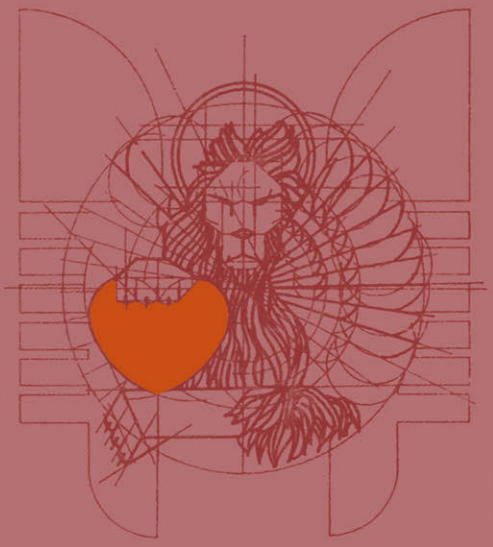
Cardiac Arrhythmias 1997



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Antonio Raviele

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Preface

This book contains the Proceedings of the "5th International Workshop on Cardiac Arrhythmias" held in Venice on October 7-10, 1997. They represent an update on the most recent advances in the diagnosis, prognosis and treatment of cardiac arrhythmias; the contributions, made by numerous well-known world leaders in the field of clinical electrophysiology and arrhythmology, cover an array of timely topics including fibrillation and other supraventricular tachyarrhythmias, diagnosis and management of ventricular arrhythmias; risk stratification and prevention of sudden death in post-myocardial infarction patients: technological advances, clinical issues and new indications of ICD therapy, update on syncope and progress in clinical pacing.

I would like to express my sincere and profound gratitude to all the Authors that with enthusiasm and devotion have allowed the realization of this book. Without their effort and excellent job this volume would not have been possible.

A special word of thanks also to the Publisher, Springer-Verlag, that with great expertise and care has followed the production process of the book.

Finally, my deepest appreciation goes to Prof. Eligio Piccolo for his example and continuous encouragement, to my present colleagues, in particular Dr. De Piccoli, Di Pede, Rigo, Bonso, Zuin and Gasparini, for their unvaluable help in preparing and realizing the workshop and to my wife and children for their patience, personal sacrifice and support.

Antonio Raviele

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Table of Contents

List of Contributors

ATRIAL FIBRILLATION: MECHANISMS AND CLINICAL ASPECTS

What Are the Electrophysiological Mechanisms of Perpetuation of Atrial Fibrillation?

M.A. Allessie, F.J. Chorro, M.C.E.F. Wijffels, F. Mast and R. Dorland

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in man, its incidence greatly increases with age resulting in a prevalence of more than 2% in the population over 60 years of age [1-3]. It therefore represents an important medical problem with a considerable impact on morbidity and quality of life, especially in the elderly. Because of thrombus formation in the left atrium and the associated risk of cerebrovascular accidents, although it is not immediately life threatening, on the long term the arrhythmia also carries a considerable mortality.

Atrial fibrillation often starts in the form of *paroxysmal* AF, but after some time its propensity for self-termination gradually diminishes until after a variable period of time the arrhythmia becomes *persistent* [1, 4]. Although some of the electrophysiological mechanisms of atrial fibrillation have been elucidated, little is yet known about the mechanisms involved in *termination* of AF. And still, from a medical point of view this is the most important aspect of the arrhythmia, since if one were certain that AF would always cardiovert within a couple of hours, the arrhythmia would not require any treatment unless the paroxysms occurred very frequently. In this chapter we will discuss the possible mechanisms involved in perpetuation and termination of AF.

Multiple Wavelet Theory

On the basis of animal experiments and computer simulations, in 1964 Moe proposed that atrial fibrillation is based on multiple wavelets propagating randomly through the atria [5, 6]. Later, mapping studies both in animals and in humans have supported this hypothesis [7-11]. When atrial fibrillation is maintained by multiple wandering wavelets, termination of AF is dependent on the statistical chance that all wavelets will die out simultaneously. If the average number of wavelets is small, the chance that this will happen is high and atrial fibrillation will self-terminate within a short time. On the other hand, if there are many

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wavelets present, the chance that they will all die out at the same time might become so small that atrial fibrillation is persistent. Direct proof that perpetuation of AF is dependent on multiple wavelets has been provided by the successful development of a surgical treatment of atrial fibrillation by Cox et al. in 1991 [8]. With the goal of obliterating the substrate for multiple reentering wavelets, they divided the total surface of the atria into various smaller segments by multiple linear incisions both in the right and the left atrium. By this procedure the normal anatomy of the atria was transformed into a *maze* of narrow pathways, which still allowed conduction of the electrical impulse from the sinus node to the AV node, but no longer provided the substrate for enough wavelets to perpetuate atrial fibrillation.

