+	±	±	±
Capture beat**	+++	–	–	–
Outcome of therapy				
Termination by cardioversion	+	–	±	±
Termination by ATP	+	–	–	±

Classification in relation to class of tachycardia: +++ = specific; ++ = always but not specific; + = frequent; ± = might occur; – = does not occur.
Abbreviations: AFib = atrial fibrillation; ATP = antitachycardia pacing; SiTa = sinus tachycardia; SVT = supraventricular tachycardia; VT = ventricular tachycardia.
* If an accessory pathway has been excluded.
† Criterion can be used only with dual-chamber ICD.
†† In the case of 1 : 1 V-A conduction.
§ In some cases VT is triggered by exercise showing only a small change of the tachycardia cycle length.
¶ Only when the tachycardia starts below the programmed detection rate and later accelerates.
** Criterion can be used only with electrogram of defibrillation electrodes.
†† Rarely a VT originating in the basal interventricular septum may be narrow.

have high tendencies to accelerate the tachycardia. Using this information, ICD therapy can be optimised. Information on the lead impedance of delivered shocks sometimes allows one to suspect or diagnose a short-circuit or lead fracture[19]. Variations of lead impedances between individuals, lead configuration and applied peak voltages have to be considered.

Evaluation of the integrity of sensing and pacing, battery check

Sensing signals can usually be telemetered on-line from the device and recorded in parallel with an ECG lead and detection markers of the ICD. The sensing signal can be compared visually to the one obtained previously, and its size can be measured for quantitative comparison. Some ICD allow the user to change sensitivity if necessary. If a right ventricular lead perforation is suspected, a change of the electrogram might be documented. When the width of the electrogram is used as an additional detection criterion, it should be measured, too, and width detection parameters should be corrected if necessary. Due to the automatic gain or threshold control, ICD are more susceptible to over-sensing than pacemakers, despite bipolar sensing[18]. Once over-sensing is clinically suspected, or device replacement is scheduled, provocative manoeuvres should be performed during recording of detection markers and/or sensing electrograms and a surface ECG lead[19]. These manoeuvres should include use of the diaphragm, skeletal muscles near the device and the submuscular or subcutaneous part(s) of the lead(s), shaking the device, and manoeuvres mimicking the exercise which have provoked the inappropriate detection. Due to the automatic gain or threshold control, over-sensing might be seen only with profound bradycardia, or if the sensing signal has deteriorated[17]. In this case the inappropriate detection typically shows a quite long RR interval followed by several short ones which are close to the refractory period of the device. However, in many cases only isolated myopotentials are detected during provocation manoeuvres (Fig. 8). An example of a

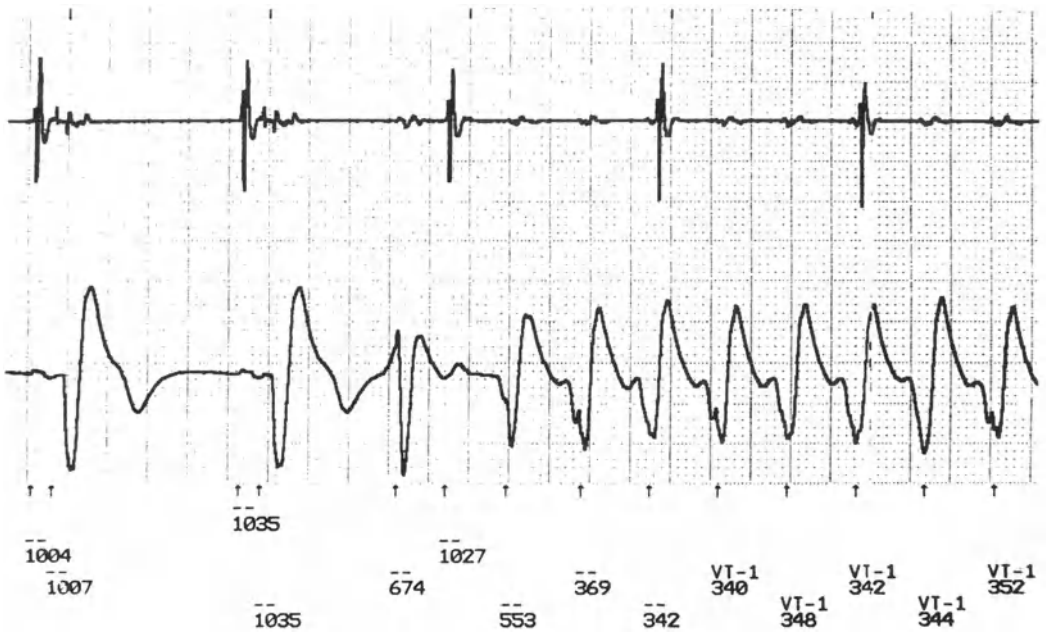

Figure 4. Interrogation of therapy history of an ICD (CPI Ventak™ AV model 1810). The onset of a ventricular tachycardia episode (175 bpm) is shown. The lower electrogram from the defibrillation electrodes shows the onset of a tachycardia with broad QRS complexes. Before the onset, P-waves precede paced (DDD, 60 bpm) broad QRS complexes. The upper electrogram from the bipolar atrial pace/sense electrode shows large atrial deflections and tiny ventricular deflections. The AV-dissociation proves that the tachycardia originates from the ventricles. Below the electrograms sensing markers, RR intervals and therapy zones, in which RR intervals have been detected, are shown.

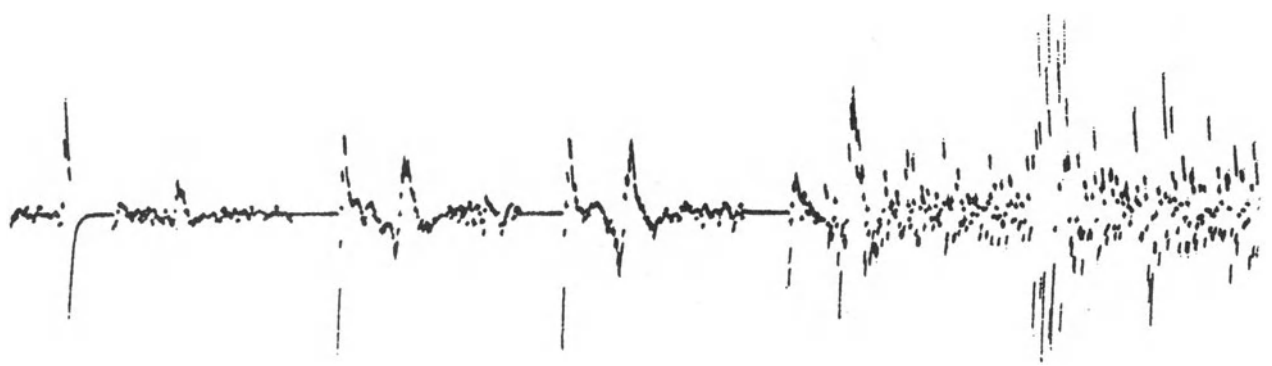

Figure 5. Interrogation of therapy history of an ICD (Ventitrex Cadence™). The electrogram of the sensing electrodes shows a regular slow rhythm which is superimposed by high-frequency myopotentials which were detected due to an insulation failure of the sensing lead.

combination of bradycardia and muscle contractions which facilitate over-sensing is the Vasalva manoeuvre used during defaecation.

Pacing thresholds and pacing lead impedances have to be determined as in ordinary pacemakers.

Battery integrity is determined directly from the battery voltage and/or by measuring the time needed for charging the capacitor. Some devices derive semi-quantitative data concerning battery integrity from this measurement (beginning of life = BOL, middle of

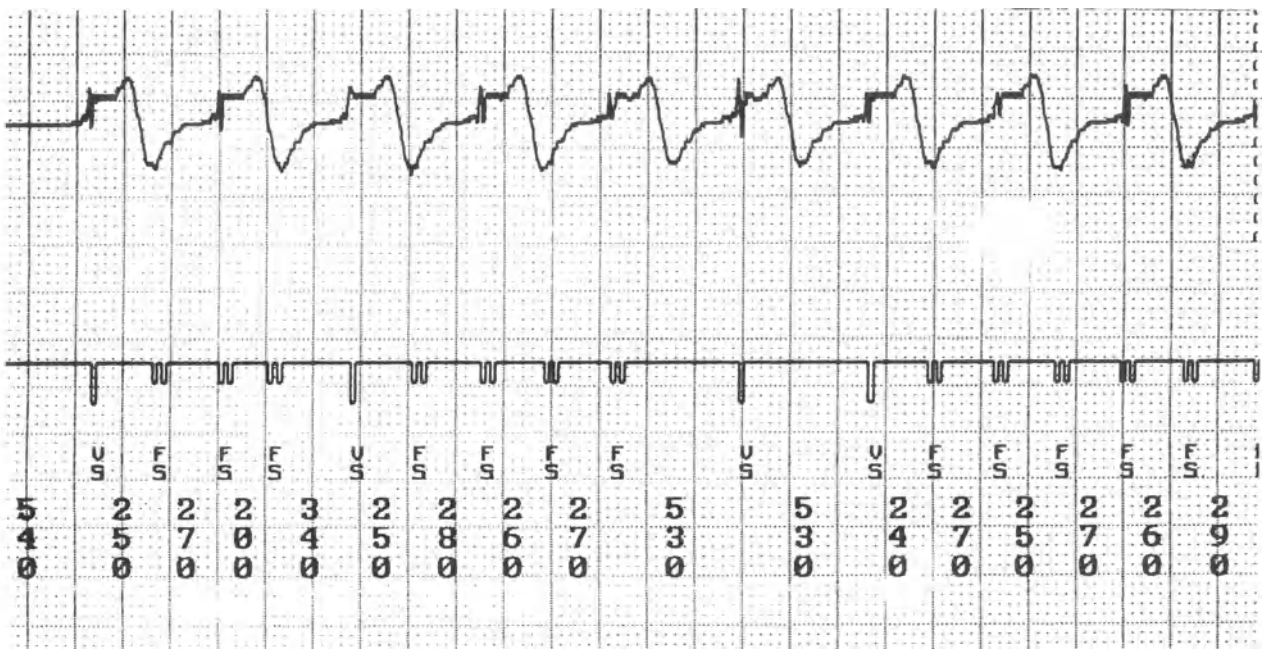

Figure 6. Interrogation of a therapy history of an ICD (Medtronic Jewel™). The endocardial electrogram shows a sinus tachycardia (113 bpm). The markers and RR intervals based on the deflections detected from the sensing electrodes by the device indicate that additional T-wave detection took place for most beats and caused an inappropriate detection within the VF zone (FS = fibrillation sense). The patient had an episode of vasospastic angina causing ST elevation.

life = MOL, elective replacement indicator = ERI, end of life = EOL). Once ERI has been reached, replacement of the device has to be scheduled within a certain period of time. The period depends on the ICD model and the patient's expected use of pacing and shocks.

Electrocardiogram

A 12-lead ECG should be recorded whenever possible to allow for definitive diagnosis of the current rhythm and to detect progression of the underlying disease. If a right ventricular lead perforation is suspected a change of paced QRS morphology, as well as of the bipolar stimulus, might be documented.

An exercise ECG should be performed if sinus tachycardia or fast-conducted atrial fibrillation is suspected as a cause of inappropriate therapies. If reprogramming was done and/or antiarrhythmic drugs were prescribed to avoid recurrent detection of sinus tachycardia or fast-conducted atrial fibrillation by the ICD, the benefit of these measures should be ascertained by another exercise ECG.

Laboratory examination

Sedimentation rate, blood count and blood cultures should be taken in the case of a suspected ICD infection; potassium and magnesium in the case of a cluster of ventricular tachyarrhythmias, especially if diuretics have been prescribed.

X-ray

Chest X-rays might be able to identify perforation, dislodgement and fracture of leads[1,22]. However, a chest X-ray should be performed only during a follow-up visit if another indicator for perforation, dislodgement or fracture of a lead exists. As fractures and dislodgements of subcutaneous or additional transvenous defibrillation leads (e.g. in the superior vena cava) may not be detected by over-sensing or changes in lead impedances, patients with these leads might routinely receive a chest X-ray after certain follow-up periods or, at least, if device replacement has been scheduled[22]. Whether a fluoroscopic examination is of additional value has not yet been shown.

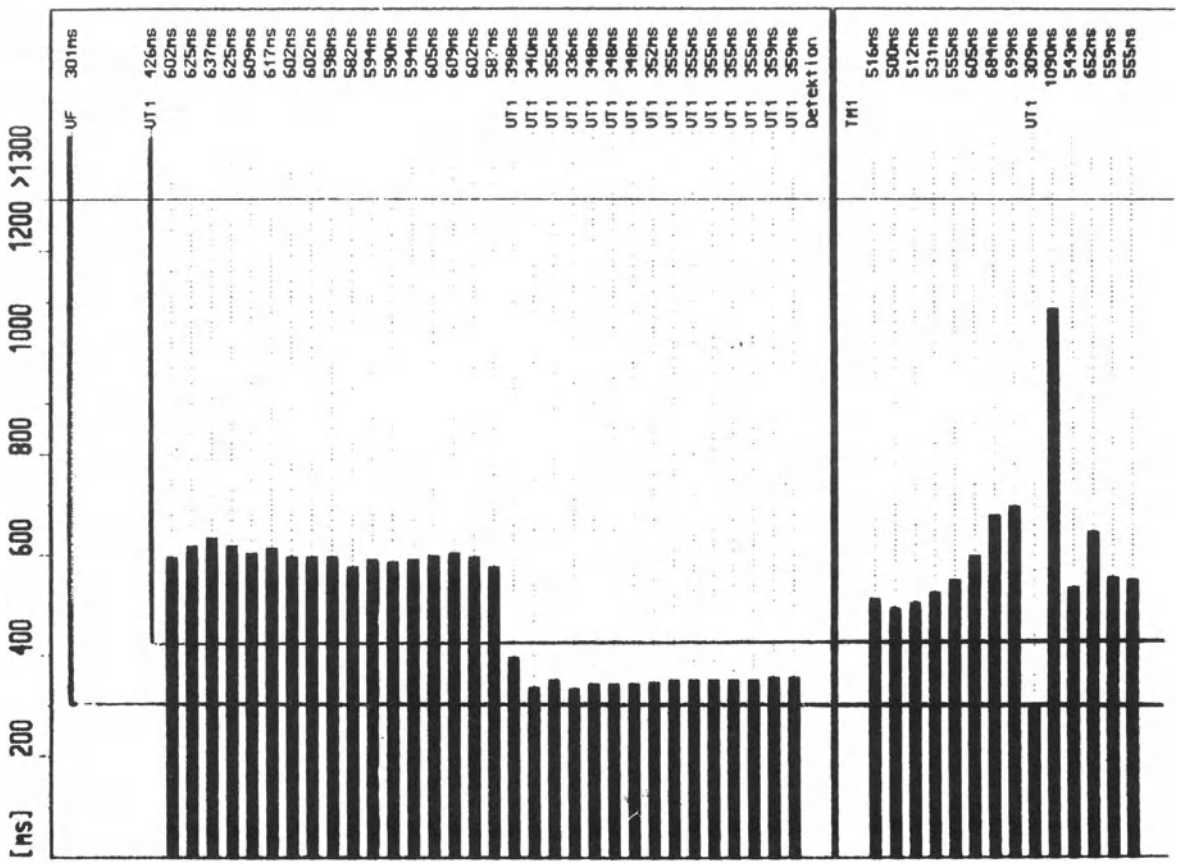

Figure 7. Interrogation of therapy history of an ICD (Biotronik Phylax 06™). An episode of ventricular tachycardia is displayed graphically by the detected RR intervals preceding the tachycardia (17 RR intervals), at the start of the tachycardia (15 RR intervals), and after ICD therapy (14 RR intervals) in relation to the programmed RR intervals for detection of VT and VF.

Echocardiography

If a cluster of ventricular tachycardias has occurred, echocardiography should be performed to rule out deterioration of left ventricular function. If a perforation of a right ventricular lead is suspected, echocardiography might show a pericardial effusion, or might visualise the perforation directly[23]. In the case of pulmonary emboli, systemic (possibly paradoxic) emboli, or suspected infection of the ICD system, a transthoracic, and if negative, transoesophageal echocardiogram should be performed to detect thrombi or vegetations attached to the leads[24].

Holter ECG

As ICD provide more and more sophisticated built-in Holter functions, Holter ECG are rarely needed in ICD patients. They still have a value if symptoms occur which can be attributed to arrhythmias, but no episodes have been detected by the ICD. Tachycardias below the programmed detection rate of the ICD, frequent unsustained ventricular tachycardias or, in patients who need permanent pacing, an intermittent exit-block or over-sensing might be detected.

Non-invasive induction of ventricular tachyarrhythmias

All current ICD have sufficient non-invasive means to induce ventricular tachyarrhythmias including programmed ventricular stimulation, high-frequency bursts and/or T-wave shocks. After induction of ventricular tachycardias and/or fibrillation, the safety and efficacy

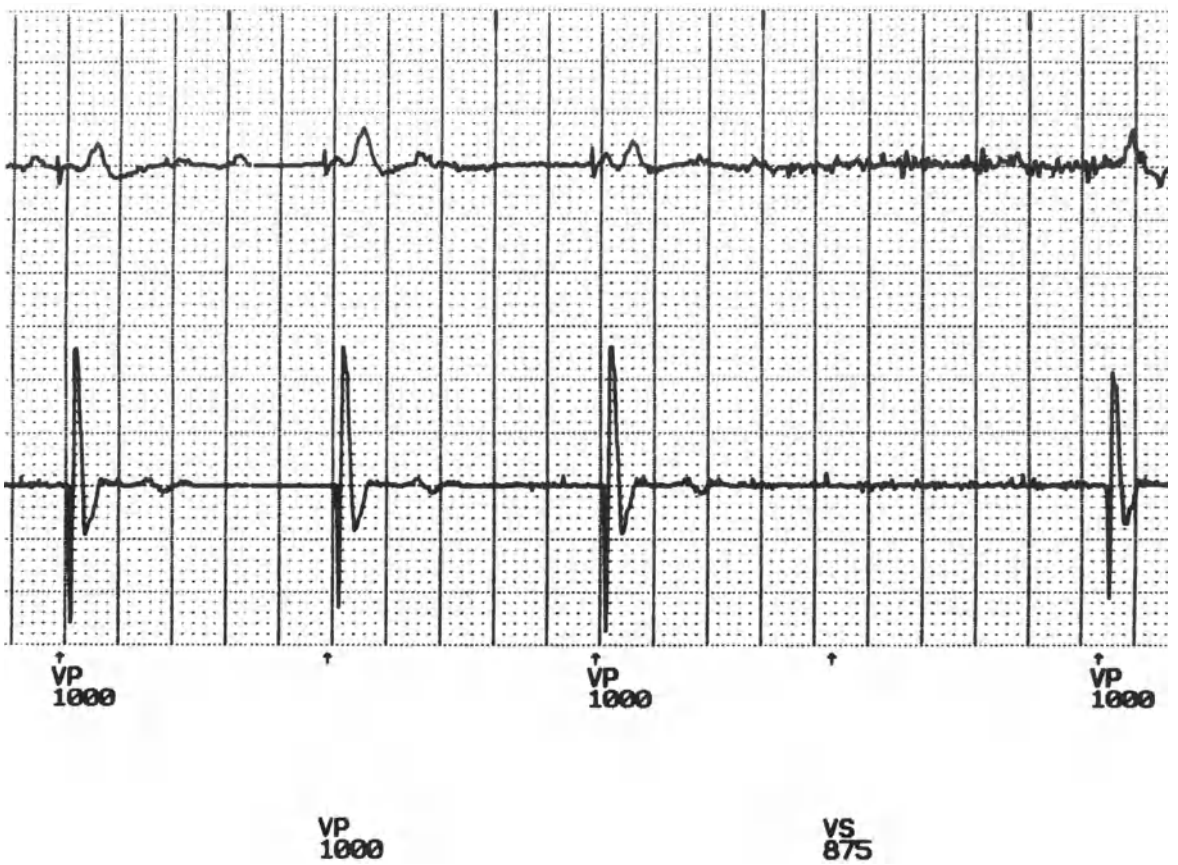

Figure 8. While provoking over-sensing by the Vasalva manoeuvre, a surface ECG lead, the electrogram from the defibrillation electrodes, and the sensing markers of the ICD (CPI Ventak™ Mini) were recorded. Myopotentials are seen after the third paced beat in the surface ECG. The ICD detected only a single myopotential late in diastole causing an inhibition of the pacemaker.

of programmed detection and therapy algorithms can be ensured. However, the procedure is stressful for the patient due to the painful shock(s) and/or the experience of a cardiac arrest[6]. Complications such as transient or permanent neurological symptoms are rare[25].

It has become common practice to induce ventricular tachyarrhythmias to ensure the ICD functions of antitachycardia pacing, cardioversion and defibrillation before the patient is discharged from the hospital after ICD implantation[26]. Some groups have advocated additional routinely performed inductions of ventricular tachyarrhythmias during early follow-up[27]. However, no studies have shown the need for routinely performed induction of ventricular tachyarrhythmias in ICD patients, and both routinely performed testing of defibrillation and antitachycardia pacing have been questioned[25,28]. General agreement exists that patients should be tested in whom a dysfunction of the ICD is suspected, or in whom a change of the antiarrhythmic drug regimen involves the risk of insufficient detection or defibrillation[26].

Follow-up visits

Predischarge evaluation

Before the patient is discharged from the hospital after ICD implantation, a routine evaluation of the ICD should be performed including a 12-lead ECG, an interrogation of the ICD, an evaluation of the integrity of sensing and pacing, a battery check, and usually a noninvasive induction of ventricular tachyarrhythmias to test safety and efficacy of programmed detection and

therapy algorithms[26]. The location of the ICD device and its lead(s) by X-ray, a 12-lead ECG during pacing by the ICD, and the endocardial electrogram(s) of the ICD during sinus rhythm and/or atrial fibrillation and induced ventricular tachyarrhythmias should be documented to allow for comparison in case of ICD dysfunctions during follow-up.

Routine follow-up visits

During routine follow-up, a 12-lead ECG, an interrogation of the ICD, an evaluation of the integrity of sensing and pacing, and a battery check should be performed. Originally, ICD follow-up visits were scheduled at 2-month intervals to perform capacitor reformation. Today's devices can do these capacitor reformations automatically, but manufacturers still recommend interrogation of their devices every 2–6 months. Frequent charging of the device due to unsustained tachycardias or over-sensing might lead to early and unexpected battery depletion. Additionally, lead or device component failures have often been detected in the past, and might have been missed with infrequent follow-ups resulting in inappropriate shocks or failures of therapy during ventricular tachyarrhythmias. Rarely power-on-reset or even deactivation of the ICD by magnetic fields have been discovered during routinely performed interrogations of the ICD. Some manufacturers call for more frequent follow-up visits once the battery is close to depletion.

Pre-ICD-replacement visit

If an ICD replacement is needed, provocative manoeuvres to detect over-sensing, careful evaluation of lead impedances, and a chest X-ray should be performed to identify lead defects ahead of surgery. An upgrade of the ICD should be considered based on previous problems. For instance, an upgrade from a shock-only device to a device offering antitachycardia pacing in case of monomorphic ventricular tachycardias detected by the ICD, an upgrade to a dual-chamber device in case of intermittent AV block III, or an upgrade to a device offering more promising ways to avoid detection of fast-conducted atrial fibrillation (stability, EGM width) in case of inappropriate shocks due to atrial fibrillation.

Emergency follow-up visit

Once a patient experiences several shocks partly within intervals of less than 1 min, or his/her first syncope after ICD implantation, he/she should see an emergency medical service immediately, or preferably a physician who is capable of interrogating the ICD[29]. Additionally, a sustained tachycardia not detected or terminated by the ICD, or a sudden onset of signs of heart failure, should indicate the patient seeing an emergency medical service[29].

Urgent follow-up visit

The patient should schedule an urgent follow-up visit with his/her ICD follow-up physician if one of the following situations occurs[29]:

1. Signs of infections of the ICD system.
2. First spontaneous shock by the ICD.
3. Several interventions by the ICD within a short period of time.
4. New irregular heart rhythm.
5. Recurrent syncopes.
6. Increasing emotional stress due to the ICD.

Summary

ICD patients experience frequent complications during follow-up. To reduce the frequency of inappropriate ICD therapies without compromising the efficacy of treating ventricular tachyarrhythmias, current ICD are multiprogrammable, have complicated detection and therapy algorithms and can store large quantities of information on tachycardia episodes. Follow-up of ICD demands sophisticated interpretation of information on tachycardia episodes retrieved from the device, skills to perform tests for over-sensing, competence to perform non-invasive induction of ventricular tachyarrhythmias to test safety and efficacy of programmed detection and therapy algorithms, knowledge on normal and irregular appearance of ICD leads on X-rays, ability to perceive signs of ICD infection or right ventricular lead perforation, and knowledge on the intervals needed for battery checks depending on the model of the ICD and the patient's use of pacing and shocks.

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PART FIVE

CARDIAC PACING

Chapter 46

The Features of a Paced Heart Beat

Lukas Kappenberger, Michel Grobéty and Xavier Jeanrenaud

Introduction

Pacemaker treatment was introduced about 40 years ago in order to avoid asystole. We should, however, remember that as early as 1809 it was mentioned that the heart could be stimulated by electricity[1], and that in 1932 a report was published describing a pacemaker which was able to control the rate in experimental animals[2]. The primary goal of electrical stimulation of the heart was the treatment of syncope, which was recognised to be due to intermittent atrioventricular (AV) block. This treatment was successfully introduced in clinical therapy in 1952[3] with an external artificial pacemaker and the first implant being performed in 1958[4]. Bradycardia pacing remained for many years the only focus of physicians, and it is still the primary one.

The second chapter in pacemaker development concerned haemodynamics. This feature attracted much attention about 20 years ago. At that time the haemodynamic effects of fixed rate, adapting rate ventricular pacing and atrial triggered ventricular pacing were reported in the literature[5]. The AV sequence and optimal pacing sites in the ventricle were carefully analysed. It was realised that pacing the left ventricle and right ventricle or septum was not the same. The AV sequence gained more and more attention as it was rapidly recognised that the atrial contribution to ventricular filling is not to be neglected and, as mentioned, atrial pacing resulted in the best ventricular performance[6]. Much attention was then given to rate adaptation. It was felt that rate might be more important than AV sequence[7] but the two together gave the best haemodynamic results[8]. This evolution clearly shows that the problem of stimulation for avoiding syncope evolved to one of stimulation for haemodynamic improvement. The indication for pacemaker implantation was, of course, restricted to use in patients with rhythmic indications for permanent treatment.

Several reports, however, mentioned interesting modifications of contraction in hypertrophic cardiomyopathy, and even a benefit of this stimulation technique for this disease in surgical patients[9]. Further anecdotal reports showed that even dilative cardiomyopathy could be improved not only by pacing at the appropriate rate but by pacing with short AV delay[10]. These last two ideas clearly show that pacing might be a tool not only for rhythm control but also for modulation of functional and haemodynamic abnormalities. Therefore it seems useful to analyse the features of a paced heart beat, which means discussing the difference between the electrically stimulated heart beat and the spontaneous heart beat.

Trigger observations

The fact that pacing influences haemodynamics in patients with hypertrophic obstructive cardiomyopathy

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(HOCM) has been observed for many years, but only recently has this idea achieved widespread acceptance as a possible therapeutic option for this abnormality. The recognition of pacing-induced outflow gradient reduction in HOCM led us to hypothesise that pacing modulates ventricular function, probably through multiple changes in all contraction parameters.

Similarly, observations in dilated cardiomyopathy stressed the importance of the AV interval and the induced changes in valvular movement. It was especially impressive to read how mitral regurgitation might be influenced by appropriate pacing[11]. Contraction asynchrony is often observed in heart failure, but not much can be done about it, unless pacing is taken into consideration. This led to the idea of multi-site ventricular pacing, and to the concept of the four-chamber pacemaker[12].

What might be the mechanisms by which pacing can favourably modify ventricular contraction in a way that leads to clinical improvement in such different diseases as hypertrophic and dilative cardiomyopathy? This chapter will focus on pacing influence in systole and diastole, and discuss the different possible mechanisms as summarised in Table 1.

Pacing-induced influences on systolic function

Pacing-induced changes in systole are summarised in Table 1. Looking simply at the ECG, it becomes evident that pacing has a major impact on activation sequence. The narrow QRS complex, which reflects the activation of the whole ventricular myocardium being accomplished within 80 ms, becomes enlarged to 200 ms and deformed, which means that the spread of activation with electrical stimulation is slow and bizarre. Epicardial activation mapping has shown that propagation from an ectopic stimulation site is much slower than in a His-Purkinje-activated heart[13]. Whatever pacing site is chosen, this spread remains the same unless capture of the proximal His bundle can be performed. Slow conduction means slow propagation, and therefore asynchrony of contraction between left and right ventricles. This feature was analysed in more detail. The regional contraction of the septal area in the left ventricle in hypertrophied hearts is significantly diminished, while apical and freewall regions compensate slightly for this loss during right ventricular stimulation. This means that in ectopic stimulation the functional loss through asynchrony can be compensated by hypercontraction in late-activated regions[14]. In this patient population as a whole ejection fraction does not change, while it might in diseased or dilated hearts. However, as in dilative cardiomyopathy, activation spread is often delayed, as reflected by the enlarged QRS complexes. This loss of synchronisation might not immediately become apparent; therefore we lack clinical reports on reduced left-ventricular function under pacemaker therapy. Ectopic activation and delayed conduction probably play key roles in the pacing-induced changes of ventricular function, and will therefore be discussed in more detail.

Table 1. Pacing influence: results in structural changes

In systole	In diastole
Activation sequence	*Relaxation sequence*
Activation time	Coronary flow distribution
Valve movement	Relaxation time
Electromechanical coupling	Filling pressures
Redistribution of wall stress	

The correlation between excitation and contraction was extensively investigated by Prinzen et al[15]. Electrical and mechanical mapping showed first the slowing of activation wavefront and in parallel delayed onset of contraction. These acute changes seem to have a chronic impact. While preload is probably homogeneous if contraction occurs simultaneously in all cardiac regions, preload is inhomogeneous in the pacing-activated heart. This observation needs further explanation. The early-activated region, around the pacemaker electrode, starts contraction before the remote regions contract. Due to the elasticity of the heart muscle, therefore, resistance to contraction, afterload, is diminished in the early-activated region. In contrast remote regions will be stretched before activation occurs, due to the contraction in the early-activated region. Increased stretch means increased preload and increased work. In other words the early-activated pacing site is unloaded while remote regions have increased workload. This may be one cause of the beneficial effect observed in acute pacing of HOCM.

The chronic redistribution of wall stress must lead to morphological changes. This was proven in various animal experiments. In the chick embryo[16] epicardial pacing showed, in the earliest-activated region, a reduction in wall thickness (Fig. 1). In the chronic dog

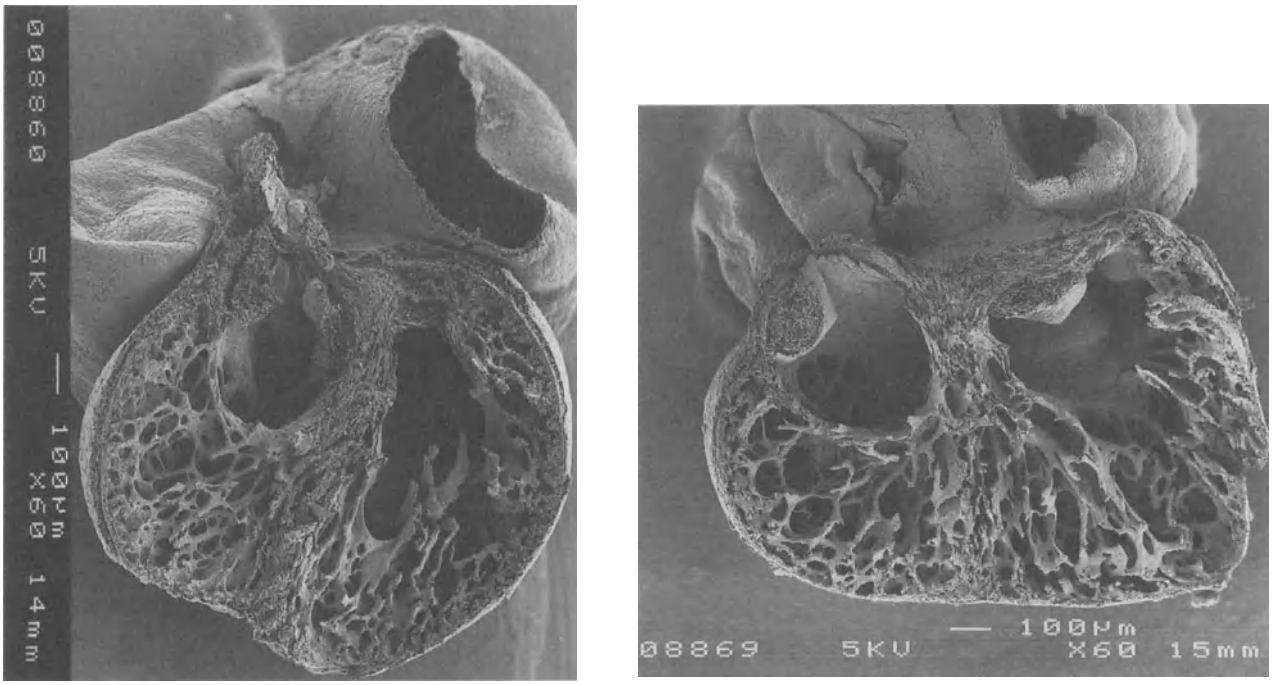

Figure 1. Modifications of chick embryo heart by pacing. **(a)** Sham-operated; **(b)** active pacing 48 h.

experiment Delhaas et al. made similar observations, and demonstrated a reduction of wall thickness in the earlier-activated region and slight but not significant compensation in the late-activated region[17]. These observations clearly show that pacing, at least in animal experiments, leads to remodelling of the heart. Pacing-induced remodelling could be an important tool in the treatment of various cardiomyopathies, and this highlights interest in the topic of modulation of ventricular function through pacing.

As a consequence of these first two parameters, activation sequence and modification of preload, the oxygen consumption in various regions might change. It has recently been demonstrated by positron emission tomography scan that, in patients with HOCM, pacing improves septal metabolism[18]. Regional coronary blood flow was investigated in a Langendorf model by Amitzur et al.[19]. These experiments showed that mean and phasic flow are reduced in the early-activated region. Under controlled perfusion pressure and intact vascular tone, ventricular pacing compromises blood flow compared with normal activation during atrial pacing. This seems to reflect a response to demand, probably explained again through the unloading of early-contracting regions. When vascular tone is eliminated by coronary injection of adenosine this effect disappears, suggesting that coronary auto-regulation is responsible for some of the observed flow shifts. The clinical correlate to this seems to be confirmed by the previously mentioned redistribution improvement in HOCM, while in patients with pre-existing perfusion defects pacing might not have the same favourable impact[20].

All these described mechanisms will modify valve movement. As shown in Fig. 2 of a patient with HOCM, the anterior movement of the mitral valve is greatly delayed during the paced beat, and valve to septum contact is significantly shortened. The result of this is a reduction, sometimes even disappearance, of mitral regurgitation in HOCM. We explain this fact through the late septal contraction and therefore delayed bulging, through the reduced narrowing of the outflow tract and therefore reduced blood flow velocity which results in diminished Venturi forces, and through earlier contraction of the papillary muscle in the paced beat.

On the other hand, pacing also influences mitral regurgitation simply by shortening AV intervals. This was the major observation made by Brecker et al[11], when

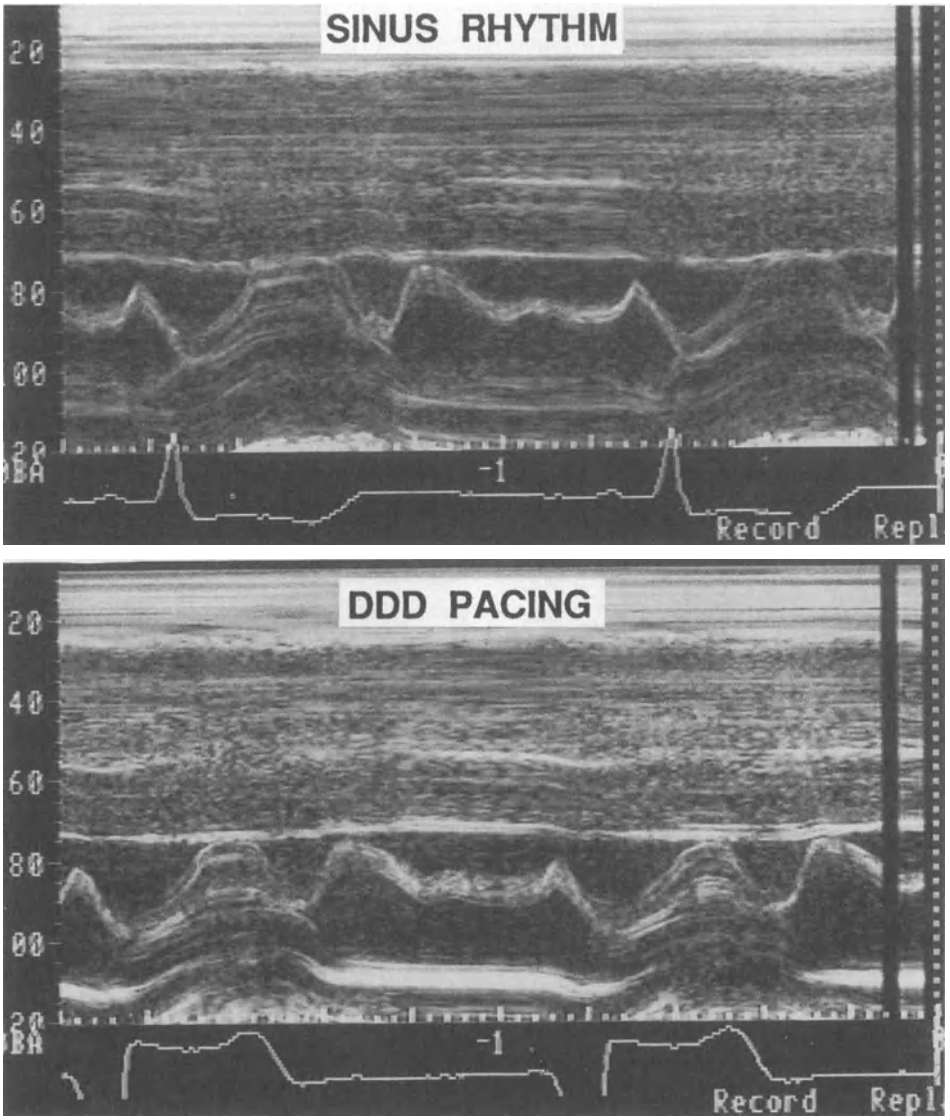

Figure 2. Modification of mitral valve systolic anterior.

studying the possible mechanisms of beneficial effects of dual-chamber pacing with short AV interval in patients with dilative cardiomyopathy. The shortening of AV delay led to an appropriate closure of the mitral valve and significant diminution of presystolic mitral regurgitation, a feature that many years ago was found to be important also in patients with complete AV block, and which disappears with well-timed VAT pacing.

In dilative cardiomyopathy, in addition to the influences on mitral regurgitation, the asynchronic activation, especially if reflected by the enlarged QRS complex, can be corrected by simultaneous pacing at different sites of the heart – multi-site pacing. Preliminary reports using this technique[12] have reported dramatic improvement in haemodynamics, and raise new interest for wider application in the treatment of heart failure.

Pacing influences on diastolic function

Diastolic filling of the ventricle is a complex process. Many interactive events can modify diastolic flow, and

it is extremely difficult to assess them in patients. The most eminent influence can be gained with appropriate AV sequence. The atrial kick increases ventricular filling by about 10–20% and therefore improves contraction and stroke volume in the normal heart, at rest but also under exercise[6]. It can be hypothesised that, in the normal heart, pacing, through the initiation of asynchronous activation and a prolonged activation sequence, will result in asynchronous and prolonged relaxation, and therefore reduction in diastolic elastic properties of the heart. The hypertrophic heart might be especially sensitive to such manoeuvres, and this has recently been demonstrated by Nishimura et al[21]. Their data indicate that dual-chamber pacing results in a deterioration of diastolic function with consecutive increase of left atrial pressure. The importance of the well-timed AV interval was again stressed, and it should be remembered that atrial filling is of the utmost importance in the presence of diastolic dysfunction. Appropriate timing of the AV interval is a major factor in the tuning of the pacemaker for patients with HOMC!

The fact that the diastolic properties are not modified in the same favourable way as the systolic abnormality in this disease is further reflected by the clinical observation which showed that dyspnoea, although significantly improved by pacing for HOCM[22], is not improved so consistently as angina. Some of the gain that should result from the decrease in the degree of outflow track obstruction might be lost in HOCM patients through delayed relaxation. To date, only in animal experiments has the influence of pacing on diastolic parameters of the left ventricle been investigated[23]. These experiments have shown that pacing from the right ventricular apex shows the rate of ventricular relaxation. Appropriate AV sequence may minimise these changes but, as expected, left ventricular asynchrony persists. It is concluded that left ventricular asynchrony reduces isotonic relaxation rate. The disturbed relaxation is most probably a reflection of the temporal dispersion of the contraction/relaxation sequence.

Conclusions

The fourth decade of pacing ends with a focus on the functional and structural reaction of the myocardium to the paced heart beat. Anecdotal observations in selected patients stimulated research in pacing-induced modification of systolic and diastolic function. While some information on acute testing is available, long-term effects of pacing with regard to global function, remodelling or histological changes have never been studied. Therefore, while the rhythmic problems of pacing seem resolved, the functional understanding of what comprises the features of a paced heart beat is a new field for research.

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Chapter 47

Clinical Evaluation of Chronotropic Incompetence: Implications for Rate-Adaptive Pacing

Demosthenes Iskos, Marcus J. Mianulli and David G. Benditt

Introduction

The introduction of sensor-based rate-adaptive pacemakers in the 1980s revolutionised the practice of cardiac pacing[1]. In particular, the availability of a means to restore heart rate responsiveness focused attention on the physiological importance of providing symptomatic patients with as normal a chronotropic response as possible. Thus, the recognition of chronotropic incompetence became a true clinical concern, and ultimately led to a new indication for implantation of cardiac pacemakers.

Despite the potential benefits of rate-adaptive pacing in patients with chronotropic incompetence (a subset of "sick sinus syndrome"), this relatively recent indication for pacing is frequently overlooked. In part this may be due to the fact that the clinical manifestations of sick sinus syndrome itself are often subtle (e.g. inability to concentrate, declining memory, personality changes), and may thus elude clinical recognition. In the same context, recognition of a causal relationship between vague symptoms such as fatigue and dyspnoea on exertion with inadequate heart rate responsiveness is often even more difficult. Equally important, however, is the current uncertainty as to how to define and measure "chronotropic incompetence" clinically.

This chapter provides an overview of the physiological significance of chronotropic incompetence. More importantly, it examines the variety of definitions which have been employed, as well as the methodology and limitations of clinical assessment of the individual with suspected chronotropic incompetence.

Importance of exercise-induced chronotropic response in normal subjects and in patients with pacemakers

The relative contributions of atrioventricular synchrony and rate responsiveness to cardiac output are well established. In normals, atrioventricular synchrony tends to contribute more to cardiac output at rest and at low levels of exertion than it does at higher levels of exertion[2]. As exercise increases in intensity, rate adaptation becomes more critical. Maintenance of atrioventricular synchrony and physiological rate adaptation are therefore complementary in the physiological setting.

For the most part, excluding patients with severe left ventricular dysfunction or ischaemic heart disease, the

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same physiological principles regarding atrioventricular synchrony and rate response apply in patients with pacemakers. Thus, among patients studied by Karloff, only 8% of the average three-fold cardiac output increase between rest and exercise was attributable to atrial transport; the majority of the increment was the result of increased heart rate[3]. Similarly, among the several observations reported by Fananapazir et al, they noted in particular that the 40% increase in exercise capacity associated with heart rate responsiveness in their patients, compared to VVI pacing, was essentially independent of whether atrioventricular synchrony was maintained[4]. These studies, as well as reports from Ausubel and colleagues and Ryden and associates, also clearly show that exercise capacity, stroke volume changes with exercise, and peak observed oxygen consumption ($\dot{V}O_2$) depend primarily on heart rate change in most patients[5,6].

The approximately linear relationship between heart rate and oxygen consumption has been validated for both maximal and submaximal exercise[7,8]. Thus, preservation of the physiological coupling between heart rate response and oxygen consumption is desirable, and reduces the need for premature encroachment on cardiac compensatory responses. Several studies have confirmed this theoretical principle by demonstrating a physiological advantage of rate-adaptive pacing in patients with chronotropic incompetence[9–14]. For example, improvement in exercise capacity by 20–50% with AAIR as compared with conventional AAI pacing has been demonstrated[9,10]. Other studies have shown an advantage of VVIR over VVI mode, DDDR over DDD mode and DDIR over DDI mode in patients with chronotropic incompetence[11–14].

Definition of chronotropic incompetence

The term "chronotropic incompetence" generally implies the inability of the heart to increase its rate appropriately in proportion to metabolic demand. Although it traditionally refers to inadequate sinus response during exercise, the term also encompasses other disturbances of heart rate response such as inadequate exertional ventricular rate response in patients with chronic atrial fibrillation, and inability of a lower escape pacemaker to respond to exercise or other autonomic changes, e.g. in patients with complete heart block[15]. Overall, chronotropic incompetence may manifest as: (i) failure or (ii) delay in achieving maximal heart rate, (iii) inadequate submaximal heart rate, (iv) rate instability during exercise, or (v) an unexpected abrupt rate drop after exercise (Fig. 1).

Although the concept of chronotropic incompetence is relatively straightforward, there is at present no widely accepted definition applicable to clinical practice. In general terms, chronotropic incompetence can be characterised using statistical methods based on studies in a normal population. Nevertheless, one cannot conclude that patients who fall outside the normal range necessarily need, or will benefit from, a rate-responsive pacemaker. Thus, on clinical grounds, chronotropic incompetence may be more appropriately conceptualised as an abnormal response of the heart rate to changing metabolic demands that, when corrected, results in functional improvement (i.e. improved exercise tolerance, improved quality of life).

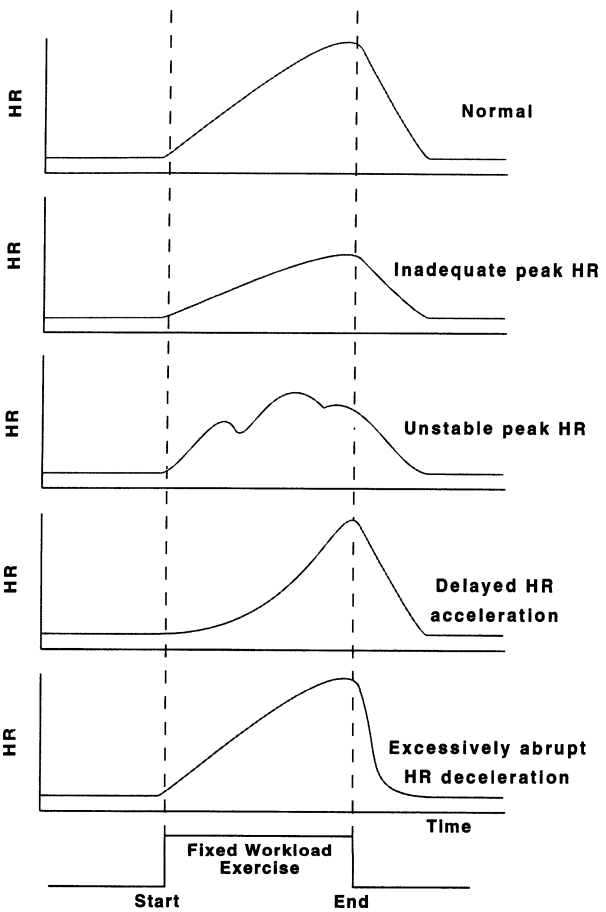

Figure 1. Patterns of chronotropic incompetence. HR = heart rate.

Incidence and clinical assessment of chronotropic incompetence

The incidence of chronotropic incompetence is widely variable depending upon the definition employed, as well as the patient population examined; rates of 5% in a general adult population to as high as 58% in pacemaker recipients and 64% in elderly patients with sinus node dysfunction have been reported[16–18]. Furthermore, chronotropic incompetence may be progressive over time[17]. It seems that the prevalence increases with age, although the effects of age, gender and fitness level have yet to be fully studied in normal populations[19]. Consequently, the real value of any apparent abnormalities of chronotropic response in the elderly may be arguable at present. A certain degree of chronotropic incompetence may represent a "physiological" accompaniment of ageing, and only advanced and symptomatic cases need to be considered for rate-adaptive pacing.

The methodology utilised to quantitate chronotropic capability, and thereby permit "diagnosing" chronotropic incompetence, is far from established, and further progress cannot be expected until there is a consensus on diagnostic criteria. Nonetheless, both exercise testing and ambulatory electrocardiographic (ECG) recordings are widely utilised for this purpose.

Cardiopulmonary exercise testing

Treadmill exercise remains the most popular instrument for evaluation of the chronotropic response to exercise, although cycle ergometry has also been used. Several exercise protocols have been used for the evaluation of the chronotropic response (Bruce, Balke, Ellestad, Astrand, Chronotropic Assessment Exercise Protocol – CAEP, Minnesota Pacemaker Response Evaluation Protocol – M-PREP, etc). All basically achieve comparable peak $\dot{V}O_2$, but at different slopes of $\dot{V}O_2$ and heart rate increment[20]. When assessing chronotropic response via exercise determination of the maximal heart rate, it is important to confirm maximal effort by objective means. Preferably, this can be accomplished by determining $\dot{V}O_2$ at anaerobic threshold and, if this is not feasible, by measuring peak observed VO_2. The anaerobic threshold indicates the point during sustained exertion where anaerobic metabolism is required to maintain the workload.

In clinical practice, determination of chronotropic incompetence by exercise testing has entailed either: (i) the evaluation of peak heart rate attained on maximal exercise or (ii) the study of heart rates at submaximal workloads. The former has been the most common approach. For instance, failure to achieve a heart rate of 100 beats/min at maximal exertion has been proposed by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force as an indicator of the need for a rate-responsive physiological pacing system[21]. However, while this somewhat arbitrary definition may be very specific, it probably represents a far too stringent definition.

In a study of 2700 subjects referred for exercise testing, Ellestad and Wan defined chronotropic incompetence as a heart rate below the 95% confidence limits for age and sex[22]. In another study of 2365 healthy adult men, Bruce et al considered the failure to reach 90% of age-predicted maximal heart rate as chronotropic incompetence[16]. In groups of patients with dilated cardiomyopathy or conduction disturbances, chronotropic incompetence was defined as inability to reach 80% of age-predicted maximal heart rate[17,23]. A statistical approach to the problem was introduced by Chin and colleagues[24]. They defined age- and protocol-specific heart rate responses for each stage of exercise, and characterised individuals as having mild chronotropic incompetence if they failed to achieve a heart rate within one standard deviation below the mean heart rate, and more severe chronotropic incompetence if they could not reach a heart rate within two standard deviations below the mean heart rate. A similar approach was undertaken by Wiens et al in a patient population with chest pain and/or suspected coronary artery disease[25].

In a study of 410 normal subjects, Wilkoff and coinvestigators described a mathematical model for the assessment of the cardiac chronotropic response at different stages of exercise[26]. This model considered the influence of age, resting heart rate and peak functional capacity. The subjects underwent treadmill testing on either the Bruce or the Chronotropic Assessment Exercise Protocol (CAEP). A plot of heart rate reserve [maximal predicted heart rate – resting heart rate (HR_{rest})] against metabolic reserve [maximally achieved workload ($METS_{peak}$) – workload at rest ($METS_{rest}$)] showed a linear relationship with an intercept at the origin (0.0) and slope of 1.0 for the regression lines. The following formula described the predicted normal heart rate for an individual at some submaximal level of exercise (HR_{stage}):

$$HR_{stage} = [(220 - age - HR_{rest}) \times (METS_{stage} - 1)/(METS_{peak} - 1)] + HR_{rest},$$

where METS = V_{O_2} (ml/kg per minute)/3.5. To classify the entire metabolic chronotropic response, the slope of this relation must be measured, and fall within the 95% confidence intervals of the normal response (Fig. 2)[27].

Assessment of activities-of-daily-living with ambulatory electrocardiography

Recently it has become apparent that heart rate responses resulting from daily submaximal activities exhibit many similarities from individual to individual; in fact, for individuals of a given age, gender and fitness, daily heart rate variations can be depicted as an expected "profile". Thus, heart rate "profiles" represent a useful characteristic of the normal human chronotropic response. Unfortunately, relatively little attention has been focused on this important issue. A few studies have assessed statistical descriptors of daily heart rates, while others have investigated the circadian response of heart rate and described significant diurnal variations. Kostis and associates reported the effect of ageing on heart rate in a sample of normal subjects, aged 16–68 years, undergoing both ambulatory ECG monitoring and maximal exercise testing[28]. They showed that the maximal but not the minimal or average daily heart rate declined significantly with increasing age. This could be explained by a higher heart rate increment in older people during submaximal activities of daily living. This observation was confirmed in a subsequent study by Kostis and colleagues, in which a positive correlation between maximal heart rate during exercise testing and ambulatory ECG was also demonstrated[29].

In a 48-h ambulatory ECG study of 57 healthy adults during routine daily activities (mean age 65 years), Mianulli observed that approximately 15% of all recorded beats were at a rate of > 90 beats/min[19]. Although the absolute number of beats over 90 was relatively small, fluctuations or excursions above this rate occurred many times a day. The mean duration of a heart rate excursion was approximately 1 min or less. Thus, daily heart rate behaviour can be summarised as generally being submaximal, but with frequent rate increments of short duration. Optimally, physiological cardiac pacing would produce similar heart rate profiles. However, because the establishment of normal values for all circumstances is unrealistic, assessment of chronotropic response during standardised activities of daily living was proposed. In this regard, Mianulli and associates analysed heart rate behaviour in 20 healthy adults performing repeated sets of specific activities such as walking, walking with a load, stair climbing, vacuuming, etc.[30]. Each event lasted 1.5–2 min, with an intervening rest period. The findings provided target heart rate ranges useful for determining whether pacemaker programming is appropriate for comparable daily activities.

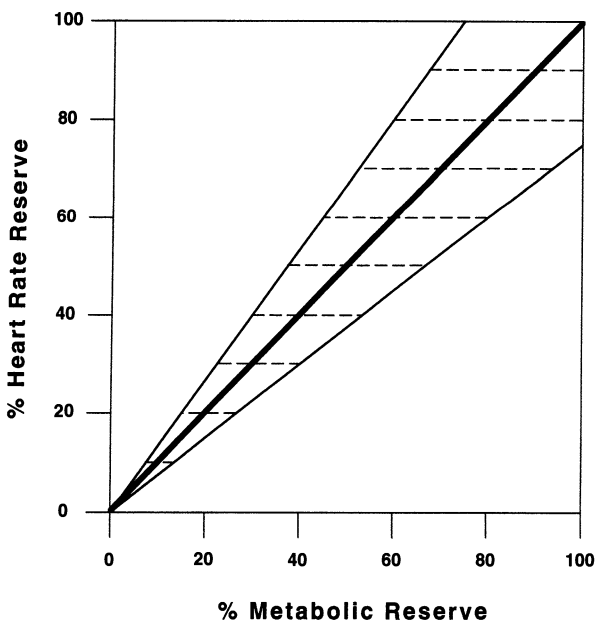

Figure 2. Using a mathematical/statistical model, chronotropic competence is defined as the response to physical exertion that results in a metabolic-chronotropic relation within the 95% confidence intervals of the normal response (shaded area). The normal response is represented by the central thicker line which exhibits a y-intercept of 0.0 and a linear slope of 1.0. Graph modified from the work of Wilkoff[27].

Limitations of current techniques

Current methods of evaluating the patient with suspected chronotropic incompetence are subject to several limitations. Most importantly, despite widespread use in clinical practice, the utility of maximal exercise testing alone for assessment of chronotropic competence (or of the physiological appropriateness of a rate-adaptive pacing system operation) is questionable. The lack of a uniform clinical definition for chronotropic incompetence based on the results of exercise testing is a

serious drawback. Simple definitions for chronotropic incompetence based on failure to achieve a predefined heart rate during maximal exercise testing (e.g. ACC/AHA guidelines) probably carry a high specificity but a low sensitivity and, if strictly applied, could lead to overlooking many patients that might benefit from rate-adaptive pacing. Methods or techniques which fail to take into account the patient's age and the slope of heart rate increase with exercise, and especially the numerous brief heart rate excursions that occur daily in normal individuals, are unlikely to be helpful clinically. Formulas, such as the one suggested by Wilkoff et al, may be useful as a guide to the expected heart rate at various stages of exercise in subjects able to exercise to maximal workload. However, this specific approach is not helpful when peak exercise cannot be achieved. In other words, in patients with physical limitations in whom $METS_{peak}$ cannot be defined, the formula may lead to an overestimation of HR_{stage} and therefore may exaggerate the magnitude of chronotropic incompetence.

From a clinical standpoint, recognition of chronotropic incompetence is most relevant only if "normalising" heart rate responsiveness (usually by sensor-based pacing) would result in a functional improvement for the patient in question. In this regard, even sophisticated methods based on sound physiological principles (such as measurement of peak observed $\dot{V}O_2$ or $\dot{V}O_2$ at anaerobic threshold), may not be sufficiently sensitive to detect certain subtle but potentially important differences among pacing systems. For instance, peak $\dot{V}O_2$ may not differ substantially in patients with "optimally" programmed rate-adaptive pacemakers, although it may be achieved promptly in one case and slowly in another (Fig. 3). Such differences in the promptness with which peak $\dot{V}O_2$ is achieved may be reflected clinically as differences in exercise tolerance.

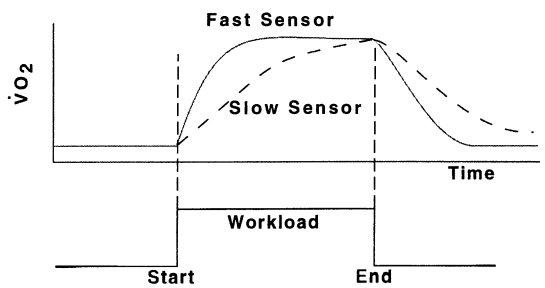

Figure 3. Comparison of two sensor-based pacing systems, one relatively fast responder and one slower. Similar peak $\dot{V}O_2$ is achieved with both, but at different slopes of $\dot{V}O_2$ rise. The ordinate indicates observed $\dot{V}O_2$ and the abscissa indicates duration of exercise. The individual sensor responses are shown.

An additional limitation of conventional exercise testing is that it does not address heart rate behaviour during periods of submaximal activity such as resting or activities of daily living. This is clearly an important issue to consider, as many patients are unable to perform maximum levels of exercise because of physical disabilities or medical illnesses such as lung disease, claudication, angina, etc. Further, even in individuals without obvious limitations, the vast majority of time in an average day is spent in performing submaximal activities. As already discussed, transient brief chronotropic demands are posed very frequently in everyday life[29]. Identifying an individual's capability to provide this form of intermittent chronotropic responsiveness may be more clinically relevant than the ability to achieve an age-related maximal heart rate.

Conclusions

Only recently have physicians come to realise that chronotropic incompetence is a frequent occurrence, and can be associated with significant clinical symptomatology. In order to further understand and manage this problem, however, we need to establish a widely accepted definition that is clinically relevant, accurate and relatively easy to use. Factors such as patient's age, gender and level of fitness must be taken into account. Quantitative characteristics such as maximal heart rate achieved, time to peak heart rate for a given submaximum exercise load, stability of heart rate increment during onset of exertion, stability at offset, as well as rate stability during sustained submaximal exertion need to be documented. Heart rate profiles related to activities of daily living, including the capacity for frequent transient heart rate excursions to relatively high rates, should be incorporated. With this information on hand we will be in a better position to focus on the most appropriate pacing modes and sensor systems for treating individual patients.

Acknowledgement

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Chapter 48

Indications for Permanent Antibradycardia Pacemakers. The Official Guidelines Should be Revised

S. Serge Barold

Introduction

The most complete and authoritative guidelines concerning the indications for permanent pacing were originally published in 1984 by a joint committee established by the American College of Cardiology (ACC) and the American Heart Association (AHA)[1]. The ACC/AHA guidelines were revised in 1991[2]. Although the past few years have seen little new knowledge in conduction system disease, the ACC/AHA guidelines need revision to address a number of important issues:

1. Shortcomings and inconsistencies in the old document need correction, especially with regard to the characterisation of conditions for which pacing may be considered; e.g. definitions of second-degree atrioventricular (AV) block. A number of controversial issues require reevaluation; e.g. the need for pacing in asymptomatic near sustained narrow QRS type I second-degree AV block.
2. Some of the recommendations for pacing need to be presented with greater precision in concert with the above, and also to reflect current and changing clinical practice.
3. Emergence of new non-bradycardic indications for pacing in the past few years.
4. Many previous recommendations of the optimal pacing mode in a variety of situations are now outmoded.

AV block

According to the definitions codified by the World Health Organisation (WHO) and the ACC (both in 1978), type II second-degree AV block should be defined as the occurrence of a single non-conducted P wave associated with constant PR intervals before and after the blocked impulse, provided there are at least two consecutive conducted P waves (i.e 3 : 2 AV block) to determine the behaviour of the PR interval[3–6]. The pause encompassing the blocked P wave should equal two (P-P) cycles[7]. Stability of the sinus rate is an important criterion because a vagal surge can cause simultaneous sinus slowing and AV nodal block, generally a benign condition, that can superficially resemble type II second-degree AV block[8].

Type II second-degree AV block invariably occurs below the AV node while type I second-degree AV block in the setting of a normal QRS complex often occurs in the AV node and rarely in the His bundle. Type II second-degree AV block is associated with

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bundle branch block in at least 70% of cases[9,10]. Type I second-degree AV block with tiny increments of AV conduction, narrow QRS and a constant sinus rate can simulate type II AV block[8]. In chronic bundle branch block and type I second-degree AV block, the site of second-degree AV block lies in the His-Purkinje system in about 30% of cases[8,9,11]. The prognosis of type I second-degree infranodal block appears similar to that of type II AV block.

Two to one AV block cannot be classified into type I or type II, an important concept clearly emphasised in the 1989 and 1995 ACC/AHA guidelines for clinical intracardiac electrophysiological studies[12,13]. Rather it is best considered as advanced second-degree AV block, as are higher degrees of block such as 3 : 1, 4 : 1, etc., according to the definitions promulgated by the WHO and ACC[5,6]. It is unclear why the 1984 and 1991 ACC/AHA guidelines make no mention whatsoever of 2 : 1 AV block throughout the documents. Furthermore the term "advanced AV block" is used to describe both second and third-degree AV block, a source of potential confusion because the term "advanced" is also used to describe a particular form of second-degree AV block.

The 1991 ACC/AHA guidelines state that "second-degree heart block may be further classified as type I (progressive prolongation of PR interval before a blocked beat) or type II (no progressive prolongation of PR interval before blocked beats) and is usually associated with a wide QRS complex. Advanced second-degree block refers to the block of two or more consecutive P waves." The definition of type II second-degree AV block in the 1991 ACC/AHA guidelines lends itself to misinterpretation because the constancy of the PR interval after the blocked impulse is not emphasised[3]. In the above definitions the wide QRS complex obviously applies to type II second-degree AV block, but it should be stated without ambiguity. Use of the plural description for type II blocked "beats" is unfortunate because constant AV conduction intervals followed by block of two or more P waves (advanced second-degree block) could be mislabelled as type II AV block. Furthermore, the ACC/AHA guidelines do not state the requirement that constancy of the sinus rate

Table 1. Indications for permanent pacing. Acquired AV block in adults*

Class I

A. Permanent or intermittent complete AV block at any anatomical level in the absence of reversible causes, regardless of symptoms.†‡
B. Permanent or intermittent second-degree AV block regardless of the type or the site of block, with symptomatic bradycardia.‡
C. Permanent or intermittent asymptomatic type II second-degree AV block.‡§
D. Asymptomatic type I or advanced second-degree AV block at intra-His or infra-His levels.‡§
E. Exercise-induced second or complete AV block regardless of symptoms but without reversible ischaemia.‡
F. Atrial fibrillation, atrial flutter, or rare cases of supraventricular tachycardia with AV block and bradycardia associated with congestive heart failure or periods of asystole $\geq$ 3.0 s or escape rate < 40 bpm or alternating tachycardia and bradycardia difficult to control pharmacologically. The bradycardia must be unrelated to drugs known to impair AV conduction.

Class II

Symptomatic first-degree AV block improved by temporary dual-chamber pacing.

Class III

A. Asymptomatic first-degree AV block.
B. Asymptomatic type I second-degree AV block at the supra-His (AV node) level.

* Adapted from ref. 2, with permission.

† Asymptomatic complete AV block, permanent or intermittent, at any anatomical site is a class II indication in the 1991 ACC/AHA guidelines when the ventricular rate $\geq$ 40 bpm in asymptomatic patients and a class I indication when the ventricular rate < 40 bpm or there is asystole $\geq$ 3 s in asymptomatic patients. The 1991 ACC/AHA guidelines classify permanent or intermittent complete AV block at any level as a class I indication when associated with: (1) symptomatic bradycardia, (2) congestive heart failure, (3) conditions requiring therapy with drugs that suppress (escape rhythm) automaticity.

‡ A number of conditions are listed in the 1991 ACC/AHA guidelines in both the section on acquired AV block and the section on bifascicular and trifascicular block (chronic intraventricular block). The same format was adopted in Tables 1 and 2, to facilitate comparison with the 1991 ACC/AHA guidelines despite repetition.

§ Class II indication in the 1991 ACC/AHA guidelines.

or P–P intervals is essential for the diagnosis of type II second-degree AV block[7].

Table 1 outlines the indications for pacing for acquired AV block in adults that best reflect current practice. Reversible causes of AV block such as Lyme disease, athletic heart, hypervagotonia, ischaemia and drug, metabolic or electrolyte imbalance must be excluded. A number of class II indications should be reclassified as class I indications such as complete AV block with a rate > 40/min in asymptomatic patients. Many experts believe that permanent pacing is indicated in asymptomatic patients with type I, type II or advanced second-degree AV block where the block is intra-Hisian or infra-Hisian (often associated with bundle branch block) because symptoms usually develop in a relatively short time. However, these recommendations should not be interpreted to indicate that all patients with asymptomatic narrow QRS type I second-degree AV block should undergo invasive testing to determine whether the site of block is in the His bundle. In contrast patients with asymptomatic wide QRS type I second-degree AV block require His bundle recordings to establish the site of AV block in order to find patients with infranodal block who would benefit from pacing.

Exercise induced AV block

Permanent pacing is recommended in patients with exercise-induced AV block even in the asymptomatic state, because almost all cases of exercise-induced or tachycardia-dependent AV block are due to disease of the His-Purkinje system and are associated with a poor prognosis. Many patients with exercise-induced AV block also demonstrate abnormal tachycardia-dependent infranodal AV block with incremental atrial pacing[14]. Exercise-induced AV block secondary to myocardial ischaemia is rare, and does not require pacing unless ischaemia cannot be alleviated.

First-degree AV block

Some symptomatic patients with marked first-degree AV block may benefit from dual-chamber pacing to restore a more physiological AV interval[15]. Such a situation represents a class II indication, and permanent pacing should be considered only if temporary pacing produces unequivocal haemodynamic improvement.

1991 ACC/AHA versus 1991 BPEG guidelines

The document entitled "Recommendations for Pacemaker Prescription for Symptomatic Bradycardia", by the British Pacing and Electrophysiology Group (BPEG)[16] recommends using the 1984 ACC/AHA guidelines (basically similar to the updated 1991 version) with the exception of two areas: malignant vasovagal syncope (now included in the 1991 ACC/AHA guidelines) and persistent asymptomatic type I second-degree AV block. The BPEG document referring to the work of Shaw et al[17], recently editorialised[18], indicates that "asymptomatic patients with either Wenckebach (type I) or Mobitz II second-degree AV block occurring during much of the day and night would qualify for pacemaker implantation as would patients with asymptomatic complete heart block." This recommendation obviously excludes the development of type I AV block resulting from heavy physical training in athletes. According to Shaw et al[17] the prognosis of this form of type I second-degree AV block regardless of QRS duration and unrelated to acute myocardial infarction is as poor as that of type II block. Despite the BPEG recommendation to pace asymptomatic patients who have narrow QRS type I block during much of the day, it seems reasonable at this time to follow the more conservative 1991 ACC/AHA guidelines until others confirm the work of Shaw et al[17].

Intraventricular conduction block

The ACC/AHA guidelines do not specifically mention right bundle branch block (BBB) because it is neither bifascicular nor trifascicular block (but really a form of unifascicular block), an important omission because all the recommendations for pacing in bifascicular block also apply to right BBB.

Trifascicular block

The ACC/AHA guidelines use the term "trifascicular block" rather loosely. Electrocardiographic documentation of trifascicular block during 1 : 1 AV conduction is rare, and occurs usually in the presence of alternating right BBB and left BBB and rarely as fixed right BBB with alternating left anterior hemiblock and left posterior hemiblock[19]. The guidelines mention neither of these possibilities. Although rare, 1 : 1 AV block conduction with alternating left BBB and right BBB carries a poor prognosis and should be a class I indication for

pacing even in an asymptomatic patient[20,21]. Table 2 shows the guidelines for pacing in patients with intraventricular conduction blocks that best reflect current practice. Many of the indications overlap with some of the conditions contained in Table 1 (acquired AV block in adults). Consequently, Tables 1 and 2 should cross-reference basically similar information, especially with regard to type II second-degree AV block (as discussed later).

Symptomatic bundle branch block

It is important to perform an electrophysiological study (EPS) in patients presenting with BBB or bifascicular block and syncope (or its equivalent)[14,22]. The guidelines should emphasise that a comprehensive EPS includes measurement of the HV interval, incremental atrial pacing, programmed ventricular stimulation for the induction of ventricular tachycardia, sinus node function tests, rapid ventricular pacing to test for the "fatigue" phenomenon in the His-Purkinje system, programmed stimulation for supraventricular tachycardia (useful if associated with hypotension), and carotid sinus massage to unmask infranodal phase 4 bradycardia-dependent block or demonstrate carotid hypersensitivity. The guidelines should advance the concept that EPS can define by a process of exclusion which patients might benefit from pacing in the presence of HV prolongation (≥ 70 ms) and no other identifiable cause for syncope. The guidelines should outline the causes of provokable AV block particularly applicable to patients with symptomatic BBB (Table 3). The role of drugs such as procainamide that depress His-Purkinje conduction to provoke HV prolongation or actual His-Purkinje block

Table 2. Indications for permanent pacing. Intraventricular conduction blocks*

Class I

A. Bundle branch block† or bifascicular block with intermittent or stable second or complete AV block associated with symptomatic bradycardia.
B. Bundle branch block† or bifascicular block with intermittent or stable type II second-degree AV block without symptoms (see Table 1 for acquired AV block).
C. Bundle branch block† or bifascicular block with intermittent or stable infranodal block without symptoms: type I second-degree, advanced second-degree, or complete AV block‡ (see Table 1 for acquired AV block).
D. Trifascicular block during 1 : 1 AV conduction regardless of symptoms such as: (1) alternating left bundle branch block and right bundle branch block, (2) fixed right bundle branch block with alternating left anterior hemiblock and left posterior hemiblock.
E. Exercise-induced second or complete AV block regardless of symptoms, but without demonstrable ischaemia as a cause of AV block.
F. Bradycardia (or phase 4) dependent second- or third-degree infranodal AV block either spontaneous or induced by carotid sinus massage or electrically induced atrial or ventricular extrasystoles during an electrophysiological study.

Class II

A. Bundle branch block† or bifascicular block with syncope that is not proved to be due to complete AV block, but other possible causes of syncope are not identified, especially when HV ⩾ 70 ms.
B. Markedly prolonged HV interval (⩾ 100 ms) regardless of symptoms.
C. Infra-His block induced by atrial pacing.§
D. Infra-His block induced by ventricular pacing (fatigue phenomenon).

Class III

A. Hemiblock, bundle branch block, or bifascicular block without second-degree or complete AV block or symptoms.
B. Hemiblock, bundle branch block, or bifascicular block with (or without) first-degree AV block without symptoms.

* Adapted from ref. 2, with permission.

† There is no need to state whether this is left bundle branch block or right bundle branch block because left bundle branch block is bifascicular block. Right bundle branch block is described as bundle branch block rather than unifascicular block, to avoid confusion with left anterior (fascicular) hemiblock or left posterior (fascicular) hemiblock.

‡ The term trifascicular block, used in the ACC/AHA guidelines to describe this entity, is redundant.

§ Functional block distal to the His bundle due to abrupt shortening of the coupling interval is not considered a positive response. Such functional His-Purkinje block represents a normal response to lengthening of the preceding cycle followed by abrupt shortening of the coupling interval. Pathological infranodal block induced by atrial pacing should occur during incremental atrial pacing without cessation of pacing before the pacing rate is increased.

Table 3. Provokable infranodal AV block

1. Exercise-induced AV block should be listed as a class I indication. This form of AV block is tachycardia-dependent and often reproducible by atrial pacing.
2. Infranodal block induced by atrial pacing should be a class I rather than class II indication (rule out functional block).
3. Infranodal block induced by bradycardia (phase IV block), e.g. carotid sinus massage or pause after electrical induction of atrial or ventricular extrasystoles.
4. Fatigue phenomenon in the His-Purkinje system induced only by rapid ventricular pacing.
5. Pharmacological challenge with drugs that depress His-Purkinje conduction (e.g. procainamide) on the HV interval in patients with syncope, bundle branch block and negative EPS.? Recommend pacing if HV doubles or > 100 ms or second- or third-degree AV block supervenes.

Table 4. Indications for permanent pacing in intraventricular conduction blocks. Proposed changes in the ACC/AHA guidelines

1. Clear definitions of intraventricular blocks.
2. Consider combining sections on acquired AV block with section on bifascicular and trifascicular block. At a minimum indicate how these two sections overlap.
3. Identification of trifascicular block on the 12-lead surface ECG.
4. Discussion of provokable AV block (Table 3).
5. Syncope. What constitutes a comprehensive electrophysiological study?
6. Indicate that many workers implant pacemakers in patients with syncope, negative EPS and HV $\geqslant$ 70 ms.
7. Concealed AV junctional (or ventricular) extrasystoles may simulate second-degree type I or II AV block. Such extrasystoles frequently coexist with His-Purkinje disease, which itself accounts for this phenomenon. The prognosis is not necessarily benign, but some patients can be treated conservatively.

in susceptible patients is still controversial in the USA[8,9,14,23]. The new guidelines should discuss this issue and establish the role, if any, for pharmacological challenge of His-Purkinje conduction.

Finally, revision of the guidelines for AV block and intraventricular blocks should remove a number of inconsistencies. One such example can be found in the section on acquired AV block where the ACC/AHA guidelines state that "asymptomatic type II second-degree AV block, permanent or intermittent, is a class II indication" (width of the QRS complex not stated) while for the same condition in the section on bifascicular and trifascicular block the ACC/AHA guidelines state that "bifascicular or trifascicular block with intermittent type II second-degree AV block without symptoms attributable to the heart block" constitutes a class I indication for pacing. Table 4 outlines some of the proposed changes that would enhance the guidelines for pacing in patients with intraventricular conduction blocks.

Pacing after myocardial infarction

Transient advanced AV block with BBB a class II indication in the 1984 ACC/AHA guidelines became a class I indication in 1991 with no new data presented to support the change. Transient second-degree or complete AV block with BBB is not necessarily a class I indication for pacing in patients with inferior myocardial infarction (MI) complicated by transient AV nodal block and permanent BBB because this situation carries a good prognosis. Consequently, transient second-degree or complete AV block and BBB in inferior MI should be relegated to a class III indication unless there is evidence of block in the His-Purkinje system, an exceptional occurrence in inferior MI[24]. The 1996 ACC/AHA guidelines for the management of patients with acute MI[25] recommend that in transient second- or third-degree AV block with BBB an EPS should be considered to assess the site and extent of heart block in uncertain cases. Missing from these new guidelines is how to interpret the data from an EPS in the decision process to implant a permanent pacemaker. However, prophylactic permanent pacing should be considered in the absence of transient second or third-degree AV block if there is alternating BBB, a situation not specifically mentioned in the 1991 ACC/AHA guidelines despite the use of the term "bilateral bundle branch block", which is not sufficiently descriptive[26].

Many believe that second and/or third-degree AV block in the His-Purkinje system in anterior MI, no matter how transient, should be a class I indication for pacing, yet the 1991 ACC/AHA guidelines and the 1996 ones for the management of acute MI require that the AV block be "persistent", a term not defined. Furthermore, the 1996 ACC/AHA guidelines for the treatment of acute MI introduced "symptomatic AV block" as a new class I indication for pacing[25]. This statement is

Table 5. Indications for permanent pacing after acute myocardial infarction*

Class I

A. Persistent or transient second-degree or complete AV block in the His-Purkinje system.
B. Alternating left bundle branch block and right bundle branch block with 1 : 1 AV conduction.

Class II

Persistent advanced second-degree or complete AV block at the AV node (longer than 16 days).

Class III

A. Transient AV conduction disturbances without intraventricular conduction defects.
B. Transient AV block in the presence of isolated left anterior hemiblock.
C. Acquired left anterior hemiblock, bundle branch block or bifascicular block with or without first-degree AV block, but in the presence of second-degree or complete AV block.
D. Transient second-degree or complete AV block and associated bundle branch block in acute inferior myocardial infarction.†

* Adapted from ref. 2 with permission.

† Transient AV block in inferior myocardial infarction is virtually always in the AV node or His bundle, and almost never requires permanent pacing even if associated with permanent bundle branch block. Therefore, transient advanced AV block and associated bundle branch block should not be classified as a class I indication as in the 1991 ACC/AHA guidelines (unless there is firm evidence of transient second- or third-degree AV block in the His-Purkinje system).

vague, and ignores the simple fact that any form of AV block in acute MI can be symptomatic before it resolves completely as in inferior MI.

AV block in inferior MI

The 1991 ACC/AHA guidelines classify persistent AV nodal block as a class II indication without defining what "persistent" means, a limitation perpetuated in the form of a class IIB indication (usefulness/efficacy is less well established in evidence/opinion) by the 1996 ACC/AHA guidelines for the treatment of acute MI[25]. It is therefore possible that pacemakers may be implanted unnecessarily considering the wide latitude of the ACC/AHA recommendation. The meaning of "persistent" can be derived only by understanding the natural history of AV block in inferior MI.

A literature search revealed only 20 studies of patients with acute inferior MI that documented the following: (1) incidence of second- and/or third-degree AV block during hospitalisation in survivors discharged from the hospital; (2) number of survivors who received permanent pacemakers; (3) maximum duration of second- and/or third-degree AV block (16 studies only)[27]. Thrombolytic therapy was used in all patients in only two studies[28,29], and only in a proportion in another two studies. In the prethrombolytic era a literature review revealed that second or third degree AV block could last as long as 16 days before return of 1 : 1 AV conduction. Although early reperfusion with thrombolytic therapy may not reduce the incidence of AV block, it seems to shorten its duration and reduce the need for temporary pacing[27]. In the 16 studies in the prethrombolytic era only 10 of 520 survivors (1.9%) who experienced second and/or third-degree heart block received permanent pacemakers. In one of these studies Dubois et al[30] reported 88 patients with acute inferior MI complicated by second and/or third-degree AV block. Six of the 67 survivors with AV block received a permanent pacemaker (9%). It seems very likely that these workers implanted pacemakers too early in the course of AV block without waiting for resolution. Excluding the data of Dubois et al[30], four of 453 survivors (0.9%) in 15 studies in the prethrombolytic era who had experienced second- and/or third-degree AV block (mostly with a narrow QRS) required permanent pacemakers. One cannot conclude at this juncture whether in the thrombolytic era fewer or more permanent pacemakers will be required in survivors of second and/or third-degree AV block[31].

The guidelines should state categorically that permanent pacing is very rarely needed in patients with inferior MI and narrow QRS AV block[24]. Even relatively uncommon intra-Hisian block in inferior MI is almost always reversible, and rarely requires permanent pacing[24]. The term "persistent" has been interpreted by some workers to mean 14–16 days, a cut-off point that seems satisfactory[27]. More conservative workers have indicated that pacemaker implantation should not be considered unless second- or third-degree AV block is present 3 weeks after MI[27]. On the basis of the 14–16-day criterion the need for permanent pacing in survivors who develop second and/or third-degree AV block should not exceed 1–2% of the entire AV block group whether or not they are treated with thrombolytics.

Other types of bradycardia

Barring AV block, the ACC/AHA guidelines for bradycardia probably need little revision. Many authorities

agree that spontaneous sinus pauses are abnormal if they exceed 3 s without intervening escape. However, the role of permanent pacing in these patients has not been established, although some workers feel that such a pause justifies permanent pacemaker insertion even in an asymptomatic patient. Is a pause of ≥ 3 s less important during sleep than in the awake state? Does a pause > 3 s or rate < 30 bpm during sleep as the only documented abnormality (in the absence of sleep apnea) constitute a class II indication in an asymptomatic patient? New guidelines should present a practical approach to these common problems. Contemporary guidelines should deal with the bradycardic complications of sleep apnoea and their resolution in most patients by specific treatment not involving permanent pacing[32]. Finally new guidelines should also mention the value of pacing in patients who are symptomatic only on effort secondary to atrial chronotropic incompetence, but exhibit no significant bradycardia at rest[33].

Antibradycardia pacing in specific situations

Clear recommendations for optimal pacing are required for patients with associated conditions such as coronary artery disease, paroxysmal atrial arrhythmias, cardiac transplantation, vasovagal syncope, implanted defibrillators and other specific clinical situations.

Non-bradycardic indications

Over the past few years several new indications for pacing have emerged. New indications in patients without conduction system disease include orthostatic hypotension, obstructive hypertrophic cardiomyopathy (OHC) and possibly dilated cardiomyopathy with severe heart failure. Many patients with OHC with at least a provokable left ventricular outflow tract gradient ≥ 30 mmHg can benefit from dual-chamber pacing with a short AV interval. However, the indications for pacing in OHC are evolving and not yet firmly established[34–38] so that the guidelines should reflect this situation. Therefore patients with drug-refractory OHC might be considered for pacing in terms of a class II or IIB[25] indication. The results of dual-chamber pacing in severe congestive heart failure (dilated cardiomyopathy or coronary artery disease) have so far been disappointing[39–41]. However, it would seem reasonable to consider patients with drug-refractory congestive heart failure due to poor left ventricular function and a long PR interval in terms of a class II indication for dual-chamber pacing with a short AV delay only if an acute study shows haemodynamic benefit. Multi-site pacing for severe congestive heart failure remains investigational at this time[42,43].

Optimal pacing modes

The ACC/AHA guidelines would benefit from a more detailed discussion of pacemaker haemodynamics as the basis for selection of the optimal pacing mode. In particular the definition of pacemaker syndrome in the old guidelines is too broad, and ignores the concept that the fundamental mechanism is inappropriate relationship of atrial and ventricular contractions[44]. The indications for the various pacing modes in the guidelines in terms of class I, II and III are awkward. Obsolete modes such as DVI do not deserve a class I designation and do not even belong in the guidelines except as a historical sideline.

The present guidelines provide only limited recommendations of the optimal pacing mode for an individual patient with a specific condition. Thus the guidelines contain little or no information to answer common practical questions such as "What is the optimal pacing mode for the patient with sick sinus syndrome?" Therefore, the revised guidelines should eliminate the classification of the various pacing modes in terms of class I, II and III. Instead they should utilise the useful format of the BPEG guidelines[16] for the *optimal*, *alternative* or *inappropriate* use of the various pacing modes in specific conditions.

Many of the recommendations for the various pacing modes are obsolete. For example, the guidelines do not specifically state that the VVI mode is contraindicated in patients with either the sick sinus syndrome and/or retrograde VA conduction as advocated by the BPEG[16] and others[45], while they do indicate that "VVIR pacemakers are particularly contraindicated in the presence of retrograde VA conduction". This statement applies equally to VVI pacing.

The role of single-chamber atrial pacemakers in the treatment of sick sinus syndrome without AV block should be presented as an acceptably safe (risk of AV block 1% per year) and cost-effective alternative to dual-chamber pacing in highly selected patients[46–48].

The ACC/AHA guidelines classify retrograde VA conduction as a contraindication to VDD pacing but acceptable for the DDI, DDIR, DDD and DDDR modes. Indeed it is odd that the guidelines promote only the DDDR mode as particularly applicable in those patients

who have persistent VA conduction. In this respect the BPEG guidelines correctly indicate that the indications for the VDD mode are basically similar to the DDD mode[16]. In a patient with normal atrial chronotropic function and retrograde VA conduction the concern of implanting a single-lead VDD system seems unwarranted with modern pacemaker technology because judicious programming of the lower rate can avoid VVI pacing (and possible pacemaker syndrome) during sinus bradycardia. Furthermore, sophisticated sensor-controlled VDD devices can now automatically programme the lower rate during sleep to a value below the slowest sinus rate to prevent loss of AV synchrony at night[49].

Frequent supraventricular arrhythmias should no longer be considered a contraindication for dual-chamber pacing (as in the 1991 ACC/AHA guidelines) because dual-chamber pacemakers may reduce the incidence of supraventricular tachycardia or facilitate antiarrhythmic therapy. The guidelines should stress that the DDI mode is uncommonly selected as the primary pacing mode in the brady-tachy syndrome because it has been superseded by DDD or DDDR devices with automatic mode switching to a non-atrial tracking mode (VVI, VVIR, DDI, DDIR) during supraventricular tachycardia to prevent rapid ventricular pacing[50,51]. The permanent DDI(R) mode should be relegated to second choice in the brady-tachy syndrome with a clear warning that it is contraindicated when the sinus rate is greater than the programmed lower rate to prevent AV dissociation, a situation that occurs in the presence of AV block[45].

Finally, the guidelines should point out the cost-effectiveness of dual-chamber pacing[52,53] and the importance of maintaining AV synchrony in the elderly (< 70 years) who derive considerably more benefit from dual-chamber pacing than do relatively young patients[45,54]. The statement in the 1991 ACC/AHA guidelines that favours the DDD mode in "active or young patients with atrial rates responsive to clinical need" is no longer appropriate.

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Chapter 49

Regional Electromechanical Coupling During Ventricular Pacing

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Introduction

Cardiac pacing can modulate heart rate, atrial filling and the sequence of electrical activation. The first pacemakers were mainly meant to normalise heart rate. More recently dual-chamber pacing enabled optimisation of the atrioventricular interval and, hence, ventricular filling. However, the effects of asynchronous electrical activation of the ventricular wall, caused by impulse conduction via muscle fibres rather than via the Purkinje system, has received little attention.

Regional abnormalities in wall thickening or wall motion have been observed in animals during ventricular pacing[1,2] and in patients during ventricular pacing and with bundle branch block or Wolff-Parkinson-White syndrome[3,4]. Although the contraction pattern, as obtained by phase imaging of radionuclide angiograms, is used clinically to assess the asynchrony of electrical activation[3,4], the exact relationship between the electrical and mechanical activation sequence has not yet been established. It is also incompletely understood to what extent the regional wall motion abnormalities relate to regional differences in myocardial work. Scintigrams in patients with left bundle branch block showed septal perfusion defects despite patent coronary arteries[5]. This could be due to modified local oxygen requirements or impairment of blood flow by the abnormal contraction pattern.

The present study was designed to validate the assessment of the sequence of ventricular activation from measurements of the onset of shortening, and to investigate whether asynchronous activation leads to a redistribution of myocardial work or to impairment of myocardial blood flow.

Methods

The studies were performed on anaesthetised open-chest dogs, as described in detail elsewhere[6–9]. In brief, after opening the pericardium, stimulation electrodes were sutured to the heart at the right atrium, right ventricular outflow tract (RVOT), left ventricular apex (LVA) and left ventricular free wall (LVFW). Left ventricular (LV) cavity and ascending aortic pressure were measured with catheter-tip micromanometers. Stroke volume was determined as aortic volume flow using an electromagnetic flow probe. ECG was derived from the limb leads.

A 192 electrode-brush (44 × 64 mm) was used for simultaneous recording of epicardial surface electrograms from the LV anterior wall. From these signals the moment of local electrical activation was determined.

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Myocardial contraction patterns were determined by measuring the mutual displacement of 40–60 video markers attached to the epicardial surface. The motion of the markers was recorded on videotape. Offline the video images were digitised and the markers were detected using image analysis software. The region under study was divided into 16 subregions (see Fig. 1), the fibre shortening of which was derived from the complete two-dimensional deformation dataset and the fibre orientation as determined by visual inspection. Changes in fibre length were expressed as natural fibre strain ($\ln(l/l_0)$), so negative strain means fibre shortening.

The onset of local fibre shortening was determined by shifting in time the tracings of fibre shortening from adjacent regions until the cross-correlation between them was optimal. In cases of low mutual correlation (< 0.85) the negative peak of the second time derative of fibre shortening was used as a time reference to assess the map of the time sequence of mechanical activation for all regions[7,10]. The electromechanical time (EM) interval was defined as the interval between the onset of shortening and the electrical activation time.

In analogy to the use of the pressure-volume area for the estimation of global LV oxygen demand, the local fibre stress-fibre strain area (SSA) was used to estimate local oxygen demand[9]. This area is composed of two parts: external work and potential energy. External work was calculated as the area of the fibre stress-fibre strain diagram from end-diastole until end-ejection. Potential energy was estimated from the area bounded by the end-systolic fibre stress-fibre strain relation and the horizontal (strain) axis. To this purpose regional fibre stress ($\sigma(t)$) was estimated from LV pressure, the ratio of LV cavity volume ($V_c(t)$) to wall volume (V_w) and regional deformation[9]:

$$\sigma(t) = P_{lv}(t) \cdot \left(1 + 3\frac{V_c(t)}{V_w}\right)^{2/3} \cdot \frac{L(t)}{L_0}$$

where $L(t)/L_0$ = local fibre length relative to the length at estimated zero cavity volume. Total mechanical power (TMP) was calculated as the ratio of SSA and the duration of the cardiac cycle. Regional oxygen consumption was calculated from regional myocardial blood flow, as determined with radioactive microspheres, and arteriovenous differences in oxygen content[9].

Measurements were performed during sinus rhythm or while pacing at LVA, RVOT and LVFW. During ventricular pacing the atrium was stimulated 30 ms before the ventricle, to assure complete ventricular capture.

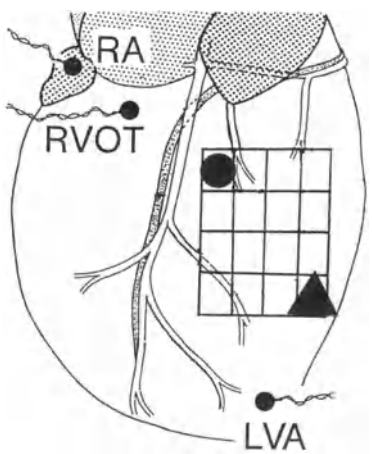

Figure 1. Schematics of the experimental setup. At the anterior LV wall measurements were performed in the regions indicated by the large rectangle. The small rectangles denote the division of this region into 16 smaller regions for determination of regional fibre shortening. The large dot and triangle indicate the anterior basal and latero-apical regions, the contraction patterns of which are depicted in Fig. 3, while the data on fibre shortening are presented in Fig. 4.

Results

Sequence of activation

Ventricular pacing increased the asynchrony of activation in the part of the anterior LV free wall studied. The maximum delay in electrical activation in this area was 8.8 ± 3.3 ms during sinus rhythm and increased to 25.4 ± 9.3 and 39.0 ± 5.3 ms during LVA and RVOT pacing, respectively (mean ± SD, $p < 0.05$). The corresponding delay in onset of fibre shortening proved to be significantly larger under all conditions, being 20.5 ± 7.3 ms during sinus rhythm, 40.1 ± 10.0 ms during LVA pacing and 50.3 ± 7.7 ms during RVOT pacing. The sequence of the onset of fibre shortening correlated fairly well with the sequence of electrical activation. This is illustrated by plotting the time of onset of fibre shortening (as indicated in Fig. 3) as a function of electrical activation time (Fig. 2). A linear relationship was observed, with a steeper slope during LVA than during RVOT pacing. In both cases the slope of this relation was larger than unity, indicating that the time interval between electrical activation and onset of

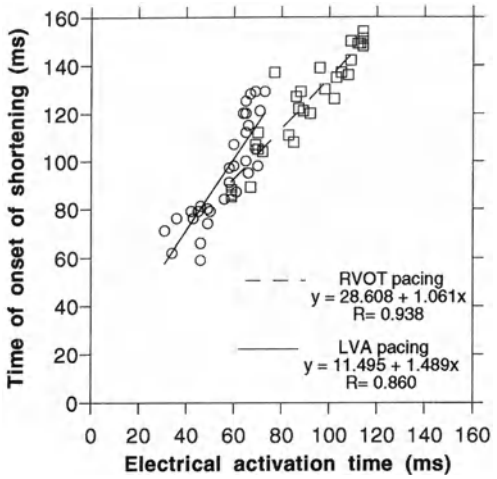

Figure 2. Relationship between electrical activation time and onset of fibre shortening during RVOT pacing (squares) and LVA pacing (circles).

fibre shortening increased when activation occurred later. This is also reflected by the differences in EM interval at the base and apex during ventricular pacing: during RVOT pacing the EM interval was 32.6 ± 10.3 ms at the base and 41.2 ± 7.9 ms at the apex ($p = 0.09$). During LVA pacing the difference in EM interval reversed: 39.9 ± 24.5 ms at the base and 23.8 ± 29.8 ms at the apex ($p < 0.05$).

Redistribution of work

During sinus rhythm and atrial pacing the patterns of regional fibre shortening were uniform, characterised by minor shortening during the isovolumic contraction phase and shortening (approximately 10%, strain –0.10) during the ejection phase. Ventricular pacing disturbed this uniform contraction pattern significantly (Fig. 3). Close to the site of pacing (anterior basal in case of RVOT pacing and latero-apical in case of LVA pacing) pronounced shortening occurred in the isovolumic contraction phase. This was followed by minor shortening, sometimes even stretching, during the ejection phase. In late-activated regions fibres are initially stretched by up to 10%, followed by pronounced shortening during the ejection phase (> 15%). Figure 4 illustrates that the length changes in the isovolumic contraction phase are inversely related to the length changes during the ejection phase. During atrial, RVOT and LVA pacing this relation was similar in different regions of the LV wall.

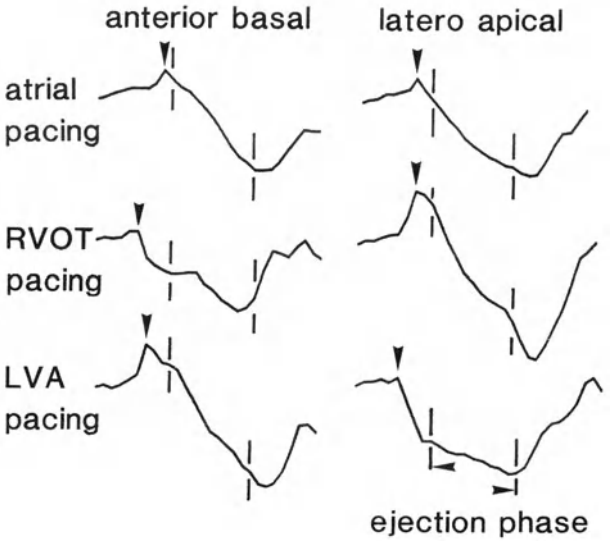

Figure 3. Patterns of fibre strain during atrial, RVOT and LVA pacing in two regions of the LV wall: anterior basal and latero-apical (for location of these regions, see Fig. 1). The vertical bars indicate the beginning and end of the ejection phase, and the arrows the onset of shortening.

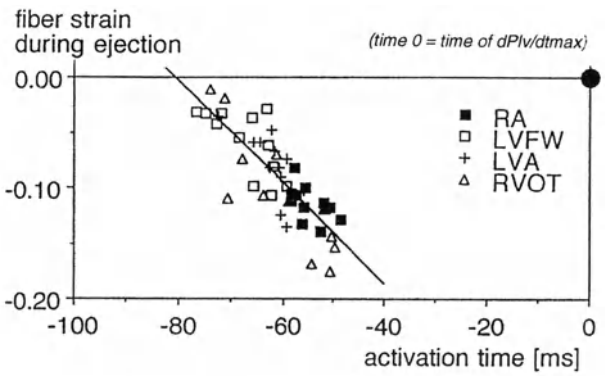

Figure 4. Relationship between strain during the isovolumic contraction phase and strain during the ejection phase while the heart was paced at the RA, LVA and RVOT (negative strains means shortening). The symbols and crosses denote mean values and SD of the data obtained at the anterior basal (dots) and latero-apical region (triangles) of the LV wall in seven experiments.

Strain during the ejection phase was also significantly related to local electrical activation time (Fig. 5). As reference moment for electrical activation the moment of maximum rate of rise of LV pressure (dP_{lv}/dt_{max}) was

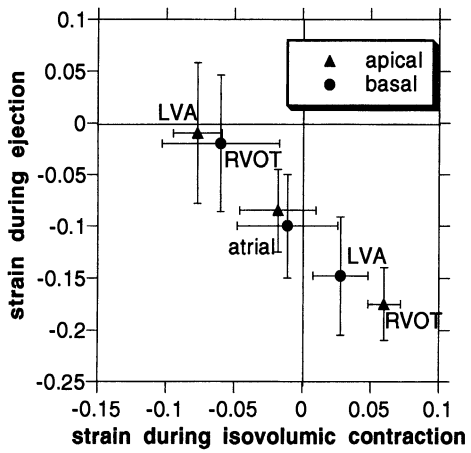

Figure 5. Plot of regional fibre strain during the ejection phase versus regional electrical activation time. The moment of maximum rate of rise of LV pressure (dP_{lv}/dt_{max}) is used as time reference. Data from all 16 regions of a heart studied during pacing at the atrium and three different ventricular sites. The regression line fitting the data points is also presented as well. Modified from ref. 8.

used. This variable resulted in a single relationship between electrical activation time and the amount of fibre strain during ejection during pacing at the various sites[8]. Linear regression analysis revealed that the slope of the regression line describing this relationship was -3.76 ± 0.73 s^{-1} and the *Y*-intercept was -0.28 ± 0.05. This indicates that a change in activation time of 30 ms is associated with a change in strain of 0.10, which is approximately the normal strain value during sinus rhythm.

Figure 6 shows maps of fibre strain during the ejection phase, maximum active fibre stress, total mechanical power (TMP) and myocardial blood flow and oxygen consumption. During atrial pacing these variables showed relatively small, random, variations. During ventricular pacing significant gradients were found for all variables presented, except for fibre stress. The regional differences in TMP were predominantly related to differences in external work: in early-activated regions the fibre stress-strain diagrams were narrow, sometimes becoming figure-eight-shaped. In lateactivated regions the stress-strain diagrams became wider than normal, due to the prestretch in these regions.

Regional oxygen uptake, as measured in 16 subepicardial regions per heart during sinus rhythm and RVOT and LVA pacing, proved to be linearly related to regional TMP, expressed by the regression equation Oxygen uptake = $a \cdot$ TMP + b, with $a = 4.94 \pm 0.31$ and $b = 24.24 \pm 1.85$ ($r = 0.68$). The slope of this regression line is similar to that of the PVA-oxygen relation, as obtained in the whole left ventricle[11,12].

Discussion

The findings of this experimental study indicate that ventricular pacing markedly influences regional myocardial performance. The sequence of electrical activation of the LV free wall may, at least qualitatively, be assessed from myocardial contraction patterns. Asynchronous activation changes local preload, being low in early-activated regions and high in late-activated regions. As a consequence local myocardial work is redistributed similarly.

Sequence of activation

Because of the sensitivity of local contraction patterns to the activation sequence, the latter parameter might be derived from the former. The electromechanical time interval in the early-activated regions during ventricular pacing (ranging on average from 23.8 to 32.6 ms) is in good agreement with the interval of about 26 ms, as found in isolated trabeculae[13]. In the latter studies the interval between electrical stimulation and force development decreases at larger sarcomere length. In our studies, however, the EM time interval was largest in late-activated regions, which were prestretched during the isovolumic phase before becoming activated. This discrepancy illustrates that the onset of local shortening is not the same as true mechanical activation. In late-activated regions the prestretch in combination with meanwhile-increased LV cavity pressure causes increased wall stress. Therefore, the level of mechanical activation (e.g. active fibre tension) has to be relatively high before shortening can be detected. The different relationship between electrical and mechanical activation during pacing from different sites may also be explained by the complex mechanical interactions between various myocardial regions. The present data, therefore, indicate that no perfect correlation exists between local electrical activation time and onset of shortening, and that the electrical asynchrony is systematically overestimated by using the onset of shortening. Nevertheless, mapping of the onset of fibre shortening gives a fair impression of the sequence of electrical activation of the ventricle.

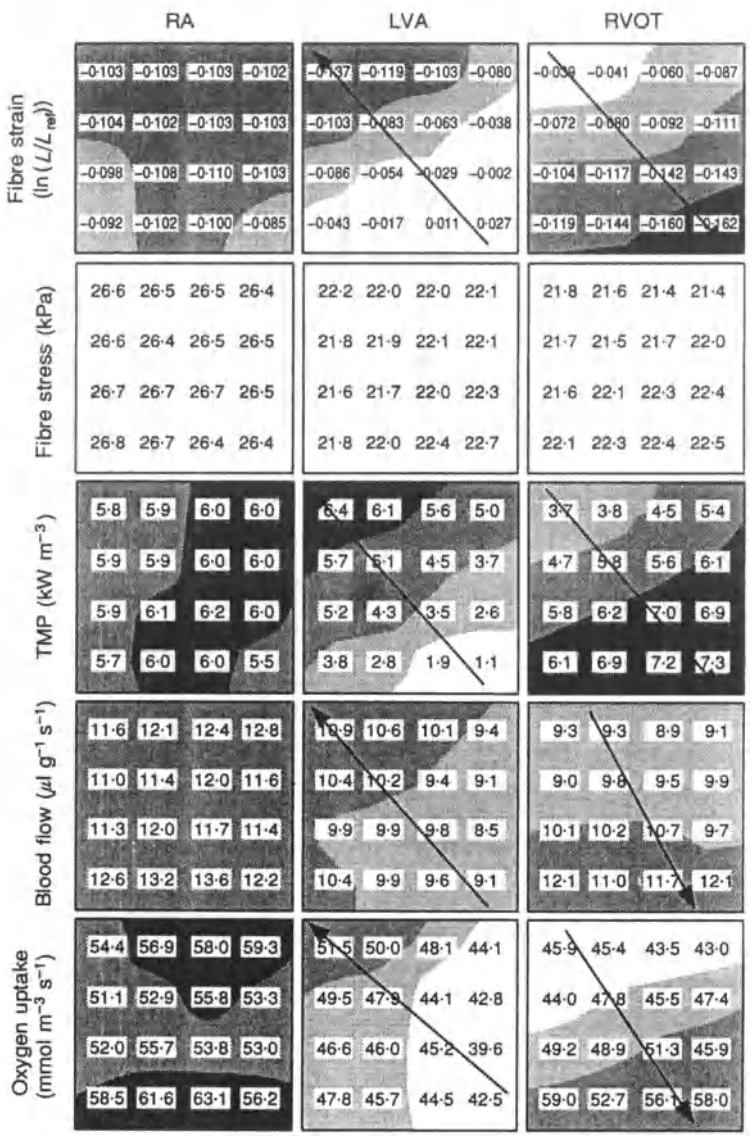

Figure 6. Mean maps of regional fibre strain, maximal active fibre stress, total mechanical power (TMP), blood flow and oxygen uptake during right atrial (RA), LVA and RVOT packing, as averaged over six experiments. Significant gradients (as tested by two-dimensional analysis) are indicated by arrows. The boundaries between different degrees of shading indicate intervals of 0.05 in fiber strain, 2 kW m^{-3} in TMP, 5 μl g^{-1} s^{-1} in blood flow and 5 mmol m^{-3} s^{-1} in oxygen uptake. Modified from ref. 9.

Redistribution of myocardial work

The finding that shortening during the ejection phase is proportional to stretch during the isovolumic contraction phase, indicates that a force-length ("Franck-Starling") relation is present at the local level. During asynchronous activation large regional variations in length at the onset of the ejection phase are present, which can be regarded as variations in regional preload. As in the entire ventricle, high preload, as in late-activated regions, is associated with increased regional myocardial work. The data presented in Figs 5 and 6, obtained from various regions of the LV wall during pacing from various sites, indicate that a close relationship exists between local electrical activation time on the one hand and regional preload and myocardial work on the other.

Regional myocardial work, in its turn, was closely related to regional myocardial oxygen consumption. The local variations in oxygen consumption were almost entirely due to local variations in blood flow, since changing of pacing site did not significantly affect local oxygen extraction[9]. This indicates that the regional differences in blood flow are due to regulation of myocardial blood flow by local metabolic need (auto- regulation) rather than impairment of local perfusion by the abnormal contraction patterns. A consequence is that perfusion defects in the septum of patients with left bundle branch block should not be interpreted as coronary artery disease. Since the septum is early-activated in these patients[14] it presumably performs less work than the remainder of the ventricle, especially the LV free wall. Therefore, the maldistribution of blood flow and glucose uptake may well reflect the abnormality in sequence of activation without any coronary artery problem.

The redistribution of work within the LV wall is, most likely, also responsible for the asymmetric hypertrophy observed during chronic ventricular pacing. In dogs, paced at the LV free wall at physiological heart rate for 6 months, selective hypertrophy (as much as 40%) has been found in the septum, but not in the LV free wall[15]. Since the septum is activated late, mechanical load is presumably high. The clinical relevance of this asymmetric hypertrophy has yet to be investigated.

Possible clinical applications

The present study shows that measurement of regional mechanical performance in asynchronously activated myocardium contains a wealth of information. The techniques used to measure deformation in the present study (epicardial markers) are not clinically applicable. However, magnetic resonance imaging (MRI) tagging is a promising technique allowing non-invasive measurement of complete three-dimensional deformation in the entire ventricular wall[16]. Recent data from an MRI tagging study, performed during RV apex and LV free wall pacing in dogs, showed patterns of shortening which were similar to those in the present study[17]. Because shortening was measured throughout the left ventricle, the observed inhomogeneities in fibre shortening and work were even larger than in the present study. Therefore, MRI tagging may become a powerful tool for functional evaluation of the (asynchronously activated) heart.