For reentry to occur without the involvement of a gross anatomically preformed pathway (leading circle reentry [12], figure of eight reentry [13], spiral wave [14], random reentry [10]), a critical tissue mass is required [15]. In this respect we earlier emphasized the importance of the wavelength (wavelength = refractory period x conduction velocity) [16, 17]. If the wavelength is short, the minimal size of a functionally determined circuit will be small and the required tissue mass for reentry can also be small. On the other hand, if the wavelength is long, the minimal dimensions of a functional circuit are larger and reentry can only perpetuate in a relatively large piece of myocardium. In a given heart of a certain size which is fibrillating, prolongation of the wavelength would decrease the number of randomly reentering wavelets and might thus lead to termination of AF [17]. This concept was recently supported by a number of studies by Nattel at al. [18, 19]. They showed that at high pacing rates, both class I and class III drugs prolonged the atrial wavelength and that termination of AF was associated with a decrease in the number of multiple wavelets. On the other hand, Swiryn's group [20] failed to find evidence for progressive fusion of wavelets prior to termination of AF in humans, and they concluded that "atrial fibrillation usually terminates directly to sinus rhythm and does so abruptly and without forewarning" and in addition, that before termination of AF "consistent trends toward more regular cycle lengths, alternating long and short cycle lengths, or progressively longer cycle lengths were not observed" [20].

Termination of AF in the Goat

Recently we have developed a chronically instrumented goat model of atrial fibrillation in which we have studied some of the electrophysiological mechanisms of spontaneous termination of atrial fibrillation [21]. Twelve goats were chronically instrumented with 27 epicardial electrodes, sutured to the left and right atrial free wall, the right and left atrial appendages, and the bundle of Bachmann. AF was chronically maintained by a fibrillation pacemaker which automatically delivered a 1 second 50 Hz burst electrical stimulus as soon as atrial fibrillation had cardioverted to sinus rhythm. While during control electrically induced AF usually terminated readily within a few seconds, after a couple of days of main-

tained AF the paroxysms became more stable and lasted for several minutes. After 1-3 weeks of maintained AF atrial fibrillation had become sustained (> 24 hours) [21].

Electrograms were analyzed recorded from 5 different areas 12 seconds before the spontaneous termination of AF. The following parameters were measured on a beat-to-beat basis: (1) local fibrillation intervals, (2) local conduction times, and (3) local conduction velocities. Local activation times were determined from the steepest negative deflection of the unipolar electrograms. Fibrillation interval histograms were made from one electrode at each of the five areas. Conduction times were measured between two neighboring electrodes (interelectrode distance 6 mm). The regional direction and velocity of propagation was measured by calculating the vector of conduction in quadruples of electrodes 6 mm apart. The quadruples were divided into two triangles and the vector of each triangle was calculated. The average of the two vectors was taken as the average direction and velocity of the fibrillation wavelet in the area of 6 x 6 mm. Only velocities in the range between 10 and 180 cm/s were taken into account. Very low and very high values were discarded because they resulted from local intra-atrial conduction block and collision or epicardial breakthrough of fibrillation waves respectively.

In Fig. 1 an example is given of an atrial electrogram recorded during the last seconds of atrial fibrillation. As it can be seen the electrogram showed clear beat-to-beat variations in configuration, but most of the time consisted of single negative deflections separated by short isoelectric segments, indicating that the atria

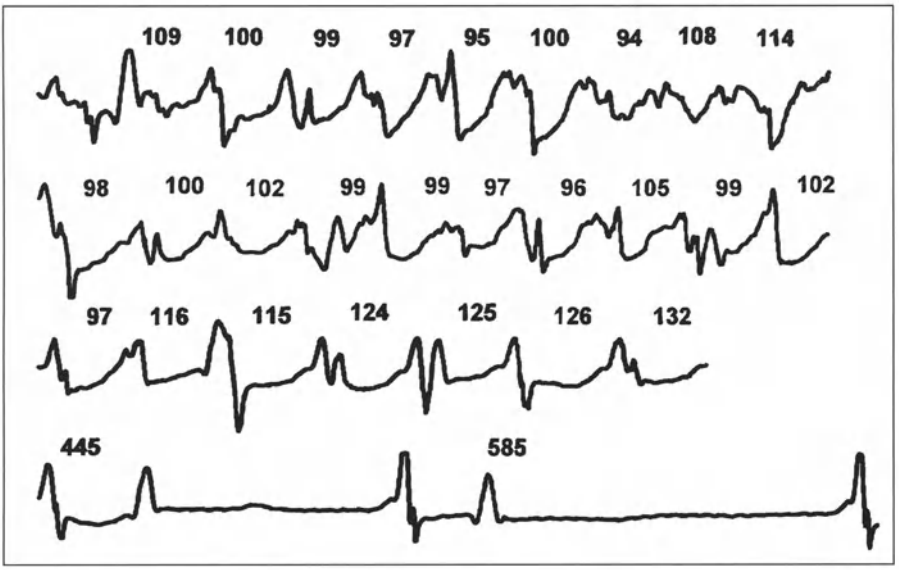

Fig. 1. Unipolar electrogram recorded from the left atrial free wall showing slowing of the rate of fibrillation prior to conversion to sinus rhythm. The individual fibrillation cycles are given in milliseconds

were still relatively uniformly activated by broad activation waves (Type I fibrillation) [10, 11, 12]. Because at this stage fragmented electrograms occurred only rarely, local activation times could be derived without too much uncertainty from the fibrillation electrograms. In this example, up to the last 7 beats prior to termination, AF showed the usual temporal variation in fibrillation intervals with a median value of 99 ms and a p5-95 of 14 ms. However, about 1 second before conversion to sinus rhythm this patterm suddenly changed and the atrial fibrillation intervals lengthened progressively to more than 130 ms. In Fig. 2 the mean fibrillation intervals are plotted recorded at 5 atrial sites during the last 17 cycles of a paroxysm of AF in 9 goats. In the whole series, the 14th interval prior to spontaneous conversion to sinus rhythm was the first AF cycle to be statistically prolonged. The average AF cycle length during the last three beats of AF were 148 ± 10, 153 ± 6, and 165 ± 7 ms (S.E.M.) compared to 113 ± 2 ms during ongoing AF (one hundred cycles prior to termination) ($p < 0.001$).

The progressive deceleration in the rate of atrial fibrillation prior to termination was associated with an *increase* in conduction velocity of the fibrillation waves.

During stable fibrillation the average conduction velocity was 68 ± 8 cm/s. About 3 seconds before termination of AF the average conduction velocity of the fibrillation waves started to increase resulting in a conduction velocity of 97 ± 20, 101 ± 17 and 99 ± 10 cm/s during the last three beats of AF ($p < 0.001$).