Conclusions

Ventricular pacing induces asynchronous activation of the left ventricle and strongly affects regional myocardial contraction patterns. These patterns can be used to assess qualitatively the sequence of electrical activation of the ventricles. Asynchronous activation changes local preload, being low in early-activated regions and high in late-activated regions. As a consequence local myocardial work and oxygen consumption are redistributed similarly. from all 16 regions of a heart studied during pacing at the atrium and three different ventricular sites. The regression line fitting the data points is also presented as well. Modified from ref. 8.

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Chapter 50

What Kind of Programming Gives the Optimal Performance in Rate-Response Ventricular Pacing

Modesto Guerola

Introduction

The answer to the question posed in this chapter title is simple: *the one that gets as close as possible to physiological sinus rate*. The problem arises when we try to achieve this setting. When programming a rate-adaptive system we need to consider three basic factors: the basal rate, the maximum rate-response (R-R) rate and the particular parameters of the selected sensor.

Considerations must be given to the type of system we wish to implant. The great advantages of activity sensor pacemakers lie in their ability to respond to a low level of physical activity and to increase heart rate rapidly. Biological sensor pacemakers display a slow initial response, but they have greater specificity and more proportional rates in the recovery phase[1–3]. Rate-adaptive cardiac pacing is limited by the inability of a single sensor to simulate the entire spectrum of normal sinus response to both exercise and rest. The combination of two sensors enables a better rate-adaptive profile, especially during exercise[4,5].

However, the clinical benefits of dual-sensor pacing over single-sensor pacing are still uncertain, although a preliminary study[6] suggests that cardiopulmonary physiology and oxygen uptake kinetics may be improved by the combination of a fast response sensor with a more proportional sensor. Do we really have the need to test sensor response? Could programming nominal sensor settings be sufficient? Is accurate R-R programming really necessary?

It is unknown whether accurate R-R programming is a necessary factor for improved exercise capacity and, hence, quality-of-life found in R-R pacing with both single- and dual-chamber pacemakers.

In 1990[7], Sulke et al published an interesting paper reporting on a study of rate-adaptive single- and dual-chamber pacemakers, in order to compare patient's exercise tolerance and general well-being with sensor programmed OFF, sensor accurate-programmed (R) and sensor over-programmed (R+). Perceived general well-being for patients using single-chamber pacemakers with an activity sensor (Sensolog) was significantly better in the VVIR mode than in either the VVI or VVIR+ mode. In dual-chamber pacemaker patients, general well-being was significantly poorer in DDDR+ than in either DDD or DDDR mode. In DDDR+ mode palpitaions were the most common complaint. Over-programming of rate response was least acceptable in both the single- and dual-chamber pacemaker

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populations. Half of the single-chamber patients and one-third of the dual-chamber patients demanded early crossover.

Under-programming in single-chamber patients was unacceptable to one-third of the studied population, but no patient requested early crossover from the under-programmed dual-chamber mode.

Over-programming of R-R is least acceptable to patients with either single- or dual-chamber pacemakers, despite improvement in exercise tolerance.

Specific subjective assessment confirmed that appropriate R-R programming was the most acceptable mode for both the single- and dual-chamber pacemaker populations, and yielded the best scores for general well-being, fewest symptoms and best functional status. Gender should also be taken in account when sensor slope is programmed, because previous studies have suggested that young and old females require faster slopes than young and old male patients[8].

Upper and lower rate limits

Upper and lower rate limits are the first parameters to select when a rate-adaptive system is programmed. The R-R curves of sensors are commonly linked to them. Accurate lower and upper rate limit selection for each individual patient requires surface ECG or Holter monitoring during rest and maximal exercise, but exercise tests have numerous limitations, e.g. third-degree atrioventricular (AV) block, sick sinus syndrome (SSS) and the physical inability of many patients. The procedure is also time-consuming and increases the cost of pacing therapy. A more simple way of selecting the upper rate limit is according to the age scale, a procedure suitable for the majority of patients without other concomitant pathologies[8,9].

The upper rate can also be set, as a rule, to 120–130 bpm in VVIR pacemakers, if we consider that highest cardiac output during exercise has been found to lie between 80 and 110 bpm although with significant individual variations[3,10–15].

Associated pathologies can introduce other upper rate limits. Special attention must be paid to patients with coronary disease. A reduction in the upper rate limit and R-R settings is recommended in such patients, because an excessively fast heart rate during exercise could trigger angina[3].

What should the lower rate be for our patients? This cannot be known for sure when the patient has third-degree AV block or atrial arrhythmia. In my opinion, as regards resting rate, the lower rate limit must be sufficiently low to allow the patient to sleep well at night, and sufficiently high to keep the patient awake during rest in daytime. In the reviewed literature most patients had mean resting rates of 81 ± 9[8,9,16]. The most commonly selected rates were 60–70 bpm with VVIR systems.

Sensor rate adaptation settings

Some type of controlled exercise is needed to select rate-adaptive sensor parameters. Ergometric tests are commonly utilised in assessing optimal rate-responsive settings, but ergometric tests do not reflect ordinary daily activities[17,18]. They are essential for clinical evaluations in which we need to repeat identical exercises in order to compare sensor response under different settings or between one patient to another.

Unconventional exercise tests which simulate daily life activities are much closer to normality, but require some kind of facility at the clinic. An exercise test for sensor programming should include rate evaluation with the patient standing still, slow walking and fast walking for periods of at least 1 min each. Jumping is a simple exercise that can be useful in determining optimal rate-responsive settings when space at a clinic is at a premium.

Old systems with manual sensor programming created an arduous, time-consuming process for the physician and patient. Selection of one sensor parameter was equivalent to one exercise test, controlled under ECG monitoring or, in the best of cases, with rate histograms. In the course of time experience brings a type of intuition that allows us, in most cases, to obtain a satisfactory response with only two or three tests.

Nowadays, automatic programming tools, such as slope selection, allow us to programme sensor settings with only one exercise test. Associated advanced R-R diagnostics enable us to tailor rate response to each patient with no need to repeat the test.

Sensor rate-versus-time histograms of these pacemakers are capable of redrawing the graphics for different sensor settings (Fig. 1). They give us the option of seeing what the sensor-indicated rate would have been under all programmable slope values, selecting the one deemed most appropriate.

Another useful tool for activity sensor threshold selection is Holter activity counters. We usually evalu-

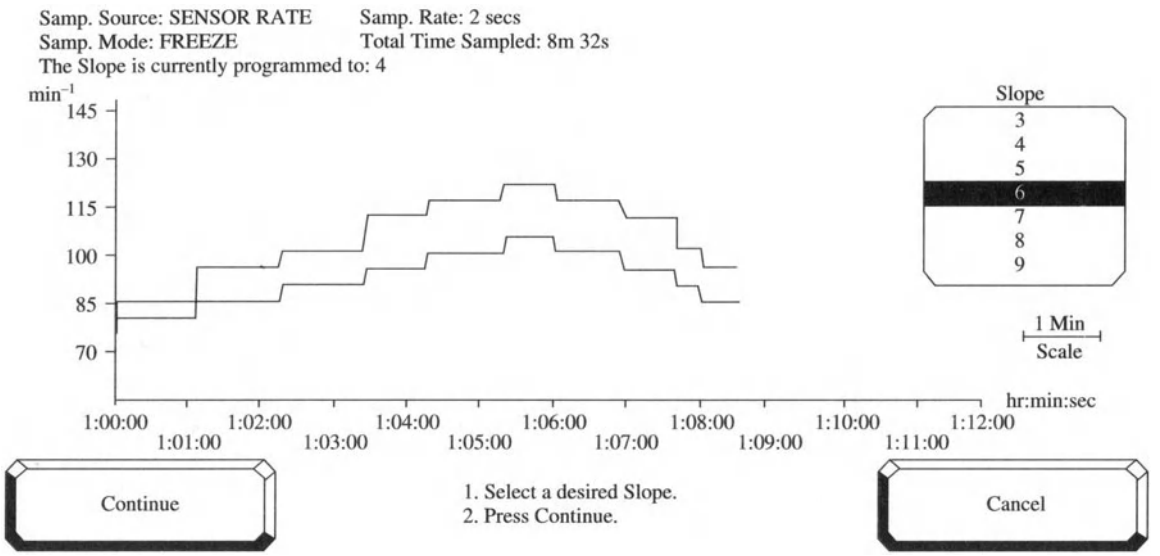

Figure 1. Once a patient finishes the exercise test with Auto-set function, a rate histogram is generated to evaluate rate adaptation with the prevailing slope. If some other sensor response is desired there is no need to repeat the exercise. A new slope is selected, and rate graphs are redrawn to the adaptive rate which would have been obtained with this slope setting.

ate activity sensing according to the sensor-indicated rate, but sensor R-R is delayed by reaction time, during which a brief activity noise does not usually evoke any sensor R-R. In other instances this noise can be present for longer periods of time, causing a rate increase and causing patient discomfort. Holter activity shows the amount of activity detected by the sensor (Fig. 2) and permits accurate sensor threshold programming with simple, 1–3 min exercises.

Automatic sensor setting adaptation

Effective initial sensor programming is sometimes not sufficient, as a result of activity or physiological

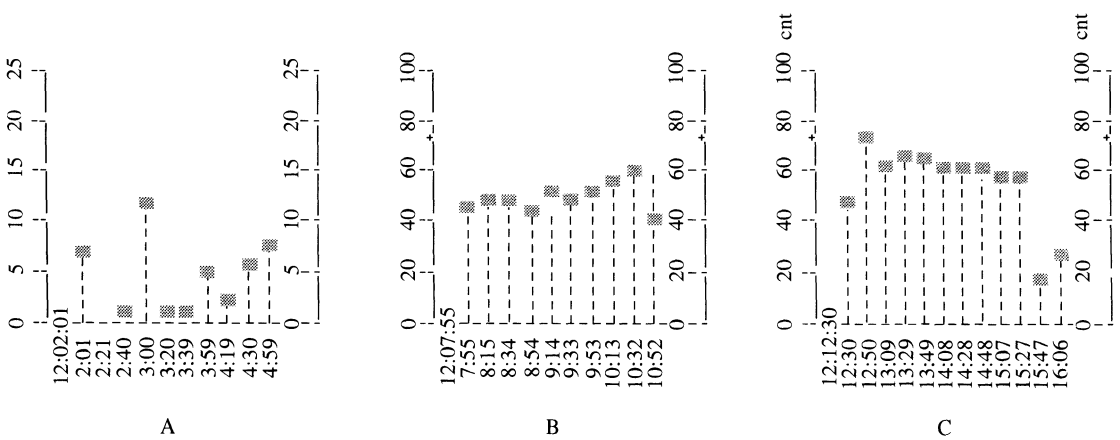

Figure 2. Holter activity counters. **A**: Activity detected while patient was seated, moving his arms normally while talking. The manufacturer recommends less than 10 counters. **B**: Activity detected during patient's normal walking. Activity counters were found between 40 and 60. **C**: Activity detected during patient's fast walking. Activity counters were found to exceed 60.

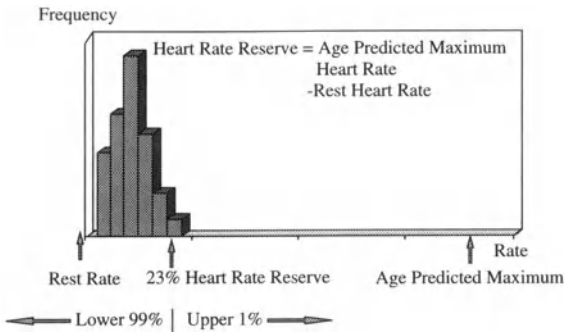

Figure 3. Normal heart rate frequency distribution.

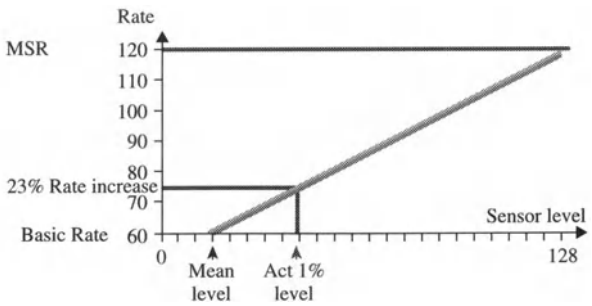

Figure 4. Automatic slope calculation. Sensor threshold establishes the activity noise detection point at which rate response begins. The slope is set according to that point and the one at which 99% of activity level corresponds to 23% of rate increase, depending on the basal and maximum sensor rates selected.

changes in patients between follow-ups. The ideal sensor should adapt on a day-by-day basis to the patient's physical or metabolic changes, according to a pre-set range.

New activity-sensing systems make a continuous automatic slope selection according to detected activity levels, which are compared to a normal heart rate frequency distribution (Fig. 3). A sensor algorithm sets a resting level, equal to basic rate plus 23% of sensor rate increase and an activity level (Fig. 4). This assumes that 99% of the daily sensor signal corresponds to resting level, and 1% to activity level (Fig. 5).

If automatic slope selection fails to provide the desired R-R because a particular patient has a different level of activity, values for automatic slope selection can be adjusted to a higher or lower sensor signal percentage breakpoint.

Things become more complex with dual-sensor pacemakers. To the individual sensor programming we must add the additional work of blending sensors so that we can obtain the individual benefits conveyed by each sensor and, by sensor cross-checking, avoid their individual backgrounds.

The activity-QT sensor combination appears to be an excellent dual-sensor system, providing a fast initial response and proportional adaptation of the pacing rate to metabolic demands, closely simulating sinus response during exercise and daily activities[16]. Diagnostic tools and daily sensor automatic regulation features make this dual-sensor system simple to control.

Nevertheless, initial sensor programming requires manual selection of activity sensor parameters. Holter activity counters permit accurate sensor threshold programming with brief and simple activity tests. One minute of testing, under normal and fast walking (Fig. 2) supplies us with this diagnostic tool, direct information of the activity sensor signal detected.

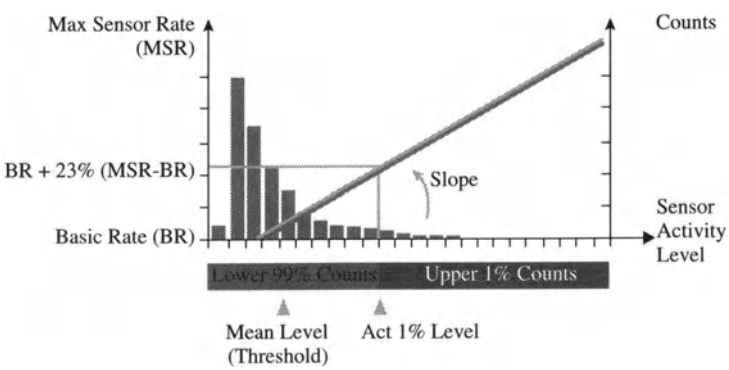

Figure 5. Sensor slope adaptation according to daily detected activity counts.

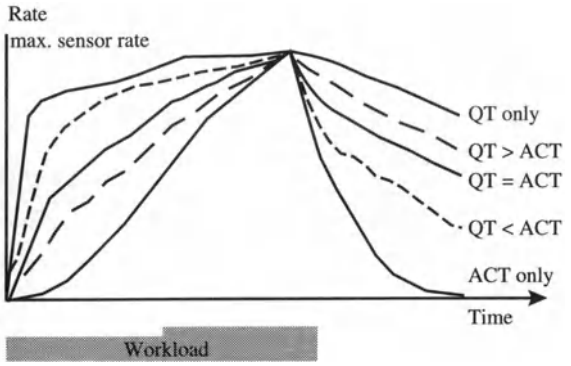

Figure 6. Influence in rate adaptation of different sensor blending.

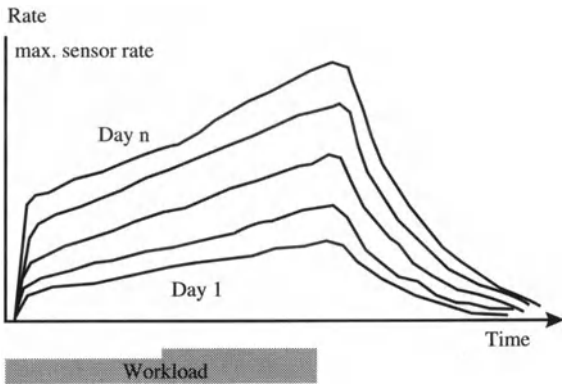

Figure 7. Daily learning of QT-ACT sensor algorithm.

Automatic QT sensor programming is the next requirement before sensor blending selection. QT slope will be set by the sensor algorithm according to basal and maximum pacing rates and shortest and longest QT interval during a short test directed by the programmer for fast QT sensor programming.

Sensor blending is a new feature that allows us to programme the influence of each sensor in the final dual-sensor indicated rate, which can be of 100%, 75%, 50%, 25% or 0%. Rate adaptation will change depending on the prevailing sensor; activity contribution will give faster and higher rate increases, while QT contribution will muffle rate increase and make it more proportional to workload[4,5] (Fig. 6).

Once dual-sensor individual settings and sensor blending have been established, an automatic sensor algorithm will match the rate adaptation to the patient's daily activities (Fig. 7).

Real dual-sensor systems mean combined sensor-indicated rate. Only in this way is it possible, by sensor cross-checking, to avoid activity sensor artefacts. The presence of physical activity is not possible without an increase in metabolic demand; therefore if there is activity noise detection, but the QT sensor does not measure QT interval changes, a dual-sensor algorithm will consider activity counters as an artefact, avoiding an inadequate fast-pacing rate.

Conclusions

Rate-responsive pacemakers should be appropriately programmed because accurate programming is more acceptable in single- and dual-chamber pacemaker patients, than is under- or over-sensor programming. Holter or patient basal ECG monitoring while resting and exercising is recommended for lower and upper rate limit selection, but this is limited to patients without third-degree AV block or SSS.

An exercise test for sensor programming should simulate daily-life activities with at least slow and fast exercising for the majority of rate-adaptive systems. Automatic diagnostic tools are valuable for more simple, fast and user-friendly sensor programming. Automatic sensor programming allows the system to adapt to changes in a patient's metabolical demands.

Dual-sensor rate-adaptive systems seem to improve cardiopulmonary physiology and oxygen uptake kinetics when adding a fast-responding sensor to a more proportional one, but R-R programming becomes more complex and time-consuming.

Further development of automatic programming is required for even more user-friendly and accurate sensor values selection. Sensor technology is improving, to give more physiological and safe rate adaptation, but at the same time it is becoming more complex, and more time-consuming for control and programming. Development of automatic features must occur at the same speed.

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Chapter 51

Atrial Septal Pacing: Synchronising the Atria

William H. Spencer III

Introduction

Permanent transvenous atrial pacing leads have been placed traditionally in the right atrial appendage. In patients with prolonged interatrial conduction time, pacing and sensing from the right atrial appendage may produce deleterious left heart timing intervals[1,2]. By pacing the left atrium one could remove any uncertainties regarding interatrial conduction time and potentially achieve appropriate left-sided timing intervals. In addition, it is possible that simultaneous depolarisation of both atria would result in a decreased incidence of reentrant atrial tachyarrhythmias[3–6]. Previous attempts at transvenous pacing of the left atrium have involved multi-site and multi-lead systems[3–6]. We present our early results of single-lead, single-site simultaneous pacing of both atria from the interatrial septum which will allow optimal left-sided timing intervals and decreased dispersion of right and left atrial activation and depolarisation.

Materials and methods

Pacemaker implantation was carried out in six male patients (average age 73 ± 3 years) all of whom had symptomatic bradyarrhythmias and symptomatic paroxysmal atrial fibrillation. Leads were implanted utilising a venogram-guided percutaneous subclavian technique. The atrial leads employed were Medtronic Model 4058 and were attached to the interatrial septum under transoesophageal echocardiographic guidance, as described below, and fluoroscopy. Once satisfactory fixation at the desired site on the atrial septum was obtained, no repositioning of the lead was subsequently attempted. The ventricular leads used were Medtronic Model 4024 and were positioned in the apex of the right ventricle. The generators used were Medtronic Model 7960. All implants were analysed using a Medtronic Model 5311-B pacing system analyser.

Transoesophageal echocardiographic studies

Positioning of the atrial pacing lead in the interatrial septum was performed with transoesophageal echocardiographic (TOE) guidance. The TOE studies were performed in the cardiac catheterisation laboratory after topical oral anaesthesia with 1% xylocaine spray and sedation with 1–3 mg of intravenous midazolam. Studies were performed with a biplane TOE probe (5 MHz) using a Hewlett Packard Sonos 1500 ultrasound imager (Andover, MA). In the last three cases a paediatric TOE biplane probe was used, which was tolerated even better than the conventional adult probe, and provided adequate imaging for positioning of the atrial lead.

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After initial insertion of the ventricular and atrial leads into the left subclavian vein, the atrial lead alone was advanced beyond the superior vena cava to facilitate identification of the lead by TOE and avoid confusion from the ventricular lead. The shaft and tip of the atrial lead were visualised by alternating the echo images between the horizontal and longitudinal planes. Knowledge of the pacemaker loop configuration on fluoroscopy facilitated identification of the spatial orientation of the lead in the right atrium and helped identify its tip. Furthermore, in contrast to the shaft of the pacemaker lead, the tip has a more dense reflection and trailing echoes, which help further in its identification (Fig. 1). Under TOE and fluoroscopic guidance the tip of the atrial lead was directed to the most anterior region of the right side of the interatrial septum, close to the area between the interatrial septum and aortic root (Fig. 1). On the horizontal plane the tip could be seen in the most anterior portion of the septum primum. On the longitudinal plane this location was identified upon clockwise rotation of the TOE probe from the view showing the ascending aorta and aortic valve to the first appearance of the interatrial septum (Fig. 1). Once the atrial lead tip was stable and in the desired position, the lead was screwed in position. After adequate pacing capture the TOE probe was withdrawn. The ventricular lead was then advanced and secured in place.

Measurement of atrial conduction times

All antiarrhythmic drugs were discontinued for at least five half-lives before the measurement of atrial conduction times. After informed consent was obtained, the patient was brought to the electrophysiology laboratory in the post-absorptive state. After sterile preparation and mild sedation, a six French quadripolar catheter was inserted into the right femoral vein and positioned in the high lateral right atrium (Fig. 2). A seven French decapolar or quadripolar catheter with a deflectable tip was inserted into the right femoral vein and positioned in the coronary sinus with the distal pair of electrodes positioned at the lateral aspect of the mitral annulus (3 o'clock) position in the left anterior oblique view (Fig. 2). The surface electrocardiogram, leads I, II, III, and intracardiac electrograms were monitored and recorded on a computer-based digital amplifier/recorder system with optical disk storage (Bard, Massachusetts). Bipolar endocardial electrograms were filtered with a bend-path of 30–500 Hz. The pacemaker was initially programmed into the AAI mode at 30 bpm, so that the interatrial conduction time during sinus rhythm could be recorded. The measurements were taken from the onset of the local electrograms recorded from the high lateral right atrium to the electrogram located from the distal pair of electrodes of the coronary sinus catheter, which is located in close proximity to the lower lateral left

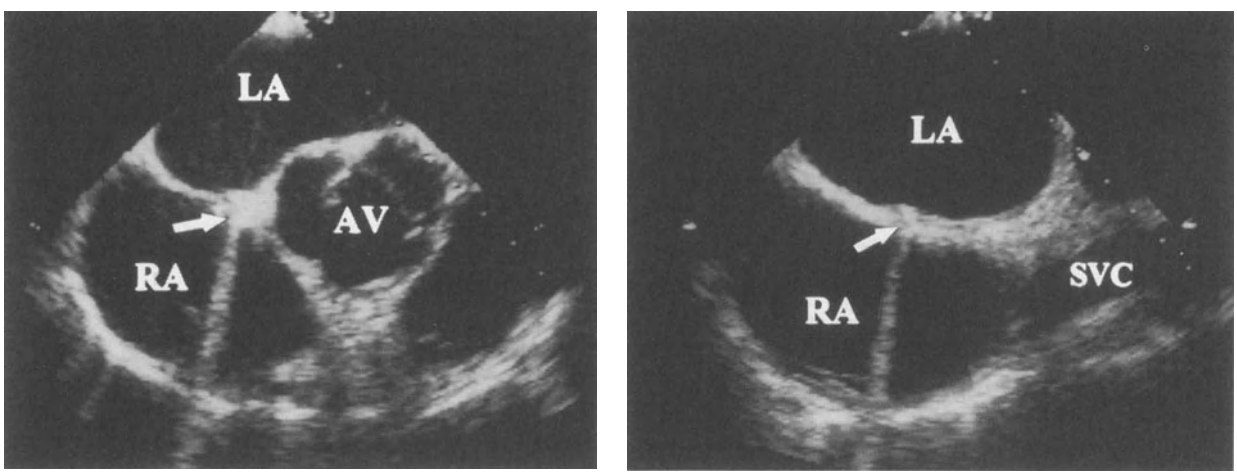

Figure 1. Transoesophageal echocardiographic images in the horizontal plane (left panel) and longitudinal plane (right panel) showing the position of the pacemaker tip in the interatrial septum (arrows). The tip of the pacemaker is at the most anterior portion of the interatrial septum, close to the aortic root. AV, aortic valve; LA, left atrium, RA, right atrium; SVC, superior vena cava.

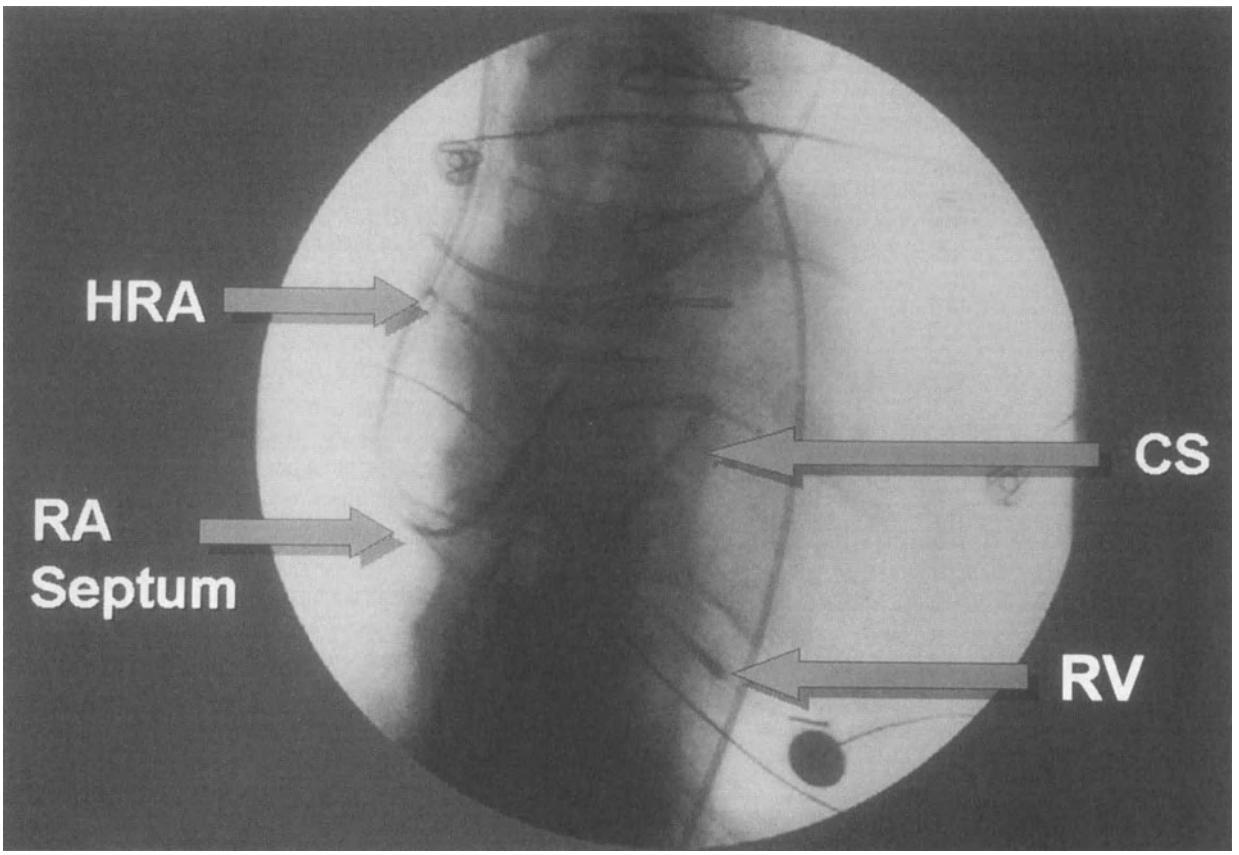

Figure 2. Locations of high right atrial catheter (HRA) and coronary sinus catheter (CS) in patient 1. The former is located in the high right atrial lateral wall in close proximity to sinus node. The CS catheter is located in the lateral aspect of mitral annulus, recording electrical activity of the lower lateral left atrium.

atrium. The pacemaker was then programmed to AAI mode at 80–100 bpm to override intrinsic sinus rhythm. During atrial septal pacing the conduction times from the septal pacing site, which was defined as the pacing artifacts to the local electrograms recorded at the high lateral right atrium and the lower lateral left atrium, were recorded. Next, the permanent pacemaker was programmed into AAT mode. The interatrial conduction time was then measured from the onset of the local electrogram recorded from the high lateral right atrium to the lower lateral left atrium.

Statistical analysis

Continuous variables are presented as mean value ± standard deviation. Student's *t*-test was used to analyse the difference of the conduction time during atrial septal pacing from the pacing artifact to the high right atrium from pacing artifact to the lower lateral left atrium. The interatrial conduction time during sinus rhythm and AAT pacing was also compared similarly. The Students *t*-value of ≤ 0.05 was considered significant.

Results

Atrial pacing thresholds, lead resistance, and P wave values obtained at implant and at 2 months' follow-up are shown in Tables 1 and 2. These include the threshold at 5 V obtained through the pacemaker programmer as well as a telemetered P wave values. All ventricular leads showed satisfactory pacing characteristics. There were no complications during the implantation. Figure 3 shows the PA and LAT chest X-rays demonstrating the position of both the atrial septal and ventricular leads in patient 1.

Table 1. Electrical characteristics of the atrial septal leads at implant

Patient	Threshold at 0.5 MS Pulse width (V)	Resistance (Ω)	P wave (mV)
1	0.6	518	5.4
2	2.0	629	2.8
3	1.0	503	1.8
4	0.9	499	5.2
5	1.3	737	1.8
6	0.8	428	3.8

Table 2. Electrical characteristics of the atrial septal leads at greater than 2 months follow-up

Patient	Threshold at 0.5 MS Pulse width (V)	P wave (Telemetered) (mV)
1	0.6	4.5
2	2.0	3.4
3	1.0	4.0
4	0.9	4.0
5	0.5	4.5
6	0.5	2.2

The PR interval in both sensed and paced modes on the surface electrocardiogram was compared during atrial septal pacing and was found to be equal in all six patients (Fig. 4), indicating that no rapidly conducting specialised tissue was paced from the atrial septal site.

The results of measurement of overall conduction times are shown in Table 3. Figures 5 and 6 show examples of the intracardiac electrograms obtained during the conduction times study in patients 1 and 4. The mean interatrial conduction time in the six patients during normal sinus rhythm was 106 ± 2 ms. The mean interatrial conduction time during AAT pacing was 95 ± 8 ms. The difference between the interatrial pacing during normal sinus rhythm versus AAT pacing was 95 ± 8 ms. The difference between the interatrial pacing during normal sinus rhythm versus AAT pacing was not statistically significant. The conduction time to the high lateral right atrium during atrial septal pacing was 57 ± 8 ms and the conduction time during atrial septal pacing to lower lateral left atrium was also 58 ± 8 ms. This finding indicated that the high lateral right atrium and lower lateral left atrium were activated almost simultaneously during atrial septal pacing.

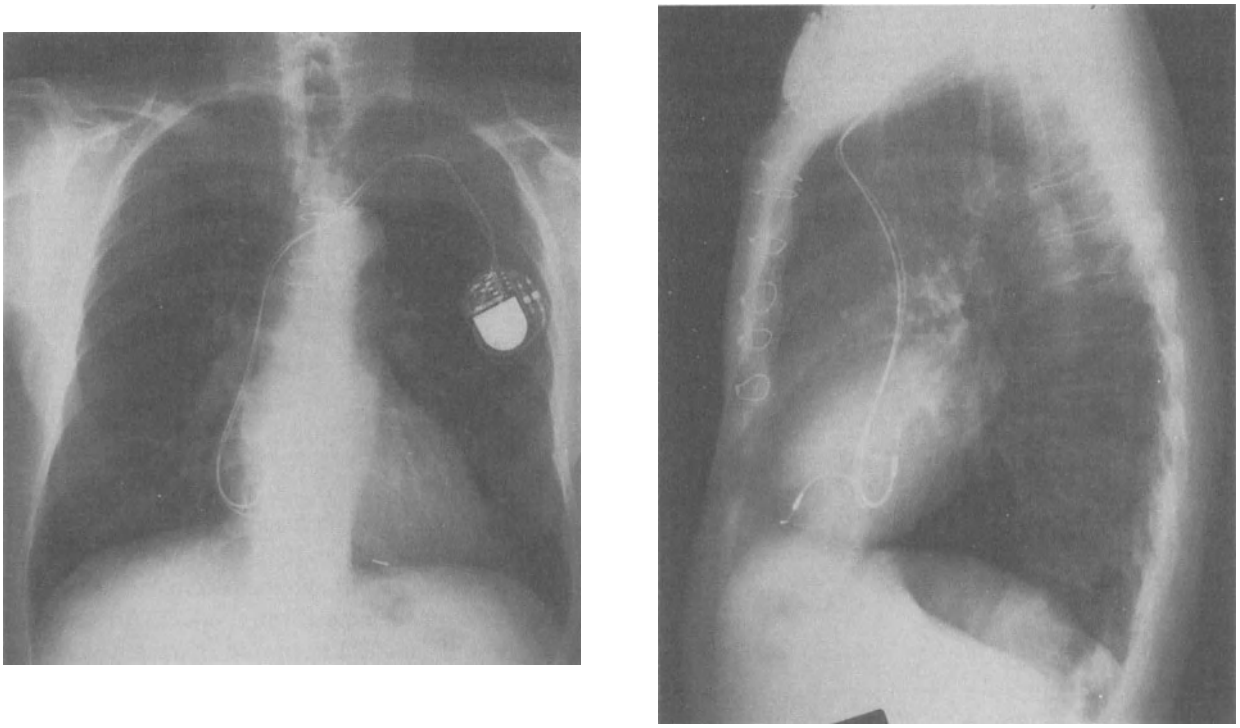

Figure 3. Posterior–anterior and lateral chest X-rays showing the position of the atrial septal lead and the ventricular pacing lead in patient 1.

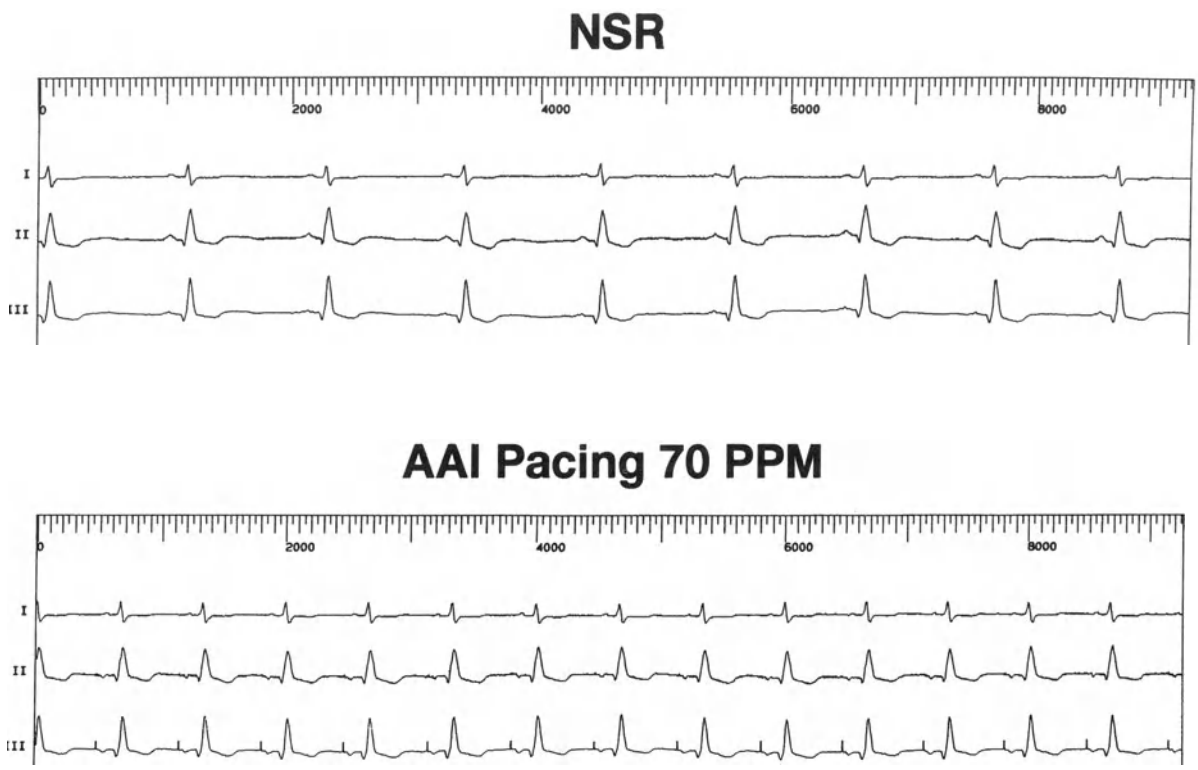

Figure 4. Electrocardiograms showing normal sinus rhythm and atrial septal pacing and normal sinus rhythm in patient 2. These ECG strips show approximately the same AV delay in both normal sinus rhythm and atrial septal pacing.

The thickness of the atrial septum at the site of atrial lead implantation was 6 ± 1 mm in width, as measured with transoesophageal echocardiography.

Table 3. Measurement of overall conduction times

			Conduction times during atrial septal pacing		
Patient	Age (years)	IACT NSR (ms)	HRA (ms)	LATLA (ms)	IACT AAT (ms)
1	73	110	52	50	90
2	72	105	52	52	108
3	78	110	47	53	91
4	70	100	62	58	98
5	72	96	60	65	96
6	68	84	68	69	84
Mean	72 ± 3	101 ± 10	57 ± 8	58 ± 8	95 ± 8

HRA = high right atrium, IACT = interatrial conduction time, LAT LA = lateral left atrium, NSR = normal sinus rhythm.

Discussion

Transvenous pacing leads traditionally have been placed in a right atrial appendage and occasionally in the right atrial lateral wall[7]. Under these circumstances pacing and sensing initially occur in the right atrium. Because of variabilities in interatrial conduction times, especially in the paced population, one cannot be certain of the all-important left-sided arteriovenous (AV) interval and often less than optimal haemodynamics are the result[1,2]. Therefore, it is desirable to pace and sense the left atrium. However, left side lead placement is not considered advisable due to the thromboembolic risk. Previous attempts to pace and sense the left atrium have involved multi-site pacing and multiple leads in unique places in the right atrium[3,4] and coronary sinus[5,6]. The current study describes single-site, standard lead atrial septal pacing in which the paced and sensed AV delay are the left-side AV delays. The interatrial conduction time during AAT pacing was shortened in two of the

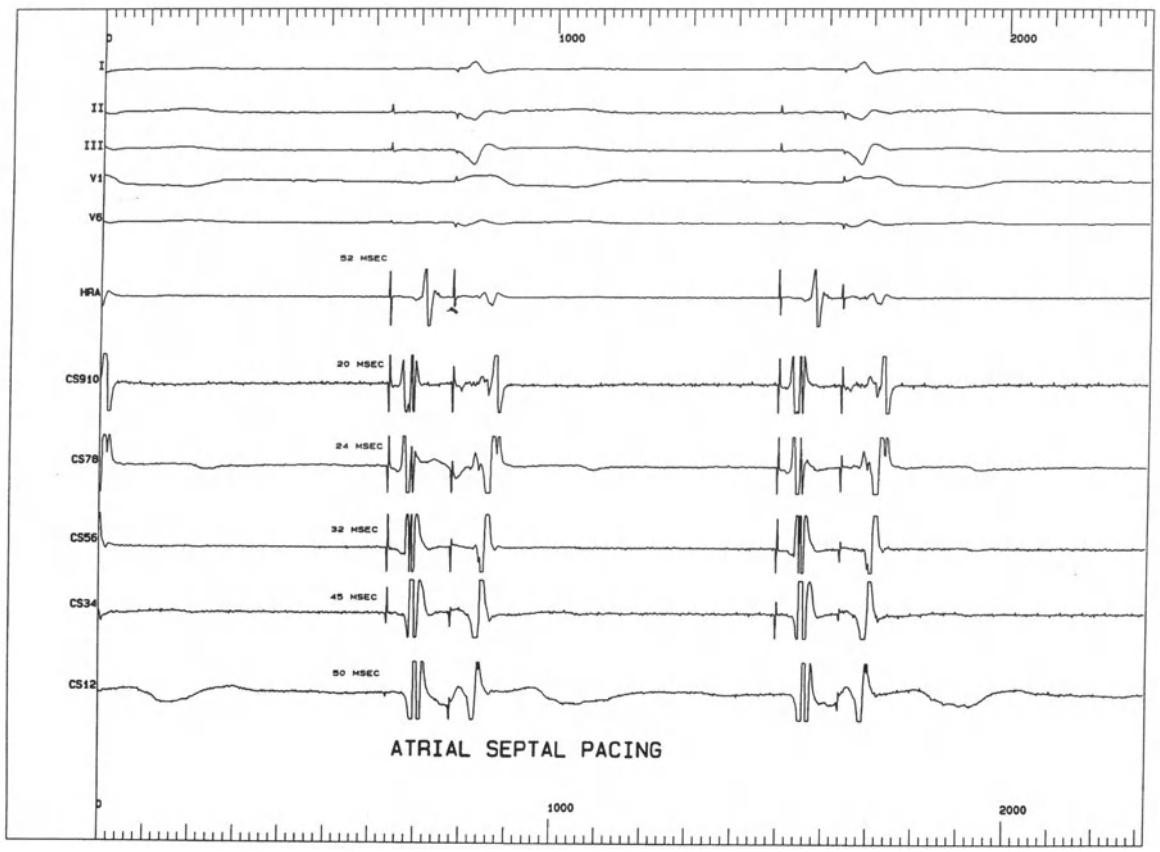

Figure 5. AV sequential pacing with atrial pacing lead positioned at the lower atrial septum in patient 1. The high right atrial catheter (HRA) was positioned in the high right atrial lateral wall in close proximity to the sinus node. The coronary sinus decapolar catheter was positioned so that the distal pair of coronary sinus electrodes (CS910) is located in the lateral aspect of mitral annulus. The proximal pair of coronary sinus electrodes (CS910) is positioned in the posterior aspect of mitral annulus. The remaining three pairs of electrodes (CS34, CS56 and CS78) are located in between. During atrial septal pacing the conduction delays to high lateral right atrium (52 ms) and to low left atrium (50 ms) are similar.

patients. The significance of this finding, and whether it relates to lead position or atrial size, is unknown. At the atrial septal site chosen for pacing in the present study, the atrial wall is several millimetres thick; presumably this short distance allows the pacing of both atria. In addition, we presume no specialised conduction tissue was paced because no shortening of the paced PR interval was observed when compared to the PR interval in normal sinus rhythm. With atrial septal pacing the AV delay should be easily adjusted to the optimal setting in a variety of circumstances. It is possible that pacing both atria simultaneously (or pacing the left atrium) may suppress reentrant atrial arrhythmias[3–6]. Synchronous depolarisation of both atria with pacing might decrease atrial extrasystoles and interfere with reentrant circuits. By combining atrial septal pacing with new algorithms, such as those providing triggered pacing on premature atrial beats, elimination of extrasystolic pauses, and overdrive atrial pacing, an atrial antiarrhythmic pacing system might result[8]. In addition, optimising left-sided timing intervals would lead to lower atrial pressures and size, and help minimise stretch-triggered arrhythmogenesis[9–11].

Because the atrial septum is several millimetres thick at the site chosen, and the helix of the current lead is 2 mm, penetration to the left side of the atrial septum is

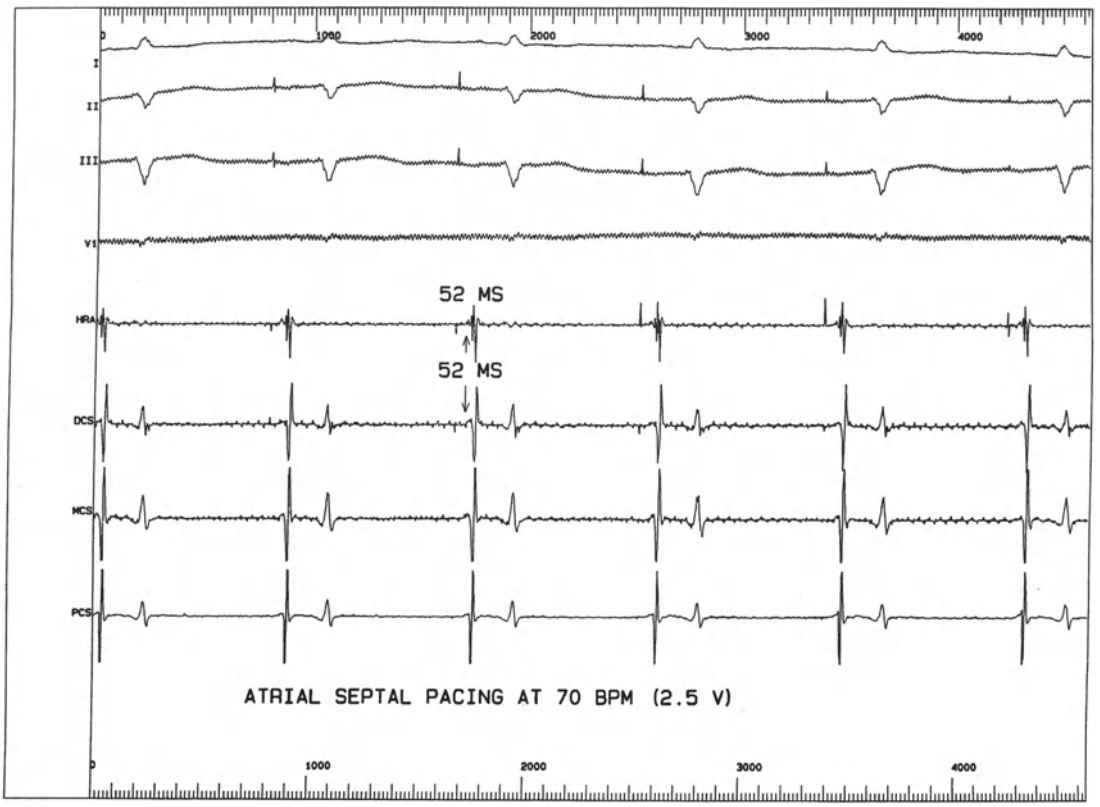

Figure 6. Atrial pacing in patient 4. Pacing leads and catheters were positioned as in Fig. 5. The coronary sinus catheter was a quadripolar catheter. In atrial septal pacing the conduction delays to the high right atrium (52 ms) and to the distal coronary or low left atrium (also 52 ms) are equal.

unlikely. Crossing a probe-patent foramen ovale must be avoided, and did not occur in our patients. In the current study, TOE, with its attendant cost, discomfort and potential for complications, was necessary to assure proper location of the lead. Hopefully, with more experience and properly designed equipment, it may be possible to place a pacing lead safely in the interatrial septum using only fluoroscopy.

We conclude that it is feasible to pace both atria simultaneously from a single site using a standard active fixation lead placed with transoesophageal and fluoroscopic guidance. Such a pacing system allows accurate timing of left-sided paced and sensed AV delays, and thereby provides the opportunity for optimal haemodynamics. By providing optimal haemodynamics and depolarising both atria synchronously, reentrant atrial arrhythmias may be suppressed.

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Chapter 52

Automatic Mode Switching in DDD(R) Pacemakers: To Make Life Easier or More Complicated?

Ali Oto

Introduction

Automatic mode switching (AMS) is an algorithm that provides automatic change of pacing mode from an atrio-ventricular (AV) synchronous to one without atrial tracking, in response to supraventricular tachyarrhythmias, to avoid non-physiologically high rates during DDD(R) pacing. Theoretically AMS gives the opportunity of implantation of dual-chamber pacemakers (recently including single-lead VDDD pacemakers), even to patients with paroxysmal supraventricular tachyarrhythmias, mainly atrial flutter and fibrillation. Although several fallback algorithms have been suggested, none of those traditional features has been satisfactory in solving the problem of such patients. On the other hand, having realised the haemodynamic benefits of atrial synchronous and possible proarrhythmic hazards of ventricular pacing, more and more patients with paroxysmal supraventricular arrhythmias, especially with sick sinus syndrome (brady and tachy episodes) have now become candidates for such devices. Therefore those patients are supposed to have the benefits of dual-chamber pacing, in terms of symptoms and increased life expectancy, and are protected from the unwanted effects of high rates.

Most of the dual-chamber devices are now available with an AMS algorithm specific to each manufacturer. Despite all these developments none of those algorithms is free of problems, and clinical experience is not yet adequate to overcome several limitations encountered during clinical pacing practice.

The available AMS algorithms vary, and each carries its own advantages and limitations. Although there are several classifications, two main categories of AMS can be discriminated[1,2]: AMS algorithms triggered by a single beat (a) (Telectronics Meta DDDR 1250 and Vitatron Diamond) and (b) AMS triggered by a series of beats (CPI Vigor DDDR, Medtronic Thera, Pacesetter Trilogy). The AMS response is slower in the second set of algorithms, and this may give rise to symptoms due to a temporarily higher ventricular rate. Inappropriate AMS due to premature beats and loss of AV synchrony during sinus rhythm could be major limitations despite an achievable quick response in the first category.

Although AMS seems to be a useful feature of a pacemaker, the true incidence of its utility in the general

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pacemaker population is not yet clear. The limitation of an external Holter recorder in predicting the frequency of AMS in a period of time is obvious. However, in some pacemakers there are mode switch counters, and it is possible to obtain data regarding the number of mode switch episodes and the maximum atrial rate achieved during those episodes. In a study performed by Love et al[3], 52 patients were implanted with a new dual-chamber rate adaptive pulse generator (Trilogy DR, Pacesetter) with a new programmable AMS feature for the frequency of AMS. Of the 52 patients evaluated 30 had the AMS enabled during the evaluation period of 6 months. In patients with mode switch enabled the AMS was utilised 66% of the time. In patients whose indication for pacing was other than atrial arrhythmias the percentage of AMS episodes over time was 55%, with the majority (17.9%) being in the atrial rate of ranges exceeding 300 ppm and 150–175 ppm, compared to patients with atrial arhythmias at 72.3% over time, with a 39.4% majority over an atrial rate of 300 ppm. Interestingly enough, these data not only confirm the frequent need for AMS in a patient with known atrial tachyarrhythmias, but also introduce the idea that an AMS algorithm might be needed even in patients without history of atrial arrhythmias. However, one should also remember the limitations of a built-in event counter.

Although AMS is designed to alleviate symptoms which may arise from unphysiologically higher rates due to atrial tracking, sometimes mode switching itself could be a source of symptoms. Those symptoms may be related to several issues, including fast-detection algorithms causing inappropriate AMS, or slow-detection algorithms due to the time needed for mode switching. In a recent study the impact of mode switch detection time on patient symptoms has been assessed in patients with paroxysmal atrial fibrillation and AV block[4]. In this particular study seven different algorithms have been used, and patient preference, based on lowest symptom frequency and severity, has been evaluated. Interestingly enough the authors described a great variability of preference, and suggested a future pacemaker should support multiple-mode switch algorithms from extremely fast to more stable detection, to suit individual patient preference.

Mode switching: effects of programming

An AMS algorithm is critically dependent on atrial sensing. The device must detect sufficient atrial signals that meet algorithm criteria for a reliable AMS. Great variation was observed among mode switch algorithms during atrial signal dropout in a study performed by a simulator with different pulse generators. Responses included delayed-onset times for mode switch (over 20 s; Vigor, Trilogy DR+, Thera) and multiple mode switch events during signal dropout (Vigor, Marathon, Telectronics 1254 and 1256)[5]. On the other hand it has been shown that in atrial fibrillation effective AMS requires more sensitive atrial settings than in sinus rhythm, and electrogram amplitude during paroxysmal atrial fibrillation can be predicted based on the amplitude in sinus rhythm. Careful positioning of the atrial lead to achieve the best atrial signal and setting has been recommended, and an atrial sensitivity with a 3–3.5 safety margin may improve AMS reliability[6,7]. Besides the atrial signal sensing, the programmed AV delay might also be important for a consistent AMS to occur. Short as well as long AV delays may interfere with AMS function[7,8].

Automatic mode switching limitations and problems

Inappropriate automatic mode switching

Inappropriate AMS refers to a mode conversion in situations falsely considered by the pacemaker to be supraventricular tachyarrhythmia. This may include sinus tachycardia, premature atrial ectopic beats, far-field sensing of the R or T wave in the atrial channel, and premature ventricular contractions with long retrograde ventriculoatrial conduction time. Programming factors that may precipitate mode switching have been shown to be a low rate response factor, a low upper rate setting a long base postventricular atrial refractory period, short atrial blanking period and a long AV delay[8,9].

Exercise is a special situation in which AMS can occur due to an inappropriate response triggered by sinus tachycardia. In those patients, when mode switches from DDDR to VVIR or DDIR, AV synchrony will be lost. This may well be tolerated in some patients, particularly if the atrial contribution is negligible during exercise. However, if the atrial contribution to the cardiac output is important, those patients would be symptomatic upon exertion. One solution would be to increase the rate limit for AMS.