The maximal number of reentering fibrillation waves during atrial fibrillation

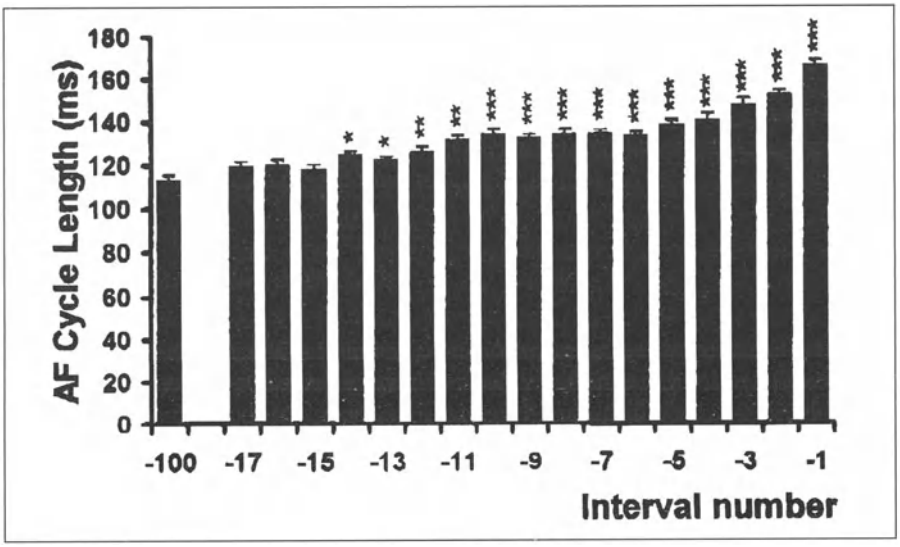

Fig. 2. Progressive prolongation of AF cycle length before spontaneous termination of atrial fibrillation in 9 goats. The mean atrial cycle length during AF (100 cycles before termination) is plotted together with the last 17 cycles before termination. During the last 14 beats of AF the cycle length progressively prolonged from 113 ± 2 to 165 ± 7 ms. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

is determined by the size of the atria and the length of the intra-atrial circuits. On the basis of the measured local conduction velocities and fibrillation cycle lengths, the average length of the reentrant pathways during AF was estimated as:

$$\text{Circuit Size}_{avg} = \text{Conduction Velocity}_{avg} * \text{AF Cycle Length}_{avg}$$

In the series of experiments given above, in their stable phase the fibrillation waves had a mean cycle length of 113 ms and an average conduction velocity of 68 cm/s. Thus, on an average, during one AF cycle the fibrillation waves propagated over a distance of 7.7 cm. Simplifying the complicated pathways of excitation during AF to simple circular-shaped circuits, during ongoing AF the average diameter of the fibrillation circuits were in the order of 20-30 mm.

In contrast, during the last three cycles before termination of AF the calculated length of the reentrant pathways had increased markedly to 15 ± 5, 15 ± 3, and 16 ± 2 cm respectively. This was due both to a prolongation of AF cycle length and an increase in conduction velocity. Assuming that no specific areas of slow conduction are involved in the intra-atrial circuits, the last reentrant pathway of AF must have had a diameter of more than 50 mm.

The observation that termination of AF was associated both with an increase in cycle length *and* conduction velocity of the fibrillation waves, suggests that conversion of AF was not primarily due to an increase in wavelength but to a progressive *widening of the excitable gap* which has been shown to exist during AF [9, 23, 24]. There are several possible mechanisms of widening of the excitable gap during AF, depending on the type of reentry involved. One possibility is that widening of the excitable gap is the result of an increase in size of the reentrant pathway. This may happen if smaller functionally determined circuits are interrupted, either by chance or under the influence of a drug, and are replaced by larger waves traveling around one or more of the atrial anatomical obstacles.

Mechanisms of Termination of AF

Although the successful abolishment of AF in patients by the maze operation [8] shows that AF will not perpetuate without a substrate for multiple wavelets, this of course does not mean that there are no other ways to terminate AF. Although the number of wavelets can be diminished by antifibrillatory drugs, it is far from clear whether multiple wavelets are the only mechanism for perpetuation of AF. On the contrary, we consider it quite feasible that during long-lasting AF additional electrophysiological mechanisms are operating. If termination of AF would solely depended on the statistical chance that the multiple wavelets die out simultaneously, atrial fibrillation would still terminate sooner or later. Mapping studies in canine and human hearts have shown that the number of wavelets during AF is certainly not extremely high and that on an average about 5-6 wavelets exist during AF [7, 8, 10, 11, 18, 19]. If one assumes an average of 5 independent waves with an individual life time of 10 cycles, the statistical chance that all wavelets will die

out during the same AF cycle is 1:100000 cycles. Thus, with a rate of 420 per minute, atrial fibrillation can be expected to self-terminate every 238 minutes. Or, in other words, AF based on multiple wavelets alone would not be persistent and sinus rhythm would resume after an average fibrillation time of 4 hours.

In Table 1 we have calculated the required life time of the multiple wavelets to sustain atrial fibrillation for a period varying between 1 minute and 10 years. The number of wavelets was assumed to be between 1 and 10. The life time of each wavelet is expressed as the number of fibrillation cycles it propagates through the atria. The assumed fibrillation rate was 420 cycles per minute.

From Table 1 it can be seen that if on an average 5 wavelets are present, the required lifetime of each wavelet to sustain AF for 1 day, 1 month, 1 year, or 10 years would be 14, 28, 46, and 73 cycles respectively. Although it is difficult to measure the exact lifetime of each fibrillation wave, mapping data of atrial fibrillation suggest that the lifetime of each wavelet is not very long. Therefore, the possibility should be considered that additional mechanisms are operative in patients with chronic AF.

Possible Additional Mechanisms for Perpetuation of AF

What other mechanisms than the multiple circulating wavelets could be involved in preventing AF from cardioverting spontaneously? There are several possibilities.

1) Apart from the unstable functionally determined reentrant wavelets also a more stable circuit can be present in the atria. In such a situation, when the multiple wavelets die out, the atria do not convert to sinus rhythm, but instead the impulse continues to circulate in this stable circuit. Indeed, in patients with AF frequent transitions between "true" AF and a more flutter-like pattern are observed. Gordon Moe designated this phenomenon with the term "atrial flitter" to indicate his belief that it was a mixture of flutter and fibrillation. But even if there are no clear episodes of flutter, the availability of an anatomically determined circuit may play an important role in perpetuation of AF by preventing the last fibrillation wave to die out. If the multiple wavelets during AF are both functionally and anatomically determined, at the moment the more unstable functional wavelets die out, at least one wave may still propagate in (the isthmus of) an anatomically determined circuit (either micro- or macroreentrant). As soon as this remaining wave exits from its circuit it will find the atria highly vulnerable to fibrillation because the different parts of the myocardium are still in a different state of excitability. Therefore the early excitation of the atria by the wave exiting from its anatomical circuit will act as an early premature beat that will immediately reinitiate the multiple wavelets and in that way prevent termination of AF. Such an event will remain unwitnessed apart from the occasional occorrence of a long fibrillation cycle.
2) Similarly, after the multiple atrial wavelets have died out, AF might be immediately reinitiated by an echo wave originating from the sinus node or the AV node, or in WPW patients from the accessory pathway.

Table 1. Required lifetime of wavelets (number of AF cycles)

	Duration of Atrial Fibrillation						
N. Wavelets	1 Min	1 Hour	1 Day	1 Week	1 Month	1 Year	10 Years
1	420	25 200	604 800	4 233 600	18 748 800	212 284 800	2 122 848 000
2	20	159	778	2 058	4 330	14 570	46 074
3	7	29	85	162	266	597	1 285
4	5	13	28	45	66	121	215
5	3	8	14	21	28	46	73
6	3	5	9	13	16	24	36
7	2	4	7	9	11	15	21
8	2	4	5	7	8	11	15
9	2	3	4	5	6	8	11
10	2	3	4	5	5	7	9

3) Another possibility why atrial fibrillation becomes persistent is that besides reentry, a form of abnormal impulse formation is also present in the atria. Recently we have shown that prolonged episodes of fibrillation trigger a process of electrical remodeling that changes the expression of ionic channels in the myocardium [21]. It therefore is not unlikely that some of the ionic mechanisms involved in early and late afterdepolarizations, triggered activity or abnormal automaticity might also be induced by atrial fibrillation. In other words, the substrate of permanent AF might not only consist of a substrate for reentry, but might also contain the trigger to automatically restart the arrhythmia as soon as it terminates spontaneously or is artificially cardioverted. This intriguing possibility has been recently supported by the finding of Haïssaguerre's group that, in a selected group of patients with AF, abnormal electrical activity was recorded from within the superior pulmonary veins. Focal endocardial ablation of these sites cured atrial fibrillation [25].

In general, we would like to propose that in patients with persistent or permanent atrial fibrillation additional mechanisms besides multiple wavelets play a role in maintaining AF. These additional mechanisms can be based on pathological micro- or macroreentrant pathways or on the presence of abnormal impulse formation in some parts of the atria, thus providing a "back-up" to restart atrial fibrillation immediately in case it might terminate.

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Vagal Tone: How Important Is It in Triggering Atrial Fibrillation?

A. Capucci, G.Q. Villani, D. Aschieri and A. Rosi

Introduction

The parasympathetic nervous system modulates the electrophysiological properties of most structures involved in normal cardiac function and in experimental and human arrhythmias. However *in vivo* it is actually difficult to evaluate the pure vagal effect since sympatho-vagal interactions are specifically involved in modulating the electrophysiological parameters. The not universally accepted concept of dividing the atrial fibrillation episodes in vagal and sympathetic induced ones is mainly based on anecdotal cases and on clinical preselected models.