Pacemaker syndrome with mode switching in ODDR pacemakers

Pacemaker syndrome occurs in association with inappropriate mode switching. It is very obvious that AV

dissociation leads to AV dyssynchrony, and patients may experience the symptoms of pacemaker syndrome if mode switching occurs during sinus tachycardia, premature atrial or ventricular beats or due to far-field sensing of the R or T waves in the atrial channel[8]. There may be several measures to avoid this problem. Since the newer algorithms allow greater flexibility for programmability it may be possible to avoid mode switching for single premature atrial contraction, sinus tachycardia and premature ventricular contraction with retrograde conduction by programming the pacemaker. Again, to programme a shorter postventricular atrial refractory period may help to prevent pacemaker syndrome in some cases. Antiarrhythmic drug therapy may be necessary to suppress premature atrial and ventricular beats and atrial tachyarrhythmias, to avoid mode switching in such conditions. Finally, reprogramming to DDD mode might be another solution.

Rate of the ventricular paced rhythm and irregularity of the heart beats

When mode switching occurs during atrial flutter or fibrillation ventricular pacing rate will be an important parameter for the patient's comfort and symptoms. A sudden change in heart rate may be disturbing in many cases, causing symptoms. There are several features in the pacemakers with automatic mode switch function to prevent sudden rate changes during mode switching, though none of them has reached an optimal setting. Some pacemakers offer the option of programming the device to a fallback mode with rate-adaptive pacing. For example in Chorus DDDR pacemakers, when programmed at rates above the upper rate limit, Wenkebach behaviour occurs. The sensor is activated as soon as the pacemaker detects an atrial rate above the upper tracking rate. The Wenkebach upper rate behaviour is allowed to function for a programmable number of cycles before the device changes mode to VDIR mode with fallback to sensor-indicated rate. As soon as the atrial rate decreases below the upper tracking limit there is a reassociation of the atria and ventricles, and return to the DDDR mode.

Rate smoothing is another feature which is aimed at preventing sudden rate change during mode switch. This is a programmable function that offers a gradual decrease in the ventricular paced rate to reach a preprogrammed ventricular fallback rate or a sensor-indicated rate (Vigor DR, Chorus DDDR). However, despite all these measures, it may not always be possible to avoid the feeling of irregular heart beats during mode switching.

Failure to detect atrial flutter

Atrial flutter due to the occurrence of every second flutter wave within the atrial blanking period could be a cause of failure for mode switching algorithms. Shortening of the AV interval, programming a shorter atrial blanking period or an attempt to increase the atrial flutter cycle length by antiarrhythmic drugs could be simple solutions[2].

Clinical experience with automatic mode switching for atrial tachyarrhythmias

Most of the newer-generation pacemakers provide mode switching algorithms. Although experience with different algorithms has been accumulated not many large series have been reported. In an earlier report Provenier et al[10] published their experience in 61 patients with Meta DDDR pacemakers, including Model 1250, 1250 H and 1254. There were 32 proper AMS to VVIR. Although they detected several inappropriate mode switches during sinus rhythm in 10 patients no inappropriate mode switch was observed in the 1254 Model. DenDulk et al[11] studied 26 patients with Vitatron Diamond DR pacemakers, with a mean follow-up of 8 months. Appropriate rate response with appropriate restoration of atrioventricular synchrony without inappropriate increase in ventricular pacing rate at the onset of, or during, atrial fibrillation or flutter were observed. On the other hand, pooled data of two studies performed with Medtronic Thera DR pacemakers documented a total of 101 episodes of appropriate AMS in 49 patients without any inappropriate AMS[6,12].

Conclusions

1. AMS is a useful algorithm to provide optimal pacing modality to patients with paroxysmal supraventricular tachycardia who need a pacemaker for bradyarrhythmia.
2. Despite the developments of new complex algorithms AMS still carries some limitations and problems, which need careful patient and algorithm selection and programming.
3. Currently available mode switch algorithms need improvement.
4. AMS algorithms generate complex ECG patterns which require a good understanding of device function for interpretation.

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Chapter 53

Neurohumoral Control of the Pacemaker and Heart System

Max Schaldach

Introduction

The human cardiovascular regulation system is composed of the central integration of the higher control centres, the cardiovascular system with the heart and the peripheral vessels, and the feedback pathways represented by the afferent fibres and baroreceptors (Fig. 1)[1]. Normally the parasympathetic (cholinergic) influence slows the heart rate and conduction velocity and decreases contraction dynamics. The sympathetic (adrenergic) nervous system has opposite effects. Both systems exert a tonic influence on the cardiovascular system, and the control of cardiac activity results from the balance between them[2].

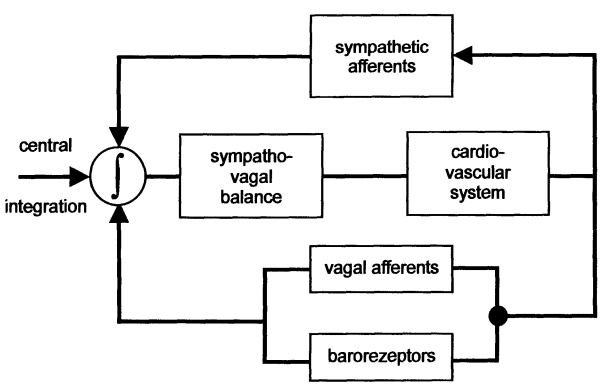

Figure 1. Schematic representation of the cardiovascular feedback loop. The feedback loop is composed by the control centres which are influenced by external impulses and the feedback fibres. The centres adjust the cardiovascular system by changing the chronotropy, dromotropy, contractility, and peripheral resistance to the actual need. (Modified from ref. 1.)

This complex regulation system adapts cardiac output by controlling sinoatrial (SA) node[3,4], atrioventricular (AV) conduction time[5,6], and atrial[7–9] as well as ventricular contractility to actual demand[10]. Pathological changes in this regulation system have important practical implications in the clinical setting. Imbalance of the vagal system may cause different kinds of arrhythmias originating from SA node arrest, as well as prolongation or even block of the AV node[11,12]. Acute myocardial ischaemia, in combination with an imbalance of the autonomic system, is already known as one of the main causes of ventricular flutter and fibrillation[13,14] and vasovagal syncope (Fig. 2)[15].

Myocardial ischaemia, in conjunction with a dominant sympathetic reflex, increase heart rate and may be responsible for ventricular arrhythmias. Dominant vagal reflexes lead either to normal rhythm or to bradycardia and hypotension.

Besides vagal effects on SA and AV nodes, efferent enervation of the ventricular myocardium may directly cause arrhythmogenic phenomena. For example significantly increased influx of Ca^{2+} into the ventricular cells caused by dominant sympathetic reflexes plays an important role in the genesis of early after depolarisations[17,18] (B Merkely et al, unpublished data, 1996)

P.E. Vardas (ed.), Cardiac Arrhythmias, Pacing & Electrophysiology, 379–388.

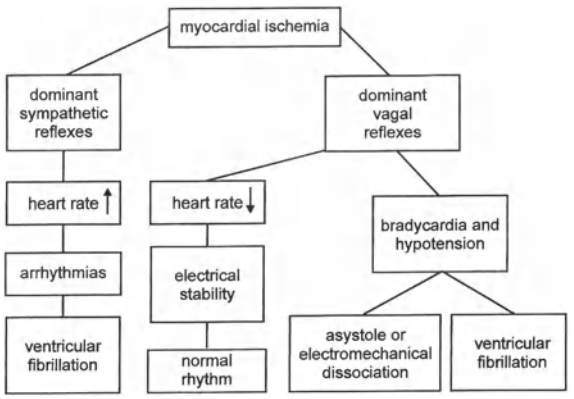

Figure 2. Effects of the autonomic reflexes on cardiac rhythm caused by acute myocardial ischaemia. Dominant sympathetic reflexes leads to tachycardias. Dominant vagal reflexes may either stabilise heart rate or may cause bradycardia and hypotension[14,15]. (Modified from ref. 58.)

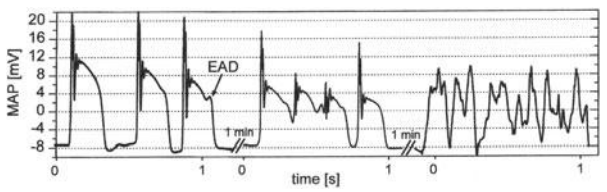

Figure 3. Early afterdepolarisation induces non-sustained ventricular tachycardias and ventricular fibrillation (VF)[19].

Each modification of the cardiovascular feedback loop, for example by an artificial pacemaker for patients suffering sickness in the heart's conduction system, may even enhance this pathological situation, as no feedback concerning the cardiac state is available to the pacemaker[20]. Thus, the ideal implant must be an integrative part of the regulation system avoiding any shifts out of vagal balance. The integration of the pacemaker or defibrillator in the cardiovascular feedback loop is a main focus of current research.

The first step towards this goal is a pacemaker which is able to monitor the vagal state of the cardiovascular system. This basic monitoring feature has been improved, and this resulted in an implant being part of the feedback system supporting sick SA or AV nodes. Additionally implementing treatment features lead to a device which modifies the imbalance of the system and avoids arrhythmias by a preventive therapy effecting the afferent feedback pathways.

Methods

The indispensable prerequisite for any of the above-mentioned implants is the monitoring of vagal state. Direct measurements of efferent vagal activity have been performed in dog heart preparations[21], but are impractical for standard implantable devices such as cardiac pacemakers or implantable cardioverter/defibrillators (ICD). Therefore the neurohumoral balance has to be monitored indirectly. In the human heart three effects can be utilised for this purpose: chronotropic, dromotropic and inotropic adaptation of the heart by the autonomic nervous system. If chronotropic response is still intact, long-term changes of vagal tone may be observed by time-domain measurements[22] and spectral analysis[19,20,23] of heart rate and its response to blood pressure changes[24,25]. For rate-adaptive pacing and other applications in which short-term characteristics of neurohumoral balance are relevant, and if excitation or conduction disturbances or both are present (which is the case in the majority of pacemaker patients), only inotropy remains to be utilised.

Various strategies have been developed to quantify the inotropic state of the myocardium (Fig. 4). If the adrenergic and cholinergic influences on cardiac action potential[26,27] are considered, alterations of the action potential plateau and repolarisation phases are of special interest for electrotherapeutic diagnosis. Although the transmembrane action potential cannot be monitored directly in pacemaker patients, it is approximated very closely by monophasic action potential (MAP) recordings, which are performed with bipolar active fixation leads in epicardial as well as endocardial settings[28,29,34,35,37]. Alternatively, the ventricular evoked response (VER) following the pacing stimulus is measured with the unipolar electrode configuration[30,33]. Similar to the surface ECG, the VER reflects the electrical field resulting from the spread of excitation all over the heart. For long-term stable and artifact-free MAP and VER recordings, fractally coated electrodes are used because of their superior electrical properties, which allow distortion-free measurements in a broad frequency range and, moreover, avoid afterpotentials after the pacing stimulus[32]. As discussed below, both signals show significant changes in morphology due to adrenergic and/or cholinergic stimulation, i.e. changes of the neurohumoral balance, which offers the physician a broad spectrum of diagnostic and therapeutic applications[10].

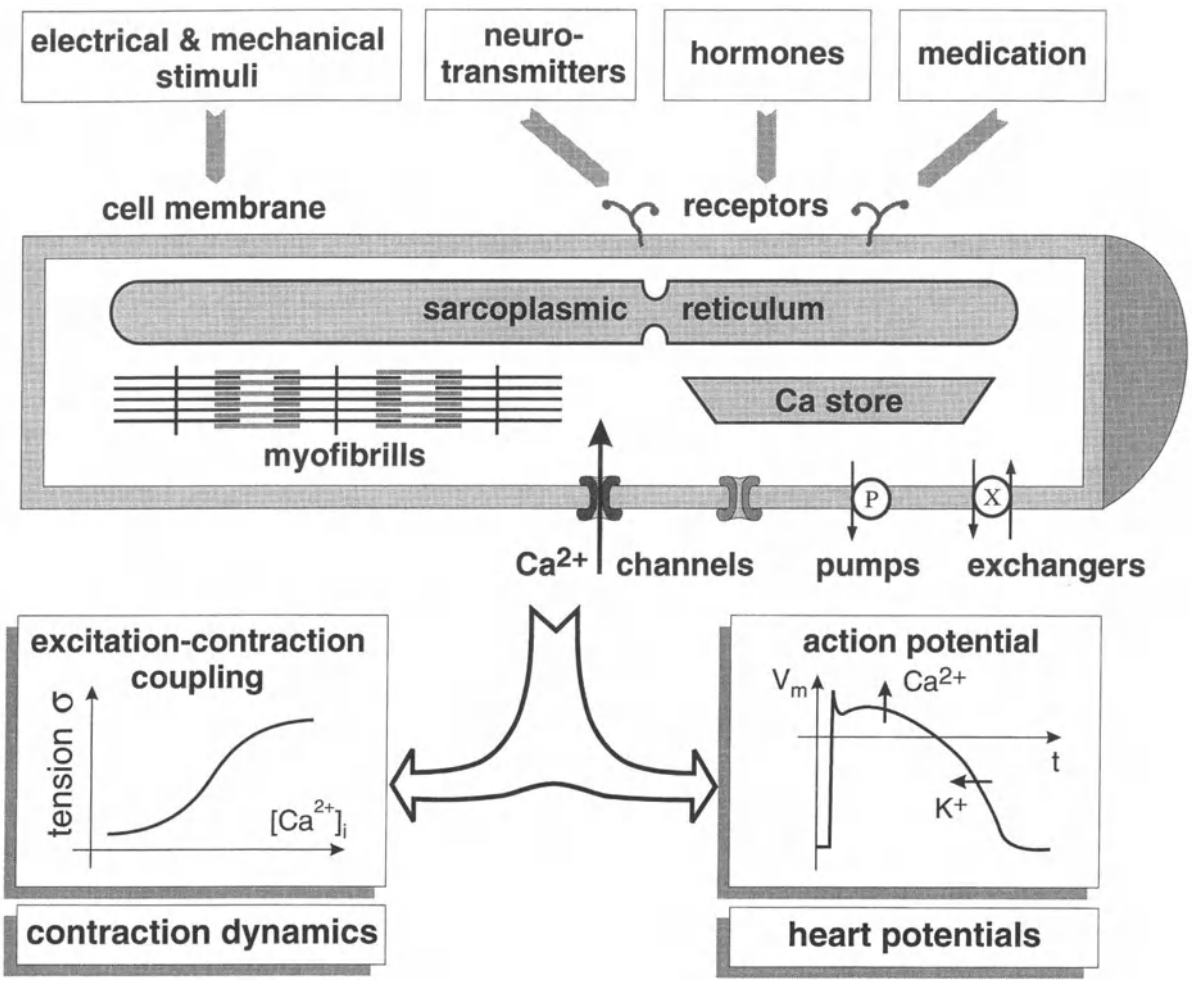

Figure 4. Different approaches to the estimation of neurohumoral activation of the myocardium.

A different approach is to monitor mechanical indicators of contractility, which is primarily defined in terms of the mechanical contraction of the heart. Due to the altered kinetics of excitation-contraction coupling, i.e. the elevated level on intracellular Ca^{2+} during systole and the changed ion channel and pump properties – that are also responsible for the changes in action potential morphology as discussed above – as well as the depressed Ca^{2+} sensitivity of the contractile filaments, contraction dynamics of the muscle fibres are changed threefold:

1. tension development occurs with a higher rate of rise, which was often quantified by the measurement of maximum rate of rise in ventricular pressure dp/dt_{max}[31,36,38];
2. a higher peak tension is reached;
3. relaxation is also accelerated, to facilitate a rapid diastolic filling.

Since conventional methods of estimating contractility are impractical for the application in implantable devices, or at least require additional sensors (e.g. dp/dt_{max}), a new sensor principle was developed. It was shown that unipolar intracardiac impedance measurement is a suitable method to obtain a measure of the contractile status of the myocardium and, therefore, to monitor the neurohumoral activation of the heart[39,40,42,43]. This is due to the fact that myocardial contraction – especially in the near vicinity of the electrode tip – is reflected in the measured impedance signal, and that different contraction dynamics result in

different signal morphologies. Unipolar intracardiac impedance can be measured with every standard pacing lead.

Thus, the clinical advantage of all of the described methods – MAP, VER and unipolar impedance measurement – is that neurohumoral balance can be monitored without the need for any additional sensor. This means that, in addition to the clinical benefit resulting from the access to neurohumoral information, implantable devices utilising one of these parameters provide high reliability, patient safety and easy implantation, since potential problems with additional sensors during implantation and follow-up will not occur.

Results

This chapter demonstrates specific changes of monophasic action potential and contractility during interventions altering the sympathico-parasympathico state, and discusses them. Furthermore the integration of a rate-adaptive pacemaker in the cardiovascular feedback system, and data relating to clinical experience with this device, are presented.

Monitoring using the monophasic action potential

The effects of carotid massage on the repolarisation behaviour of the MAP were investigated in seven patients (five male, aged 63 ± 17 years). Temporary MAP leads were positioned at epicardial sites at right atrium and ventricle during routine heart surgery, similar to conventional heart wires[44]. In the post-operative course changes of MAP were documented. Additionally, interventions such as carotid massage and infusion of dopamine were performed, to test sympathetic-parasympathetic reflexes of patients[45]. In Fig. 5 cycle length and MAP duration during carotis sinus massage in an 65 year old woman are represented. Heart rate decreased by 32 bpm about 6 s after the beginning of interventions and increased again thereafter. MAP duration shortened, with its minimum 6 s later, indicating that sympathetic effects on MAP duration have longer time constants rather than vagal effects on heart rate, as already reported in the literature[45]. To eliminate rate effects on MAP duration rate-corrected MAP duration was calculated, showing a rate-independent lengthening by 71% for MAPd90 and by 68% for MAPd50, respectively. These described effects of carotid massage were observed only in three patients without sotalol medication, indicating that this drug minimises vagal influences on MAP duration. It is assumed that patients treated with the β-blocker sotalol already have dominant vagal reflexes; therefore, no effects of vagal stimulating carotid massage are observable.

Effects of dopamine bolus, which significantly influences the ventricular contractile state[46], were investigated in the same patient group. In Fig. 6 heart rate and MAP duration are depicted for the minutes following bolus. Dopamine medication increased heart rate and shortened MAP duration at the 10%, 50%, and 90%

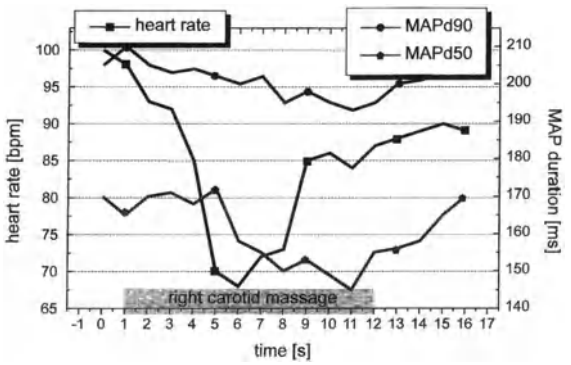

Figure 5. Effects of carotid massage on heart rate and MAP duration. The heart rate driven by the faster parasympathetic reflexes decreased within 6 s, while the sympathetic-influenced MAP duration shortened more slowly, reaching the minimum 11 s following the start of massage.

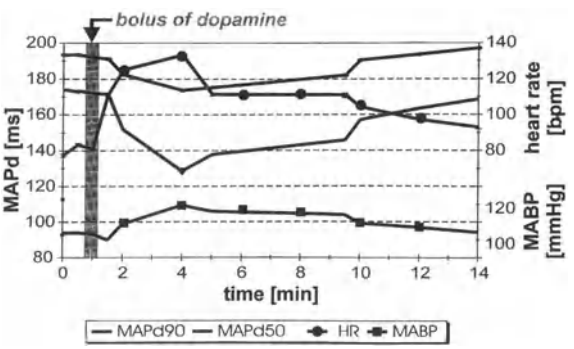

Figure 6. Effects of dopamine bolus on heart rate, MAP duration, and mean arterial blood pressure. Dopamine increased heart rate, shortened MAP duration and affected higher blood pressure. The rate-corrected lengthening of MAP duration marks increased sympathetic state and enhanced contractility.

repolarisation levels.Maximum heart rate and minimum MAP duration were observed 4 min following bolus. Simultaneous recorded mean arterial blood pressure rose in temporal correlation to other observed effects by at least 23%. About 15 min after bolus effects on MAP duration disappeared.

Rate-corrected MAP duration was calculated, demonstrating that mainly MAPd25 were lengthened by 35%. The lengthening of the plateau phase indicates higher influx of Ca^{2+}, resulting in a more elevated contractile state of the heart, as reported in literature[47]. Additionally MAP leads were implanted in a further 15 patients, and MAP were observed in the postoperative course. Six of these patients suffered atrial fibrillation (AF) during the observation interval[48]. Onset of AF was in all patients between 6 and 8 a.m. on the second postoperative day (A.M. Pichlmaier and V.A. Lang, unpublished observations). High sympathetic tone during first mobilisation, indicated by a shortened repolarisation course and distorted sinus rhythm, may support the occurrence of AF (Pichlmaier and Lang, unpublished). Specific and reversible alterations of MAP before onset of AF are used clinically for prediction of atrial tachyarrhythmias during the postoperative course, with high sensitivity and specificy (see Fig. 7). (Pichlmaier and Lang, unpublished).

The data presented above clearly demonstrate that the influence of the autonomic nervous system on the monophasic action potential was successfully monitored during carotid massage, medication, and AF. Monitoring the autonomic state with implantable MAP leads, using the repolarisation behaviour of the myocytes, is already used in the clinical setting.

	reduced repolarization duration		atrial rhythm distortions		
		without AF	AF	without AF	
patients with AF	5		2		7 of 7 (100 %)
patients without AF		2		0	2 of 15 (87%)

- Sensitivity: 100%
- Specificity: 87%

Figure 7. High sensitivity and specificity for prediction the onset of AF using MAP.

Monitoring using contraction dynamics

The recording of changes in contraction dynamics relative to a reference value for the individual patient can be obtained by intracardiac impedance monitoring[40]. This method is suitable for assessment of the current performance level of the myocardium, requested by circulation centres. Therefore, changes in cardiovascular feedback during any investigation can be monitored by intraoperatively applied temporary leads, or with an implanted device that measures contraction dynamics.

Results of these investigations are used for basic research relating to cardiovascular feedback behaviour during any short-term interventions[56]. However, the most obvious application is the control of therapeutic devices, that avoid excessive myocardial stress and cure certain malfunctions of cardiovascular regulation, as discussed below. Monitoring of contraction dynamics is demonstrated by two examples: documentation of the effect of drugs and of regional ischaemia on the contraction dynamics.

Monitoring drug effects. The efficacy of acute application of inotropic effective drugs is reflected by changes of myocardial contractility, and can be observed by contraction dynamics monitoring. Figure 8 shows the sensor signal during and after intravenous injection of a β-blocker (10 mg metoprolol). For this investigation pacemakers (Diplos-PEP, Biotronik) of eight patients (seven female; one male, aged 45.8 ± 9 years) were used for recording of the sensor signal[50]. All investigations were performed at rest in the supine position, and ECG and blood pressure (MABP) were monitored.

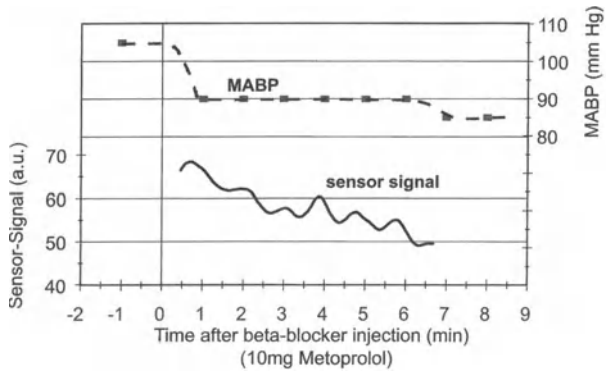

Figure 8. Effect of β-blocker injection (10 mg metoprolol) on contraction dynamics and mean arterial blood pressure (MABP).

The effect of metoprolol on myocardial contraction dynamics is directly observed in the time course of the sensor signal; β-blockers cause an effect on the signal almost immediately after injection, and a further decrease over a period of several minutes, corresponding to the expected decrease in myocardial contractility. The efficacy of drug application is validated by the observed decrease of mean arterial blood pressure.

Monitoring of regional ischaemia. The effect of occluding a coronary artery, that mainly supplies the left ventricle, during percutaneous transluminal coronary angioplasty (PTCA), induces a reaction of the cardiovascular regulation loop during a situation similar to the beginning of a myocardial infarction: a regional ischaemia located in the left ventricle (Fig. 9). In 10 patients (aged 53 ± 4 years) contraction dynamics was monitored during regular PTCA of arteries supplying mainly the left ventricle[50]. During occlusion of the ramus circumflexus, causing a regional ischaemia in the left ventricle (Fig. 9) and accompanied by angina pectoris and significant ST deviation in the ECG, a signal increase is observed with a time course similar to sinus rate. The mechanism for this behaviour is a reactive increase in sympathetic tone and a decrease in vagal tone, due to the reduced pumping efficiency of the left ventricle, and to angina pectoris of the patient during the occlusion[49]. The sympathetic and vagal tones increase right ventricular contractility, resulting in the observed signal behaviour.

These two examples demonstrate the ability of contraction dynamics to provide real-time access to cardiovascular feedback for diagnostic purposes, and for basic research. The next section discusses one application of this signal for controlling a therapeutic device, namely a rate-adaptive cardiac pacemaker.

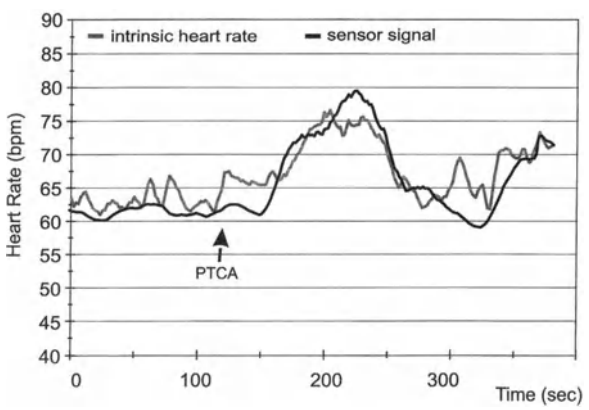

Figure 9. Intrinsic sinus rate and contraction dynamics signal before, during and after provoked regional ischaemia in the left ventricle.

Therapy

For patients suffering from chronotropic incompetency, one of the two branches for increasing cardiac output is strongly reduced in its dynamic range. This causes an imbalance between contractility increase- and sinus rate increase. Even for relatively low exercise levels the inotropic reserves of the myocardium are forced to their limits, resulting in a low maximum load and excessive stress on the myocardium, even for small exercise levels[45]. In this case the benefit for the patient arising from an implant that removes this imbalance become obvious: an implant that monitors both current sinus rate and contraction dynamics is able to identify the imbalance, and to adapt the therapy by pacing at the appropriate rate. As a result the negative influence of chronotropic incompetence on quality of life, maximum load level and overstressing of the myocardium is compensated.

In the next sections the integration of such a pacemaker into the body's cardiovascular regulation loop is validated, and the results of the clinical evaluation of this system are shown.

Validation of closed-loop integration

The main purpose of cardiovascular closed-loop regulation is compensation of disturbances that influence the blood perfusion of the organs and, thus, mean arterial blood pressure[49]. This behaviour was clinically tested in order to demonstrate the integration of a contraction dynamics controlled pacemaker into the cardiovascular feedback loop[56].

Patients with implanted rate-adaptive pacemaker (Inos^2 DR, Biotronik) are programmed in contraction dynamics-controlled DDDR mode. The patients are at rest in the supine position during the entire investigation, in order to provide stable conditions. After reaching a steady state a permanent artificial offset of 10 bpm is added to the paced heart rate. The behaviour of the pacemaker and heart system after this external disturbance is monitored. After 2 min the offset is removed by changing the pacemaker programme again. In an open-loop system the offset would cause a permanent increase in heart rate, that disappears only when the dis-

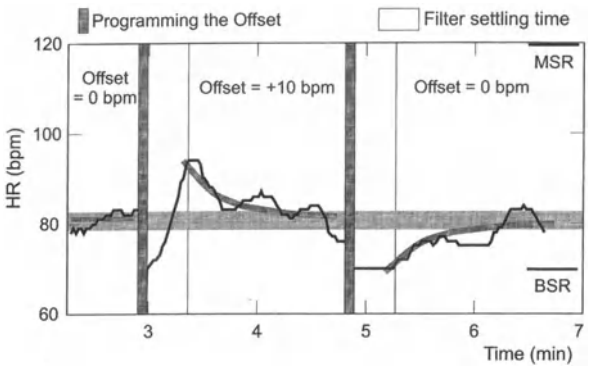

Figure 10. Observed behaviour of the paced heart rate of the contraction dynamics-controlled pacemaker with artificial offset changes of ± 10 bpm (the horizontal grey bar and the thinner grey lines are visual guides.)

turbance is again removed. In this case the resulting imbalance between heart rate and contractility is persistent during the effective time of the disturbance; but in a closed-loop system the pacemaker/heart system identifies that the balance of heart rate and contraction dynamics is disturbed, and starts to compensate by reducing the heart rate nearly to its original rest value. The disturbed balance is corrected, although the disturbance itself is still active. Since this behaviour is observed clinically (Fig. 10), the functioning of the pacemaker/heart system as a closed regulation loop is verified[51].

Establishing this closed regulation loop with integration of the pacemaker results in unique benefits for the patient, as demonstrated in the following clinical studies.

Clinical evaluation of contraction dynamics-controlled pacing

Dual-chamber pacemakers using this sensor principle for rate adaptation have been implanted in 176 patients (64 Inos DR, 112 Inos² DR, Biotronik) with an average age of 64 ± 14 years[52]. Prior to implantation, 72% of the patients had an indication for rate-adaptive pacing due to chronotropic incompetence (sick sinus syndrome: 59%, bradycardia: 13%). An AV block was diagnosed in 44% of the patients. Most of them (70%) suffering AV block III. The patients were exposed to various types of exercise to evaluate the sensitivity of the sensor principle. Ambulatory tests provided various load levels during slow and brisk walk, as well as stairs-down and stairs-up climbing. In 11 patients additional mental stress tests were performed, to evaluate the rate response of the pacemaker system to psychological load. Pacemaker 24 h Holter function recorded heart rate during non-rate-adaptive DDD mode, as well as during DDDR pacing in the same individual. The heart rate increased compared to rest during slow walking (9 ± 4 bpm) and brisk walking (29 ± 10 bpm), as well as stairs-up (28 ± 14 bpm) and stairs-down (18 ± 10 bpm) climbing, showing reasonable values which are comparable to those of healthy subjects[52,53] (Fig. 11).

Accordingly, the rate-adaptive principle is sensitive to major aspects of the patient's daily life and, additionally, highly specific to the circulatory demand, e.g. stairs-up climbing leads to higher pacing rates than stairs-down climbing. In addition, the investigated pacemaker system is sensitive not only to physical load but also to mental stress. The performance of a standardised arithmetic stress test[54] is followed by a distinct increase in pacing rate. The increase of pacing rate (12 ± 4 bpm)

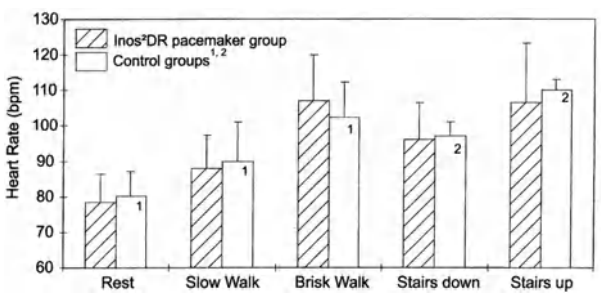

Figure 11. The adaptive pacing rate during ambulatory exercise is compared to the heart rates of healthy subjects (1 = ref. 52; 2 = ref. 53).

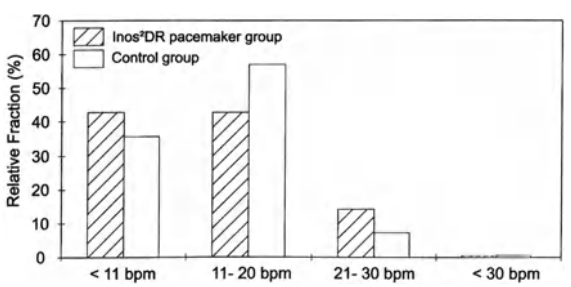

Figure 12. During an mental arithmetic stress test the pacing rates of Inos² DR pacemaker patients (n = 11) and sinus rates of healthy subjects[54] increased by comparable amounts.

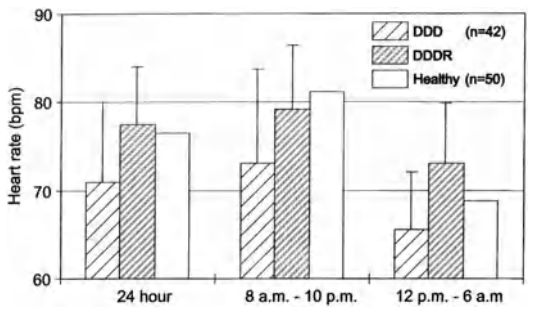

Figure 13. Average heart rates during daytime (8 a.m. to 10 p.m.), night-time (12 p.m. to 6 a.m.) and 24 h in chronotropically incompetent patients during non-rate-adaptive and rate-adaptive pacing, as well as in elderly healthy subjects[55].

was found to be comparable to that of the heart rate of a healthy control population (14 ± 2 bpm, Fig. 12)[54].

Diurnal heart rate variation is a well-known phenomenon in healthy subjects with average heart rates of 81 bpm during daytime (8 a.m. to 10 p.m.) and 68 bpm during the night (12 p.m. to 6 a.m.)[55]. As Fig. 13 shows, average heart rates during day and night are lower in chronotropically incompetent patients in non-rate-adaptive pacing mode. After switching to rate-adaptive mode the average rate values are significantly closer to the values for healthy subjects.

The behaviour of the pacemaker/heart system observed in these patients for several types of exercise as well as non-exercise conditions, like diurnal variation of the heart rate, compares well to the well-known behaviour of healthy subjects under the same circumstances. The quality of life for the patients and their maximum workload are improved accordingly. This result is due to the straightforward concept of integration of a therapeutic device into the cardiovascular regulation loop.

Discussion

The above results show that monitoring of the autonomic state is clinically feasible using contraction dynamics and a repolarisation course. The unipolar impedance measurement serves well as a tool for monitoring the contractile status of the myocardium, which directly reflects neurohumoral aspects. Further monitoring of adrenergic and cholinergic effects for a broad range of diagnostic and therapeutic applications is provided by the monophasic action potential. Sympathetic-parasympathetic alterations, due to effects such as medication and vagal stimulation, are successfully recognised, yielding additional treatment features and thus an improved quality of life. Both signals are acquired using standard implantable pacemaker leads, obviating the use of an additional sensor and standard dual-chamber pacemaker (Inos^2 DR and Physios CTM01, both Biotronik, Germany). This provides easy handling and avoids complexity, thus facilitating reliability of the system. Furthermore the contraction-controlled pacemaker Inos^2 DR not only serves as a monitoring device, but already uses the neurohumoral information for rate adaptation. Thus, this implant fulfils major criteria for integration into cardiovascular regulation.

The results regarding prediction of atrial fibrillation mainly confirm that research must focus on therapeutic concepts modifying active the vagal or sympathetic state to avoid arrhythmias[57]. The available technology currently allows only modifying chronotropy and dromotropy[58] to increase and decrease sympathetic and parasympathetic reflexes. It is technologically feasible to combine monitoring systems such as pacemakers with implantable medication pumping devices treating the autonomous nervous system with standardised drugs. But the best way is to stimulate directly afferent fibres, treating imbalance of the autonomic nervous system.

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Chapter 54

SINGLE-LEAD VDD/DDD PACING

I. Eli Ovsyshcher and Alan B. Wagshal

Introduction

Single-pass (SP) leads which provide P wave synchronous ventricular pacing (VDD) have recently become commercially available. They sense atrial activity while floating in the atrial blood pool, and provide right ventricular pacing and sensing in the usual manner. In this chapter we will describe the basic mechanisms by which atrial sensing may be achieved from floating atrial electrodes. We will also examine the clinical data available on the reliability of such pacing systems. Finally, we will briefly discuss some recent creative designs for an SP lead capable of atrial pacing in addition to atrial sensing.

Development of SP-VDD leads

The earliest designs for an SP-VDD pacing lead date back to the early 1970s from Chamberlain's group[1]. In 1979 a unipolar, SP-VDD lead was first tested in humans by Antonioli and colleagues in Italy, in 20 patients with complete heart block undergoing temporary pacing[2,3]. In the mid- to late 1980s extensive experience was accumulated using the unipolar lead in Italy[4–6]. These studies demonstrated the feasibility of SP-VDD lead pacing, although atrial sensing was still suboptimal in many patients and the well-known disadvantages of unipolar sensing (myopotential and other far-field signal over-sensing) were particularly bothersome in these pacemakers because of the need for a very high atrial sensitivity. These problems led to the development of SP-VDD leads incorporating bipolar atrial sensing[7–9].

Basic physics and technical aspects of atrial signal detection in bipolar SP-VDD systems

Establishing adequate and consistent atrial sensing from a lead floating in the atrial blood pool is obviously more difficult than sensing from a fixed point of attachment to the atrium as is done with conventional atrial leads. The sensed atrial depolarisation will necessarily be a combination of action potentials from many different points in the atrium, with the electric currents carried through the blood pool to the electrode. The resulting wanted atrial signal (itself a "far-field" signal) must then be differentiated from unwanted far-field signals, including the ventricular electrogram, in order to produce reliable VDD pacing. Finally, since the lead is floating and not attached, increased variability in atrial sensing is liable to occur with physiological manoeuvres such as respiration, cough, and positional changes. Nevertheless, recent applications of sensing technology have allowed the development of SP-VDD pacing systems with excellent clinical reliability.

There are several factors influencing atrial signals detected by a floating dipole. These factors may be divided into two groups. The first group includes pre-existing factors, that is factors which we cannot influence, such as shape of the atrium, ageing, fibrosis

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and sequence of impulse propagation. The second group includes factors which depend on the design of the atrial part of the lead; that is factors which can be manipulated to maximise atrial sensing, such as distance between atrial wall and electrode, electrode size, space between electrodes, and dipole orientation. Only appropriate interaction between these two groups of factors will provide a suitable A-signal. We now discuss each of the factors from the second group.

Regarding distance between atrial wall and electrode, it is obvious that the greater the distance, the smaller the amplitude and the lower the frequency and slew rate. As one moves further away from the source of the wave of depolarisation, the field strength diminishes, much as the ripples from a stone thrown in water diminish in amplitude and frequency (waves per second), the further they move away from their source.

Small electrodes deliver high-quality discrete signals recorded only from nearby myocardium; larger sensing electrodes ("antennas") can record signals from further away, but at the expense of recording decreased signals close to the atrial wall and increased unwanted far-field signals. The optimal electrode size is a function of the wavelength of the signal being detected; if the electrode length is equal to a considerable portion of the signal wavelength, the electrode will detect the signal at various times and phases along its course leading to widening of the signal and decreasing its amplitude at any given time point ("damping"). High-frequency or near-field signals (more waves per second) will more readily be averaged out, whereas far-field signals of a lower frequency will be less affected (since over the course of the electrode length less phase variation is produced by the lower number of waves per second of a far-field signal). This reduces the ratio of the high-frequency content to the low-frequency content of the resultant detected signal and lowers the overall slew rate and peak amplitude. Therefore, the ideal electrode for detection of the optimal atrial signal would be small, theoretically infinitestimally small.

Too small an electrode, on the other hand, although producing excellent discrimination of near-field from far-field signals, acts only as a small antenna with a small detection field. It may be adequate or ideal for detecting signals of tissue where there is direct contact; but for detection of atrial signals from the atrial blood pool, larger antennas are required for adequate signal strength. Thus, the optimal electrode size will, of necessity, be a compromise between the opposing factors.

Another potential disadvantage of small electrode size is that small electrodes will intrinsically have a higher sensing impedance (Z_s) which tends to reduce the voltage of the signal sensed by the pulse generator. In order to overcome this problem, one must use special high-input impedance (Z_{amp}) amplifiers which allow the quotient representing the total system impedance $[Z_{amp}/(Z_{amp} + Z_s)]$ to approach one and avoid further diminution in amplitude of the detected signal.

The effects of varying inter-electrode spacing are somewhat analogous to the effects of varying electrode size: the larger the inter-electrode size the bigger the sensing antenna, but at the cost of decreased specificity. In other words, the larger the inter-electrode separation, the more the bipolar lead system behaves like a unipolar system.

The key breakthrough which led to clinically reliable SP-VDD lead systems, and which is integral to all current SP-systems, was the development of the differential amplifier. Instead of adding together the signals from the two bipolar electrode poles, a differential amplifier subtracts one signal from the other. If the separation of the electrodes approximates one half of the signal wavelength, the signal amplifier effect will result in doubling of the signal $[V - (-V) = 2V]$ while at the same time lower frequency, higher wavelength far-field signals will be sensed approximately equally by the two electrodes and cancel each other out. An example of how this works in clinical practice is shown in Fig. 1. More details on the physics and electronics of SP-VDD lead sensing may be found in several recent reviews in the literature[10,11].

Based on these principles, three major types of electrode dipole orientation in bipolar SP-lead designs have been developed over the past 15 years.

1. The SP-VDD system developed by Goldreyer and co-workers[8,9] utilises small orthogonally opposed semi-circumferential or split half rings directly opposite each other in an effort to exploit all the theoretical advantages of small electrodes for sensing (Fig. 2A). As would be expected, this lead design provided excellent signal-to-noise ratio and very high frequency atrial signals but, unfortunately, the signals recorded from the atrial blood pool were often too small to allow reliable detection. In the model of this lead developed by CPI, Inc., St Paul, MN, USA, atrial sensing was adequate in only 58% of patients and implantation time was significantly

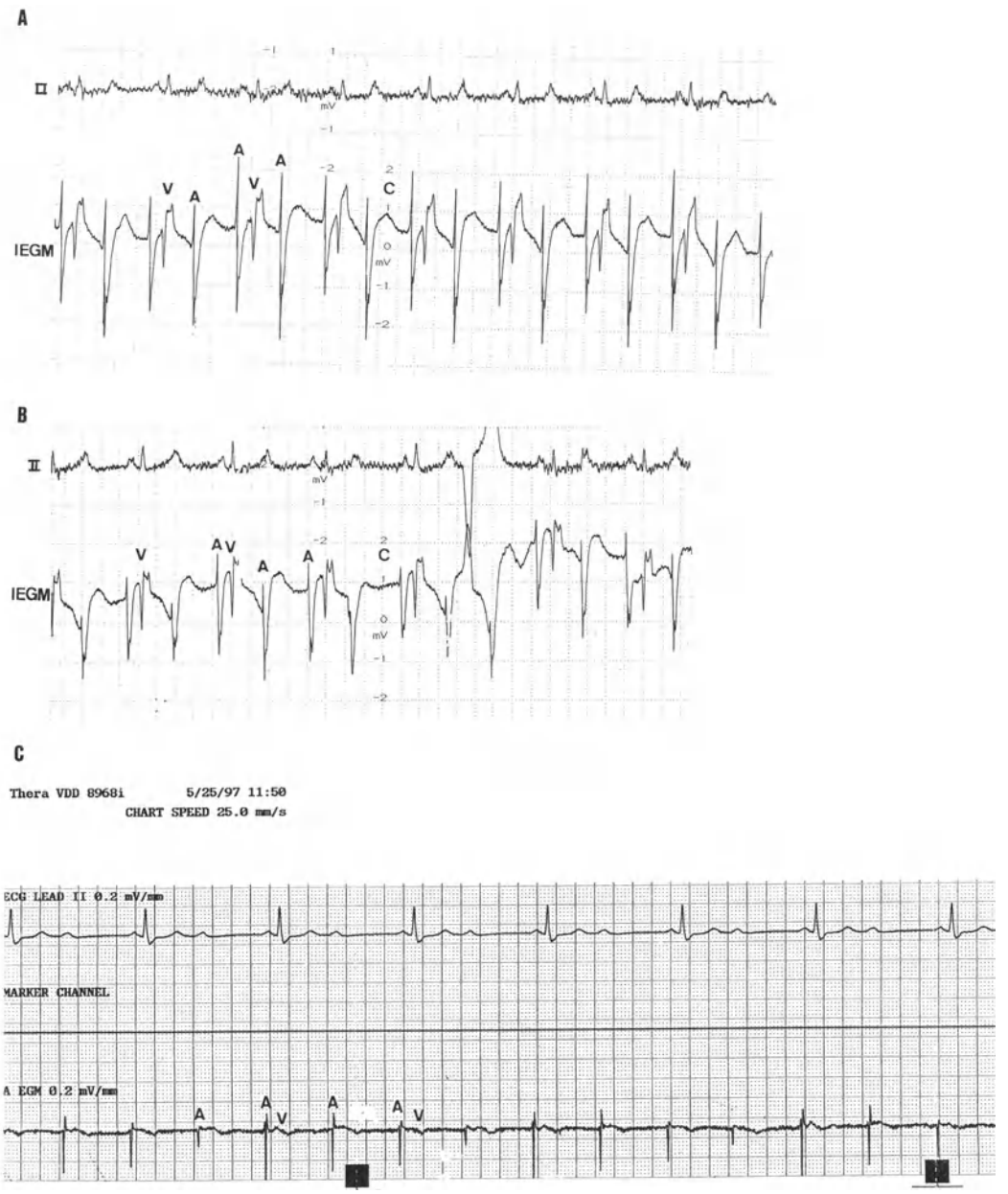

Figure 1. Example of sensing qualities of the bipolar VDD lead (Medtronic VDD lead). At implant unipolar electrograms were obtained by connecting the distal (panel **A**) and proximal (panel **B**) atrial sensing electrodes to the V_1 ECG lead. The resulting intracardiac electrograms (IEGM) are shown together with surface ECG lead II. Note the significant far-field ventricular sensing (approximately 50% of the atrial sign amplitude) for both the proximal and distal electrodes. The measured atrial EGM (A) amplitude (note the calibration C provided in the tracing) was 3.0 mV with the far-field ventricular (V) signal amplitude being 1.5 mV for the distal electrode and 2.5 mV and 1.4 mV for the atrial and ventricular electrograms respectively in the proximal electrode. Panel **C** shows the telemetered atrial electrogram from the implanted pacemaker immediately after implant. A high-quality discrete atrial EGM is recorded with an amplitude of between 7 and 17 mm (1.4–3.4 mV). Note the significant rhythmic respiratory induced variation in EGM amplitude. There is only a very low-amplitude and low-frequency far-field ventricular signal which cannot be sensed by the pacemaker. All tracings are 25 mm/s.

longer than with conventional leads[12]. It was explained that the extremely small size of the orthogonal electrodes led to significantly decreased sensing[13], and this lead has not been approved for use in clinical practice.

2. The diagonal atrial bipolar or DAB leads consist of two small split rings separated by either 5 or 7 mm (Fig. 2B). CCS, Inc. (Cardiac Control Systems, Inc.), Sulzer-Intermedics, Inc., TX, USA and LEM Biomedica, Italy all produce similar examples of this lead. The theoretical principle behind DAB electrodes is that, since the electrodes are opposite each other and differential bipolar sensing is used, "near-field" atrial sensing will be preferentially detected in only one of the electrodes (the one facing the atrial wall that is the source of the signal), while ventricular far-field signals will be detected essentially equally by the two electrodes and will tend to be subtracted out.
3. The total ring pair electrodes exist in two configurations: a short inter-electrode distance of about 10 mm (Fig. 2C) is available in leads manufactured by Biotronik, Medtronic and Vitatron (the last two leads are identical), and a long inter-electrode distance of up to 30 mm which is available in those made by Medico Italia, Sorin Biomedica, Pacesetter of St Jude and ELA Medical.

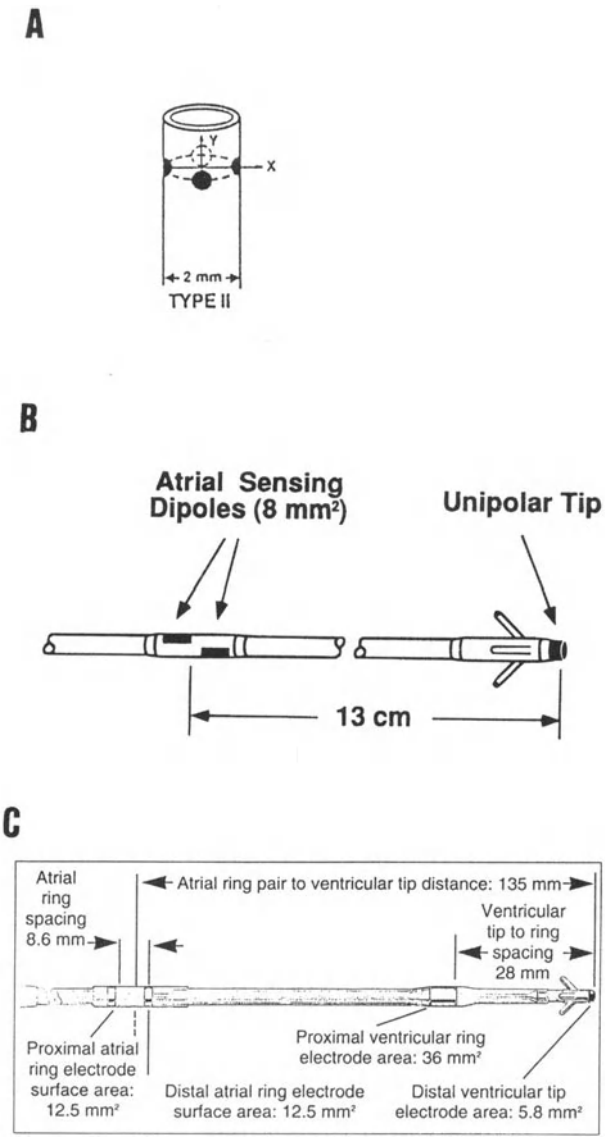

Figure 2. Diagrams of three major varieties of SP-VDD leads: multiple orthogonal semi-circumferential electrodes (panel **A**) (reproduced with permission from Futura Publishing Co., Inc.[9]); Intermedics Uni-Pass™ lead (panel **B**) which utilises two closely spaced (5 mm) diagonally arranged dipoles (8 mm² each) for atrial bipolar sensing (reproduced with permission from Futura Publishing Company, Inc.[20]); and the Medtronic Inc. CapSure™ VDD lead (panel **C**) with bipolar total ring electrodes 8.6 mm apart (reproduced with permission from Medtronic Inc. MN, USA).

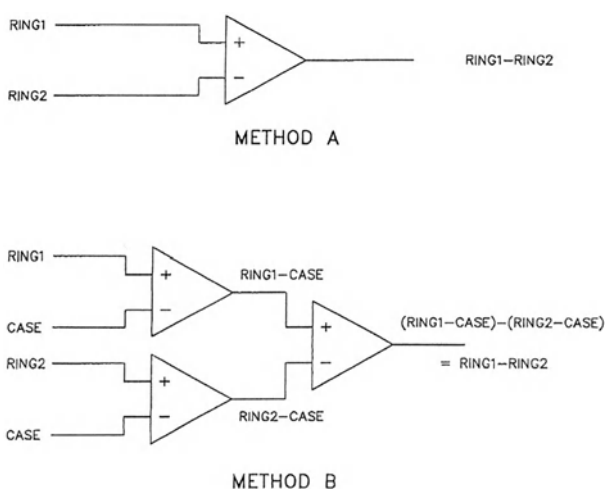

Figure 3. Diagram of two amplifier designs. Medtronic (method A) treats the two electrodes as two parts of a bipolar system and directly subtracts signals of one electrode from the second. Method B, used by the Intermedics device, processes the signals from two bipolar electrodes as if they were individual unipolar electrodes and only afterwards subtracts one signal from the other.

As was mentioned above, DAB and total ring systems both make use of a differential amplifier, although in a slightly different way, as shown in Fig. 3. Medtronic (method A in Fig. 3) treats the two electrodes as two parts of a bipolar system and directly subtracts signals of one electrode from the second. Method B, used by the Intermedics system, processes the signals from two bipolar electrodes as if they were individual unipolar electrodes and only afterwards subtracts one signal from the other. Although the systems are different, the results are basically of equal value. Method B requires more circuitry and battery power.

Clinical sensing performance and long-term results

At present two bipolar SP-VDD configurations are in clinical use: total and split ring (DAB) systems. Medtronic's and Intermedics' SP-VDD devices, as typical representatives of these VDD systems, were directly compared by Lau et al[14] and were shown to be equally efficacious. Some degree of atrial under-sensing could be demonstrated either by Holter monitoring, physical manoeuvres, or exercise testing in 13% of the patients with the Intermedics pacemaker and in 14% of patients with the Medtronic pacemaker. No evidence of atrial over-sensing (even at the most sensitive settings) was seen with either device. At 6 months post-implant the mean atrial sensitivity for patients with the Intermedics device was 1.2 ± 0.5 mV versus 0.8 ± 0.4 mV for the Medtronic device, although, as the authors point out, these atrial sensitivity measurements are obtained in different manners by the two devices and are not directly comparable. Furthermore, since both devices contain amplifiers capable of detecting atrial signals as low as 0.10 mV (Intermedics) or 0.18 mV (Medtronic) the A-signal amplitudes recorded above still allow for a significant margin of error.

We have undertaken extensive analysis of the Medtronic VDD system, publishing our initial single-centre results[15], the results of a multicentre investigation of the lead[16] and direct comparison of the two lead systems[17]. In agreement with Lau et al[14,18] we also showed that, despite the different sensing strategies used in the two lead systems, the two were essentially equivalent (atrial signal amplitude at implant of 3.7 ± 1.6 mV for the Medtronic system and 4.1 ± 2.1 mV for the Intermedics system and corresponding 6-month atrial sensing thresholds of 1.5 ± 1.4 mV versus 1.4 ± 0.3 mV). Most importantly, adequate atrial sensing was obtained in between 96% and 98% of patients, and maintained with 2 years of follow-up[16].

Others studies also demonstrated the long-term reliability of bipolar atrial sensing in various SP-VDD systems[16,18–24]. The performance of VDD leads has been studied specifically during exercise by using the CCS device[25]. The authors demonstrated a 5.9% to 59.4% decrease in atrial signal amplitude during peak exercise in most of the patients (the other patients having either no change or a slight increase in atrial signal amplitude) but nevertheless excellent atrial tracking was maintained during exercise. The variation in atrial signal amplitudes has recently been shown with the aid of "P wave" amplitude histograms available in the Vitatron Saphir™ VDD pacemaker[26]. Atrial signal amplitude showed great variation with changes in posture, respiration and during exercise. During exercise the mean A-signal amplitude fell by 37% ± 31% compared with the resting value, with a difference of up to 200% in every fifth patient. During daily activities, 23% of "P wave" amplitudes recorded on the histogram were < 0.5 mV.

The issue of long-term VDD performance requires, in addition to long-term successful sensing as discussed above, the maintenance of a physiology appropriate for VDD pacing, in particular without the onset of atrial fibrillation (AF) or chronotropic incompetence. In this regard the study of Crick is important[19]. Crick examined the long-term outcome of 1002 patients with intermittent or chronic heart block with no contraindications for VDD pacing, who were implanted with SP-VDD systems as part of a European multicenter study. Ninety-eight per cent atrial synchronisation was seen by Holter monitoring in 97%, 95%, and 94% of patients at hospital discharge, 3 months and 6 months, respectively. More importantly, 92.5% of the pacemakers functioned satisfactorily in the VDD mode, with only about 2% of the patients dropping out for either lack of atrial sensing, development of chronotropic incompetence requiring temporary VVI pacing to maintain an adequate heart rate, or AF with a follow-up of 90–1895 days (mean = 430 days). A similar rate of AF was observed in DDD patients with heart block and predominantly atrial sensing[27] and in SP-VDD patients in other multicentre studies[16,28,29] The rate of development of AF in these patients is significantly lower than the rate of AF development for patients with sick sinus syndrome and VVI pacing. This is undoubtedly the result of a predilection for the development of AF in patients

with sick sinus syndrome; a predilection not so commonly seen in patients with lone complete or high degree heart block who are the typical candidates for the VDD device.

Indications for single-lead VDD pacing

Single-lead VDD pacing is indicated for patients with intact sinoatrial (SA) node function and various degrees of heart block. Heart block may be a manifestation of generalised fibrosis, calcification, and dysfunction of the conduction system; it can also be congenital, a postoperative complication of valve surgery, or the result of surgical repair of complex congenital heart disease. In all these cases there is no particular reason for coexistent SA node disease. We use a practical rule-of-thumb in evaluating patients with acute complete heart block: the sinus rate should be elevated to reflect the altered haemodynamics of complete heart block, usually both before and after temporary VVI pacemaker placement, to a value of about 100 bpm at rest; sinus rates of only 70 or 80 bpm should raise the suspicion of coexistent SA node dysfunction or chronotropic incompetence. In some patients with high degree or complete heart block, Holter monitoring may be performed. It should be noted that Holter monitoring in patients temporarily bed-ridden (due to acute heart block) has little weight in influencing decisions regarding choice of pacing mode. When possible, an appropriate stress test should be performed – walking with maximal rate for a given patient.

Finally, while most of the advantages of obtaining AV synchrony with just a single lead are obvious, there are certain situations in which SP-VDD leads may be particularly advantageous. These include patients with one or more pre-existing leads already in place, and paediatric patients[16], in whom there is a particular advantage in minimising the number of leads implanted. Physicians who routinely use the cephalic vein for one lead can avoid the need for subclavian vein puncture altogether when using a SP-VDD lead. The ability of VDD systems to offer the benefits of AV synchrony with a single lead is particularly noteworthy in light of the fact that over 80% of pacemakers world-wide are single-lead systems[30,31].

Practical aspects of lead positioning and pacemaker programming

Most VDD leads are available in several different lengths to accommodate patients with longer or shorter right atrial to right ventricular apex separations, with the standard separation being 13 cm for most leads. The decision to implant a lead with a longer or shorter AV separation may be made empirically (very large or tall patient and/or significant right-sided cardiac enlargement versus children). A simple fluoroscopic technique may also be used to predict the best lead size by laying a test electrode over the chest of a supine patient and positioning it under fluoroscopy to approximate the expected intracardiac course of the lead[32].

In terms of actual placement of atrial electrodes, the optimal position for atrial dipole should theoretically be in the area of the SA node. Depolarisation of the atria normally begins with depolarisation of the SA node area and spreads in a wavefront towards the AV node. This fact notwithstanding, non-uniformity of atrial anatomy due to the complex shape and boundaries of the chambers, and also due to changes related to ageing and fibrosis, could lead to a complex uncoupling of transverse conduction between fibres in a muscle bundle. Therefore, individual propagation may be very unpredictable. This multiform depolarisation in the atria may complicate the prediction of individual propagation and sensing of the atrial signal by the pacemaker lead. In clinical practice, Antonioli and several other *implanters of VDD leads*[6,11,21,22,25,33] *observed optimal* A-signal in the upper right atrium (RA), i.e. in close

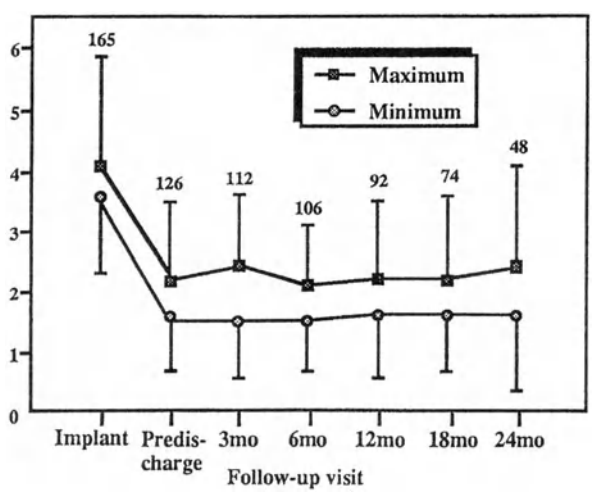

Figure 4. Mean and SD of maximal and minimal atrial signal amplitude during implant and follow-up period for 24 months. Note a decrease in atrial signal in the postoperative period compared with implant and stability of atrial signal over time. (Reproduced with permission from Futura Publishing Company, Inc.[16]).

proximity to the SA node. Our experience from our initial use of implantation of VDD leads was different. Using mapping of the RA during implantation with atrial electrodes of single leads, we observed, for the most part, optimal A-signal in the lowest parts of the RA and very infrequently in proximity to the SA node. Other investigators (about 300 implantations of SP-VDD leads) also observed that the optimal A-signal was most frequently found in the mid- and lower parts of the RA[16,18,29].

For VDD lead placement we use the following technique. First the lead is placed securely in the right ventricular apex in the traditional manner and adequate ventricular pacing and sensing performance is verified. Next, in order to obtain an optimal atrial signal, atrial sensing is assessed by atrial mapping: the proximal part of the lead is either bowed to move the atrial dipole distally towards the lower part of the atrium, or straightened to relocate the dipole in a superior orientation towards the upper part of the atrium. A-signal amplitude is evaluated either with a pacing systems analyser (PSA) or by connecting one or, preferably, both of the atrial poles of the implanted lead to a properly grounded ECG recorder. One advantage of this approach is that it allows a visual estimation of the bipolar atrial signal and the amount of ventricular far-field sensing, although in general the differential amplifiers provided in the pacemaker circuitry eliminate most of the ventricular far-field sensing signals (Fig. 1). The lead is slowly moved while assessing the A-signal amplitude after every slight change, until the location of the maximum atrial signal is verified. Redundancy in the heel of the lead helps provide lead stability as well as to more closely approximate the lead electrodes to the atrial endocardial surface. At the optimal location, stability of atrial sensing should be assessed using manoeuvres such as deep breathing and coughing. The assessment of atrial sensing, as well as ventricular sensing and pacing, should be made with the stylet completely or at least mostly withdrawn from the lead, since the presence of the stylet can affect the sensing performance of the lead quite dramatically. Particular caution must be exercised in order not to move the lead during fixation in the pacemaker pocket once the optimal position is found, since very often the positioning is quite delicate and slight movements one way or the other can significantly reduce the sensing values obtained.

It should be emphasised that placing the electrode pair near the sinus node may provide acceptable (although usually not optimal!) atrial signal. However, the A-signal in this position is usually unstable and its amplitude can drop significantly due to migration of the dipole to the superior vena cava (SVC) during inspiration or patient movement. Similarly, atrial electrodes placed close to the tricuspid valve will tend to be pulled distally into the ventricle by the heart's contractions, particularly if there is a large redundant loop after the atrial electrode pair. This is particularly so in the Intermedics VDD lead, which tapers to a very thin unipolar lead body distal to the atrial sensing part.

Another important issue during implantation of VDD leads is minimal acceptable amplitude of the atrial signal. As has been demonstrated with the Medtronic VDD system[15,17], as well as with Intermedics VDD lead[17,18,20] and in the multicentre, study with Dromos SL VDD device, Biotronik, Inc.[34], there is an approximately 50% diminution in atrial signal amplitude between values obtained at implant with a PSA and the actual atrial sensing threshold detected by the pacemaker (Fig. 4). Because of this diminution, and also because of respiratory variation in atrial sensing, effort should be made at the time of implant to search for the optimal A-signal in terms of stability and amplitude. This variation in atrial signal amplitude from measurements made during pacemaker implantation with a PSA to measurements obtained with the programmer immediately after, or a day after, implantation is not unique to VDD systems, having also been described for standard atrial leads[35]. Although one cause for this may be subtle changes in lead positioning or lead tip orientation early after lead placement[35], in the case of VDD leads a more likely explanation is the difference in atrial signal processing between the PSA and the pacemaker itself, since the difference is already evident immediately post-implant and atrial sensing remains fairly stable afterwards[15,16] (Fig. 4). Therefore, the minimal acceptable A-signal amplitude during implantation should be at least twice the desired long-term A-signal. As mentioned above, atrial signal may decrease up to 200% (mean 37% ± 31%) during exercise or other physiological manoeuvres[25,26]. This would suggest that it is necessary to employ a large margin of safety. Programmable atrial sensitivity that can provide appropriate atrial sensing should be at least twice, or more, that measured supine at rest. Such diagnostic features as atrial signal amplitudes histograms can provide further help in adequately programming atrial sensitivity. In our institution during implantation of VDD leads we adopted a rule

that minimal *acceptable* atrial signal amplitude measured by ventricular channel of the PSA, Medtronic, Inc., Model 5311, should be at least 2 mV. After implantation, and during follow-up, most of our patients are programmed at close to the highest sensitivity (0.1–0.25 mV, but not more than 0.3–0.35 mV, even in patients with A-signal 2–3 mV and more) unless at least a 3-fold sensing threshold at a higher setting can be demonstrated both at rest, and particularly during coughing and while standing. In terms of programming other parameters, careful attention should be paid to the following: PVARP (which must include retrograde P wave if recorded), AV interval[36], and lower rate – which should be lower than the patient's lowest sinus rate determined by Holter monitoring or by rate histogram recorded through the diagnostics of pacemaker.

SP leads for pacing and sensing

The major limitation of all VDD leads is that they cannot provide atrial pacing with the same success as they provide sensing. Nevertheless, attempts have been made to apply the same benefits of SP-VDD lead technology with the goal of achieving atrial pacing as well as sensing. A multicentre study presented at the NASPE '97 and Europace'97 meetings, using the Medico Phymos™ 830-S SP-VDD lead, reported successful atrial stimulation on implantation in 76% of 315 patients, albeit at a high threshold (mean threshold 3.2 ± 1.5 V at 0.5 ms pulse width)[37]. At 6 months follow-up, 51% of the patients were responsive to atrial pacing without side-effects with threshold up to 5 V/0.5 ms. Similar results were reported during Europace'97[38] in the summarised experience of 16 Italian centres using OLBI (overlapping biphasic impulse) stimulation with the Dromos SL device (Biotronik, Inc.). The possibility of long-term atrial stimulation by atrial dipole in patients with chronically implanted VDD leads was investigated by Papouchado et al[39]. They assessed patients undergoing pulse generator replacement who had had a Medico Italia SP-VDD lead implanted for at least 5 years. In 43% of patients atrial pacing was obtained at > 1.5 V and in another 43% of patients atrial pacing was achieved at > 4 V; while in the remaining 12% of patients atrial pacing was not possible at 10 V. The authors concluded that present VDD leads are not suitable for atrial pacing. Thus, although the ability to pace the atrium with VDD leads is a useful feature for patients with AV block who are already implanted with an SP-VDD system, and who later require atrial pacing, the high pacing threshold would preclude its *a-priori* use in patients needing atrial pacing. As a result there is considerable interest in modifying SP-VDD leads so that direct atrial contact can be achieved for reliable atrial pacing. Actually, the first design of an SP-DDD lead dates back to 15 years ago when the "Crown of Thorns" SP lead was introduced for DDD pacing[40]. Although this lead did maintain good atrial sensing and pacing function, it was mechanically unreliable and prone to dislodgement.

At least four SP-DDD lead designs are currently being studied. Medtronic is currently conducting initial clinical testing of an SP lead[41] which has a pre-shaped L-curve with a protruding electrically active side tip, 13 cm proximal to the ventricular electrode, and which is designed to lodge in the atrial trabeculae (pectinate muscles) (Fig. 5). The lead is in the early stages of clinical evaluation. Pacesetter, St Jude, has designed an 8 French atrial J lead with a 5 French ventricular limb that offshoots 1 cm proximal to the atrial J and can be positioned in the RV apex[42]. A single long stylet which straightens the atrial J portion is used, and is removed after placing the distal electrode in the RV apex to allow the J to form for placement in the atrial appendage. This lead was easily placed in dogs, and achieved long-term atrial pacing thresholds of less than 1 V. Hirschberg et al[43], also from Pacesetter, have designed an SP-DDD system in which the distal tip is an atrial electrode, and

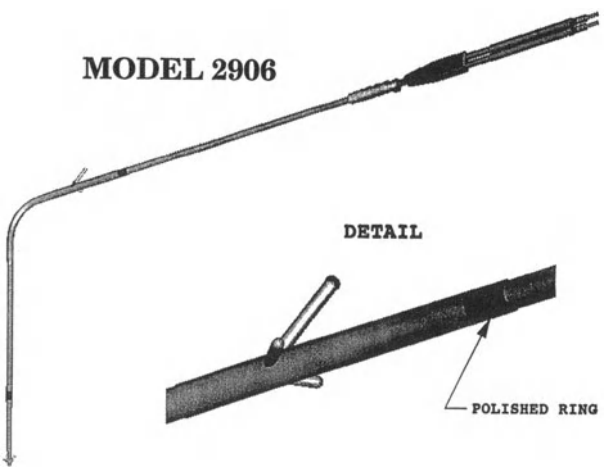

Figure 5. Schematic of the Medtronic SP-DDD lead (Model 2906) with a separate atrial tip electrode for sensing and pacing and two nearby *tines* to aid in fixation to the pectinate muscles of the right atrium (reproduced with permission from Medtronic, BRC).

has an active fixation. The ventricular electrode is a ring placed 12 cm from the tip. According to data from an animal study, the implantation of this lead is quite simple: the distal tip was easily placed in an optimal atrial position and the lead body was backed into position in the apex of the ventricle. Another type of DDD SP-lead has been designed by CCS Inc. and has two pre-formed S-shape curves: one at the level of the SVC and the other at the level of the mid- to lower RA[44]. The lead is still in the early stages of evaluation in animals.

Conclusions

VDD pacing with SP leads is clearly a reliable pacing alternative for patients with various degrees of AV block and maintained SA node function. It offers long-term reliable atrial sensing and makes the implanter's job both simpler and quicker. SP-VDD pacing has been officially recognised as an appropriate pacing system in the latest Guidelines for Implantation of Cardiac Pacemakers[45]. It offers a convenient alternative for the large pacing community worldwide who currently use only VVI systems. All available VDD leads provide appropriate acute and long-term atrial sensing, and pacing physicians could use the type of lead with which they feel most comfortable. It seems fair to say that, no matter what lead configuration is chosen, if acutely adequate sensing is obtained, with very few exceptions one can be assured of long-term successful sensing performance. However, to obtain appropriate long-term atrial sensing it is important to place the atrial part of the VDD lead at a site within the RA, where it exhibits the optimal sensing of the A-signal.

The major limitation of all VDD leads is that they cannot as yet provide appropriate atrial pacing. Proposed models of SP-DDD leads are very interesting, but they are still in their infancy. There is good reason to hope that, in the near future, one or more SP systems capable also of appropriate atrial pacing will be available. We believe that SP-DDD leads might also be particularly suited for incorporation into future universal pacemaker/defibrillator devices for the optimal treatment of brady- and tachyarrhythmias.

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Chapter 55

Clinical Trials in Cardiac Pacing: Justification, Design, and Preliminary Results of the United States Trials

Gervasio A. Lamas

Introduction

Over 440 000 permanent pacemakers were implanted worldwide in 1995, at a cost of several billion dollars. It is unlikely that Drs Elmqvist and Sewing, who placed the first fully implantable pacemaker in 1959, could have foreseen the technological advances that now allow pacemakers to restore optimal haemodynamic function, enhance exercise capacity, and improve the quality of life. The continuous upwards spiral of technology is not without its economic cost, however. The development of dual-chamber pacing, rate-adaptive pacing, mode switching, and other programmable features has encouraged pacemaker physicians, particularly in North America and parts of Europe, to implant the most technically advanced devices. However, the clinical data used to encourage the use of the most sophisticated technology for all pacemaker recipients is very often flawed. This chapter will briefly examine some of the major retrospective clinical studies which have demonstrated superiority for more advanced technology, and review some of the United States-based prospective trials designed to answer key clinical questions posed by the retrospective studies.

Brief review of major retrospective studies

Retrospective studies comparing dual-chamber to ventricular pacing are based on the seductive hypothesis that preservation of atrioventricular synchrony will prevent clinical events such as stroke, heart failure, and overall mortality. This concept first gained attention and then acceptance following the publications of Rosenqvist and co-workers[1,2], who reported on patients implanted with VVI or AAI pacemakers for sinus node dysfunction in two Swedish hospitals. In one hospital, all patients received a VVI pacemaker. In the other hospital, patients underwent an atrial pacing test to assess atrioventricular conduction. Those patients with normal atrioventricular conduction were implanted with an AAI pacemaker. Although baseline demographic characteristics were not significantly different for the AAI and VVI groups, their clinical outcomes were dramatically different. After 4 years the incidence of atrial fibrillation was 47% for the VVI group and 6.7% for the AAI group ($p < 0.001$). Congestive heart failure and death also were less frequent in the AAI group (heart failure in VVI 37%; in AAI 15% ($p < 0.001$); death in VVI: 23%; in AAI: 8% ($p < 0.005$). However, in a retrospective

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analysis such as this there are potential sources of bias that must be taken into account.

The principal problem with this interesting study is that the two groups under study were potentially not comparable, because AAI-paced patients, not VVI-paced patients, had "passed" an atrial pacing test prior to selection for AAI mode, and because the outcome of those patients who did not "pass" the atrial pacing test is unknown. Although this might seem a trivial point, the presence of atrioventricular or intraventricular conduction disturbances may signify more severe underlying cardiac disease[3], even when differences in left ventricular function are controlled. Such patients were systematically excluded from the AAI group, and not from the VVI group. Thus, less sick patients may have preferentially received AAI pacemakers and this may, in part, account for some of the clinical differences between groups.

Many other retrospective studies have been subsequently published (Table 1)[4–20], all of which are flawed by the use of retrospective clinical data; and nearly all of which conclude that atrial-based pacing is superior to ventricular pacing. The largest of these is worth reviewing[20] because it carefully defines the great differences in clinical characteristics of dual and ventricular-paced patients in the United States. This retrospective analysis randomly selected 36–312 pacemaker recipients aged 65 years or older as a representative sample of all Medicare patients undergoing initial pacemaker implantation from 1988 to 1990 in the United States. Pacemaker mode selection was not randomised, and was by attending physician choice. Mortality at 1 year in dual-chamber-paced patients (13.7%) was significantly lower than in

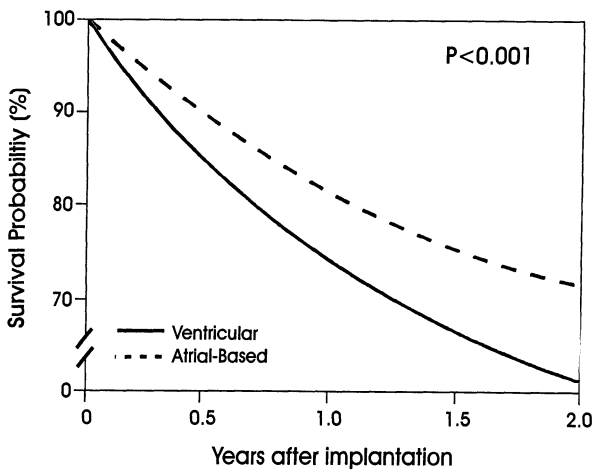

Figure 1. Kaplan-Meir survival plots in a Medicare population-paced VVI or DDD ($p < 0.001$). Adapted from ref. 5.

Table 1. Studies comparing VVI versus atrial-based pacing in patients with sinus node dysfunction

First author	Months [n]	VVI [n]	A/AV [n]	VVI AF (%)	A/AV AF(%)	VVI CHF (%)	A/AV CHF (%)	VVI death (%)	A/AV death (%)
Rosenqvist[1]	24	79	89	29.5	3.4	23	7	10	5.6
Rosenqvist[2]	48	79	89	47	6.7	37	15	23	8
Markewitz[6]	32	87	136	30	7				
Alpert[7]	60	79	49					43	25
Sasaki[8]	50	34	41	44	17	21	2	35	12
Santini[9]	54	125	214	47	7			30	14
Bianconi[10]	43	150	153	7.9	4.8			6.3	3.8
Feuer[11]	44	70	61	25	11				
Sethi[12]	49	47	40	21	2.5			14.9	10
Zanini[13]	40	57	53	10	2	3	1	17.5	9.4
Grimm[14]	69/32	67	14	42	0				
Stangl[15]	53	112	110	19	6			28	17
Kosakai[16]	60	51	144					21	7
Witt[17]	96	3 440	1092					22.6	10.9
Hesselson[18]	96	193	366	26	5.7			24	22.6
Sgarbossa[19]	66	112	395	17.5	5			39	21
Lamas[20]	48	15 145	5813					15.5	11.2
Totals	885	19 848	8770	24	6	20	3	34	23

A/AV = AAI or DDD pacing; AF = atrial fibrillation; CHF = congestive heart failure.

VVI-paced patients (18.3%; $p < 0.001$; Fig. 1). A multivariate analysis demonstrated that pacing mode was an independent predictor of survival (odds ratio 0.82). Nonetheless, the purpose of presenting these data in greater detail is to underline the extent and depth of the selection bias which is always inherent in the clinical choice between two different technologies. Many non-clinical and non-pacing-related characteristics were independently associated with the selection of a dual-chamber pacing system, including younger age, male gender, higher socioeconomic status, atrioventricular block, no history of atrial fibrillation, the absence of peripheral vascular disease, and the presence of fewer non-cardiac co-morbid conditions. Dual-chamber devices also were more likely to be implanted in hospitals that were urban, privately owned, over 500 beds in size, and had a cardiac catheterisation laboratory. Although multivariate analyses can control for the identified sources of bias, the extensive *reported* differences between the two groups are too great. The presence of other confounding variables which were uncoded and could not be controlled, such as living in a nursing home, dementia, or general debility, certainly account for at least part of the clinical results.

Our review of the pacemaker literature has led us to the conclusion that the available retrospective data have painted an overly rosy picture of the benefits of dual-chamber or atrial-based based pacing[20]. Only carefully designed prospective studies will permit an accurate definition of the benefits of any technological innovation in cardiac pacing.

Review of the first prospective study

In fairness, a small prospective trial of pacemaker mode selection has already been published by Andersen and co-workers[21]. These investigators studied 225 patients with sinus node dysfunction, all of whom had passed an initial screen to confirm normal atrioventricular conduction. Patients were randomly assigned to receive AAI ($n = 110$) or VVI ($n = 115$) pacing. An average follow-up of 2.7 years revealed no striking differences in the mode-related incidence of atrial fibrillation, stroke, or survival (Fig. 2). However, there were fewer embolic events in the atrial-paced group (AAI pacing: 5%; VVI pacing 17%; $p = 0.005$).

However, the correct interpretation of this largely negative study requires careful consideration in light of its small size (115 control patients), the small number of

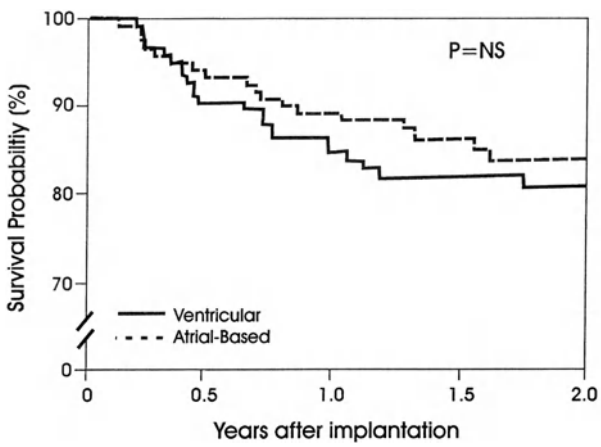

Figure 2. Kaplan-Meier survival plots in patients randomised to VVI ($n = 115$) or AAI ($n = 110$) pacing (not significant). Adapted from ref. 21.

events (25 control group deaths), and the relatively short follow-up (2.7 years). The calculation of statistical power reveals that there was only a 19% likelihood of detecting a 30% decrease in AAI-group mortality. Consequently, *this important study did not have enough statistical power to exclude a small, or moderate, but important, survival benefit of atrial-based pacing*. A later analysis with more follow-up, and therefore more events, is said to show results favouring atrial pacing, but has not yet been published. However, multiple reanalyses increase the likelihood of misinterpretation of results. Therefore, large-scale randomised clinical trials *with enough statistical power* to provide a conclusive answer must be designed and carried out, lest a significant therapeutic benefit of atrial-based pacing be missed.

Review of the United States studies

Pacemaker selection in the elderly (PASE)

We[22,23] have reported preliminary results of the Pacemaker Selection in the Elderly trial. Preliminary analyses have suggested interesting trends in clinical endpoints. However, this 407-patient study was designed as a pilot study, and was planned to have adequate statistical power for a quality-of-life endpoint, and not for a mortality endpoint.

The Pacemaker Selection in the Elderly (PASE) trial was designed as a quality-of-life study in 407 patients aged 65 years or older who underwent permanent pace-

maker implantation for any diagnosis. Patients underwent implantation of a DDDR pacemaker which had been randomly programmed to VVIR or DDDR. The primary endpoint of the study was quality of life measured using the Medical Outcomes Study Short Form 36 Item Questionnaire. The study had > 80% power to detect a clinically meaningful difference in quality of life between modes. Secondary endpoints included composite total mortality, stroke, heart failure hospitalisation, any diagnosis of heart failure, development of atrial fibrillation, and development of pacemaker syndrome. Patients were followed for a median duration of 1.5 years. Although preliminary results have been presented, as of July 1997 the final paper is still undergoing peer review.

In the overall group of 407 patients there were no consistent, significant differences between ventricular pacing and dual-chamber pacing in any of the SF-36 subscales at 3 months, 9 months, or 18 months. Athough there were no significant early differences in the average Specific Activity Scale class between groups at either the 3-month or the 9-month assessment, a significant difference favouring dual-chamber pacing was evident at the 18-month visit. A different reponse to dual-chamber pacing was observed in the subgroup of patients with sinus node dysfunction as the implant diagnosis. Longitudinal analyses demonstrated better emotional role ($p = 0.001$) and social function ($p = 0.02$) in the dual-chamber-paced patients throughout the course of follow-up. A longitudinal analysis of Specific Activity Scale demonstrated a significant difference favouring dual-chamber pacing ($p = 0.022$).

Clinical events

There were no significant differences between the ventricular-paced and dual-chamber-paced groups in total mortality, stroke, heart failure hospitalisation or development of atrial fibrillation. There was, however, a significant reduction in the clinical endpoint of any diagnosis of heart failure, or stroke, or death (VVIR 32% versus DDDR 23%; $p = 0.03$). Patients with sinus node dysfunction as the implant diagnosis demonstrated numerical benefit favouring dual-chamber pacing of borderline statistical significance, in the endpoints of total mortality, stroke or death, heart failure hospitalisation, and the development of atrial fibrillation. There was a significant reduction in the combined clinical endpoint of any diagnosis of heart failure, or stroke, or death (VVIR 34% versus DDDR 21%; $p = 0.03$). In patients with atrioventricular block as the implant diagnosis, no statistically significant benefit of dual-chamber pacing could be detected in either clinical endpoints or in quality of life.

PASE was a well-powered study of pacemaker mode selection in the elderly which showed that dramatic mode-unrelated improvements in health-related quality of life occur following pacemaker implantation. However, quality-of-life benefits associated with dual-chamber versus ventricular pacing are clearest only in the subgroup of patients with sinus node dysfunction. This interpretation of the quality-of-life results must be tempered by the crossover rates from ventricular pacing to dual-chamber pacing, and by trends towards clinical benefit in dual-chamber-paced patients with sinus node dysfunction.

Thus, although PASE was correctly powered for a quality-of-life endpoint, the results still encourage the performance of an adequately powered clinical trial to assess the clinical benefits of atrial-based pacing. There are three such trials in progress at the present time. The US and Canada-based Mode Selection Trial (MOST), for example, has nearly 1000 patients enrolled out of a total projected of 2000 pacemaker recipients with sinus node dysfunction. MOST will have 90% statistical power to detect a reduction of 25% in the primary endpoint of non-fatal stroke or all-cause mortality. Furthermore, MOST has a strong quality-of-life and cost-effectiveness team that will be able to answer many of the questions posed above.

Rate-modulated pacing and quality of life

DDD pacemakers provide modulation of the heart rate in response to exercise or other physiological stress by tracking spontaneous atrial activity and pacing the ventricle after the programmed atrioventricular delay. However, optimal physiological function of DDD pacemakers may be limited by chronotropic incompetence, which is estimated to be present in 20–58% of pacemaker recipients[24–27]. In the presence of chronotropic incompetence, the ability of the DDD pacemaker to increase heart rate in response to physiological stress may be limited. The use of rate-modulated sensor-driven dual-chamber pacemakers (DDDR) has been proposed for patients with chronotropic incompetence[28,29]. Thus, DDDR pacing is expected to produce a clinically meaningful improvement when compared to DDD pacing by means of having the patient reach higher heart rates during exercise.

Heart rate increase may be responsible for as much as 75% of the increment in cardiac output achievable with exercise[30]. Studies by Fananapazir et al[31] and others[32] have suggested that AV synchrony may add little to exercise cardiac output if rate response is preserved. An increase in heart rate may therefore be a more efficient and effective way to increase exercise cardiac output than would be increasing stroke volume at a fixed heart rate. These physiological data suggest that DDDR pacing should be preferable to DDD pacing for many pacemaker recipients. Another argument in favour of using DDDR pacemakers for all new dual-chamber implants is that chronotropic incompetence may develop after the pacemaker has been implanted. Gwinn et al[27] studied 38 patients followed in a pacemaker clinic with exercise treadmill testing to assess chronotropic competence. The incidence of chronotropic incompetence was 58%. However, in patients paced longer than 4 years the incidence of chronotropic incompetence was greater than 70%. The correlation between chronotropic incompetence and the duration of time since pacemaker implantation was most striking in patients with atrioventricular block. Thus, the prevalence of chronotropic incompetence may increase with time after pacemaker implantation.

However, despite convincing data showing the importance of rate response to exercise stress and the high prevalence of chronotropic incompetence, clinical investigators have found an inconsistent improvement in the exercise capacity of DDDR-paced patients when compared to DDD patients. For example, Capucci et al[32], in a crossover study of eight patients randomised to DDD or DDDR pacing for 3 weeks each, found higher maximal heart rates, V_{O_2} max and V_{O_2} at the anaerobic threshold in patients programmed to DDDR. However there were no significant differences in average exercise time. In a report of 17 patients with maximal heart rates below 100 bpm, Sutton et al[33] found that only 60% of those patients derived clinical benefit from DDDR pacing. Jutzy et al[34] studied exercise capacity and gas exchange ratios during DDD, DDDR, and VVIR pacing. Although cardiac output during exercise increased by 23% in chronotropically incompetent patients, exercise duration increased only by 4%. These investigators postulated that maximum duration of exercise is too crude a measure to assess the relative benefits of different pacing modes.

The lack of uniform improvement in peak exercise capacity with DDDR pacing when compared to standard DDD pacing is an interesting finding which may simply reflect the effect of patient selection bias in small studies, and non-cardiac limitations to exercise in others. Thus, peak exercise capacity may be too crude a measurement of functional benefit in an elderly paced population. Quality of life may be a more sensitive indicator which can be used to assess the benefits of rate-modulated dual-chamber pacing.

Small crossover studies in highly selected patients have already suggested that DDDR pacing leads to superior quality of life. Sulke et al[35] compared four rate-responsive pacing modes in a double-blind crossover study of 22 patients with high-degree AV block. All subjects had previously implanted DDDR units with a motion-activity sensor. Chronotropic incompetence was present in 17/20 patients. Patients were randomly programmed to VVIR, DDIR, DDD or DDDR modes, each for 4 weeks. DDDR mode had the highest acceptance rate (59%). In addition, when DDDR paced, patients had improved perception of well-being, increased exercise capacity and better functional status than when programmed to VVIR or DDD modes. The investigators concluded that DDDR pacing was superior both objectively and subjectively to other variable-rate pacing modes (VVIR, DDIR and DDD) in this small number of chronotropically incompetent patients. Although these small crossover studies of highly selected, chronotropically incompetent patients are suggestive, they do not provide definitive support for the concept that all patients who need dual-chamber pacing should have a DDDR pacer implanted. Indeed, how to properly balance the increased complexity of DDDR pacing with the potential for added clinical benefit remains an important question in the clinical practice of cardiac pacing.

The Rate Modulated Pacing (RAMP) trial is a randomised, controlled trial of DDD versus DDDR pacing in 400 patients with any standard diagnosis for cardiac pacing. The primary endpoint will be quality of life as measured by the 36-Item Medical Outcomes Study Short Form General Health Survey. Cost-effectiveness, chronotropic incompetence, cardiovascular functional status with the Specific Activity Scale, and composite clinical events (atrial fibrillation, congestive heart failure, stroke, death, ischaemic events) will also be analysed. At the present time nearly 350 patients have been enrolled in the trial from 30 clinical centres. Given the blinded nature of the study, no results are available yet.

Discussion

Need for definitive studies

Randomised controlled trials are the premier tool currently in use to test therapeutic modalities. Clinicians can be shown to accept the results of these trials and promptly change their clinical strategies[36]. Retrospective studies have generated many hypotheses regarding the benefits of atrial-based pacing, but selection biases render these studies inconclusive. Furthermore, the strategy of routinely implanting the highest-technology (and most expensive) device in each patient, instead of matching the technology to the patient, is no longer tolerable, not even in the United States. Finally it is also essential to consider that safety concerns constitute one of the more important costs of excessive technology. Patient safety issues such as those faced by recipients of the Telectronics Accufix atrial lead[37] have gone a long way to rendering a blanket recommendation for dual-chamber pacing in all pacemaker recipients with sinus rhythm unjustified. However, the above randomised clinical trials may yet demonstrate that the global utilisation of atrial-based pacing improves clinical outcome, or that the global utilisation of rate modulation leads to improved quality of life in all dual-chamber pacemaker recipients (Table 2). If so,

Table 2. Ongoing clinical trials in pacing

(a) Small studies

Study name	Principal investigator(s)	Implant diagnoses	Number of patients	Primary endpoint	Modes tested	Status as of October 1996
Andersen	Andersen	Sinus node dysfunction	225	Mortality + embolism	VVI vs. AAI	Published[6]
Andersen	Andersen	Sinus node dysfunction	200	LA and LV size and function	AAIR vs. DDDR	Enrolling
PAC-A-TACH	Wharton	Sinus node dysfunction	200	Atrial fibrillation	VVIR vs. DDDR	Follow-up
PASE	Lamas, Orav, Goldman	All diagnoses	407	Quality of life (SF-36)	VVIR vs. DDDR	Completed
RAMP	Lamas, Orav, Goldman	All diagnoses	400	Quality of life (SF-36)	DDD vs. DDDR	Enrolling
STOP-AF	Charles, Garratt, Stafford	Sinus node dysfunction	300	Recurrent atrial fibrillation	VVI(R) vs. DDD(R) or AAI(R)	Enrolling

LA, left atrium; LV, left ventricle; PAC-A-TACH, Pacemaker Atrial Tachycardia Trial; PASE, Pacemaker Selection in the Elderly; RAMP, Rate Modulated Pacing and Quality of Life; STOP-AF, Systematic Trial of Pacing for Atrial Fibrillation.

(b) Large studies

Study name	Principal investigator(s)	Implant diagnoses	Number of patients	Primary endpoint	Modes tested	Status as of October 1996
CTOPP	Connolly, Kerr	All diagnoses	2450	Mortality	VVI(R) vs. AAI(R) *or* DDD(R)	Enrolment complete
MOST	Lamas, Lee, Goldman	Sinus node dysfunction	2000	Mortality + stroke	VVIR vs. DDDR	Enrolling
UKPACE	Skehan, Camm, deBono, Toff	High-grade AV block	2000	Mortality	VVI *or* VVIR vs. DDD	Enrolling

CTOPP, Canadian Trial of Physiologic Pacing; MOST, Mode selection Trial in Sinus Node Dysfunction; UKPACE, United Kingdom Pacing and Cardiovascular Events Trial.

then the application of the highest-technology devices to all eligible pacemaker patients would be medically sound and economically defensible. Nevertheless, until the results of these trials are known, we must endeavour to judiciously utilise biomedical technology and match the pacemaker to the patient.

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Chapter 56

CAN PACING BE MORE PHYSIOLOGICAL?

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Introduction

Although the superiority of dual-chamber (DDD) pacing in terms of haemodynamic and clinical benefits has well been established compared to single-chamber ventricular (VVI) pacing modality, especially in some conditions such as recurrent atrial tachyarrhythmias and congestive heart failure, much still remains to be done to reach a truly physiological way of pacing the human heart. The optimal pacing system should mimic the native physiological functioning of the conduction system as closely as possible. In reality, current pacing systems are far from reproducing the function of the normal heart. If in some cases clinical benefits can paradoxically be obtained by means of an "unphysiological" pacing (e.g. pacing the right ventricular apex to reduce left intraventricular gradient in obstructive cardiomyopathy), in the vast majority of cases pacing with the current technology and configuration produces detrimental effects on several aspects of cardiac functionality, and does not allow maximal benefits to be obtained[1]. The normal sequence of electric activation of the ventricles is largely disrupted by pacing the right ventricular apex; the normal sequence of atrial activation is modified by the current method of pacing in the right atrial appendage causing intra-atrial delays; the optimal temporisation of atrial and ventricular contraction would require atrioventricular (AV) delay adjustments; the current single-sensor technology only in part resembles the physiological sinus node response to metabolic, activity and emotional requirements.

Towards a physiological ventricular activation

Ventricular shape, mass, contraction and relaxation, and consequently ventricular functionality, are greatly affected by the pattern of ventricular activation. In one study[2] on 228 patients with left bundle branch block, the early-activated septum proved to be significantly thinner than the late-activated posterior wall, and the reduction was more pronounced (10%) in 28 patients with paradoxical septal motion; moreover, in the same study, on six dogs submitted to epicardial left ventricular pacing for 6 months, the early-activated anterior wall decreased in thickness by 20%. Thus a mass redistribution is induced by chronic early activation of a specific ventricular zone. In another study[3], the different effects of right ventricular pacing and classic left bundle branch block on left ventricular function have been compared in 48 patients equally distributed between the two groups. QRS duration ($p < 0.01$) and electromechanical delay ($p < 0.001$) were longer, whereas contracion time and relaxation time were shorter ($p < 0.01$) in right ventricular pacing. Leclerq et al[4] performed a radionuclide and haemodynamic study in 11 patients with a DDDR pacemaker. During atrial-inhibited (AAI), compared to DDD

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pacing modality, the ejection fraction was significantly higher both at rest (61% versus 58%, $p < 0.05$) and during exercise (65% versus 60%, $p < 0.05$), and the improvement was principally due to the increase in septal ejection fraction. Furthermore, cardiac output, pulmonary wedge pressure, left ventricular stroke work index and systemic vascular resistances all ameliorated when the normal activation sequence was preserved.

As well as systolic function, diastolic function is also affected by the pattern of ventricular activation. In a recent study[5], Doppler echocardiography has been used to assess whether diastolic function was affected by ventricular activation sequence in 13 patients. The pre-ejection time and the isovolumic relaxation time were longer during VVI pacing compared to AAI pacing, while an isovolumic relaxation flow was recorded during the course of VVI pacing, indicating prolonged asynchronous relaxation. Therefore, maintaining a close-to-physiological way of stimulation is important, especially in some situations. In heart failure it is crucial to maintain the optimal functionality of the residual left ventricle. Some conflicting results concerning the usefulness of DDD pacing with short AV delay in congestive heart failure could be due to mechanical problems related to apical activation masking benefits. In the light of this theory a more physiological method of ventricular activation can be provided by septal pacing. In one study[6], on 15 patients with congestive heart failure, the haemodynamic effects of septal and right ventricular activations were compared at several AV delays. Apical ventricular pacing did not increase cardiac output, whereas septal ventricular pacing resulted in a significant increase ($p = 0.037$). Similar results have been obtained by Rosenqvist et al[7] on six dogs, comparing proximal septal pacing and apical pacing at several AV delays. Positive and negative dP/dt was higher during septal pacing, while left ventricular activation time was significantly shorter ($p < 0.001$), indicating improved cardiac function.

On the basis of the above results a further step forward is the realisation of the contemporary pacing of both ventricles, i.e. so-called biventricular pacing. In one study[8], biventricular pacing has been evaluated on an acute basis in 18 patients after coronary artery surgery using epicardial pacing electrodes. Simultaneous biventricular pacing was documented by fusion morphology on the surface electrocardiogram, and by isochronal epicardial activation mapping. Atrio-biventricular pacing increased cardiac index and decreased systemic vascular resistances compared with atrial pacing, and with atrio-right ventricular or atrio-left ventricular dual-chamber pacing ($p < 0.05$). From the perspective of an increasingly physiological way of artificially pacing the human heart, initial studies on biventricular pacing using transvenous electrodes have been carried out[9,10]. A specifically designed thin coronary sinus electrode has been advanced through the coronary sinus in a lateral cardiac vein over the left ventricular free wall in 15 patients. In 11 patients the procedure was successful, with good acute pacing threshold and good ventricular electric signal. After 6 months of follow-up all leads were functioning and no complications were observed[9]. In a second study on 24 patients with end-stage heart failure[10] cardiac performance improved substantially, and functional class ameliorated in a stable fashion in 14 patients who survived a follow-up of 10 months.

Towards a physiological atrial activation

Dispersed atrial refractory periods that can be found in sinus node disease with bradycardia-related supraventricular tachyarrhythmias can be resynchronised by atrial pacing, thus restoring a more physiological electrical atrial pattern. Therefore, drug-resistant paroxysmal atrial tachyarrhythmias have become an accepted indication for atrial pacing in selected patients[11,12]. However, for this purpose a relatively high pacing rate must be used, often causing patient discomfort. Moreover, the presence of an intra-atrial block, slowing conduction between right and left atrium and causing left atrial delayed retrograde activation, can be at the origin of paroxysmal supraventricular arrhythmias[13,14]. In reality the current method of pacing the right atrium, placing the catheter in the right atrial appendage, is often the source of delayed intra-atrial conduction delays and discoordinate left and right atrial mechanical function[15]. Simultaneous pacing of both atria is a novel approach, under investigation by some authors, that can offer advantages. Daubert et al[16] implanted a DDD pacer in 19 patients with a double atrial electrode (Y connected) fixed in the right appendage and in the coronary sinus for left atrial stimulation, obtaining an evident atrial resynchronisation (P wave duration decreased from 209 to 108 ms during right atrial and biatrial pacing, respectively). At a follow-up of 34 months, 84% of patients improved, no longer needing antiarrhythmic drugs. There is a concern, moreover, on

the usefulness of multi-site atrial pacing in uselected patients. As atrial pacing starts to show induced benefits in terms of prevention of recurrence of atrial fibrillation, even in patients with non-bradycardia-related arrhythmias, recent reports indicate the feasibility and efficacy of multi-site atrial pacing in a setting of unselected patients with paroxysmal atrial fibrillation also. Saksena et al[17] performed a prospective crossover study to evaluate single- and dual-site right atrial pacing in 15 patients with drug-refractory atrial fibrillation and bradyarrhythmia. Dual-site atrial pacing was performed in the right appendage and in the coronary sinus ostium. Pacing lower rate was programmed at 80 ppm in 14 patients. After each 3-month period of single and dual-site atrial pacing the rate of recurrence of the arrhythmia was lower in dual-site pacing ($p = 0.03$). In addition, atrial pacing resulted in a marked decrease of arrhythmia recurrence ($p < 0.001$) and of antiarrhythmic drug use ($p < 0.01$).

Physiological rate responsiveness

Symptomatic disturbances of sinus node response account for 50% of all pacemaker implantations. Thus, incorporating artificial sensors in the pacers, to provide appropriate heart rate responsiveness, is mandatory in most patients in order to increase cardiac output during exertion. Currently the most-employed sensors are those reacting to motion and vibrations transmitted by the muscles and the skeleton to the device, using a piezoelectric effect; other sensors react to the QT interval; others to the minute ventilation, central venous temperature, or central venous oxygen saturation. Some other sensors, sensitive to changes of right ventricular stroke volume or pre-ejection interval, are employed less often. In reality the ideal sensor is still under research, since in its complex response it should mimic sinus node activity, which is a very complex-functioning apparatus reacting to metabolic requirements in the course of physical activity, as well as emotions. The combination of more sensors implemented in the same pacemaker might improve the physiological response of the system, but can also cause complicated interactions. The association between multiple sensors must be carefully assessed. Multiple sensors cause increased battery drain but, on the other hand, can be used to assess pacing threshold and to save energy. In addition, the follow-up of the device can become quite complex and the costs can be augmented. However, some multiple-sensor pacers do not require much additional technology (e.g. activity plus QT or plus ventilation).

In comparison with single-sensor devices, multiple-sensor devices offer advantages, especially during daily activities. The current strategy for multiple-sensor pacing has been to match a rapidly responding sensor such as an "activity" with a slower but more proportional sensor such as QT or minute ventilation. Few devices have these systems implemented, but clinical results suggest that the sensor combination provides heart rate profiles similar to the healthy sinus node, and a better mean response time to abrupt-onset physical activity[18–20].

In the field of new sensors an endocardial accelerometer has recently been developed. It measures endocardial acceleration from its position on the tip of the electrode. The resulting signal (the so-called PEA – peak endocardial acceleration) is correlated mainly to the left ventricular dP/dt and reflects changes in overall contractile state. The clinical results are promising for a useful utilisation of this sensor to drive rate responsiveness in a physiological manner, and also for a convenient adjustment of AV delay[21,22]. New fields of utilisation are in the monitoring of contractile cardiac function.

Physiological AV delay

The adjustment of the AV delay according to the functional ventricular characteristics of the patient, and with different pacing rates, is fundamental for a physiological pacing modality. The contribution to the cardiac output of an optimal AV delay is between 13% and 40%. Consequently, both in patients with normal hearts and in patients with cardiac failure, optimising the AV delay is of great importance, and may improve function and long-term prognosis, as well as systolic and diastolic dysfunction[23,24]. On the other hand, empirical programming of the AV delay can result in a significant deterioration of functional class. In one study[15], empirically selected AV delay was compared to optimal AV delay as detected by its effects on cardiac output in 19 patients with a DDD pacemaker. Optimal AV delay pacing increased cardiac output from 7% to 32% ($p < 0.0001$) compared to empirical AV delay pacing. Very short AV delays are deleterious because they cause atrial contraction to occur after mitral valve closure, while over-long AV intervals can cause diastolic mitral regurgitation. Therefore, systems to evaluate cardiac function in paced

patients are fundamental in assessing an optimal setting of AV delay. Echocardiography can offer assessment of systolic and diastolic parameters as well as reliable cardiac output variations estimation, but future will necessitate having cardiac output estimation implemented in the pacer, to produce real "on-line" evaluation, with the possibility of changing the programming automatically during varying daily activities. A promising step in this direction is impedance cardiography, which is a reliable non-invasive method for cardiac output estimation which has been proposed for implementation in the pacing device[15]. Another novel system for AV delay optimisation currently under investigation is use of a recently developed sensor for rate responsiveness, i.e. the endocardial accelerometer. As mentioned above, the sensor offers estimation of left heart contractility which is used by the algorithm of the programmer to plot a curve with automatic variations in AV delay, by means of which optimal AV delay is calculated[22].

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Chapter 57

IMPROVED FOLLOW-UP PROCEDURE

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Introduction

Since the inception of implantable cardiac pacing, regular follow-up controls have been mandatory[1,2]. Goals and methods of pacemaker follow-up, however, have changed substantially over the past four decades. During the first era of cardiac pacing (1958–1974), implanted devices had no telemetry or programmable options[3]. There was nothing to adjust during follow-up sessions, only evaluation of the wound for comfort and freedom from infection, detection of eventual lead displacement, and identification of signs of (impending) failure of pacing system components[1,2], which was not simple using only external ECG recorders, oscilloscope and X-ray images.

By the end of the second era of cardiac pacing (1974–1990)[3], pacemaker programmability and telemetry of battery voltage, lead impedance, electrograms and marker annotations gained widespread use. With these tools implemented, pacemaker programmers allowed for a relatively easy evaluation of battery status, pacing system functionality and the nature of the observed malfunction. On the other hand the number of programmable parameters was growing. Programmed values could improve or compromise patient safety, haemodynamic and rhythmic benefit. The improved flexibility of pacing therapy was welcomed, but it created new difficulties for the follow-up physician. Evaluation of the appropriateness of the programmed values, elucidation of intermittent patient symptoms and resolving more subtle problems usually required that patients were subjected to a range of additional clinical tests and repeated 24-h Holter ECG recordings. Such procedures were intricate, time-consuming and expensive, and provided information on pacemaker performance only for a limited period of time.

Pacemakers of the third era (1990 onwards)[3] provide a broad range of diagnostic data on how pacemaker and patient interacted over time, which may reduce follow-up time by eliminating the need for clinical testing. Novel pacemaker algorithms are increasingly sophisticated, and have the potential to increase patient safety and therapeutic benefit automatically.

Novel and improved follow-up tools

A large array of follow-up tools have been devised and used in clinical practice. Some pacemaker models are accompanied by physician manuals containing hundreds of pages of explanation of device features, follow-up tools and diagnostic data collection options. As it is not possible to address all the existing tools in a limited publication of this type, we will focus on relatively new, interesting follow-up possibilities in the following four categories.

P.E. Vardas (ed.), Cardiac Arrhythmias, Pacing & Electrophysiology, 411–419.

Monitoring battery and leads

What was once the most difficult task of pacemaker follow-up – detection of impending battery depletion – is nowadays a very easy one, thanks to the availability of telemetered battery voltage and the elective replacement point notice on the programmer screen[1]. In newer devices details of the remaining battery life, in months, are also available on the screen, calculated from telemetered battery and lead impedances, programmed output values, and historical percentage paced data (counters) (Fig. 1). Many units display telemetered battery current drain (μA), lead current (mA), and pulse charge (μC), which are instrumental in evaluation of the influence of various factors on battery consumption rate[4].

Pacemakers may monitor lead impedance between follow-up sessions and provide a tabular or graphical report on the observed impedance variations and trends (Fig. 2). In some units the bipolar lead configuration may be automatically reprogrammed to unipolar if an out-of-range bipolar impedance value is detected, or other criteria are met[5]. Impedance trends are useful not only for assessment of lead functionality, but also in clinical studies of new high-impedance leads, reducing the need for follow-up visits[6].