Anatomy and Physiology

The efferent pathways responsible for cardiac parasympathetic control are derived primarily from the ventro-lateral region of the nucleus ambiguous, the dorsal vagal nucleus and the intermediate zone between nuclei. The preganglionic cardiac vagal fibers are connected to ganglia adjacent to the pulmonary veins, inferior vena cava - inferior left atrial junction and A-V groove. The vagal fibers cross the A-V groove and are located in sub-endocardial regions [1]. Experimental studies have established that at least two types of receptors are found in the heart that are carried by vagal afferent fibers [2].

Acetylcholine is the neurotransmitter that is crucial to the functioning of the preganglionic and postsynaptic neurons; its cardiac action is mediated by interaction with one of the several subtypes of muscarinic receptors [3].

Electrophysiology

The parasympathetic system influences the heart electrophysiology by modulating several cardiac ionic channels:

1. The dromotropic effect of vagal stimulation on the sinus node and the A-V

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node is mediated by influences on K_{Ach} channels. Its activation results in cell hyperpolarization with a short delay cardiac effect [4]
2. Acetylcholine inhibits the inward current (If) that in sinus node cells is activated by hyperpolarization and tends to depolarize these cells [5]
3. Acetylcholine inhibits the voltage and time-dependent calcium current. This effect is mediated by inhibition of cAMP synthesis [6].

The vagal stimulation shortens the atrial refractory period and increases the dispersion of the atrial refractoriness in experimental models [7, 8]. This effect is more evident if combined with additional modifiers of refractoriness such as hypothermia [9].

Nevertheless the action of the parasympathetic system may be attenuated or facilitated by the sympathetic system. Vago-sympathetic interaction is the consequence of the anatomic proximity of the nerve terminals of the two systems [10]. The final effect is a result of the non-uniform anatomic distribution of nerve endings and the temporal heterogeneity of nervous stimulation. Consistent data suggest that atrial vulnerability to vagal stimulation depends on the shortening of the wavelength [9], while micro re-entry, automatic and triggered activity are more likely to occur as a consequence of sympathetic stimulation [11].

Atrial Fibrillation in Experimental Studies

Several investigators have noted that in experimental models vagal stimulation (administration of acetylcholine or methylcholine, direct vagal stimulation) may induce sustained atrial fibrillation [12, 13]; this effect is related to the activation of acetylcholine K+ channels or to the inactivation of cAMP calcium channels. Different electrophysiological effects are involved in the mechanism of atrial fibrillation induction: a shortening of atrial myocardial refractory period with dispersion of refractoriness, a production of intra-atrial conduction delays and the accompanying bradycardia favor the formation of re-entrant circuit. Furthermore, the negative inotropic effect of cholinergic stimulation leads to atrial distension that may alter cellular electrophysiological properties and predispose to arrhythmia [14].

However, the membrane effect of acetylcholine is dependent on the underlying electrophysiological conditions. The muscarinic agonist plays a protective action against the profibrillatory effect of isoprenaline or glucagon but has no effects against dibutyril-cyclic AMP, ouabain or electrical stimulation [15].

Atrial Fibrillation in Human Observations

Coumel et al. first described a syndrome of recurrent paroxysmal atrial fibrillation which was very homogeneous from the clinical and ECG point of view [16]. The condition developed slowly over a period of years towards a maximum incidence of several short daily attacks of an arrhythmia which alternated between

atrial fibrillation and atrial flutter which were usually not completely nocturnal. Vagal overactivity was considered the precipitating cause of these attacks on the basis of the onset pattern of arrhythmia. The beginning of each attack was accompanied by a progressive slowing of the sinus rate down to threshold level.

The following observations allowed the authors to characterize the pattern of atrial fibrillation of vagal origin (Table 1):

- Absence of underlying heart disease (lone atrial fibrillation);
- Predominance of young men over women (ratio 4:1);
- Attacks starting at night, during rest or after meals;
- Arrhythmia preceded by progressive sinus rate bradycardia with further slowing before the atrial fibrillation onset;
- Frequent mixed picture of atrial fibrillation and flutter;
- Presence of the sensation of incoming arrhythmia (atrial premature beats);
- Atrial fibrillation may be prevented by exercise.