Improvements in pacing threshold determination and output setting adjustment occurred in two areas. One direction was towards increased programmer assistance during follow-up controls. For example, some units allow the clinician to perform autothreshold measure-

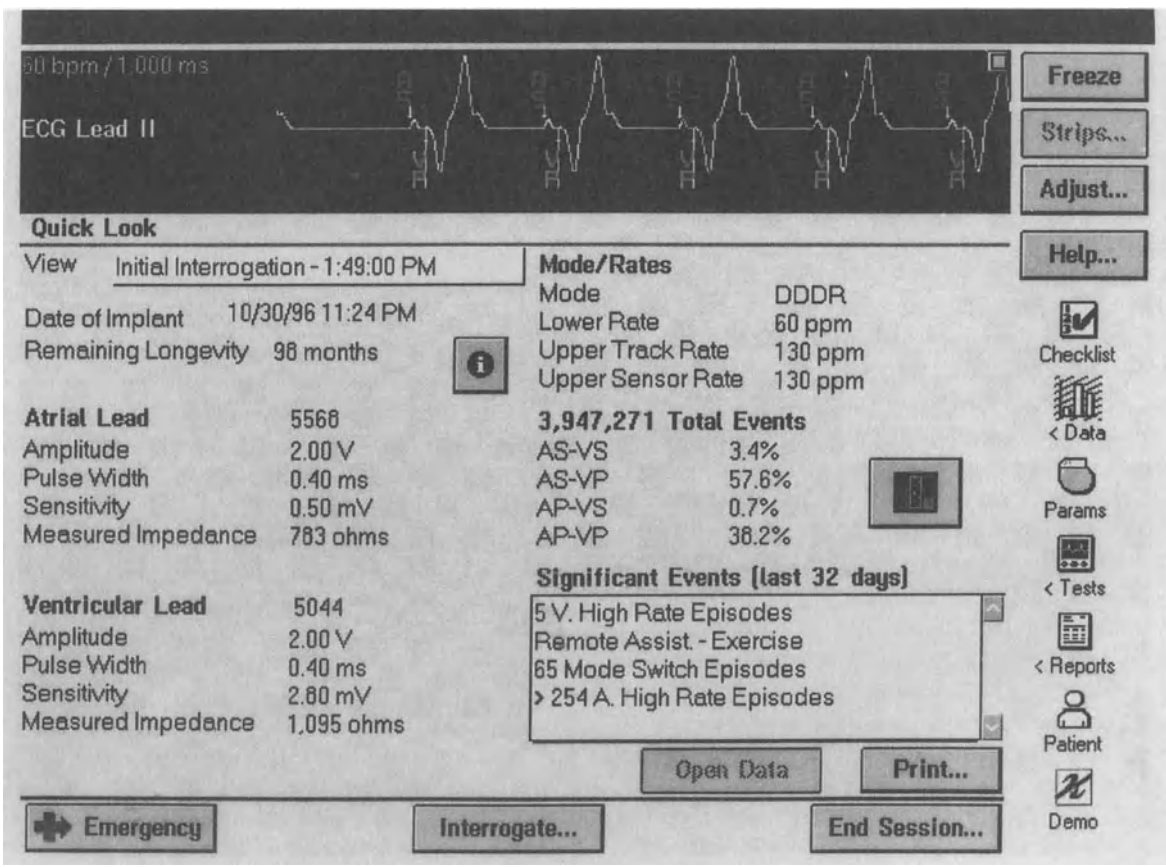

Figure 1. Modern devices provide, on the initial interrogation screen, a succinct report on the most important information concerning device performance (remaining battery longevity, major programmed values, lead impedances, AV association counters) and significant events that mostly involve arrhythmia episodes. This should give an instantaneous hint to the physician as to whether pacemaker and patient interacted properly. Further screens are available with detailed diagnostic data on a variety of subjects. V = ventricular, A = atrial, S = sense, P = pace.

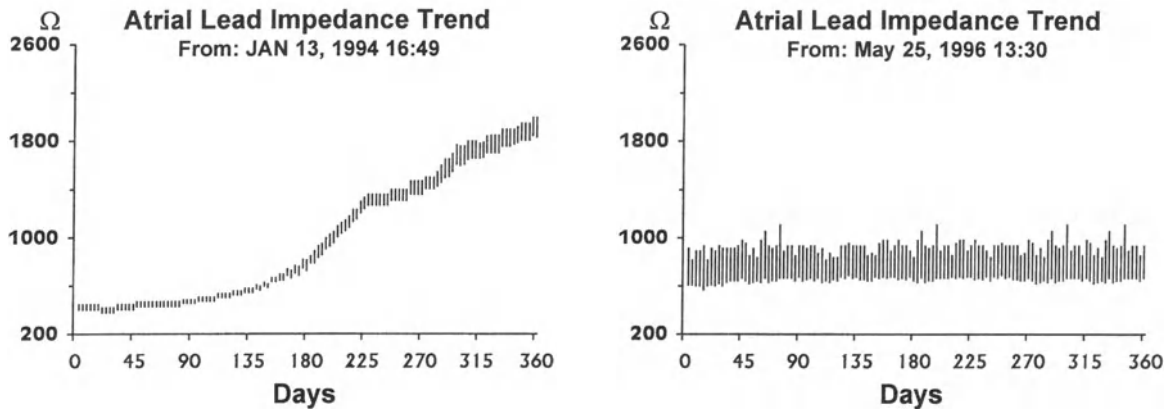

Figure 2. The left panel shows climbing lead impedance which probably indicates impending lead fracture. The right panel illustrates that large, consistent, up to 500-Ω daily impedance variations (bars) may be observed in leads with excellent long-term performance. In this case impedance variations are non-indicative.

ment at two different points, with graphical presentation of the strength-duration curve and output zones maintaining certain safety margins (2 : 1 or 3 : 1, etc.)[7]. An "optimal" output setting is suggested for the measured threshold value and selected safety margin. The other direction was continuous capture verification by the implanted units, by monitoring the evoked response, with output settings adjusted on the basis of periodic pacing threshold search, e.g. every 8–12 h (Fig. 3)[8]. Reliable performance of the AutoCapture has been obtained only in the ventricle, which is sufficient to improve patient safety and battery longevity.

Some pacemakers include a function that monitors the patient's intracardiac signal amplitude to provide the necessary adjustment of sensitivity values to compensate for potential fluctuations in intracardiac signals resulting from the patient's activity, medications, and other factors. This feature may reduce episodes of under/over-sensing, and the physician no longer needs to perform sensing threshold tests during follow-up visits. As with pacing thresholds, amplitude trends may be displayed[9].

Tailoring rate and haemodynamic profiles

Modern tools for evaluation of spontaneous heart rates and artificial sensor-indicated rates have been histograms and trends, suitable for long-term and short-term evaluation, respectively. Very detailed data of this type are available from the state-of-the-art pacemakers (Figs 4 and 5). In addition to increased diagnostic data storage, tailoring of rate profiles has been facilitated by increased programmer assistance during follow-up sessions, and through self-adjustment of rate-responsive parameters over time (Fig. 5). Earlier, only the slope was automatically reprogrammed between follow-up controls according to target specifications. Nowadays, pacemakers can perform multiple rate-responsive parameter self-adjustment based on comparison of actual rate histogram and desired rate histogram[10].

Paced atrioventricular (AV) delay is automatically shortened during exercise, but the resting AV delay must be selected by the physician[11,12]. Based on AV association counters (Fig. 1) and AV conduction histograms (Fig. 6), the AV delay can be better tailored to the individual patient.

By programming the sinus preference zone the frequency of P-wave tracking is increased, haemodynamic benefits improved, and battery energy conserved. Sinus preference diagnostic data nowadays include the total number of episodes detected, the percentage of time in sinus preference, the duration of the episodes, the sensor rate of the beginning of the episodes, etc.

Episode monitoring

Around 1990, episodes of high atrial and ventricular rates were indicated rather vaguely by counters of single premature contractions, runs of premature contractions, and rate histograms. In modern pacemakers a large number of episodes is documented with the exact time, date and duration of the episode; trend of atrial/

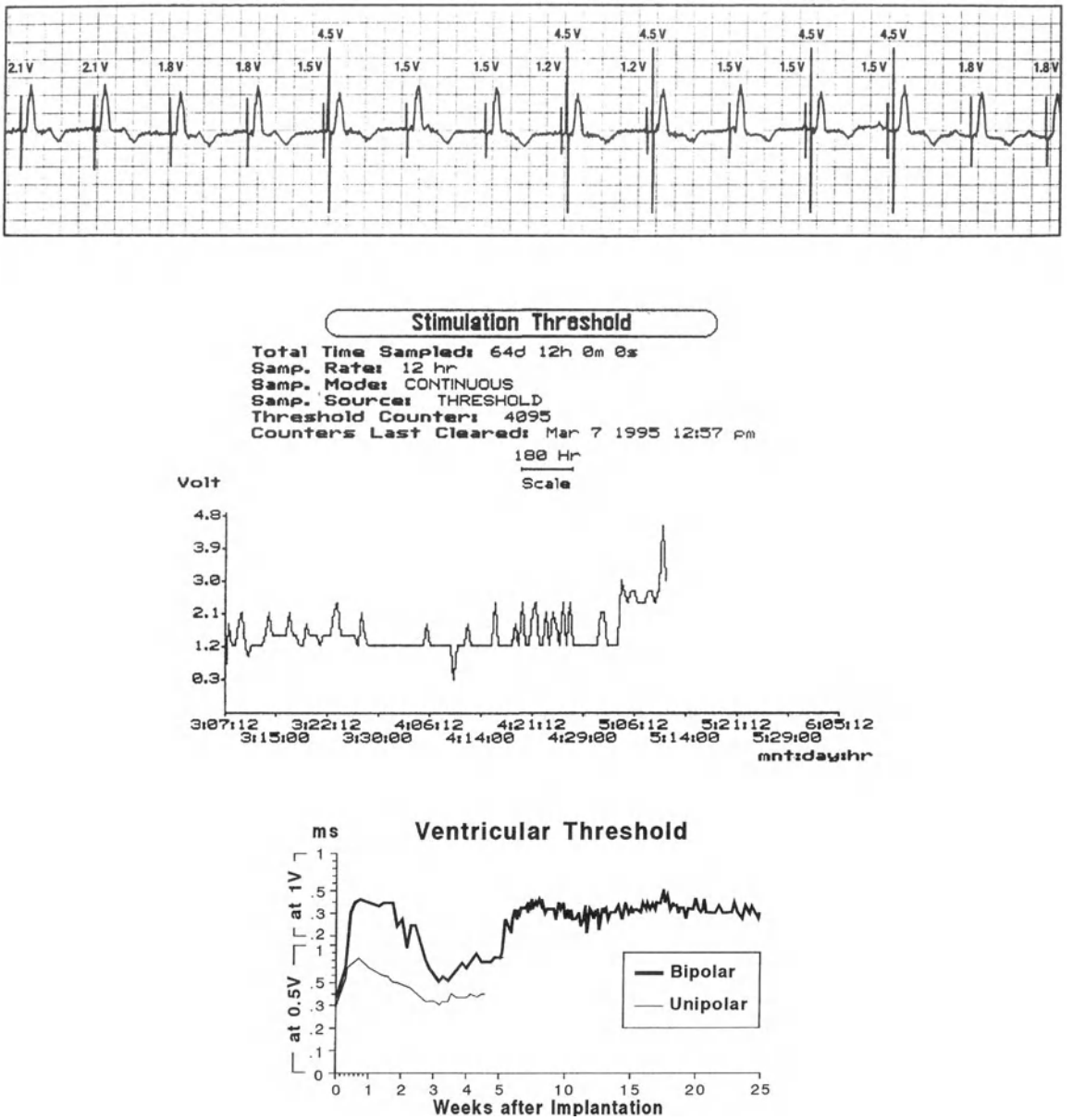

Figure 3. The upper panel demonstrates an automatic periodic search for pacing threshold in the ventricle by an implantable pacemaker incorporating AutoCapture feature, and the subsequent self-adjustment of pacing output at slightly above the threshold level. The middle panel displays long-term voltage threshold trend (at 0.31-ms pulse width) recorded by an implantable pacemaker incorporating AutoCapture function. The lower panel shows a high resolution pulse-width threshold trend recorded by an ordinary pacemaker (without AutoCapture function). Pacing threshold in this pacemaker was measured for scientific purposes by means of special additional algorithms down-loaded via telemetry links in the memory of the implanted pacemaker (see "Special follow-up" section).

ventricular rates or PP/RR intervals prior to, during, and after the episode (Fig. 7). These data help in evaluation of the incidence and extent of patient problems, and in tailoring pacemaker (mode-switching) and drug therapy[13,14]. They also have a good psychological effect, making the patient more relaxed and confident to the

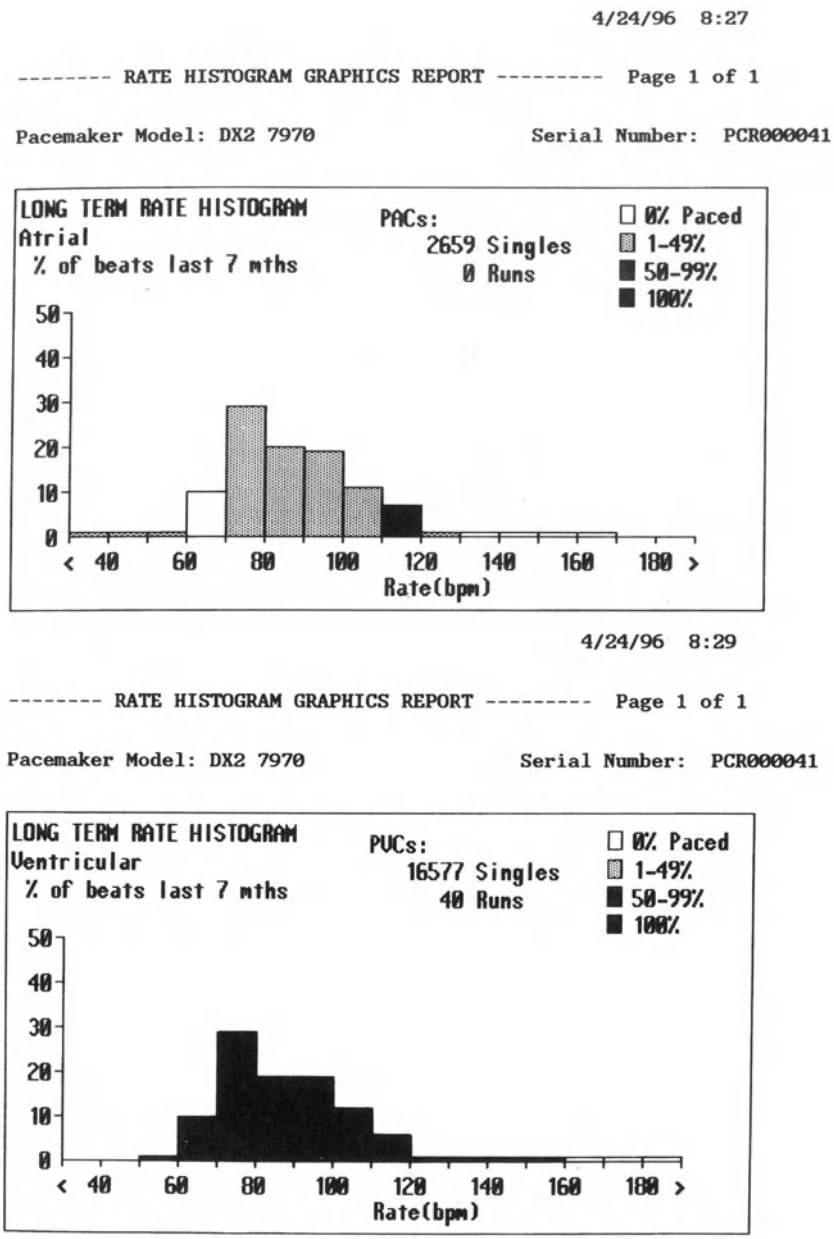

Figure 4. Detailed atrial (upper panel) and ventricular (lower panel) rate histogram with the indication of AV association.

physician, who can cite the exact time, dates and durations of each individual's problems and adjust the therapy according to the findings.

Recently, systems have been developed for increasing pacing rate, and hence cardiac output, initiated by a gradual drop in heart rate preceding neurocardiogenic syncope. Records on episode details and associated rate profiles are automatically collected[15].

A brief summary report on arrhythmia occurrence has become an integral part of the initial interrogation data screen (Fig. 1). Thanks to this, the clinician's attention can be shifted from the pacemaker and the lead to other

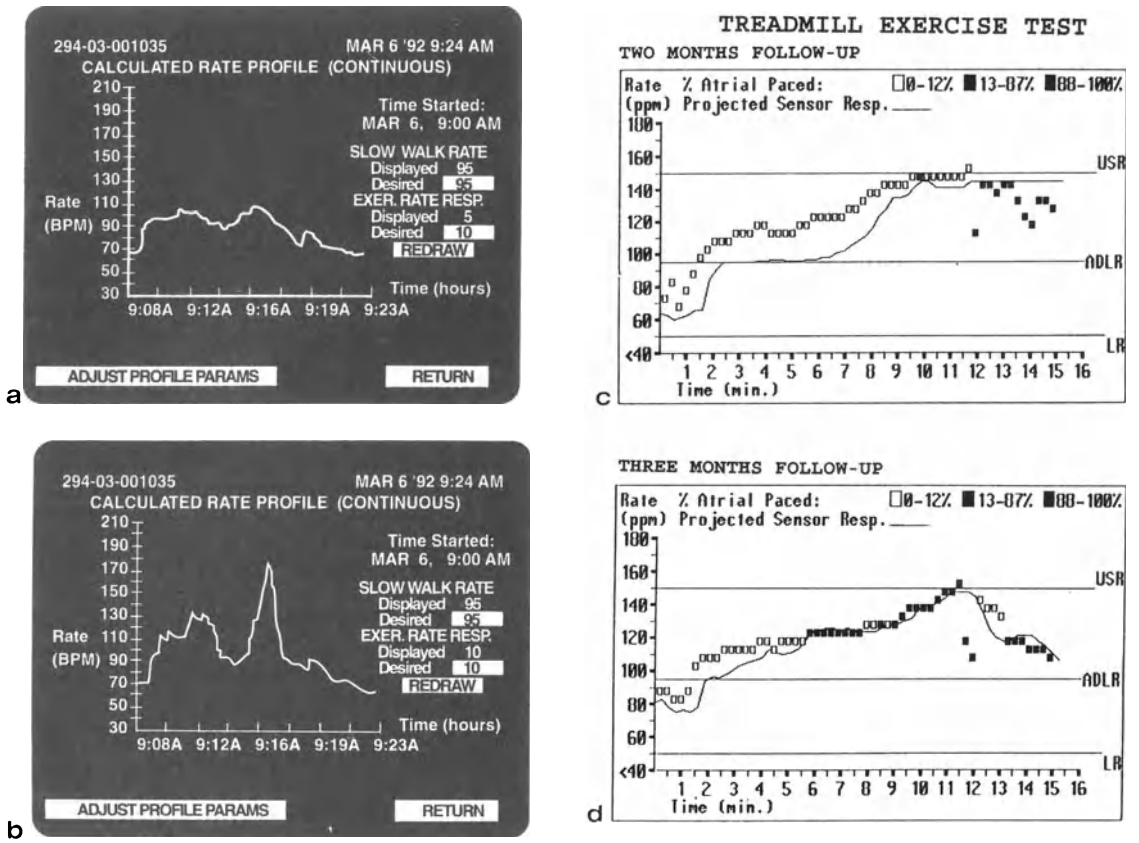

Figure 5. Sections **(a)** and **(b)**: redrawing rate profile option. Calculated rate profiles are designed to assist in optimising rate-responsive parameters through the redraw option. This allows the physician to graphically depict the effect of alternate rate-adaptive parameter setting without having the patient undergo additional exercise tests. Sections **(c)** and **(d)**: projected sensor response compared to sinus rhythm during an exercise test at 2- and 3-month follow-up points. During this period the sensor-indicated rate and paced rate are in good concordance. Black squares = paced beats, open squares = intrinsic rate, sensor rate is indicated by line. LR = lower rate, ADLR = activity of daily living rate, USR = upper sensor rate.

aspects of treatment which can further improve the patient's medical condition.

Special follow-up

Newly available patient-triggered event recorders may assist the physician in revealing the underlying cause of vague patient symptoms experienced outside hospital, such as fatigue, palpitations, pounding in the chest, "skipped beats", etc.[16]. In pacemakers incorporating this feature, atrial and ventricular electrogram, event recorder or/and detailed short-term heart rate trend run continuously. Upon the patient's application of a magnet or a remote assistant device over the pulse generator, a portion of these recordings immediately before and after the application (triggering) is stored in pacemaker memory for later retrieval and evaluation by the physician (Fig. 8).

Special algorithms that may be temporarily downloaded into the implanted pacemakers via telemetry links, and removed when no longer needed, have become feasible due to a substantial pacemaker memory (RAM) extension[3]. These algorithms allow for collection of additional information of scientific or clinical value which is not available in standard devices; for instance, automatic recording of pacing thresholds, additional information on arrhythmia episodes, etc.[17–19]. Down-loadable pacemaker algorithms and data collected by these algorithms can be conveniently distributed via Internet[20].

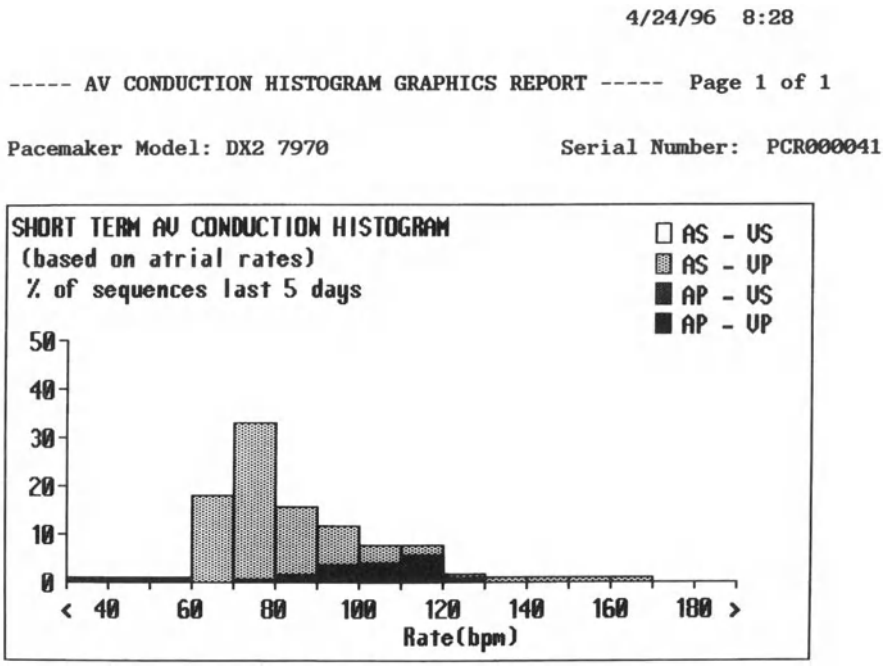

Figure 6. Example of an AV conduction histogram.

Ancillary pacemaker functions may include monitoring of physiological parameters such as cardiac contractility, oxygen saturation, right ventricular pressure, ejection fraction, etc.[21–26]. In the past, insufficient RAM memory did not allow for massive amounts of physiological data to be collected in pacemaker memory for physician evaluation. In the future, however, with more automated pacemaker performance, clinicians will probably focus more on physiological data and their implications than on pure follow-up of the devices.

Conclusion

With the majority of modern pulse generators the clinician still plays an active role in device programming for safe and optimal therapy and maximum longevity. This task has been greatly facilitated by diagnostic data accumulated between follow-up sessions, and by sophistication of pacemaker programmers that are nowadays of more assistance to the physician in making clinical decisions. Automation of lead-related and rate-responsive parameters is ongoing.

The amount of pacemaker diagnostic data that may be collected, and the complexity of automated pacemaker algorithms, are presently restricted by limitations in battery current drain. Increased microprocessor operating time and RAM size, associated with the extended diagnostics and automatic functions, may double or even triple battery current drain. Therefore, no commercially available device embraces all of the features mentioned in the foregoing. However, trends in circuitry technology progress in the past and present[3] imply that the options mentioned will almost all be incorporated in nearly every pacemaker, in only a few years. With more automated pacemaker functions, monitoring of the patient's physiological parameters by implanted devices will probably receive more attention.

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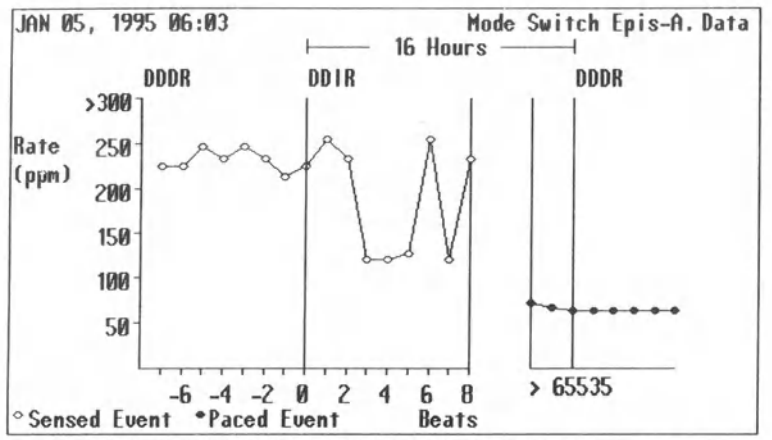

------- MODE SWITCH EPISODE SUMMARY TABLE REPORT -------- Page 1 of 2

Pacemaker Model: Thera DR 7940 Serial Number: PAF004005
Type: Mode Switch Epis-A. Collected: JAN 06, 1995 09:34
Method: Rolling Episodes Detected: 13
Mode: DDDR LR: 50 UTR: 120 Act RR: 6 Thresh: Medium

Epis	Date/Time	Duration (units)	A. Tachy Rate
1	JAN 05, 1995 06:03	16 Hours	>400 ppm
2	DEC 29, 1994 03:09	2 Minutes	>400 ppm
3	DEC 27, 1994 00:21	13 Hours	>400 ppm
4	DEC 17, 1994 05:54	62 Hours	>400 ppm
5	DEC 06, 1994 02:35	40 Hours	>400 ppm
6	NOV 22, 1994 22:58	5 Hours	>400 ppm
7	NOV 12, 1994 02:59	7 Hours	>400 ppm

Figure 7. *Upper part*: example of the atrial rate trend recorded at the onset and after termination of an atrial tachyarrhythmia lasting for 16 h. LR = lower rate, UTR = upper tracking rate, Act RR = activiting rate response, thresh = threshold. *Lower part*: summary report on mode-switching episodes during 2-month period (date/time and duration of each episode, maximum atrial rate during the episode). Additional detailed data on each episode are obtainable from pacemaker memory.

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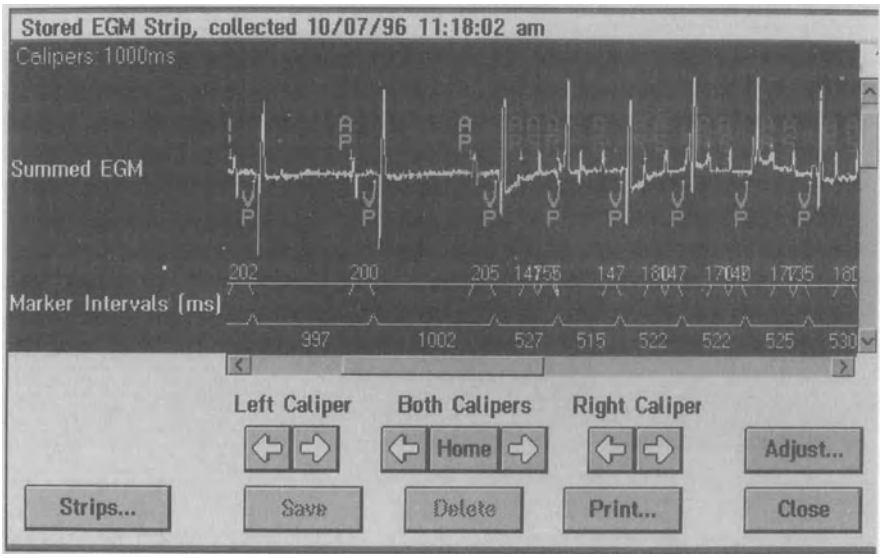

Figure 8. Patient-triggered event recording. The passage of summed (atrial + ventricular) electrogram (EGM) and marker intervals that are collected prior to patient activation are displayed in the figure, revealing that patient symptoms in this case were associated with the onset of an atrial tachyarrhythmia.

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Chapter 58

DEVELOPMENT OF A TRUE PACEMAKER HOLTER

S. Serge Barold, Gene Bornzin and Paul Levine

Introduction

A Holter recording is generally defined as the electrocardiographic registration of all cardiac cycles usually for a period of 24 h. Other monitoring methods cannot be considered true Holter recordings except for intracardiac electrographic (IEGM) data.

Time-based pacemaker event counters

Time-based counters that place each event in temporal relationship to the prior event require extensive memory capability. Each piece of data must have a time reference and cannot be dumped into a rate or pacing state bin.

Many pacemakers are designed to store information about output and sensing. In this way sequential events can be recorded in terms of atrial pacing (Ap or A) atrial sensing (As or P), ventricular pacing (Vp or V), ventricular sensing (Vs or R) or ventricular extrasystole (VE or PVE). The limitations of such marker chains are well known[1]. For example, a predominance of Ap-Vp or As-Vp combinations may indicate complete atrioventricular (AV) block and normal pacing, an AV delay too short to allow conduction through the AV node, while Vp may be a fusion or pseudofusion beat or there may be total loss of ventricular capture with intact AV conduction, a situation in which the conducted QRS is not sensed because it falls in the pacemaker ventricular refractory period. In the memory of the Pacesetter Trilogy DR+ pacemaker (Pacesetter, Sylmar) each symbolic representation (AV, AR, PV, PR, PVE) requires one byte of storage for the event and for the cardiac interval or rate. In this system sampling every 26 s provides 59.2 h of memory, sampling every 1.6 s gives 3.7 h and sampling every event yields approximately 2.3 h of memory[2].

Do we need a true pacemaker holter?

Although marker chains are useful, the IEGM in certain clinical circumstances provides critical information that cannot be adequately obtained in any other way. In contrast to implanted cardioverter/defibrillators (ICD) clinical experience with this diagnostic modality in pacemakers is so far limited, and the duration of IECG recordings remains very short. Clinicians need to tell pacemaker manufacturers what duration of IEGM recording is realistically useful, and how best to use it by means of programmability in various clinical situations.

Microprocessor memory

Microprocessor-based pacemakers store information in bits or units of basic information. Bits can have values of either 1 or 0. Bits are stored and accessed in electronic memory in convenient "packets of eight bits"

P.E. Vardas (ed.), Cardiac Arrhythmias, Pacing & Electrophysiology, 421–426.

called bytes. Bytes can be used to store numbers or encoded symbols. When information is read or stored in electronic memory it is done byte-by-byte. Memory is measured in units called Kilobytes (K). One K = 1024 bytes.

Each byte of data is stored at a specific address. The computer writes the data to a given address, and when it wants that information it goes to that address and reads the information. This type of memory, called random access memory or RAM, allows fast, direct and specific reading of and writing to addresses. RAM can be lost if the voltage of the power source drops below a critical value. (Read-only memory or ROM cannot be lost by a drop in the voltage supply from the power source.) Data stored in the RAM addresses include IEGM, control information for programmable functions (pacing mode, rate, AV delay, etc.), event records (including patient-triggered events), histograms, other diagnostic information (such as automatic mode-switching data), patient data, etc.

Sampling

Sampling rate for IEGM recording is based on the Nyquist criteria, which state that, in order to register all the information in a signal, one must sample the signal at ×2 the maximal frequency component[3] (Fig. 1). The latter can be established by doing Fourier analysis for power spectral estimation. Actually for clinical purposes only recognition of the waveform is needed. During ventricular tachycardia and fibrillation, containing a lot of high-frequency data, sampling at 256 samples/s is good practice because it allows good reproduction of the rapid signal transitions and narrow inflections. Each sample requires one byte of memory (Fig. 1). Sampling at 256 samples/s or half this value is convenient because it is related to the frequency of the crystal oscillator that regulates the timing functions of devices. The number 256 is obtained by using a circuit that divides down the 32 kHz crystal oscillator by a factor of 2^N where $N = 7$ ($2^7 = 256$). Some ICD sample at 190 samples/s. In pacemakers a sampling rate of 128 samples/s provides a readily recognisable signal and can be used to yield longer data storage. A lower sampling is not advisable.

Let us consider an ICD with 128K memory totally dedicated to IEGM storage.

1 sample = 1 byte
128K × 1024 bytes/K = 131 072 bytes
With sampling 256 bytes/s
(131 072 bytes)/256 bytes/s = 512 s = 8.5 min.

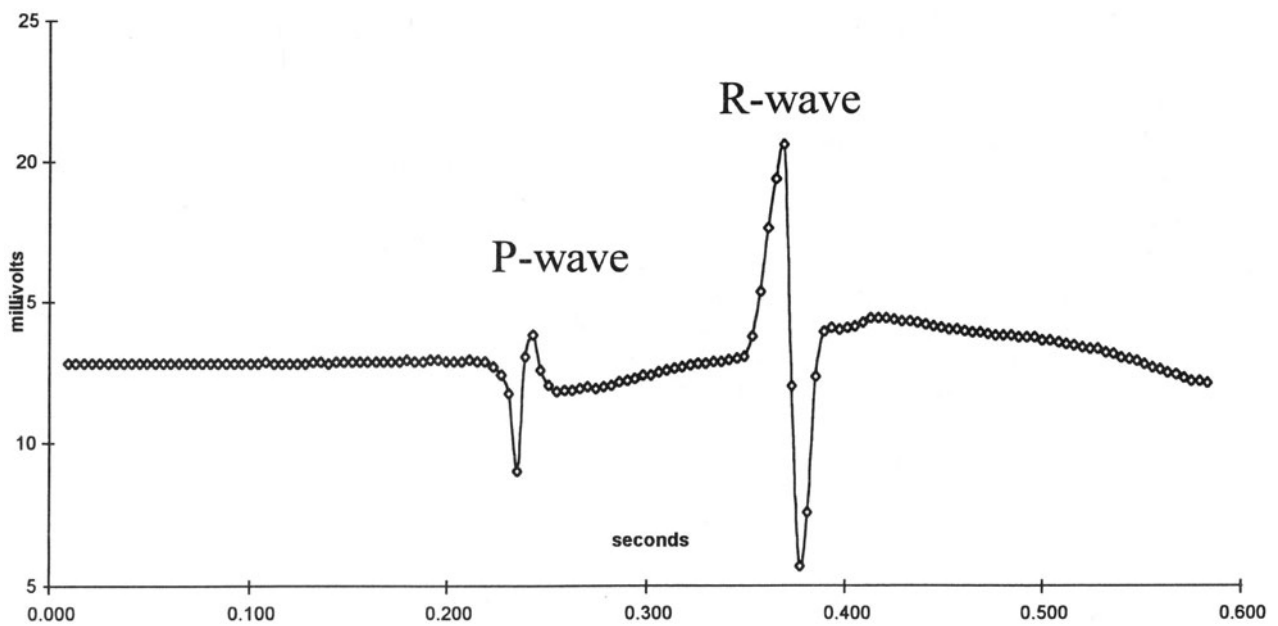

Figure 1. Digitised IEGM A-tip to V-tip captured with the Pacesetter Affinity dual chamber pacemaker implanted in a dog. The IEGM was immediately stored in the RAM of the pacemaker. Each dot or sample corresponds with one byte of data storage. Each byte is stored at a specific memory address for retrieval at a later time. In this situation the samples were stored at a rate of 256 bytes/s.

IEGM recording would therefore take 8.5 min to fill the RAM memory. The Pacesetter Affinity pacemaker (to be released soon) has been designed with an 8K memory for IEGM recording.

8K × 1024 bytes/K = 8192 bytes
With sampling 128 bytes/s, the continuous recording of IEGM is equal to 64 s.

Redundancy and compression algorithms

Redundancy is present in the IEGM signal in the form of repeated sequences such as the baseline. One can take advantage of redundancy in the signal to increase the amount of IEGM that can be stored in a given amount of memory. With one form of compression the actual diagnostic changing waveform is unaltered, but a persistent baseline can be represented as a duration of zero rather than wasting many samples, each storing identical data. In other words, a counter keeps track of how many data samples fall on a line with the same slope (V/s) so that less memory can be expended to store this type of data (Fig. 2). Thus, by eliminating unnecessary redundancy, longer durations of IEGM can be stored in a given fixed memory range.

By encoding the signal with compression the amount of memory required to store a given section of IEGM can be reduced by 2–10-fold. Recovery of the signal is achieved by running the signal through a decompression program that "reinflates" the signal to its original form. Compression algorithms are very useful because they effectively multiply memory availability without actually increasing the chip size and without increasing power requirements for larger memories.

In the previous example a 64-s IEGM recording capability without compression is expanded to 320 s with 5 : 1 average compression. Compression algorithms as a rule do not "compress" the diagnostic waveform (such as QRS). Because compression does not occur evenly for the entire IEGM signal, the compression ratio only describes an average value for the entire cycle. The duration of IEGM recording in a given RAM memory specified by a manufacturer is only an arbitrary value because the degree of compression is affected by the nature of the recorded signals. Consequently a signal with substantial zero baseline (such as marked sinus bradycardia) that undergoes substantial compression will provide an actual IEGM recording longer than the specified value by the manufacturer.

Requirements for 24-h recording of IEGM

This can be calculated as follows:

24 h/day × 60 min/h × 60 s/min = 86 400 s/day
128 samples/s × 1 byte/sample × 86 400 s/day = 11 million bytes/day.

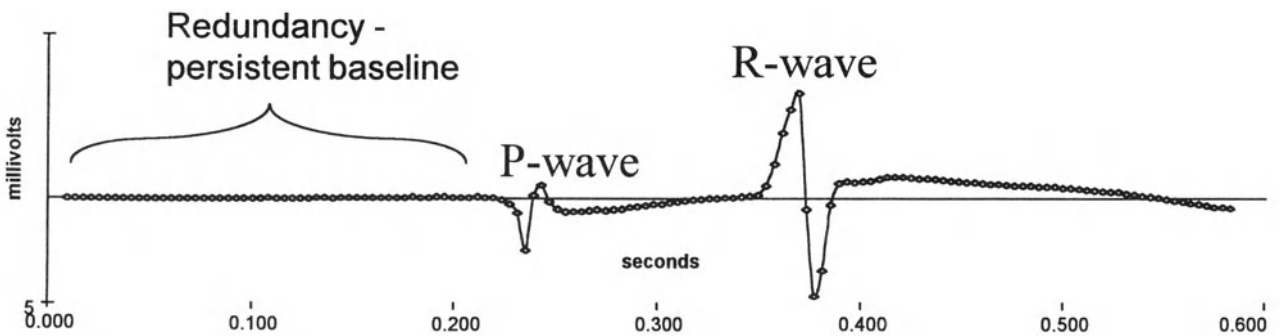

Figure 2. Redundancy and compression of IEGM sampled at 256 samples/s. Each sample is stored in memory as one byte of data. Thus the data can be stored at 256 bytes per second. However, a substantial portion of the IEGM signal displays repeated values near the zero baseline (redundancy). Signals with a relatively large amount of redundancy can be stored in much less memory. In this example the first 0.2 s could be stored as 50 bytes by sampling at 256 bytes/s. However, a simple algorithm may be used to detect the persistence of baseline values. The algorithm simply stores a marker byte (reflecting a given value). The marker byte is then followed by a count byte that indicates the number of repeated baseline values. Using this approach, 50 bytes of persistent baseline can be replaced by only two bytes: a marker byte that indicates the fixed value of a series of repeated baseline values and a count byte indicating the number of repeated values. This process allows storage of longer IEGM durations in relatively less memory.

Using a 3 : 1 compression ratio this yields 3.6 million bytes of RAM or 3516K. Even at a 10 : 1 data compression ratio over 800K of RAM would be required to store a 24-h IEGM.

Memory capacity for IEGM recordings: pacemakers versus defibrillators

Defibrillators use lithium silver vanadium oxide (LSVO) batteries that provide a voltage of 3.2 V (Fig. 3). This voltage is sustained throughout the life of the ICD and the voltage drops below 2.7 V only at the very end of its useful life. LSVO batteries are suited to ICD because they have a low internal impedance that permits the battery to deliver a large current (in terms of amperes). This large current goes to a circuit for recharging the high-voltage output capacitor to hundreds of volts. The current flow must be high because recharge must take place in seconds. In contrast the resistance of the electrolyte in a lithium-iodine cell used in pacemakers increases during its life from a few hundred to a few thousand ohms. This limits its application to uses that do not require very high bursts of current as in a defibrillator. Pacemakers require only tens of microamperes to operate, so that the low current supplied by lithium batteries is ideally suited for pacing.

Tests on present commercial RAM show that a minimum of about 2.7 V is required to retain memory. In commercial devices (computers, instruments, etc.) there is no problem achieving voltages of 2.7 V or more. Manufacturers do not make low-voltage RAM because there is little demand. A low-voltage 128K RAM chip will probably be soon commercially released, and it is likely to find its way into pacemakers before the end of the century. Defibrillators can utilise commercially available 128K static RAM chips because the LSVO battery provides 3.2 V. Such RAM is very reliable, and manufactured in large quantities by companies expert in this area. Hitachi is one manufacturer. In pacemakers the voltage provided by the lithium-iodine battery starts off at 2.8 V, but long before the recommended replacement time the voltage drops below 2.7 V (Fig. 3). (At replacement time the voltage is usually 2.4 V, and 2.2 V at end of life.) Consequently, the voltage characteristics of the lithium battery influence the type of RAM that can be used in pacemakers. RAM chips in pacemakers must generally be custom-made to function at < 2.7 V.

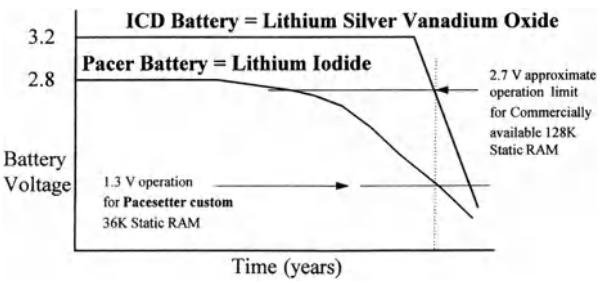

Figure 3. Diagrammatic representation of voltage characteristics of ICD and pacemaker batteries (see text for details).

The question arises as to whether a pacemaker could be designed to function with a presently commercially available 128K chip using existing technology. We believe it is possible, but manufacturers have been dissuaded because of a number of disadvantages that include: (1) use of a voltage doubler with the lithium-iodine power source provides an inefficient arrangement; (2) large size of the 128K chip; (3) increased current consumption requiring larger batteries and pacemaker size. For memory retention a 28K static RAM requires 0.5 μA (about 3% of the lifetime current budget) while a 128K static RAM in an ICD consumes about 10% of the current budget in the new smaller defibrillators. These drawbacks can be overcome by using larger batteries, but it is worth it? Pacemaker manufacturers need to be convinced of the relative value of increased memory to decide on these trade-offs.

Interpretation of stored IEGM

It seems likely that present and future devices will record only one channel of IEGM data. A right ventricular IEGM does not usually register diagnostic atrial activity. Pacesetter has designed cross-channel IEGM recordings to overcome this problem. In effect this provides a compound electrogram in a single channel (Atip-Vtip, Atip-Vring, Aring-Vtip, Aring-Vring, etc.) that displays near-field information from both the atrium and the ventricle (Fig. 4A, B). Such a system eliminates the need to store atrial and ventricular IEGM independently. In ICD the superior vena cava electrode can be used to form a similar compound electrogram.

The diagnostic value of IEGM recordings would be enhanced by the simultaneous display of appropriate markers, a function that does not consume much memory. During atrial pacing the demonstration of successful atrial capture in the stored IEGM is feasible by utilising low-polarisation leads and high-performance digital circuitry for recording the evoked response[4].

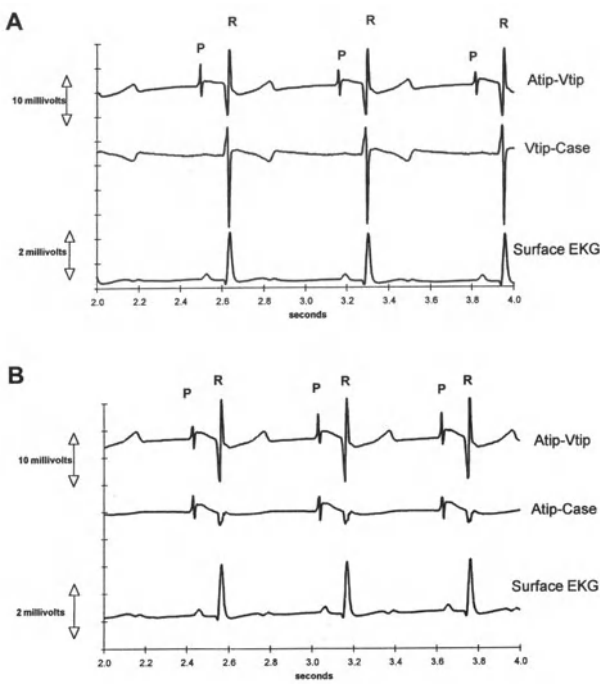

Figure 4. A: Advantages of cross-channel IEGM recordings. The uppermost tracing is the cross-channel IEGM. The sensing configuration was programmed Atip-Vtip resulting in a compound IEGM with near-field representation from both chambers with clear P and QRS delineation. The cross-channel IEGM displays atrial events much more clearly than the surface ECG. Note that atrial events are not clearly discernible in the unipolar ventricular IEGM (Vtip-Case) in the middle tracing. **B:** Advantages of cross-channel IEGM recordings. The cross-channel tracing (Atip-Vtip) is on top and is similar to that in **A.** The middle tracing shows the unipolar atrial IEGM (Atip-Case). Note that the cross-channel electrogram depicts ventricular activity better than the unipolar atrial IEGM.

Storage modes

The IEGM memory can be filled using two different methods.

1. Freeze the first events that fill the memory. The memory is filled once for a given recording set-up. The first events will be stored and they will not be written over by subsequent events. Once the memory is read it may be cleared for future event recording.
2. Store the most recent events (rolling or continual looping with writing over). This memory is a form of continuous data storage. Since memory can be written over indefinitely, the pacer can be set up to fill the *n*K of IEGM memory in a loop so that new events overwrite old ones automatically. This method gives access to only the most recent events; older events are lost because they are written over. For instance if automatic mode switching is used to trigger a recording of the atrial rhythm that activated this particular function, the atrial IEGM must be continuously recorded in a looping memory[5]. In such a looping memory scheme, about 7–15 s of IEGM could be continuously stored and then written over. When an event triggers recording, the memory is frozen so that the last 7–15 s of IEGM leading up to the triggering event are available for subsequent review.

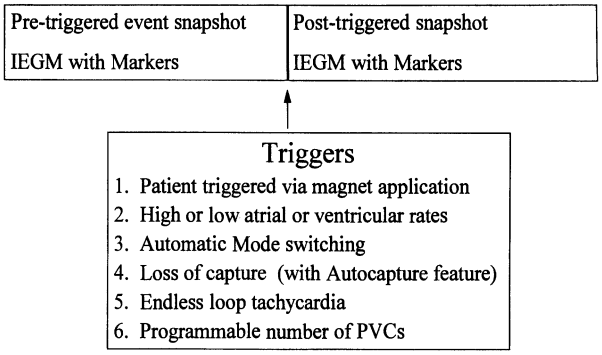

Figure 5. Triggers for snapshot IEGM recordings. IEGM storage before and after a specific trigger provides important diagnostic data. Pre-trigger allows storage of events leading to trigger. PVC = premature ventricular contraction (see test for details).

There are several other potential triggers (Fig. 5). The patient could trigger an IEGM snapshot recording with magnet application. The physician could program the device to trigger IEGM recording at high or low rates, with loss of capture (with autocapture programmed on), endless loop tachycardia, etc. Such IEGM snapshots record events leading up to the trigger, as well as events after the trigger.

Telemetric transmission of IEGM data

Transmission of IEGM to the programmer must be achieved accurately and quickly. Transmission of a few seconds or snapshots of IEGM do not take long. In fact, new higher-speed telemetry that transmits 8 Kilobits per second will be available in the next generation of Pacesetter pacemakers (Affinity). Down-loading four

12-s snapshots of uncompressed IEGM or symbolic event recordings that sample every event for at least 2 h will require only about 12 s of telemetry time to download. However, there would be little clinical interest in down-loading many hours of IEGM data from many megabytes of memory if the transmission time were in terms of hours. The need for even higher-speed transmission of data is obvious. Transmission of data is associated with many engineering trade-offs. The transmission of data to the programmer requires more current than the continuous retention current used to keep the data in the stand-by mode within the device memory. Furthermore, the higher the telemetry transmission speed, the greater the current drain. If the data transmission rate is made too high, the process could impose a heavy load on the pacemaker battery by requiring huge surges of current with a resultant marked drop of battery voltage and interference of pacemaker function. Thus there is a trade-off between data transmission rate and the amount of current that the battery can supply.

Programmable memory capability: exchangeable software

Despite the spectacular advances in pacemaker technology, microprocessor-based devices still contain limited RAM capacity. A substantial portion of the RAM is dedicated to functions other than IEGM recording. Because RAM is flexible, certain functions can be removed via standard telemetry to create space for the introduction of new temporary algorithms into the RAM, such as additional IEGM storage[6–9]. In this way the IEGM memory capability can be enhanced temporarily until the original algorithms are returned by telemetry[10–12]. The design of programmable memory functions is very complex and therefore more likely to cause problems than fixed memory systems in devices equipped with more (non-programmable) RAM dedicated to a particular function. Future pacemakers with extensive RAM capability will make programmability of memory obsolete for the enhancement of a particular function.

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Chapter 59

Electromagnetic Interference in Current Implantable Devices

Werner Irnich

Introduction

Since the beginning of synchronised pacing there must have been the problem of irritation of the sensing mechanism by electromagnetic interference (EMI). That it was not detected earlier than 1968[1] may be explained in several ways:

1. The number of patients with atrial synchronised ventricular pacemakers (VAT) was very limited during that decade (1961–1969). If at all, interference of that type caused the pacemaker to speed up its rate up to 120 ppm, which was probably not noticed by every wearer.
2. Though the very first demand pacemaker of the inhibited type (VVI) was very sensitive, and without any interference-detecting and protecting means[2], the few (mostly elderly and sick) patients were seldom exposed to EMI, except to a few sources in their domestic environment, with which they learned to live.
3. The number of EMI sources was far fewer than today; the devices were also less powerful.

It is surprising that the first demand pacemaker, which had no interference protection (like today's implantable cardioverter/defibrillators – ICD), was produced from 1966 onwards for over 5 years, although the first reports on false synchronisation and on total inhibition appeared as early as 1968[1].

The reported examples were considered episodic ("very rare") by pacemaker manufacturers, and clinically insignificant by physicians. If a pacemaker patient experienced dizziness during usage of an electric toothbrush or an electric razor the solution was simple: return to conventional non-electric means. Nobody at that time would have asked for better protection of pacemakers against EMI by improved circuitry or by shielding.

The situation has largely changed since then. Mobile EMI sources such as mobile telephones, stationary sources such as electronic identification systems (electronic article surveillance EAS, personel access systems, electronic write-off systems, weapon detectors) are everyday items. As the numbers of pacemaker and defibrillator wearers have increased dramatically, the judgement "very rare" or "clinically not relevant" must be looked at critically. So far there is no juridical verdict as to which party in this game of EMI interaction is responsible for impairment of the patient: the field producer or the producer of insufficiently protected implants. Figure 1 demonstrates the problem graphically. There is an overlapping area between fields produced and susceptible implants. Increasing the resistance to EMI, or decreasing the fields, would reduce or disarm the problem of interference.

If one asks how the problem of interference is handled today, one can outline insufficiencies in brochures from manufacturers and hospitals:

P.E. Vardas (ed.), Cardiac Arrhythmias, Pacing & Electrophysiology, 427–436.

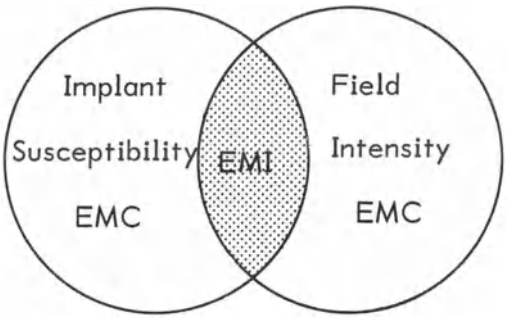


Figure 1. Electromagnetic interference EMI occurs where field intensity surpasses the implant's interference threshold. Electromagnetic compatibility is possible in two ways: either to reduce susceptibility or to reduce field intensity.

1. Avoid places with potentially hazardous electromagnetic fields! How can patients identify such fields and how can they judge the potential reaction?
2. Ask your physician for advice! Which physician is meant, and what advice can he or she give?
3. Reduce EMI fields if possible! Who knows to what extent this must be done?

The request to reduce pacemaker susceptibility to EMI by engineering solutions has not been made in the past. It is our intention, in this chapter, to give an overview of the current situation with respect to EMI sources and EMI susceptibility of implants, and to advise, where possible, as to how critical situations could be avoided or mitigated.

Clinical relevance

Implanting physicians often state that the problem of interference is one more of intellectual than of clinical relevance. This may be true, though safety considerations are always a matter of intellectuality based on rare cases, or on imagining case possibilities. Our daily life is determined by rules derived from imaginary risks. This includes the possibility that safety measures are exaggerated, but who would seriously claim that safety measures in aviation, in shipping, in motor cars or in bridge construction (the list could be prolonged indefinitely) should be reduced under risk/benefit considerations.

The situation in EMI and implants is very similar: should one wait until the first victim has to be complained? This more statistical view, of how often something has to occur before gaining relevance, has one deciding disadvantage, as it claims that rare cases must be tolerated by the pacemaker community. Nobody, no association, no society has yet determined.

1. How many lethal cases due to EMI are allowed?
2. What degree of impairment must be tolerated by the pacemaker patient?
3. How often and how long are prolonged pauses due to EMI tolerable in pacemaker-dependent patients?

The first question mainly addresses the situation of non-dependent pacemaker patients which exists if the pacemaker switches over to a non-synchronising interference rate, which is called by manufacturers the "safety rate". If the lethality were 1 in 100 million non-synchronised pulses, would this be of clinical relevance?

There is a recent tendency to change the safety philosophy from case or statistic orientation towards intellectual considerations. The best proof of this is discussion of the EMI capability of mobile telephones and pacemakers. Though there is no report of a realistic interference situation (case) so far, all investigations are based on provocation tests; the "clinical relevance" is no longer the foundation on which advice is given to pacemaker patients and to the public. We appreciate this change in safety philosophy, but claim that other interference situations, such as electronic article surveillance (EAS) gates, AM radio transmitters, or magnetic fields in daily life are looked at similarly. However, we strongly claim that elevated consciousness of EMI should not be realised to the debit of the patient, in that prohibitory signs constrict that patient's daily life to a degree that clinical relevance is reached and surpassed. Is it tolerable that pacemaker patients are excluded from certain medical procedures which could be life-saving, such as high-frequency surgery, magnetic resonance imaging, lithotripsy or therapeutic radiation? All new technologies, which have decisively changed and improved pacemaker therapy, have left the problem of EMI as it was in the beginning. On the other hand, why should implant producers develop and explore new methods of interference detection and protection, if

physicians declare the problem to be clinically irrelevant. This attitude of the implanting and care-taking physician is probably the greatest obstacle on the way to increased compatibility.

The mobile telephone problem

It is really surprising that the following questions are asked in connection with mobile telephone application:

1. Are they influencing pacemakers?
2. Do they really impair patients?
3. What is the safety distance, to avoid every influence?
4. What advice should be given, and to whom (implanting physician, patient, public)?

During the last three meetings of the North American Society of Pacing and Electrophysiology (NASPE) there were in total 15 posters or presentations, and *PACE* in 1996 devoted one issue to this topic, with two editorials and six original papers[3].

If one considers the different physical characteristics of the different mobile telephone nets, as listed in Table 1, it is understandable that a generalisation of the problems which mobile telephones could cause is undue. The carrier frequencies of the three German mobile phone nets are: 450 MHz for the C-net, 900 MHz for the D-net, and 1800 MHz for the E-net. Information is coded by frequency modulation in the C-net, but digitally coded in the D- and E-nets. Transmission is continuous for the C-net, but pulsed in the D- and E-nets. Transmission power for hand-held phones (there are also portables with higher power in C- and D-nets) is variable according to the distance to the nearest base station, and may have a maximum up to 2 W in the C- and D-nets, and 1 W in the E-net. The so-called "demodulation product", while mostly the source of interference, is virtually the envelope of the transmission signal. There are few pulses with an average frequency of 0.5 Hz in the C-net, while D- and E-nets may have a mixture of 2, 8, and 217 Hz under special conditions.

Table 1. Characterisation of the German mobile telephone nets

	C-net	D-net	E-net
Carrier frequency (MHz)	450	900	1.800
Information coding	FM	Digital	Digital
Transmission	CW	PW	PW
Maximum power (W)			
Hand-held phones	2	2	1
Portable	15	8	–
Frequency of demodulation product (Hz)	0.5	2*/8*/217	2*/8*/217

*In DTX mode = user is silent or during call organisation.

Table 2. Results in abridged version

Interference	C-net	D-net	E-net
Influence possible	Yes	Yes	No
Impairment possible	No	Yes	No
Manufacturers with unaffected models	3	6	20
Models affected	71 (30.7%)	79 (34.2%)	–

Our *in-vitro* investigations with 217 pacemaker models from 20 manufacturers were published elsewhere[4]; the main results are collated in Table 2:

1. Using the C-net 2 W output power, 30.7% of all models were influenced, yielding up to five prolonged pulse periods during call organisation. We deem this sort of interference as being no impairment for its wearer. Three out of 20 brands were resistant; an indication that sufficient protection is possible.
2. Using the D-net 2 W output power 34.2% of all models were influenced, yielding either false inhibition or atrial rate tracking (over-sensing) or false stimulation (under-sensing). Six brands were resistant in all models, 11 brands were resistant in the majority of models.
3. Using the E-net no interference was seen.

If the results are broken down (see Table 3), and the numbers of models are converted to the estimated number of living patients wearing this model, a possibly realistic figure is gained, showing that about 27% of all D-net patients could be influenced by our provocation test. Line 6 of Table 3 shows further that slightly more "old" pacemaker models (32.5%) are affected, as compared to the "new" ones (35.1%); however, the number of patients concerned is lower for the "old" models.

Is the D-net really impairing a pacemaker patient with a non-resistant pacemaker? Table 4 answers this question separately for pacemaker-dependent and non-dependent patients. As the demodulation product is different for different call modes one can identify

Table 3. Breakdown of interference samples: patient numbers were estimated using the implantation numbers for every model as registered by the German Pace-makers Registry

Tested pacemakers	All (n = 231)		1–6 years* (n = 83)		7–12 years* (n = 148)	
Corrected patient numbers†	111.811		55.877		55.934	
	Pacemakers (%)	Patients (%)	Pacemakers (%)	Patients (%)	Pacemakers (%)	Patients (%)
(1) By C-phones alone	10.4	7.0	8.4	8.8	11.5	5.2
(2) By D-phones alone	15.2	15.4	14.5	16.7	13.5	14.1
(3) By C+D-phones	20.4	11.6	18.1	12.6	21.6	10.6
(4) Sum (1) + (3)	30.7	18.6	26.5	21.5	33.1	15.5
(5) Sum (2) + (3)	34.2	27.0	32.5	29.3	35.1	24.8

* Of function time estimated.
† Of living patients with these models estimated.

Table 4. Effects of GSM telephones (D-net) on pacemaker patients if close enough to the pacemaker (breast pocket)

	Mobile telephone-dependent	Non-dependent
Call organisation, 3 s	False inhibition	Inhibition
Ringing	Stimulation	False stimulation†
Speaking*	Stimulation	False stimulation†
Silent phase*	False inhibition	Inhibition
Dialling*	False inhibition	Inhibition

* Distance normally too large for interference.
† Asynchronous stimulation with the (rare) possibility of fibrillating the heart.

possible effects on the pacemaker and its wearer. Pacemaker-dependent patients can be influenced negatively only in the phase of call organisation lasting 3 s. The non-dependent patient may experience false stimulation (under-sensing) when speaking. Is this situation dangerous? The answer to this question is of great importance from the viewpoint that all other interference situations would and should also be affected by this new philosophy:

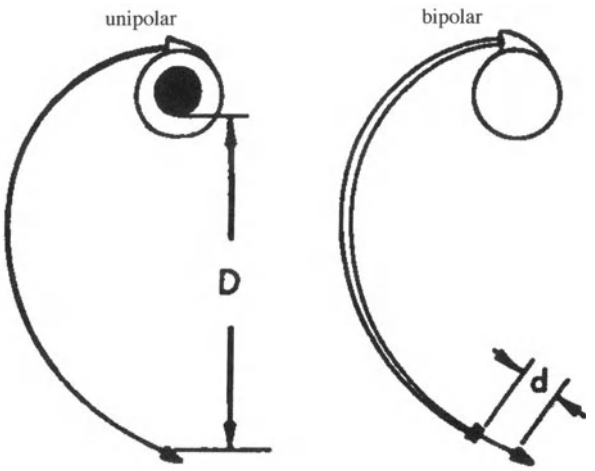
One result should be noted: there is no advantage in bipolar over unipolar pacemakers in mobile telephone interference.

To conclude this chapter on mobile telephone interference we can summarise for the D-net:

1. Twenty-seven per cent of all pacemaker patients can be influenced if the mobile telephone is brought in closest vicinity combined with maximum output.
2. During the 3 s call organisation before ringing false inhibition can occur in pacemaker-dependent patients with a mobile telephone in the breast pocket. Is this still tolerable?
3. Impairment of pacemaker-dependent patients is further possible, if the patient leaves the mobile phone after start of ringing or puts a mobile telephone into his or her breast pocket, just over the pacemaker, during the silent phase of the call. (Why should he or she do so?)
4. Impairment of non-dependent patients is possible only when speaking due to unsynchronised stimulation with "safety rate". However, the distance between antenna and pacemaker in this case is larger than 10 cm and, therefore, no longer influencing.

Coupling of interference

Interference to pacemakers may be coupled into the lead system either galvanically, or electrically by external electric fields, or magnetically by magnetic fields[5]. In all cases the lead configuration in the frequency range up to 10 MHz is of paramount importance. One can estimate that the voltage across different and indifferent electrodes is proportional to distance, so that the bipolar configuration offers an interference rejection ratio over unipolar



Interference rejection ratio:

$$\frac{\text{bipolar}}{\text{unipolar}} \cong \frac{D}{d}$$

Figure 2. Lead configuration and interference: In the frequency range up to 10 MHz, bipolar leads offer an interference rejection whose value is equal to the ratio of distances D:d.

(see Fig. 2), which is approximately the ratio of the respective distances, or assuming 15 cm distance for unipolar, 1.5 cm for bipolar, the rejection ratio is 10. An ICD system with 0.3 mV sensitivity will experience the same interference as a 3 mV unipolar ventricular pacemaker.

For magnetic fields the loop area formed by the electrode is important, as the voltage induced is proportional to it. In this respect a right pectoral implantation site is much better than a left-sided one (see Fig. 3). The rejection ratio of right over left site is about 4 to 5.

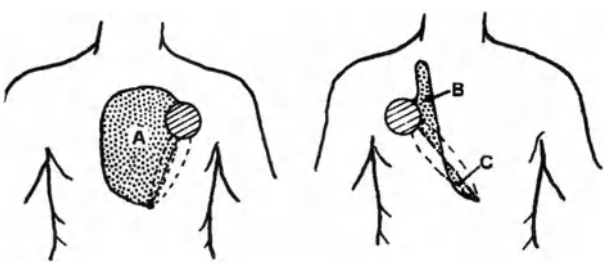


Figure 3. Pacemaker site and magnetically effective area: right side implantation reduces interference by a factor of 4 to 5 (i.e. area A is approximately four or five times greater than area B–C).

Interference sources

Pacemakers react sensitively to all types of amplitude-modulated fields. This is the reason that frequency-modulated (FM) transmitters for radio or television do not cause interference. Bossert has shown[6] that, under unfavourable circumstances, a powerful long-wave transmitter may interfere with a sensitive pacemaker at distances up to 600 m, with medium-wave transmitters up to 1500 m, and with short-wave transmitters up to 10 000 m. Such a worst-case scenario is the result of combining the most powerful transmitter, together with its directional antenna, with the most sensitive pacemaker. The minimum electrical field necessary for interference is about 10 V/m.

Less powerful, but sometimes also amplitude-modulated, are electronic article surveillance (EAS) systems. Their frequency range covers all frequencies between some hundreds of Hertz and 13 MHz. There are so many different systems that one should be cautious in interpreting the results. Whereas Dodinot et al[7] found interference, others did not. In any case, if the gate is passed at normal walking velocity a single signal of sinusoidal shape is created which could, if strong enough, simulate a single heart beat. Such an effect is not unusual in a pacemaker patient's daily life, as was found by 24 h ECG monitoring by Bethge and colleagues[8]. In the rare situation in which patients are forced to stop in or just outside the gate, the EAS system may produce under-sensing or over-sensing, as happened in 1992 in Hamburg, a case which aroused much public interest.

One other source may exist in the future, when induction ovens are present in some private kitchens. They are nowadays found only in professional kitchens. The electrical energy is transferred to the ferromagnetic bottom of a pot or pan by magnetic fields at around 25 kHz. Under certain, not so realistic, conditions the fields are so large in the environment that sensitive pacemakers could be influenced. We can confirm that, at least in Germany, manufacturers of these ovens try to avoid the problem by suitable technical measures.

The most common source of interference is, in our opinion, still the 50/60 Hz magnetic fields produced by household appliances: for instance a microwave oven, electric tin-opener, hand drill, electric pad, and so on. In industry, magnetic field producers such as degaussian coils or plates, annealing furnaces, or electric steel furnaces must be mentioned.

A very special case arises if electrosurgery is carried out in combination with a pacemaker that is older but

below elective replacement indication (ERI). The strong HF field reaching the input, and creating a voltage of more than 4 V, can permanently switch off the pacemaker. The electronic circuitry is thus brought to a low-ohmic intermediate state during HF application. After cessation of interference the battery voltage is not sufficiently high, due to voltage drop across the battery resistance, to move the circuit out of this intermediate stage. Older pacemakers with battery resistance ≥ 10 kΩ can be affected. In a few cases application of a magnet has restored normal operation.

EMI sensitivity of pacemakers

To guess at which field of which frequency can influence a pacemaker, it is necessary to measure the influencing voltage of a sufficiently large population, to ensure one has not overlooked the most sensitive element. Very typically the cumulative interference distribution is always an S-shaped curve, which indicates the broad range of reaction covering normally one, and sometimes more than two, decades between the most sensitive and most resistive pacemaker. Figures 4–8 demonstrate our findings in the range between a static magnetic field[9] and 130 kHz[10]. Without going into detail there is always a big difference between continuous and pulsed interference, which is sometimes ten times more sensitive for pulsed than for continuous waves. It is also interesting to note that a not-yet-harmonised CENELEC standard requires minimum reaction thresholds, below which pacemakers must remain uninfluenced. These are already met by the majority of pacemakers today. One can similarly state that between 40% and 50% fulfil requirements which are posed by standards for the general public. This provokes the question of why a specific interference standard for pacemakers with limiting values below those for the general public is necessary or desirable.

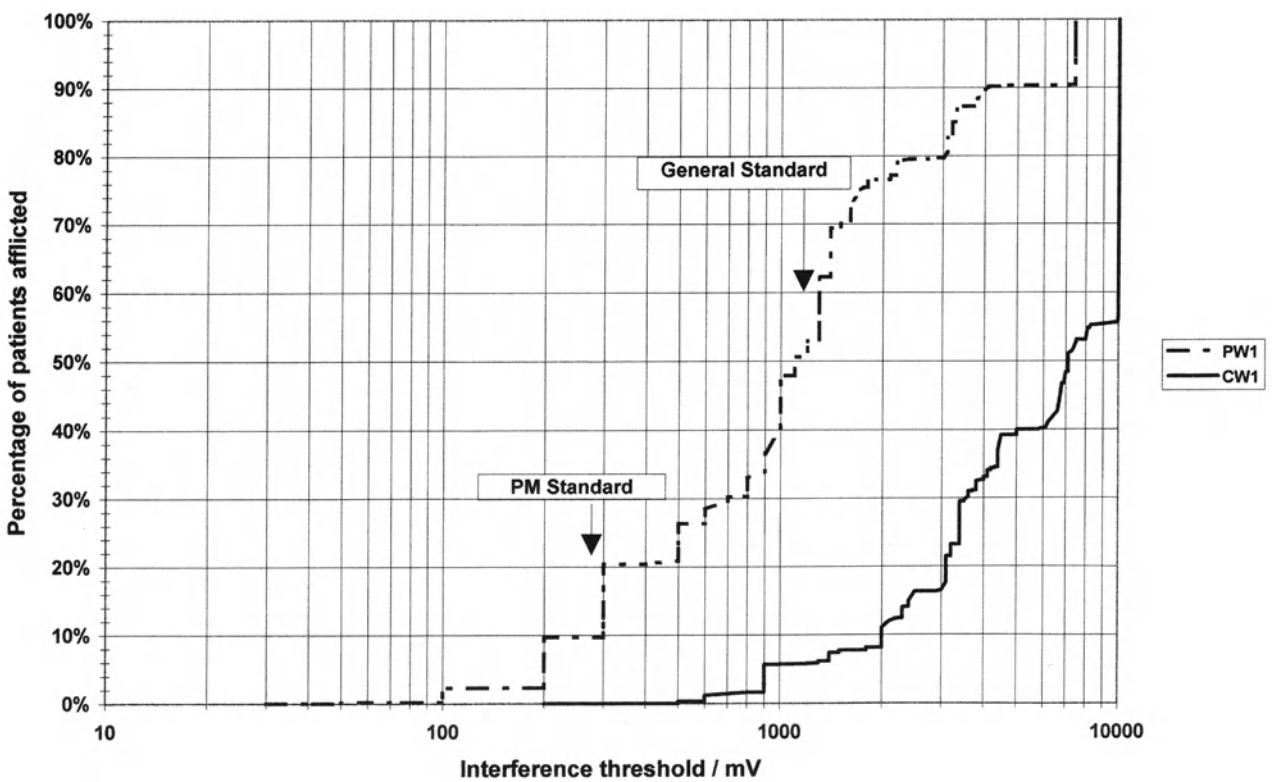


Figure 4. Cumulative distribution of interference sensitivity (130 kHz, pulsed (PW1) according to EN 50 061/A1). Arrows characterise: *left*: sensitivity due to EN 50 061/A1, *middle*: highest level for normal population calculated with 250 cm² electrode area (CW1 = continuous).

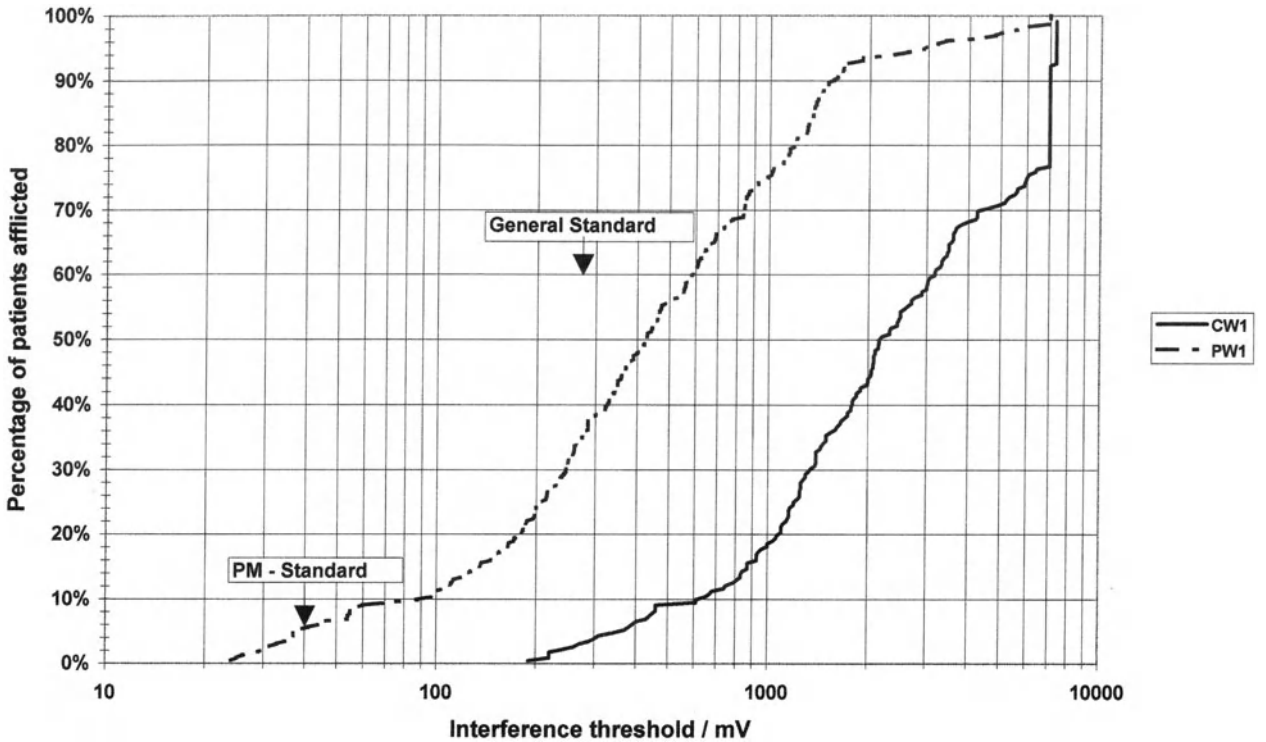


Figure 5. Cumulative distribution of interference sensitivity (25 kHz, pulsed (PW1) and continuous, CW1).

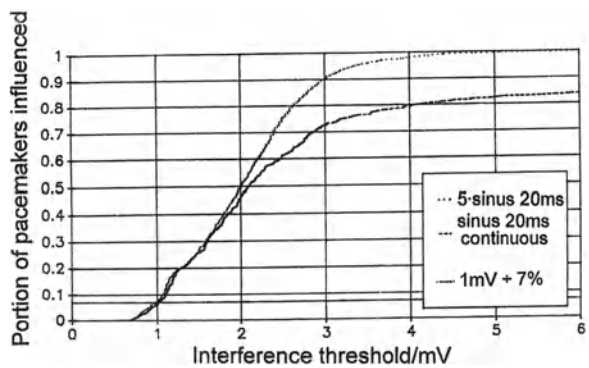


Figure 6. Cumulative distribution of interference sensitivity (50 Hz, pulsed and continuous (lower curve); n = 1000).

Why are pacemakers so different in EMI sensitivity? This question has never been answered by professionals. We believe that it is more or less unintentional. In any case, if all devices below the CENELEC value were withdrawn from the market, no loss in quality would occur, or, expressed differently, the high EMI sensitivity is not counterbalanced by high pacing quality.

ICD and EMI

In general, ICD possess bipolar sensing leads so that they are less prone to EMI. However, as the sensitivity is very high (0.3 mV or less), and as the distance between different and indifferent can be large (the mid-point of the coil electrode is relevant), useless shocks due to EMI cannot be excluded. Episodes of such shocks, called "anectodal" by manufacturers[11], are:

1. operating an electrical radial arm saw[11];
2. operating a large orbital electric sander[11];
3. operating a 70 MHz remote control mechanism of a model ship[12];
4. playing slot machines[13];
5. standing close to an EAS detection gate[14];
6. exposed to ≥ 0.25 mT (semi-bipolar) or ≥ 1.6 mT (bipolar)[15].

ICD have so far proved resistant against mobile telephones.

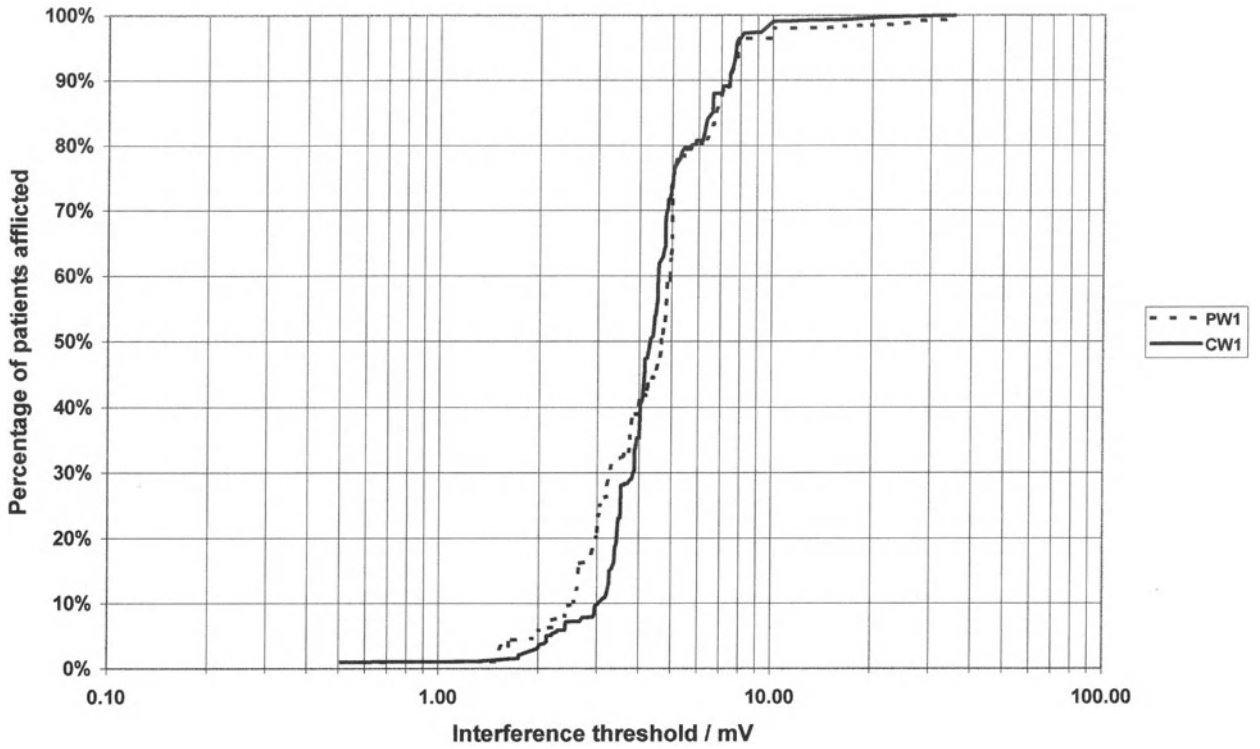


Figure 7. Cumulative distribution of interference sensitivity (16 2/3 Hz pulsed, PW1, CW1 = continuous).

Standardisation of interference behaviour of implants

Obviously, each party engaged in the field of electromagnetic interference expects that the other side should be active in avoiding interference. While pacemaker manufacturers are of the opinion that field producers have a duty to reduce their fields to harmless amplitudes or, if not possible, would warn pacemaker wearers, field producers correctly think that this would be impossible as long as implant manufacturers do not disclose their sensitivity characteristics. This conflict can be overcome only by standardisation. Since 1984 a CEN/CENELEC Working Group on Active Implants has tried to find a solution to the problem, which yielded a CENELEC standard EN 50 061/A1, which was accepted in 1992. At that time the Foreword contained the date 1 March 1998, at which time the standard should come into force. Moreover, the standard has not yet been harmonised according to the EU rules, which makes it rather ineffective, as it is not a prerequisite for CE certification. Meanwhile there is a draft of another vertical standard within the horizontal standard for active implantable medical devices (AIMD). When this draft (which is nearly identical with the above-mentioned and already accepted standards) will become official cannot be guessued at, but, on the basis of our own experience in such standardisation committees, we estimate that validity and harmonisation will not occur in this century.

If we repeat our proposal that the pacemakers of tomorrow should have an interference behaviour which is equal to that of the top 50% of today's pacemakers, one can develop a borderline below which no pacemaker should be influenced, and above which no field producer should be active (without warning). This borderline characteristics for the CENELEC test signals are depicted in Fig. 9. Especially at or below 130 kHz (frequencies for identification systems) the approximation function based on 50% sensitivities would solve practically all existing problems. The two circles in Fig. 1 would no longer overlap, and an EMI problem would no longer exist. Pacemaker standard values are surprisingly low, and there is no reason why they should

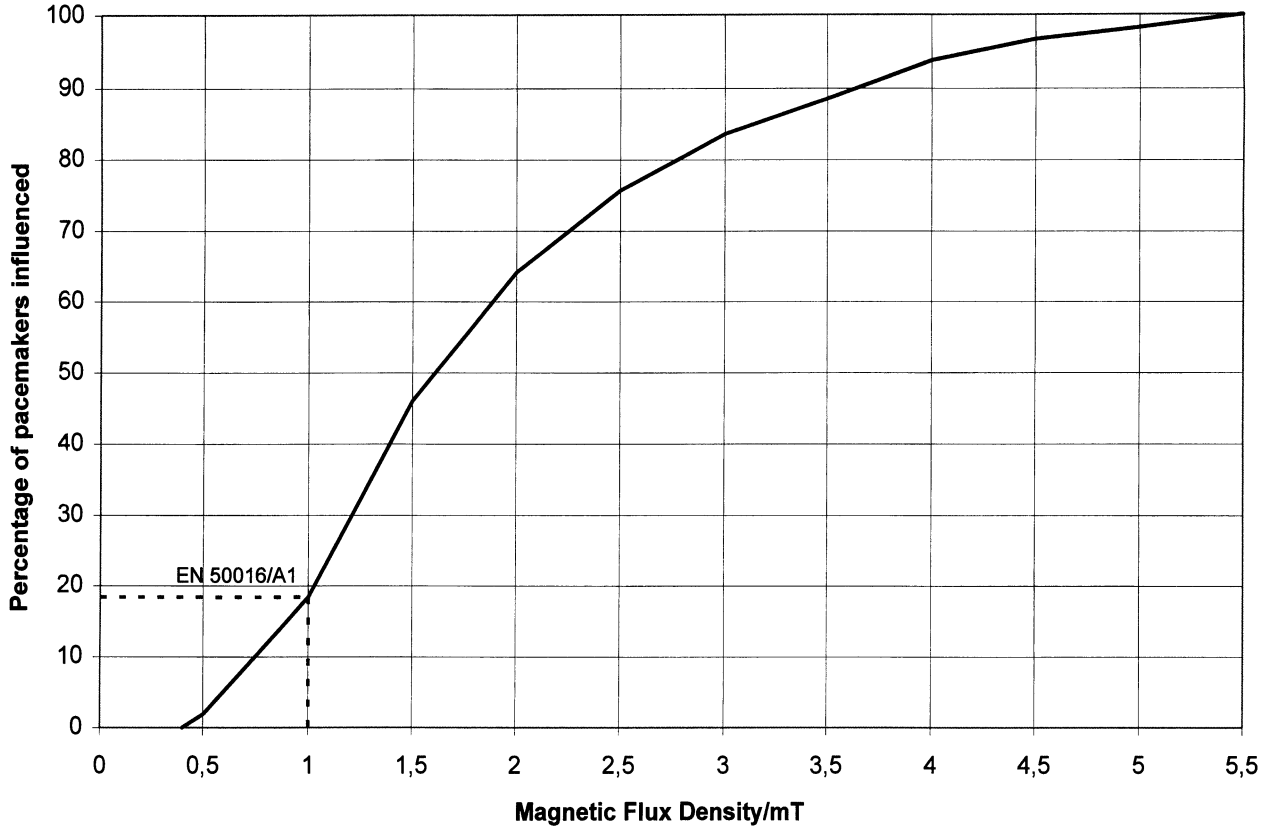


Figure 8. Cumulative distribution of interference sensitivity for static magnetic fields. The standard EN 50 061/A1 demands 1 mT or more. It is general practice in magnetic resonance imaging to warn pacemaker patients at 0.5 mT (5 Gauss), though about 3% of pacemakers react between 0.3 and 0.5 mT.

remain so low. The dotted line in Fig. 9 characterises a pacemaker sensitivity to interference which would be activated in fields normally not allowed to the public.

Conclusions

Except for mobile telephone interference nearly all other forms of interference, described above, are almost nonexistent in bipolar pacemakers. In view of the other disadvantages of bipolar leads, one is led to demand that pacemakers should be improved in such a way that unipolar units would remain a suitable alternative. For today's implantable systems we can state:

1. Even if rare, a problem of EMI exists, reaching from static magnetic fields (activation of reed switch) up to the highest frequencies of mobile telephones.
2. It is unrealistic to expect that field producers would respect the minority of implants susceptible to EMI.
3. Susceptibility of implants to EMI would be eliminated if the technology of the top 50% of pacemakers were mandatory for all.
4. As long as mandatory standards do not exist, EMC can be improved only, if physicians demand it. Why not ask for a mobile telephone compatible pacemaker?

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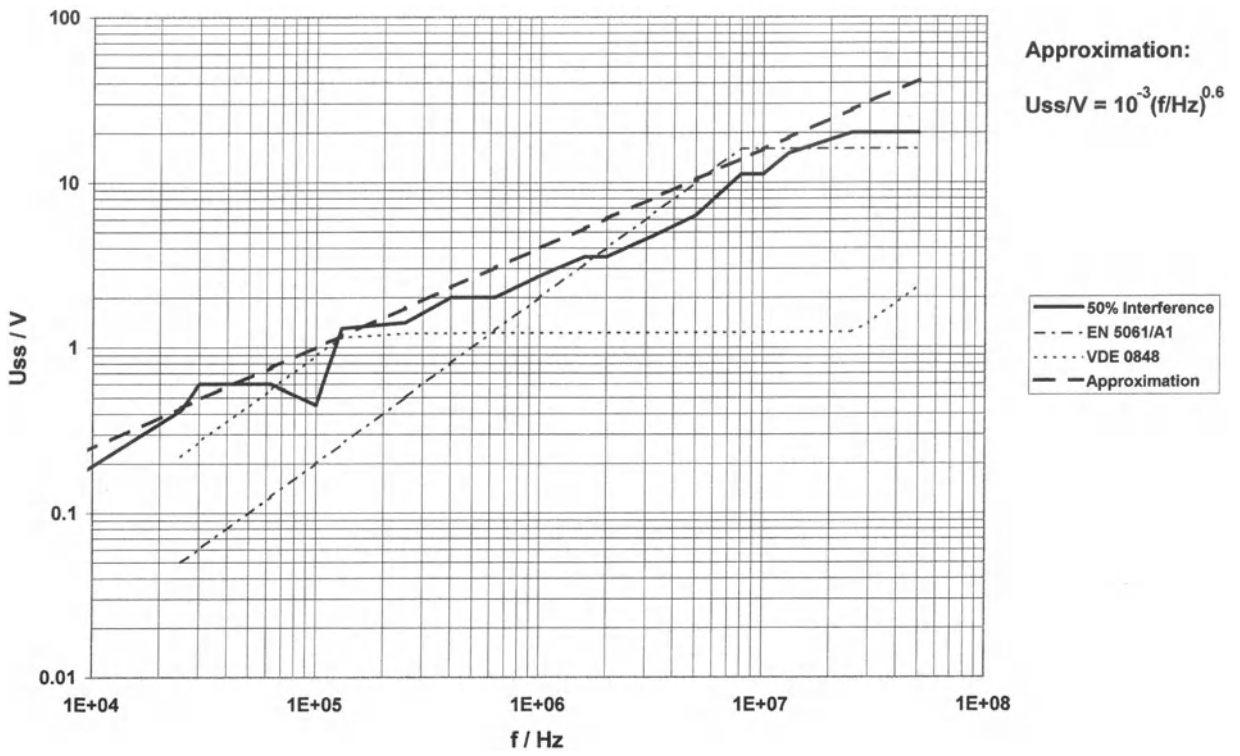

Figure 9. Fifty per cent interference sensitivity as a function of frequency (bold line). The dotted lines represent: (a) the pacemaker standard EN 50 061/A1; (b) VDE 0848 which is very close to IRPA and ANSI standards for the normal population. The sensitivity of approximately 50% of all today's pacemakers lies above the standard line for the normal population. A simple-to-remember approximation for the 50% sensitivity is: $U_{ss}/V = 10^{-3}$ (f/Hz)$^{0.6}$. The 50% values are taken from our own measurements, or from a study carried out by CETECOM[16].

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Chapter 60

Potential Impact of Pacing in the Treatment of Dilated Cardiomyopathy

Richard Sutton

Introduction

The time has come to talk of many things: of shoes – and ships – and sealing wax – of cabbages – and kings – and why the sea is boiling hot – and whether pigs have wings[1] and of heart failure for pacemaker physicians! This field has developed in parallel to that of pacing and, in general, there has been little overlap because the heart failure complicating the course of pacemaker patients often responds to the correctly chosen pacing mode. If it occurs later it can frequently be attributed to the onset of atrial fibrillation and is treated along conventional lines. Regrettably, the heart failure that pacemaker physicians may cause by retrograde atrioventricular conduction from ventricular stimulation[2] or, simply, by stimulating at the right ventricular apex[3,4] has all too commonly not received proper attention. It is necessary now to approach heart failure due to dilated cardiomyopathy of any aetiology with a fresh mind, to address the questions of whether some of these patients can be helped by pacing; if so which are they, what pacing system is best, how should benefit be assessed and if there is improvement, is it extension of a better quality of life or is it prolongation of life itself?

The first publication in the field is recognised as that by Hochleitner et al in 1990[5], where she and her colleagues drew attention to an apparent prognostic benefit of dual-chamber pacing with an atrioventricular delay of 100 ms in 16 patients who were either awaiting cardiac transplantation or who were deemed unsuitable for it on grounds of age or complicating diseases. Hochleitner et al were unable to account for the improvement then, or in their later publication in 1992[6], but they did notice that patients who were bradycardiac before pacing tended to increase their heart rates when pacing in VDD mode, and those who were tachycardiac tended to slow their rates. Some of the patients had conduction tissue disease and there was a possible benefit of pacing in this regard. This work triggered considerable interest around the world, but in 1997 it is fair to state that the role of pacing is still not understood, and its possible value is certainly not accepted by heart failure physicians.

The available evidence concerning pacing

The initial work of Hochleitner et al[5,6] was followed by carefully structured attempts in several centres to identify which patients stood to benefit from pacing. All were small series, selecting patients on slightly different criteria; very few were controlled and no consistent pattern emerged. Kataoka[7] reported one patient who experienced quite dramatic improvement with dual-chamber pacing. Brecker et al, in their publications of 1992[8] and 1996[9], using atrioventricular intervals of around 70 ms, gave logical arguments for the reasons why benefit may

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occur, and encouraging preliminary results, although longer-term follow-up has been less persuasive (P. Kelly, personal communication, 1997). These data await publication. Both Auricchio et al[10], in 1993, and Nishimura and co-workers[11], in 1995, found similarly that the most important aspect of pacing was the imposed reduction in atrioventricular interval, with only a subset of the latter group's patients gaining benefit when presenting with long PR intervals and pacing shortening them to between 100 and 120 ms. In contrast, Linde and her group[12] in 1995, as well as Gold et al[13], in the same year, (the latter in a controlled study), showed no significant improvement during medium-term follow-up. Furthermore, the work of Innes et al in 1994[14], examining acute haemodynamic data in a randomised controlled format, found no benefit of 100 or 60 ms atrioventricular intervals using the VDD mode of pacing in 12 patients, for whom pacing was not indicated on conventional grounds, despite the desired increase in left ventricular filling times.

In summary, these reports are of heterogeneous patients in that, for some, pacing was conventionally indicated and, for others, it was not; moreover, the assessment criteria were diverse, and probably too many were only acute in nature. In this field lack of acute benefit may not assumedly be followed by a similar lack of improvement in the longer term. Studies tended to concentrate upon haemodynamics, and gave too little attention to features such as quality of life and extension of exercise time, or improvement in maximal oxygen consumption.

Possible mechanisms of benefit of pacing

This aspect has been most fully appraised by Brecker and Gibson[9]. They not only drew attention to the classical cardiological means of assessment, but also pointed out the importance of a broad view of the electrophysiological and electromechanical interactions between a pacing system and a very diseased heart. This begins with pacing and sensing in the right atrium. Leads are usually placed in the right atrial appendage, which results in delay in sensing the P wave and an abnormal activation pattern when pacing. This problem may be overcome by placing the electrode at the crista terminalis. Secondly, these patients may have important conduction defects in their atria determining delayed left atrial activation which, occasionally, may occur so late as to coincide with left ventricular systole activated by pacing from the right ventricle[15]. The solution, here, may be to include the left atrium in the pacing system, either by a left atrial lead in the coronary sinus[16] or an electrode at the mouth of the coronary sinus[17]. Right ventricular pacing from the apex has been criticised for years as a stimulation site[18], but has come under more intense adverse scrutiny in the recent past[4]. Changing the stimulation site to the outflow tract has been advocated as a better alternative[19], but controversy remains as to its true benefit. Lastly, there may be delayed activation of the left ventricle and, certainly, this chamber's activation pattern is grossly abnormal[9]. Stimulation of the left ventricle, as recommended by Cazeau et al[20], Daubert et al[21] and Blanc et al[22], may offer a solution to some of these problems if an optimal site can be found. This will always be a compromise between what is technically feasible and what is electrophysiologically desirable. It may eventually be demonstrated that, for optimal activation of the left ventricle, multiple stimulation sites are necessary. Pacing via the venous system, as used in the majority of Daubert's 24 patients[21], rather than an epicardial approach, is generally considered better for the patient, but at the present time access of an electrode to, and stability within, the coronary venous system must be regarded as a major challenge to the pacing community, both industrial and medical.

It must now be clear that pacing in dilated cardiomyopathy is a complex endeavour and, furthermore, benefits cannot be assessed until the electrophysiological and electromechanical abnormalities are to the fullest possible extent surmounted. The most encouraging aspect of pacing in dilated cardiomyopathy is that a few patients show quite dramatic benefit, e.g. Cazeau et al's report in 1994[20], but when a fault has developed in the pacing system the patient has returned equally dramatically to pulmonary oedema and New York Heart Association class IV. Once the fault has been corrected improvement has recurred.

As regards the haemodynamic features of these patients, those that will be candidates for pacing show a restrictive diastolic filling pattern with increase in the *e* wave, decrease in the *a* wave of the mitral valve Doppler flow velocity and in the most severe cases there is a left atrial pressure increase without any detectable flow across the valve. In conjunction with these findings there is a long PR interval and an indeterminate bundle branch block QRS on the electrocardiogram and, clinically, sinus tachycardia with a summation gallop at rest. When the PR interval is sufficiently prolonged there is an effective reduction in diastolic left ventricular filling,

which is often associated with diastolic mitral regurgitation. In systole the prolonged QRS complex is associated with delayed left ventricular contraction and relaxation, and the dysynergetic contraction pattern leads to functional atrioventricular valve regurgitation, which extends throughout the so-called isovolumic phases of contraction and relaxation. Thus, the great duration of systole prejudices diastolic time.

Brecker and Gibson[9] have stated their criteria for consideration of pacing: duration of functional mitral regurgitation of > 450 ms and left ventricular filling of < 200 ms. Caution is advised in patients who show obvious functional tricuspid regurgitation of long duration, because shortening of this by pacing, unaccompanied by any improvement on the left side of the heart, can lead to pulmonary oedema. All these assessments are made by echocardiography at rest; on exercise further shortening of diastole must be expected with further compromise of left ventricular filling.

Potential impact of pacing in dilated cardiomyopathy

If the technical and medical difficulties can be overcome the benefits to the patient seem unlikely to be immediate, and unlikely to be measured in classical haemodynamic terms. They may be appreciated in increase in tolerance of low levels of exercise and, purely, quality of life. It must also be borne in mind that these patients die suddenly, and some of these deaths are due to bradycardias rather than ventricular tachyarrhythmias. However, if the latter feature transpires as the only benefit, pacing will not stand up to critical cost-benefit analysis. Patients who will be considered for pacing will have some or all of the presenting signs, symptoms and findings given by Brecker and Gibson[9], will be in New York Heart Association classes III and IV and furthermore, will be unsuitable for other forms of treatment such as cardiac transplantation or cardiomyoplasty. These may constitute 10% of patients presenting with dilated cardiomyopathy.

If pacing offers benefit

If pacing offers benefit, pacemaker physicians will be required to understand better the condition of heart failure, and its epidemiology as it relates to this type of patient. Heart failure has been defined as a condition which develops as a consequence of cardiac disease, and is recognised clinically by a constellation of symptoms and signs produced by complex circulatory and neuroendocrine responses to cardiac dysfunction[23]. The incidence of heart failure in the population is estimated to be one to five cases per 1000 per year, but in those over the age of 75 years the incidence rises to no less than 40 cases per 1000 per year[24]. The prognosis of heart failure can be portrayed in many different ways: in terms of population studies a mortality of 34% in the first year after diagnosis or up to 75% within 5 years has been reported; hospital studies indicate mortality rates between 21% and 48% and > 50% in 5 years; pharmacological trials reveal some information about prognosis by examination of the placebo groups in which 14–52% mortality has occurred; 267 000 death certificates were issued for heart failure in the United States in 1988 with the rates being 8.8 and 13.2 in white and black males and 6.3 and 10.1 in white and black females[24]. Causes of death are most usually divided equally between sudden, presumed arrhythmic, and due to pump failure[24]. In terms of the demand on hospital facilities, in Scotland in 1990 there were 210 hospital discharges per 100 000 population in which heart failure was coded as the primary diagnosis[24]. If pacing were to benefit 10% of these presenting patients there could be as many as 30 new pacing systems implanted per million population per year for this indication.

Conclusions

The status of pacing in the treatment of dilated cardiomyopathy so far, after 7 years experience, is that no study has yet shown consistent benefit in patients without standard indications for pacing. Optimisation of the atrioventricular interval is an attractive concept, but it has not always yielded the desired result; perhaps because the pacing approach has lacked total amelioration of both the electrophysiological and electromechanical abnormalities. There is some consensus that conventional VVI pacing is always deleterious. The limited studies performed so far not only lack the technical equipment, but also have been too small and have not, in every case, had clearly and appropriately defined end-points. The next steps must be studies of carefully selected patients using dual, triple or quadruple chamber pacing including, at least, stimulation of the left ventricle or both ventricles, and possibly also with synchronisation of the atria. In these studies special attention must be paid to the end-points and the modes of assessment, depending greatly on exercise testing,

maximum oxygen consumption or the 6-minute walk, and measures of quality of life rather than haemodynamics. At the present state of knowledge a reduction in mortality cannot be expected.

Returning to the quotation from Alice through the looking glass[1], the walrus and the carpenter had a very large and long feast of oysters during their discussion of many things. This, we may anticipate, will also occur in the field of pacing in dilated cardiomyopathy with a feast of scientific work, for we have a long way to go.

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Chapter 61

Can Reliable Pacing be Achieved in Hypertrophic Obstructive Cardiomyopathy with Normal Conduction?

Daniel Gras, Dominique Pavin, Philippe Mabo and Claude Daubert

Introduction

DDD pacing has recently been proposed for the treatment of patients with hypertrophic obstructive cardiomyopathy (HOCM) and cardiac symptoms refractory to conventional drug therapy[1,2], including β-blockers and verapamil. The results from open studies[3–5], and more recently from randomised studies[6,7], have demonstrated an improvement in symptoms and a significant decrease in left ventricular outflow tract (LVOT) gradient.

The precise mechanisms by which clinical and haemodynamic benefit is obtained are still unclear. However, there is general agreement that complete and permanent ventricular capture (VC) by the pacemaker is of critical importance. The right ventricular (RV) preexcitation is responsible for a delayed septal activation, resulting in an enlargement of the LVOT area during systole, and in lower forces acting on the anterior mitral valve leaflet. Another beneficial haemodynamic effect can be a decrease in mitral regurgitation[8], which is more likely to be observed in patients without structural valve alterations.

Our first observations[9], as well as the study reported by Sadoul et al[10], also suggested a trend of continuing improvement beyond the initial period of pacemaker therapy. In some patients, however, the beneficial effect is not seen for weeks or even months, which may account for failures of acute pacing studies to identify responder patients. A possible explanation for this delayed response is long-term left ventricular remodelling[11,12]. This hypothesis is supported by the usual presence of a lower gradient, or even its disappearance, at follow-up during sinus rhythm (the pacemaker being turned off), compared with that measured before implantation, and by a trend towards a long-term decrease in the thickness of the left ventricular wall, particularly the septum. However, the question of left ventricular remodelling remains controversial.

Conditions for successful pacing therapy in HOCM

Various conditions are required to achieve the expected benefit from DDD-pacing therapy in HOCM patients (Table 1). First, the ventricular lead has to be placed at

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Table 1. Conditions for successful DDD pacing therapy in HOCM patients

Right ventricular pacing site: the very apex
Selection of pacemaker device
AV delay hysteresis, rate-adaptive AV delay
Protection against electronic tachycardias and atrial arrhythmias
Rate-response algorithm
Sophisticated Holter function
Individual AV delay programming

the very apex of the RV[13], in order to produce the maximal delay for septal activation. This may sometimes be difficult to achieve, particularly in patients in whom hypertrophy also reaches the RV. Concerning the atrial lead, there is a preference for a bipolar electrode, the rationale being to optimise atrial sensing not only during sinus rhythm, but also during exercise. In case of atrial arrhythmia occurrence it may also facilitate arrhythmia detection from the pacemaker, and then an appropriate switch mode episode. Placement of the atrial electrode close to the sinus node may contribute to a decrease in electromechanical delay, and then to optimisation of atrioventricular (AV) synchrony, particularly during effort.

The selection of pacemaker device is also of crucial importance. The implanted model should have at least the following parameters: independent sensed and paced AV delay with ultra-short values (< 50 ms), a linear rate-adaptive AV interval in order to maintain a complete VC during exercise, a specific algorithm dedicated for diagnosis and termination of pacemaker-mediated tachycardia, and sophisticated Holter function to collect important information regarding the natural course of the disease (atrial arrhythmias, ventricular arrhythmias, chronotropic incompetence etc.). A rate-responsive algorithm can also be very useful in cases of chronotropic incompetence, which may develop in up to 30% of patients[14].

As soon as the patient is implanted with the appropriate system it is necessary to select the optimal AV

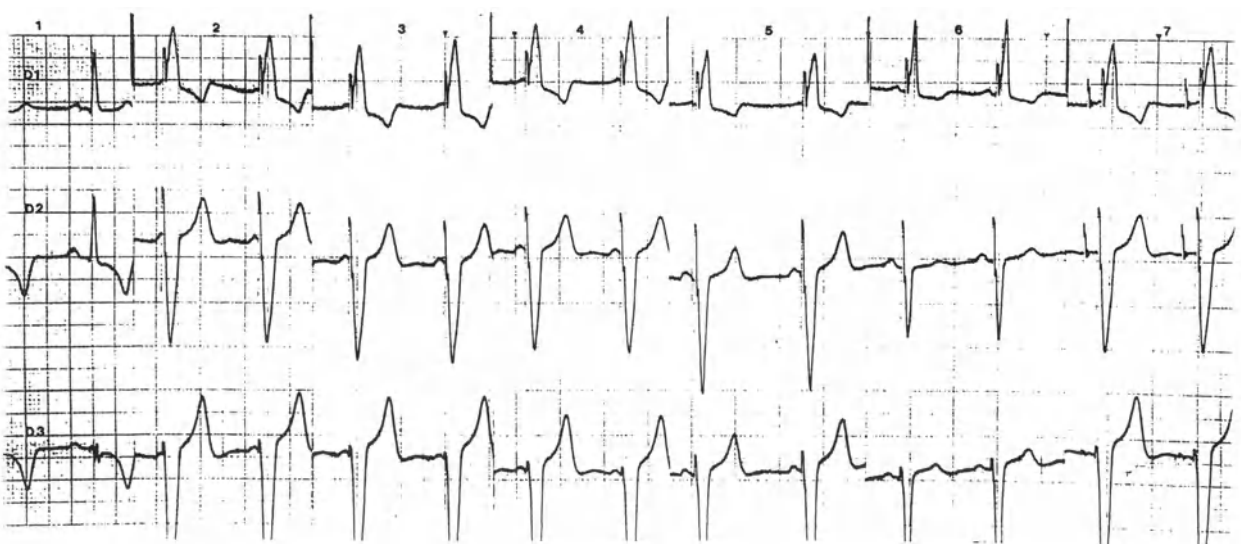

Figure 1. Selection of optimal AV delay programming during DDD pacing for the treatment of HOCM. Panel 1: surface ECG (leads I, II, and III) recorded during sinus rhythm. Panel 2: single ventricular pacing in VOO mode used as a reference to check that the duration of paced ventricular complexes is similar during both DDD and VOO pacing modes. Panels 3, 4: selection of optimal sensed AV delay in DDD mode, using programming with various AV delays, at 50 and 70 ms respectively. The best AV interval is defined by the longest one that maintains a complete ventricular capture. Panels 5, 6: when choosing a longer AV interval, of 90 and 110 ms respectively, duration of paced ventricular complexes becomes shorter because of a fusion. Panel 7: in the same way, selection of the best AV interval is made on paced atrial events, with respect to the electromechanical delay. The optimal value is 130 ms, so the hysteresis of the AV delay is 60 ms.

delay programming. In patients with normal AV conduction the best AV interval is defined by the longest one that maintains a complete VC, on both paced and sensed atrial cycles (Fig. 1). Complete VC is determined by reference to the duration of paced QRS complexes, recorded during VOO mode with a lower rate programming 10 beats higher than the intrinsic rate. Then, a rate-adaptive AV delay algorithm is activated in order to ensure a complete VC, not only at rest but also during exercise.

How to define optimal AV delay programming in HOCM

In our initial experience we investigated 32 patients with drug-refractory HOCM, in whom all the pre-cited conditions for successful pacemaker therapy were fulfilled. Then we divided this population into two groups, taking into consideration the effect of DDD pacing with optimal AV delay programming on LVOT gradient. The drug regimen remained unchanged during this first evaluation. Group I consisted of responder patients ($n = 18$) in whom the gradient was decreased by more than 50%. Group II consisted of non-responder patients ($n = 14$) in whom the LVOT gradient remained unchanged or slightly decreased, by less than 50%. Comparison between the two groups demonstrated that non-responder patients were, on average, younger, had higher gradient at baseline and shorter PR intervals during sinus rhythm. Consequently, the mean "optimal AV delay", defined as described above, was significantly shorter in non-responders than in responders (Table 2).

These results clearly show that, despite a complete VC, very short AV delay programming is more likely associated with a failure of pacemaker therapy (Fig. 2). The short AV interval required to preempt normal AV conduction, particularly in young patients, may severely compromise the haemodynamic effect of atrial contraction, and therefore LV filling[15]. Finally, this potential impairment in diastolic function[16] may counterbalance the expected positive effect of VC, so patients may not respond to DDD pacing therapy despite the programming of an optimal AV delay.