In these patients vagal maneuvers or administration of vagotonic drugs may artificially trigger the arrhythmia and this effect can be prevented by atrial pacing at a relatively rapid rate. Furthermore, anecdotal experiences suggested the beneficial effects of anticholinergic antiarrhytmic drugs (disopyramide, quinidine, flecainide) and the clinical worsening with digitalis treatment (subsequent to its vagotonic electrophysiological effect).

Table 1. Clinical differences between vagally mediated and adrenergically mediated atrial fibrillation (AF)

Vagally mediated atrial fibrillation	Adrenergically mediated atrial fibrillation
• Male predominance, age 30-40	• No sex or age predominance
• Absence of structural heart disease	• Any cardiovascular disease
• Attacks at night, never in the morning, favored by rest, alcohol, digestion	• Attacks occurring in daytime, favored by stress, exercise
• Preceded by HR decrease and/or increase of high frequency HRV	• Preceded by HR acceleration and/or increase in low frequency HRV
• Mixed picture of atrial flutter/AF	• Mixed picture of atrial tachycardia/AF
• Vagal maneuvers may induce AF	• Catecholamines may induce AF
• β-blockers/digoxin contraindicate type IA/IC (except propafenone) and/or amiodarone	• β-blockers ± digoxin: indicated ± type IA/IC drugs (propafenone) ± amiodarone
• Atrial pacing may be useful	• No indication for atrial pacing

Murgatroy et al. [17] proposed an "Autonomic Profile Questionnaire" in order to evaluate the frequency of the vagal and sympathetic pattern amongst the population of atrial fibrillation patients, based on the agreement between arrhythmic symptoms and various activities (Table 2). When the questionnaire was pro-

Table 2. The autonomic profile questionnaire proposed by Murgatroy and Camm [17]

My attacks tend to start...“	Score (unweighted)*	Score (weighted)*
... shortly after waking	A	2A
... after meals	V	V
... after alcohol	A	A
... after tea or coffee	A	A
... during exercise	A	2A
... after exercise	V	V
... with twisting of the neck/shoulders	V	V
... resting or going to sleep	V	2V
... during sleep	V	2V
... with emotional stress	A+V	A+V

Never = 0 points; Rarely = 1 point; Sometimes = 2 points; Often = 3 points; Usually = 4 points.
*A: points count toward adrenergic score; V: points count towards vagotonic score; 2A: points are doubled before counting toward adrenergic score; 2V: points are doubled before counting toward vagotonic score.

posed to 38 patients, it appeared that symptoms were commonly associated with factors causing increase in vagal rather sympathetic tone, suggestive of a greater importance of vagal modulation as the arrhythmic trigger.

Nevertheless a direct correlation between clinical observations and vagal activity is still a matter of debate and has to be proved.

An autonomic imbalance might also play a role in atrial fibrillation occurring after cardiac surgery. Indeed, epidemiological studies reported that this arrhythmia complicates up to 40% of cardiac surgical procedures [18]. Recently Frost et al. investigated the impact of preoperative autonomic balance and atrial ectopic activity on the risk of atrial fibrillation after aorto-coronary artery by-pass surgery, analyzing the heart rate variability by 24-h Holter monitoring. A reduced cardiac vagal modulation (lower day-night difference in the mean RR level) was considered a stronger predictor of arrhythmia occurrence (relative risk 4.50, confidence index 1.40-14.5) [19].

Camm et al. performed baroreflex testing in 28 patients with “vagal” paroxysmal atrial fibrillation using the phenylephrine bolus method. No relationship was found between vagal score and baroreflex sensitivity, leading to speculation that in these cases the abnormality must reside in the response of the atrium itself rather than in the autonomic system [17].

Recently we evaluated in 35 patients with lone paroxysmal atrial fibrillation the sympatho-vagal balance response to tilt-test and the electrophysiologic substrate by P-Triggered Signal Averaged ECG. A blunted response to tilt-test was demonstrated in atrial fibrillation patients. This result was mainly due to the presence of a subgroup of arrhythmic patients with lower HF%, which is an index of sympathetic prevalence [20].

Capucci et al. studied 15 consecutive patients with prevalent nocturnal atrial fibrillation episodes and without any detectable organic heart disease, performing a sleep monitoring by simultaneous recording of electroencephalogram, electrooculogram, systemic arterial pressure, ear oxymetry and continous ECG recording by Holter system. The highest probability of atrial fibrillation onset was in sleep phases 1-2 and not in phases 3-4 where there is a prevalent vagal tone. In addition, the HRV analysis of the 2 minutes before atrial fibrillation onset pointed out both a prevalent vagal and sympathetic tone, probably reflecting a sympatho-vagal imbalance [21].