The concept of "optimal AV delay" needs clarification in this particular indication for cardiac pacing. The truly optimal AV delay is one that responds to two opposite criteria: first a complete VC to obtain the maximum reduction in LVOT gradient, which usually necessitates selecting a short AV interval; secondly an optimal AV synchrony to avoid alteration in LV filling, which is already severely impaired in HOCM; this usually requires a longer AV interval than the one selected on the basis of a complete VC. Taking this dual prerequisite into consideration we found that truly optimal AV delay programming did not exist in 44% of HOCM patients treated with DDD pacing.

So, the answer to the question expressed in the chapter title is as follows: in our experience reliable pacemaker therapy can be achieved in 66% of HOCM patients with normal conduction. In the remaining 44% of HOCM patients inappropriate AV delay programming may be responsible for a submaximal decrease in LVOT gradient and/or for an alteration in diastolic function, thereby leading to an intermediate beneficial effect, or even to the absence of positive clinical effect.

How to optimise benefit of pacemaker therapy in HOCM

In most HOCM patients treated with DDD pacing, who experience a slight benefit or no benefit, pacemaker therapy may be optimised. First, it should be verified that the RV lead is correctly located at the very apex. In our population we followed one patient who did not benefit from DDD pacing, and in whom the RV lead was placed at the inferior wall in between the tricuspid annulus and the apex. This location was selected to

Table 2. Comparative data at baseline in "responder" and "non-responder" patients with HOCM treated by conventional DDD pacing with "optimal AV delay" programming

Patients ($n = 32$)	Responders ($n = 18$)	Non-responders ($n = 14$)	p-Value
Age (years)	65 ± 14	47 ± 14	0.013
Gradient (mmHg)	99 ± 34	135 ± 14	0.024
PR interval (ms)	143 ± 23	115 ± 15	0.015
AV delay (ms)	92 ± 20	43 ± 19	0.0001

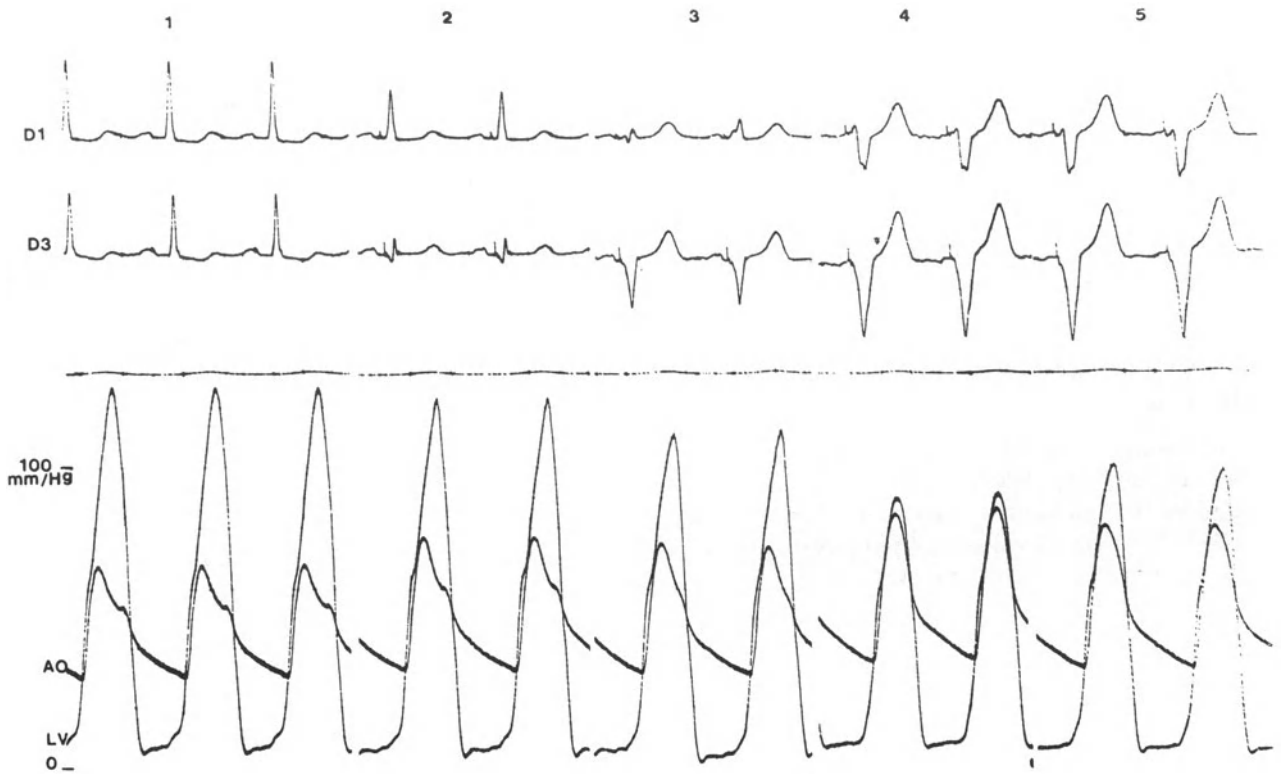

Figure 2. Acute haemodynamic study showing changes in LVOT gradient recorded during sinus rhythm (panel 1) and during temporary DDD pacing with various AV delay programming (panels 2, 3, 4, 5). The AV delay programming is progressively shortened to the optimal interval (panel 4) where paced QRS duration is the longest and LVOT gradient is abolished. A further decrease in AV interval (panel 5) results in reappearance in LVOT gradient (due to alteration in left ventricular filling), despite the maintenance of complete ventricular capture, as demonstrated by similar duration in paced QRS complexes.

achieve good pacing and sensing thresholds. Repositioning the ventricular lead to the very far apex (where pacing thresholds were poor) was associated with disappearance of LVOT gradient in parallel to a clinical improvement.

ECG Holter monitoring may also be very useful in checking that there is a permanent complete VC. Frequent fusion beats or transient loss of VC may lead to underestimation of the potential benefit of pacemaker therapy. This was the case in a patient whose ECG Holter monitoring demonstrated frequent loss of VC (Fig. 3). Surface ECG recorded during such an event demonstrated that there was competition between a normal sinus rhythm and an ectopic atrial rhythm, originating from the inferior right atrium (Fig. 4). Because the ectopic atrial rhythm was close to the AV node the PR interval was shortened, so that AV delay programming became too long to maintain ventricular preexcitation from the pacemaker. Benefits were restored after performing radiofrequency ablation of the AV junction.

In non-responder HOCM patients AV synchrony is frequently altered due to the short AV delay programming. In such cases we attempt drug prolongation of the PR interval by using a combination of cardiodepressor drugs (most often β-blockers plus verapamil). Drug tolerance is undoubtedly facilitated by DDD pacing support. Furthermore, there is probably a synergy between the myocardial effects of optimised drug therapy and DDD pacing. Out of the 14 non-responders, drug prolongation of the PR interval was obtained in six, permitting us to optimise AV delay programming (Fig. 5). This was further associated with a decrease in LVOT gradient by more than 50%, and with

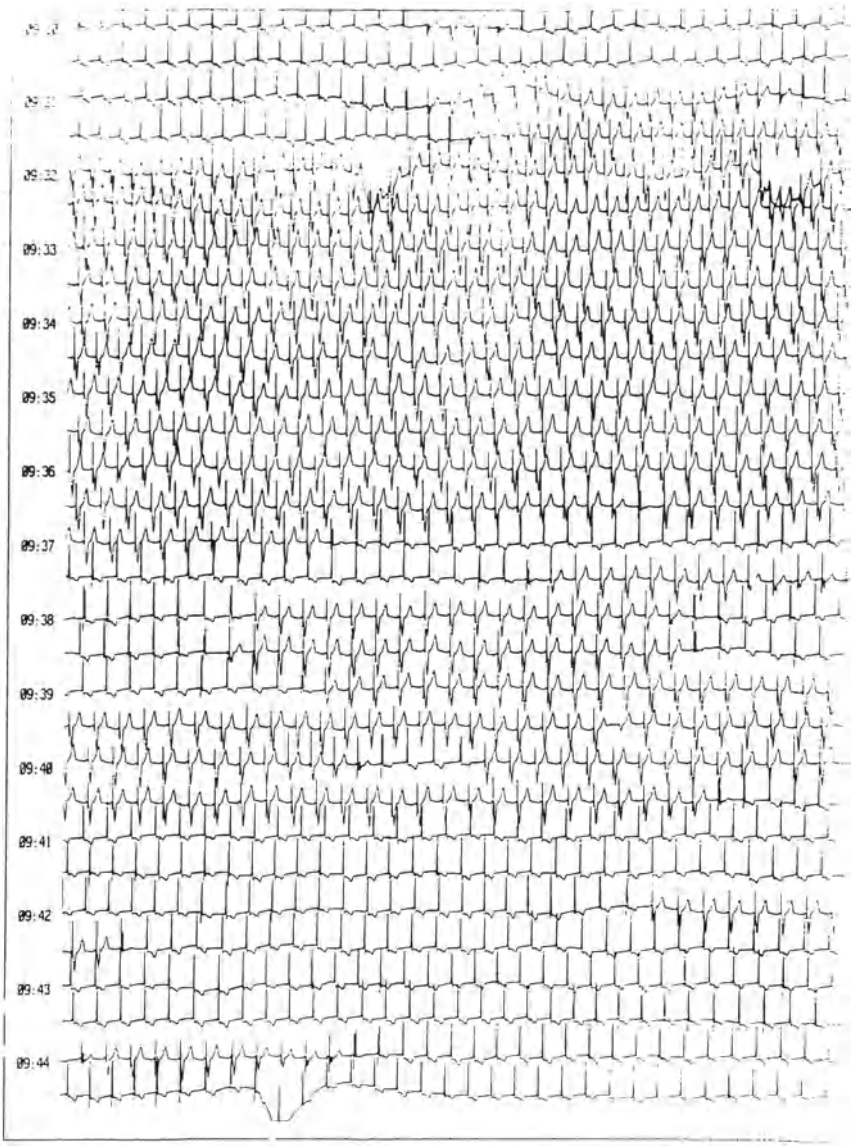

Figure 3. Control Holter monitoring showing intermittent loss of ventricular capture, recorded in a patient who deteriorated after a long period of improvement from pacemaker therapy.

improvement in cardiac symptoms. However, long-term benefit persisted in only two patients.

Radiofrequency ablation of the AV junction was performed in 12 of the 14 non-responders[17], including eight patients who failed to benefit from drug prolongation of the PR interval and four patients who escaped to optimised drug therapy. The radiofrequency ablation procedure was successful in all 12 patients, preserving a mean escape junctional rhythm of 42 ± 9 bpm (35–50). The optimal AV delay was reassessed in all cases, taking into account the AV interval associated with the lower LVOT gradient and the more physiological transmitral blood flow during echo Doppler analysis. The reassessed optimal AV delay programming was significantly longer when compared to the initial interval (145 ± 10 ms versus 42 ± 18 ms). The longer AV delay was paralleled by a major decrease in LVOT gradient (82 ± 27 mmHg to 17 ± 9 mmHg), by an important

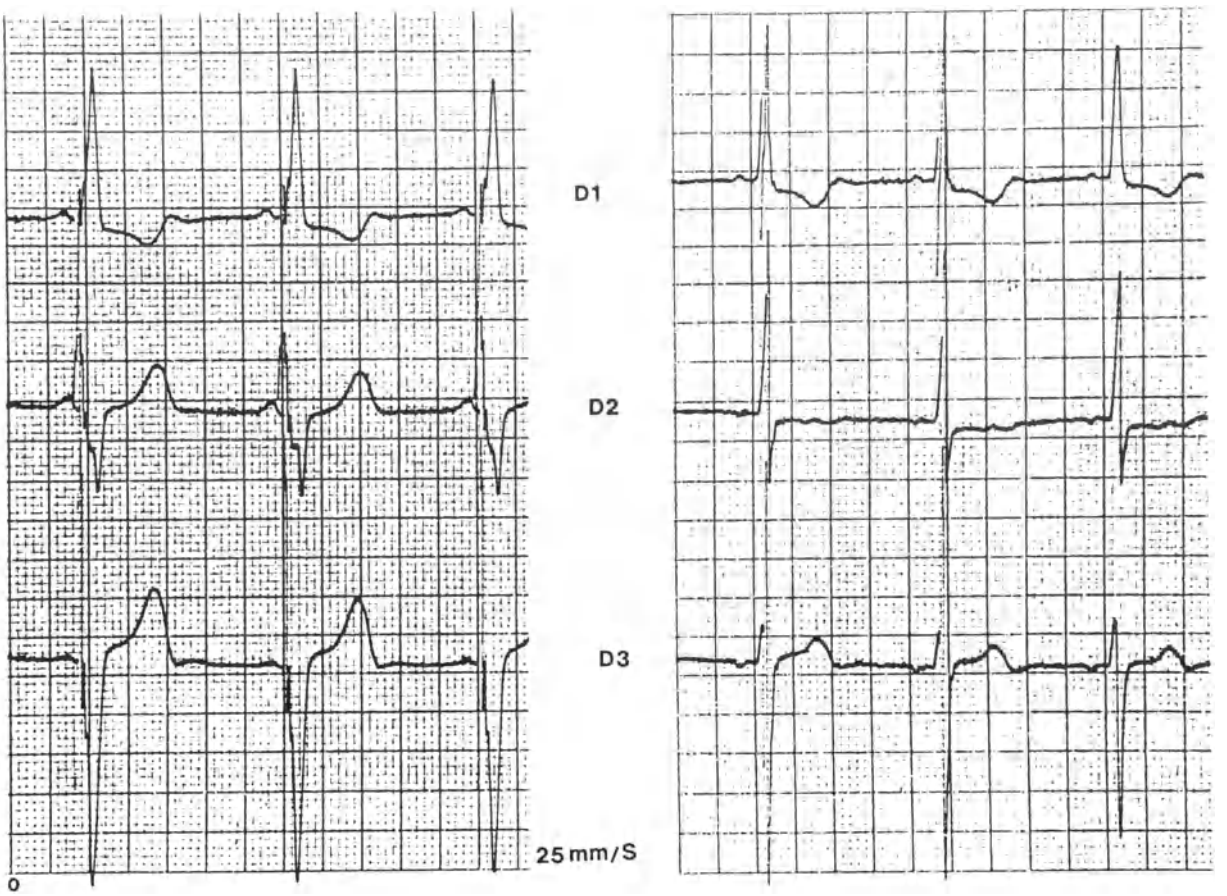

Figure 4. Surface ECG (leads I, II and III) showing competition between normal sinus rhythm (left panel) and an ectopic rhythm originating from the inferior right atrium (right panel), during which the PR interval is shortened so that the AV delay programming becomes too long to maintain ventricular preexcitation from the pacemaker.

diminution in mitral regurgitation in six patients and by an improvement in NYHA functional class status (3.3 ± 0.6 to 1.4 ± 0.5) (Table 3).

In the whole group of non-responder patients optimisation of AV synchrony led to the same final results as observed in responder patients, in terms of functional improvement, LVOT gradient reduction and mitral regurgitation diminution (Fig. 6). These data underline the paramount importance of preserving an optimal electromechanical AV synchrony in the left heart of HOCM patients treated with DDD pacing. In these particular patients the quality of LV filling depends greatly on the timing and performance of LA contraction. These data also suggest that DDD pacing may be effective in most patients with HOCM, provided that physiological AV synchrony is preserved.

Another perspective to improve AV synchrony in HOCM

If radiofrequency ablation of the AV junction is beneficial in HOCM patients for optimal LV capture and filling, it also raises the problem of permanent pacemaker dependency. For this reason we considered an alternative strategy to ablation, that could optimise LA contribution to LV filling while preserving natural AV conduction. This new technical solution consists of a new pacing system combining biatrial synchronous pacing and classical DDD pacing in a triple-chamber pacemaker configuration[18].

The pacing system necessitates three leads, two of them being placed classically at the high RA and at the very apex of the RV, the third one being inserted into

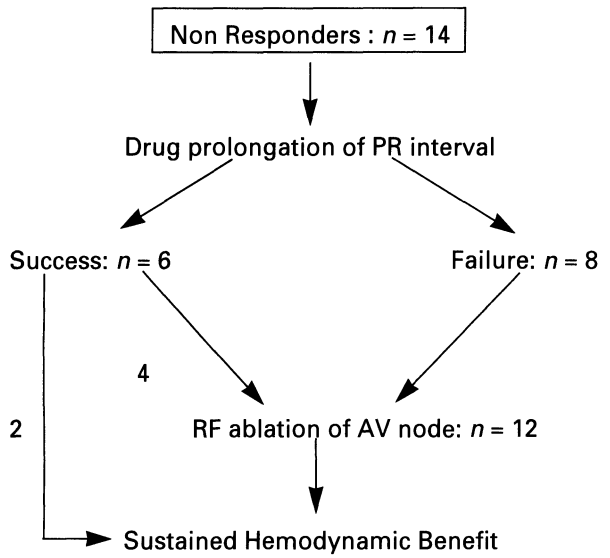

Figure 5. Chart of AV synchrony optimisation in the group of "non-responder" patients.

Table 3. Comparison of optimal AV delay programming (AV delay), NYHA functional class. LVOT gradient and mitral regurgitation (MR) > grade I, before and after RF ablation of AV junction (RF ablation) in 12 "non-responder" patients with HOCM treated by DDD pacing

Patients (n = 12)	Before RF ablation	After RF ablation	p-Value
AV delay (ms)	42 ± 18	145 ± 10	< 0.0001
NYHA class	3.3 ± 0.6	1.4 ± 0.5	< 0.0001
Gradient (mmHg)	82 ± 27	17 ± 9	< 0.0001
MR > grade I	8	2	< 0.01

the coronary sinus to pace and sense the LA (Fig. 7). This last lead (SP 2188) is specifically designed by Medtronic to provide good tissue contact with the coronary sinus wall. The two atrial leads are then connected to the pacemaker device through a Y adaptor, with the high RA lead as the cathode and the coronary sinus lead as the anode. The Y adaptor is further connected to the atrial port of the device, as well as the ventricular lead to the ventricular port.

A special algorithm for permanent atrial resynchronisation is then down-loaded into the RAM memory of a DDD(R) Chorus pacemaker (ELA Chorus 6234 or 7034). With the algorithm switched on, every atrial-

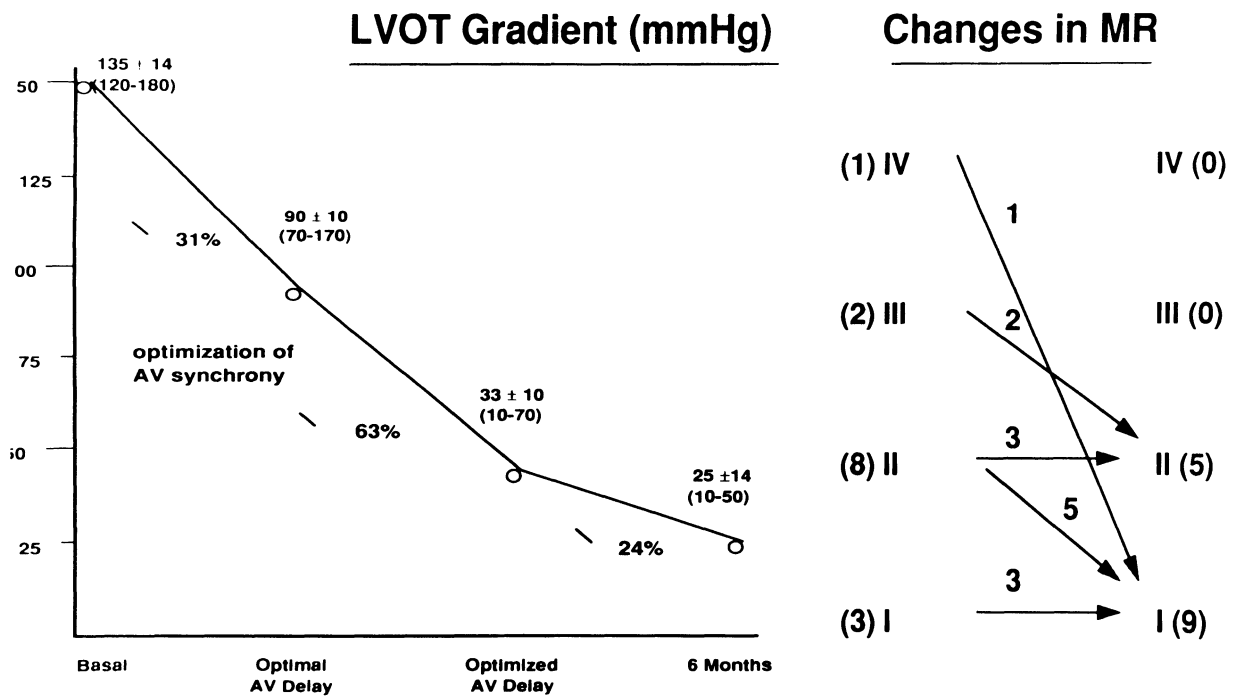

Figure 6. Changes in LVOT gradient and in mitral regurgitation grade in "non-responder" patients (n = 14) after optimisation of AV synchrony (drug prolongation of PR interval or radiofrequency ablation of AV junction).

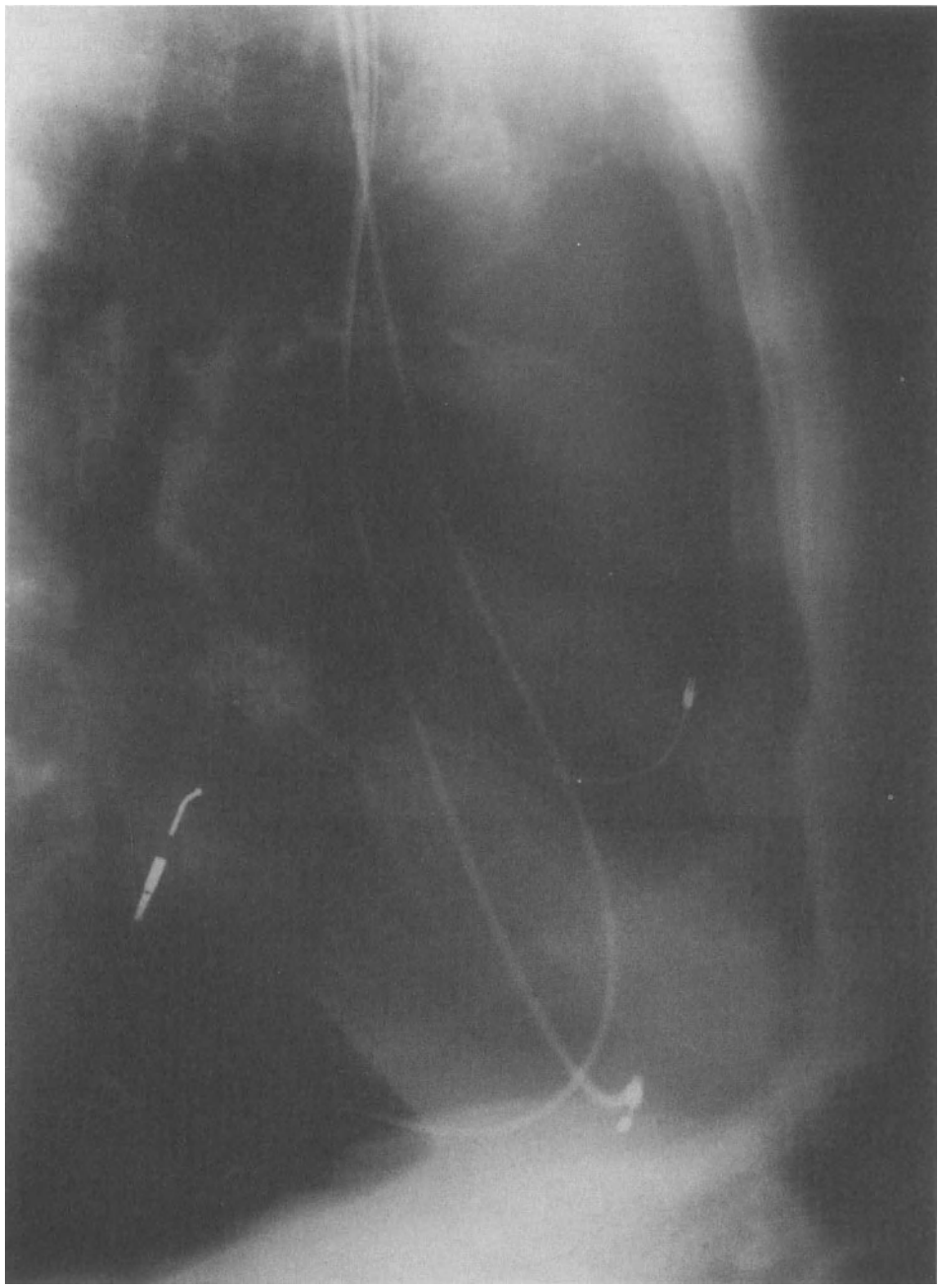

Figure 7. Chest X-ray. Lateral view showing a triple-chamber pacemaker with three leads placed respectively in the high right atrium, in the coronary sinus (to sense and to pace the left atrium), and at the very apex of the right ventricle. Note the double angulation of the terminal part of the Medtronic SP 2188 lead, which is specifically designed for left atrial pacing through the coronary sinus.

sensed event (sinus seat, right or left extrasystoles) immediately triggers biatrial pacing. In the particular case of HOCM treated by cardiac pacing, the purpose of biatrial synchronous pacing is to advance LA contraction according to individual inter-atrial conduction time, and thus to facilitate programming of a very short

AV delay without impairing AV synchrony in the left heart. If the results of this new alternative approach are encouraging, regarding haemodynamics and functional improvement, further studies will be required to validate this proposed therapeutic strategy.

Another privileged indication for biatrial synchronous pacing is in patients with inter-atrial conduction abnormalities who are at high risk of DDD pacemaker syndrome. This is explained by the delay in left atrial activation with the resultant left atrial systole occurring during ventricular systole, when the mitral valve is already closed. This can reproduce a situation analogous to that of VVI pacing with one-to-one retrograde conduction, which should be poorly tolerated in a patient with HOCM.

Conclusions

Because DDD pacing is a simple and low-risk treatment, associated with an improvement in symptoms that is comparable to that obtained with surgery, it should be considered as first-line therapy in drug-refractory HOCM patients. However, obtaining the best results depends greatly on permanent maintenance of complete ventricular capture and of physiological AV synchrony. These two goals can be achieved only through individual selection of optimal pacemaker parameters. In a number of patients who first present as non-responders to pacing therapy, a beneficial effect can be obtained only after optimisation of AV synchrony, which can be achieved by using drug prolongation of the PR interval or, in case of failure, by radiofrequency ablation of the AV junction. Biatrial synchronous pacing is a promising approach that could be considered as an alternative to ablation in the near future.

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Chapter 62

AV Node Ablation and DDD Pacing in Hypertrophic Obstructive Cardiomyopathy

Nicolas Sadoul, Bernard Dodinot, Daniel Beurrier, Christian de Chillou and Etienne Aliot

Introduction

Clinical improvement with dual-chamber pacing has largely been reported in patients with drug-resistant hypertrophic obstructive cardiomyopathy (HOCM)[1–5]. This clinical improvement is mainly related to the ability to bypass the normal atrioventricular (AV) conduction system in order to obtain a complete and permanent right ventricular capture. Some patients, however, experience only minor benefits with DDD pacing. This lack of improvement is probably due to incomplete right ventricular capture and/or deleterious effects of short AV delays on AV synchrony and left ventricular filling. Instrumental AV node modulation or ablation may be indicated in this subgroup of patients. Another indication of AV node ablation in HOCM is the occurrence of atrial fibrillation in order to restore adequate and permanent right ventricular capture. This chapter will focus on the rationale, the technical problems and results of AV node ablation in HOCM.

Background: importance of AV delay programming

The clinical efficacy of DDD pacing in HOCM is mainly related to the ability to bypass the normal AV conduction system in order to obtain a complete and permanent right ventricular capture. This approach is based on the fact that the left ventricular outflow tract (LVOT) obstruction is not fixed but dynamic. The most commonly accepted mechanism for LVOT gradient postulates that blood passes at increased velocity through the narrowed left ventricular outflow tract, creating a Venturi effect, responsible for the existence of the systolic anterior motion (SAM) of the mitral valve leaflet towards the interventricular septum and for impaired closure leading to a variable degree of mitral regurgitation[6]. The most commonly, although probably incomplete, accepted mechanism for left ventricular outflow tract gradient reduction after DDD pacing in HOCM remains the inversion of the contraction sequence of the left ventricle as a consequence of the primary activation from the right ventricular apex. The contraction of the left ventricle is hence initiated from the apex and not via the His-Purkinje system. This leads to: (1) a widening of the left ventricular outflow tract; (2) a decrease in the Venturi effect; and (3) a decrease in the SAM associated with a reduction of the degree of mitral regurgitation[7] (Fig. 1). These three combined mechanisms lead to a decrease in the gradient. In order to maintain efficacy it is paramount that the ventricles

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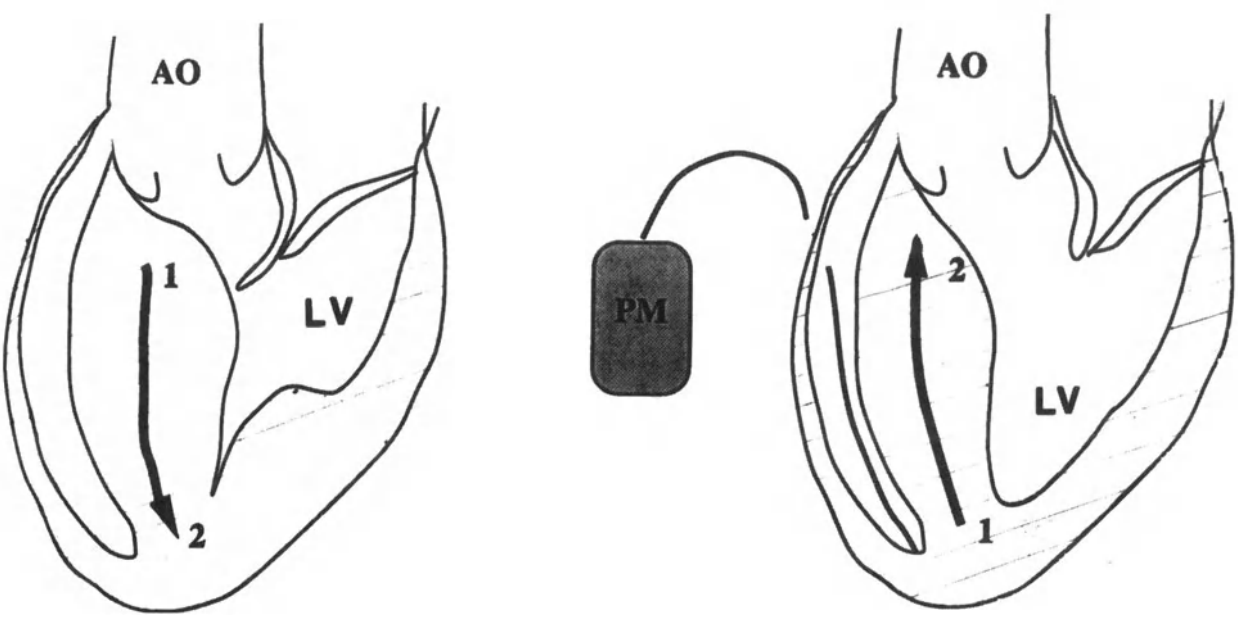

Figure 1. Mechanism of left ventricular outflow tract gradient reduction with DDD pacing. On the left panel (without pacemaker), the left ventricular contraction begins by the septum, followed by the apex of the ventricle. On the right panel, with DDD pacing and complete right ventricular capture, ventricular contraction begins at the apex of the right ventricle, followed by the apex of the left ventricle and finally by the septum. This leads to a widening of the left ventricular outflow tract, a decrease in the Venturi effect and a decrease in the SAM. See text for explanation. (From Sadoul et al[7])

are permanently and completely activated from the right ventricular apical site. Apical pre-excitation of the right ventricle is probably not the sole explanation for gradient reduction, since DDD pacing has also been reported to decrease the LVOT and to improve symptoms in patients with pre-existing left bundle branch block (LBBB)[8]. However, it must be emphasised that the mechanical pattern of the left ventricular activation in patients with LBBB does not exactly mimic the contraction pattern induced by pacing with right ventricular apical capture[9]. The last explanation is that gradient reduction occurs as a consequence of reduced systolic function and chronic ventricular dilatation, which has been speculated as a hitherto unforeseen deleterious long-term effect[10].

Pacemaker therapy in HOCM requires implantation of an atrial synchronised ventricular pacing device capable of being programmed to a short AV delay in order to ensure that the normal cardiac conduction system is bypassed by pre-excitation of the right ventricular apex[3–5]. On the other hand, it is also recognised that patients with HOCM frequently have coexisting left ventricular diastolic dysfunction. In these patients the atrial contribution to left ventricular filling is of critical importance in order to maintain a proper cardiac output and to minimise left ventricular hypertension[4]. It is also well recognised that, if the systolic gradient decreases as AV delay shortens, below a certain value, a further shortening of the AV delay is associated with a re-increase of the systolic gradient[7] (Fig. 2). The optimal AV delay can hence be defined as the *longest* AV delay that ensures complete right ventricular capture[3] at rest or during exercise, and that is not associated with impaired left ventricular filling. These optimal AV delay values are much shorter in patients with HOCM, who are often young with a normal AV conduction, than in "conventional" dual-chamber pacing. For example, in a multicentre European study devoted to pacemaker therapy in 33 patients with HOCM, the mean AV delay value was 90 ± 38 ms. Of these 33 patients, eight had undergone His bundle ablation, which allowed programming of a "normal" AV delay value in these eight patients[11]. This further underlines the necessity of programming ultrashort AV delays. In most patients short

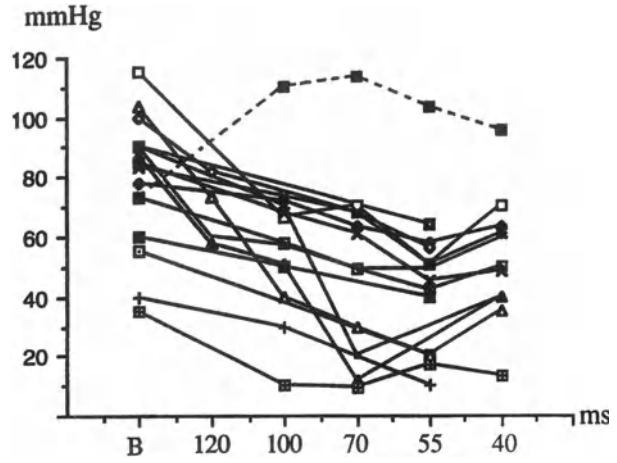

Figure 2. Changes in the systolic gradient induced by AV delay shortening during temporary dual-chamber pacing in 16 patients with HOCM. Note that there is a progressive decrease in the systolic gradient in 15 out of 16 patients when the AV delay is shortened up to a critical value ("optimal AV delay"). A further shortening is associated with a new increase in the systolic gradient. See text for explanation. (From Sadoul et al[7])

AV delays are associated with a dramatic clinical improvement due to systolic gradient reduction, and are well tolerated. In most cases the drug regimen remains unchanged after pacemaker implant. This drug regimen includes β-blockers and verapamil, which slow native AV conduction and facilitate right ventricular capture[12]. However, a minority of patients experience little or no improvement with DDD pacing. This lack of improvement is probably due to incomplete right ventricular capture and/or to the deleterious effect of short AV delays, which jeopardise left ventricular filling. In these particular patients prolongation of AV conduction can be proposed.

AV ablation or AV modulation in patients with normal sinus rhythm

The purpose of AV conduction prolongation is to obtain a complete and permanent right ventricular capture with an AV delay which is compatible with adequate left ventricular filling. This can theoretically be obtained either by AV node ablation or by AV node "modulation"[13] (i.e. creating a first-degree AV block). In theory this latter solution seems ideal. The ablation catheter is positioned at the site of maximal His bundle electrogram and is then withdrawn several millimetres proximally. The target site is characterised by an atrial/ventricular ratio greater than 1, with a His bundle amplitude less than 0.1 mV. The endpoint of radiofrequency current application is a PR prolongation by about 50% from baseline[13,14]. Energy delivery must be interrupted immediately if a non-conducted P wave is observed. Of 40 patients who received DDD pacing for drug-refractory HOCM in our department, two patients who were not improved underwent AV modulation. The lack of improvement was due to the inability to obtain complete right ventricular capture without compromising left ventricular filling. ECG before and after the ablation in one patient is shown in Fig. 3[15]. This particular patient developed a transient complete AV block during ablation. Radiofrequency delivery was immediately stopped and AV conduction resumed within 5 min with a prolonged PR interval (240 ms). After a follow-up of 3 months the patient had dramatically improved and the "chronic" PR interval was 250 ms. This improvement was not due to an important reduction in the systolic gradient, which remained unchanged, but was mainly due to improved left ventricular filling (Fig. 4). It must be emphasised that this technique, which has been initially proposed for ablation of the fast pathway in patients with reentrant tachycardia, and as an alternative to AV node ablation in patients with drug-resistant atrial arrhythmias, is associated with a 10% incidence of complete AV block[13,16]. On the other hand, it is also well established that a permanent first-degre AV block is often difficult to obtain with a high recurrence of normal AV conduction[13].

For these two reasons most authors perform conventional AV nodal ablation. Since most patients who require AV node ablation for optimising AV delay are young, particular care is taken in order to perform a "proximal" AV node ablation, which results in a complete AV block with narrow QRS and junctional escape rhythm. In our experience such a procedure was necessary in two patients only. In other studies the incidence of AV ablation is much higher. Gras et al[17] reported their experience of the long-term effects of DDD pacing in 16 patients with HOCM. Patients were divided into two groups, according to their haemodynamic and clinical response to DDD pacing. Group 1 included 11 patients in whom DDD pacing was associated with an important reduction in the systolic gradient (104 ± 33 mmHg before pacing vs 25 ± 13 mmHg after DDD pacing), a reduction associated with a major clinical improvement. Group 2 included five patients who

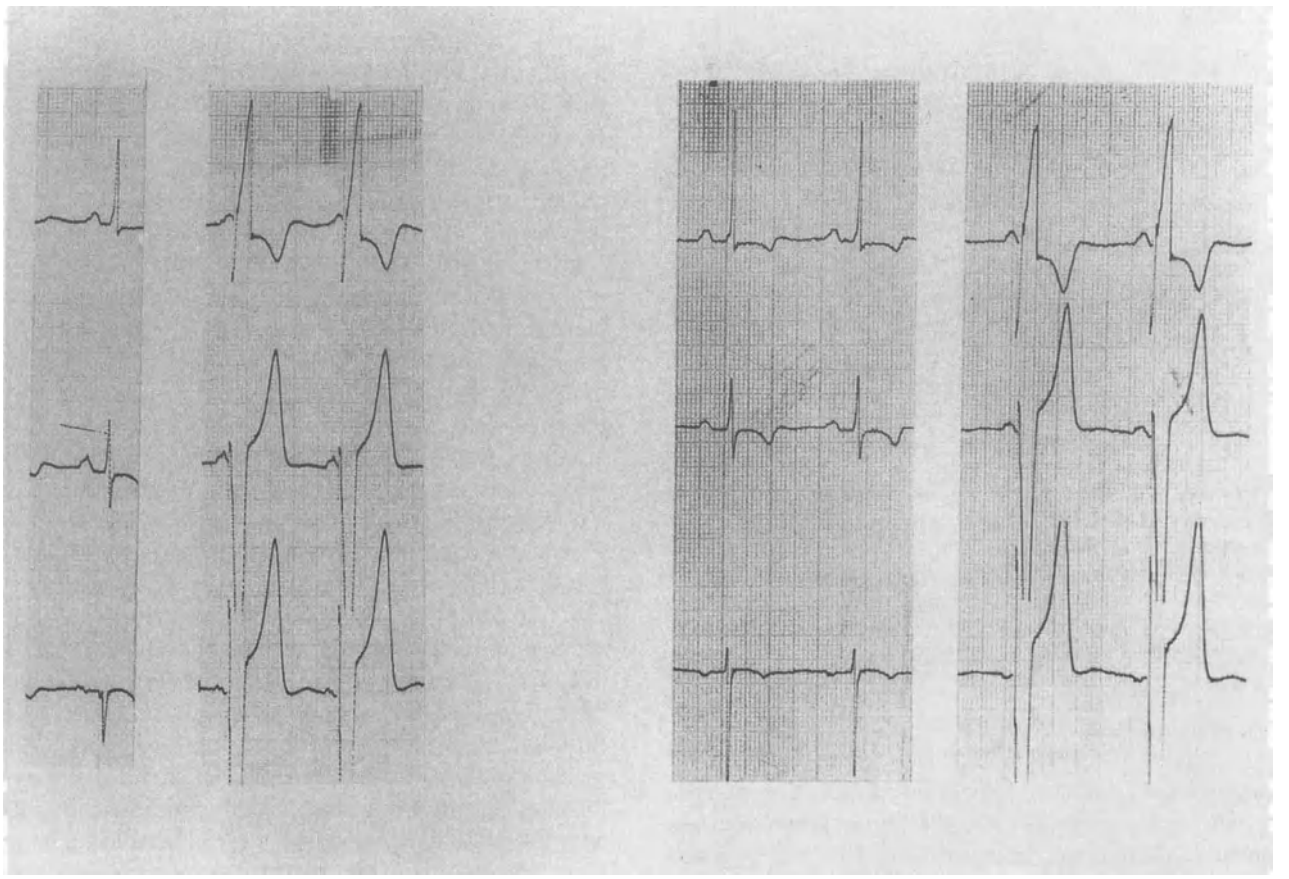

Figure 3. ECG prior (two left panels) and after (two right panels) AV modulation in a patient implanted with a DDDR pacemaker. (From Sadoul et al[15]). On the left panels note that, despite a baseline PR of 180 ms, complete right ventricular capture can be obtained only with a sensed AV delay of 40 ms, resulting in a P wave buried in the paced QRS complex. On the right panels the PR interval is prolonged to 240 ms after AV node modulation. This allows complete right ventricular capture with a sensed AV delay of 100 ms, resulting in a P wave separated from the paced QRS complex.

experienced a smaller reduction in the systolic gradient (132 ± 13 mmHg before pacing vs 88 ± 25 mmHg after DDD pacing) and little clinical improvement. The mean PR interval and the mean PV delay were respectively 140 ± 23 ms and 91 ± 22 ms in group 1 patients vs 110 ± 10 ms ($p = 0.016$) and 38 ± 25 ms ($p = 0.001$) in group 2 patients (Table 1). AV node "optimisation" was necessary in the five group 2 patients (31%). This AV node "optimisation" was possible using pharmacological agents in order to prolong AV nodal conduction in two patients (high doses of β-blockers and verapamil), but required AV node ablation in the remaining three patients, in whom the "optimal" AV delay had to be programmed to 20 ms prior to the ablation procedure, thus jeopardising left ventricular filling. This AV node "optimisation" was associated with a reduction in the systolic gradient from a mean of 88 mmHg before drug or RF AV prolongation to a mean of 26 mmHg at 1 week after the procedure (Fig. 5). Gras et al[18] have also reported their further experience of AV node ablation in a consecutive cohort of 32 patients implanted for drug-refractory HOCM. They performed such a procedure in 12 of them (37.5%). In their series the escape rhythm was 42 ± 9 beats. The optimal AV delay after ablation was 145 ± 10 ms as compared to 42 ± 18 ms prior to the procedure. AV node ablation was associated with an 80% reduction in the gradient (17 ± 9 mmHg vs 82 ± 27 mmHg). Symptoms improved in all patients

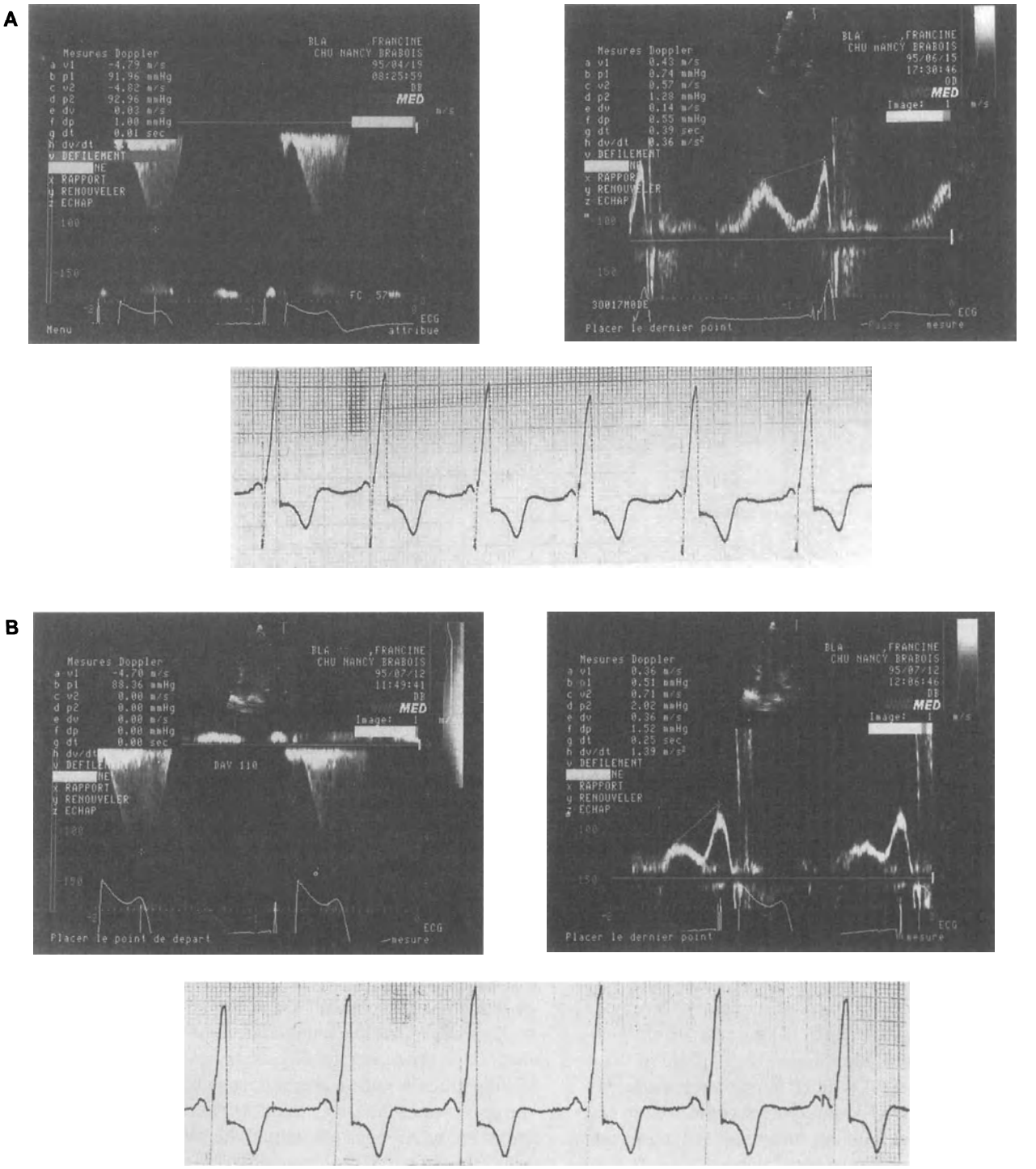

Figure 4. Systolic gradient and mitral flow before (A) and after (B) AV node modulation and "optimal" AV delay programming. Same patient as in Fig. 3. (From Sadoul et al[15]). **A:** before AV node modulation, with a sensed AV delay of 40 ms, the systolic gradient is decreased to 92 mmHg compared to 167 mmHg before pacing. This represents the longest AV delay associated with the maximum gradient reduction. Such a short value is, however, associated with a decrease in A-wave duration. **B:** AV modulation allows the programming of a longer sensed AV delay (100 ms) resulting in the same ECG pattern. The reduction in the systolic gradient is unchanged (88 mmHg). The clinical improvement can hence only be related to an improved atrial contribution to left ventricular filling, as evidenced by an increase in A-wave duration.

Table 1. Values of PR interval, programmed AV delay and systolic gradient in responders (group 1) and non-responders (group 2) to DDD pacing. See text for explanation

Patient no.	PR (ms)	PAVD (ms)	Systolic gradient (mmHg)	
			Sinus rhythm	DDD mode
Group 1				
1	140	80	90	20
2	160	90	140	20
3	120	100	170	60
4	130	100	80	30
5	120	80	120	20
7	140	80	100	10
8	180	100	70	20
10	120	70	60	20
12	180	150	80	20
15	120	80	130	30
16	130	80	100	30
Mean ± SD	140 ± 3	91 ± 22	103 ± 33	25 ± 13
Group 2				
6	120	70	140	90
9	120	60	120	70
11	110	20	150	130
13	100	20	120	80
14	100	20	130	70
Mean ± SD	110 ± 10*	38 ± 25†	132 ± 13	88 ± 25

PR = baseline PR interval; PAVD = programmed sensed AV delay; mean ± SD = mean ± standard deviation. Comparison of PR interval (*: p = 0.016) and programmed PV delay († = 0.001) between group 1 and group 2 patients. From Gras et al[17].

(NYHA = 1.4 vs 3.3). For these authors this clinical improvement was due both to the reduction in the gradient and to the recovery of physiological AV synchrony with an improvement of ventricular filling. It must be emphasised that AV node ablation was not performed immediately after pacemaker implantation, but when long-term pacing associated with pharmacological AV node prolongation had failed to relieve symptoms. This is in agreement with the Lausanne Group[19], who performed AV node ablation in two of the patients who were initially improved, but subsequently developed severe symptoms at 2 and 11 months after pacemaker implantation. Radiofrequency AV node ablation resulted in permanent AV block in one patient and prolonged AV interval (310 ms) in the second. Pacing was thereafter associated with an immediate and significant clinical improvement related to permanent left ventricular capture[18].

Fananapazir et al[20] also reported their experience of long-term DDD pacing in a consecutive cohort of 84 patients with HOCM. All of these patients were implanted with DDDR devices: Medtronic Elite ($n = 60$), Pacesetter 2020 or 2022 ($n = 23$) and CPI 1224 ($n = 1$). AV node ablation was performed in eight patients (9.5%) in sinus rhythm and normal AV conduction, in order to allow the programming of a longer and more physiological AV delay.

AV node ablation in patients with atrial fibrillation

Atrial fibrillation (AF) is a common complication in the clinical outcome of HOCM. In patients treated with dual-chamber pacemakers this arrhythmia has two consequences: either pacemaker inhibition due to rapid intrinsic ventricular rate, or pacemaker tachycardia. For these reasons AV node ablation may also be indicated in the presence of AF. According to Fananapazir et al the incidence of AF does not seem to be prevented by dual-chamber pacing[19]. Furthermore, it has been reported by the same group that radiofrequency of the AV node coupled with rate-responsive VVI pacing results in a satisfactory symptomatic and haemodynamic outcome in HOCM patients with AF[21]. In his paper concerning the clinical outcome of 84 patients, Fananapazir per-

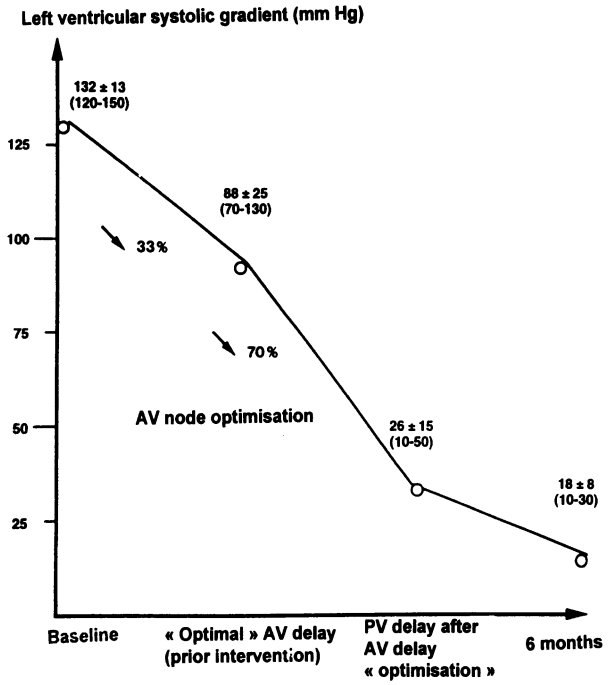

Figure 5. Haemodynamic changes in group 2 patients, before ("optimal AV delay") and after "AV delay optimisation" (drug-induced in two patients and radiofrequency AV node ablation in three patients). See text for explanation. (From Gras et al[17])

formed AV node ablation in nine of these patients (seven for chronic AF and two for paroxysmal AF) in order to reduce ventricular rate and to obtain permanent capture[19].

In our experience, of 45 patients four developed drug-refractory AF. AV node ablation was performed in three of them in order to allow permanent right ventricular capture. The last patient was not ablated since he had pre-existing complete AV block.

Conclusion

Pacemaker programming in HOCM results in a compromise between systolic gradient reduction and left ventricular filling. In most patients the systolic gradient reduction is associated with a major clinical improvement. Instrumental AV node prolongation is indicated after failed drug prolongation of the AV conduction time, and when a reduction in the systolic gradient cannot be obtained despite short AV delays, or when such programmed AV delays are associated with the loss of atrial contribution. The second indication for AV node ablation in HOCM is the occurrence of chronic atrial fibrillation.

It should be emphasised, based on Fananapazir's and our personal experience, that AV node ablation is evenly distributed between "haemodynamic" and arrhythmic (AF) indications, and that the percentage of patients requiring such a procedure is low (around 10%). This differs from the experience of other groups who performed purely "haemodynamic" AV node ablation in a much higher percentage (around 40%) in order to improve both right ventricular capture and left ventricular filling[17].

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