In conclusion, although the vagal influence has been found to be able to trigger atrial fibrillation in an experimental setting, there is no strong scientific proof of the same effect in humans. Observation of atrial fibrillation onset during sleep and with the HRV evaluation does not support the idea of a pure vagal activation even in this condition. We think that the existence of a vagal pattern of atrial fibrillation in humans is still to be proven and therefore any classification of sympathetic and vagal atrial fibrillation merely based on clinical parameters does not have any scientific value.

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Tachycardia Induced Atrial Fibrillation: What Incidence? How to Diagnose and Treat It?

P. Delise, L. Corò, P. Scipione and M. Fantinel

Atrial fibrillation is the most common supraventricular arrhythmia in the clinical setting. Some patients present both atrial fibrillation and other supraventricular tachycardias such as focal atrial tachycardia, common and uncommon atrial flutter, atrioventricular reentrant tachycardia related to an overt or a concealed Kent bundle, or atrioventricular nodal reentrant tachycardia. E.N. Prystowsky [1] suggested that all the above mentioned forms of paroxysmal supraventricular tachycardia can trigger atrial fibrillation, a phenomenon he referred to as "tachycardia-induced tachycardia". Potential factors affecting conversion of sustained atrial and nonatrial tachycardias to atrial fibrillation include tachycardia cycle length [2, 3], particular electrophysiological characteristics of the triggering arrhythmia [1] and contraction-excitation feed-back [4]. As to the latter phenomenon, it has been demonstrated that after the onset of some supraventricular tachycardias, a sudden dilatation of the atria can occur [1]. Subsequently, as changes in mechanical stress can alter cardiac membrane potential (contraction-excitation feedback), it is possible that sudden dilatation of the atria affects cardiac membrane potential and leads to atrial fibrillation.

The diagnosis of tachycardia-induced tachycardia is not always easy because the triggering arrhythmia is not always recorded by electrocardiogram. Regarding treatment, it has been recently suggested that in some patients the elimination of the triggering arrhythmia by surgery or by radiofrequency catheter ablation is able to prevent also atrial fibrillation [2, 3, 6-9]. The possible triggers of atrial fibrillation and the usefulness of their treatment will be analyzed separately.

Focal Atrial Tachycardia

A rapid atrial tachycardia may be responsible for sustaining atrial fibrillation in patients with paroxysmal and chronic atrial fibrillation, and the elimination of atrial tachycardia can restore sinus rhythm [6]. The incidence of this condition is unknown but probably quite rare. The diagnosis can be reached only through electrophysiologic studies and detailed biatrial mapping. The ablation of atrial

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tachycardia may require a transatrial puncture if atrial tachycardia is localized in the left atrium.

Common Atrial Flutter

Patients with common atrial flutter frequently also present with atrial fibrillation. The exact incidence of this association, however, is not well established. Radiofrequency ablation of the isthmus between the inferior vena cava orifice and the tricuspid annulus, or between the coronary sinus ostium and the tricuspid annulus is able to prevent atrial flutter in about 80%-90% of cases [10,11]. A major problem is represented by the recurrence of atrial flutter which is described in about 10%-30% of cases. About 10% of patients who have only atrial flutter before ablation, can present with not previously documented episodes of atrial fibrillation after ablation, despite the elimination of atrial flutter. In these cases it is not clear whether the lesion produced by ablation may have facilitated the occurrence of atrial fibrillation or if atrial fibrillation is simply a concomitant arrhythmic event related to the underlying atrial disease.

A controversial issue is the usefulness of ablation of the atrial isthmus (between the tricuspid annulus and the orifice of inferior vena cava and/or between the former and the os of the coronary sinus) in patients who present with both atrial flutter and atrial fibrillation in the basal state. In our experience [12] in these cases the ablation of the cited isthmus is able to prevent atrial flutter but not atrial fibrillation. In fact among 24 patients with atrial flutter-treated by radiofrequency ablation, 9 (37%) had both atrial flutter and atrial fibrillation (Group I) while the remaining 15 (63%) had only documented atrial flutter. Radiofrequency ablation eliminated atrial flutter during a follow-up of 14+/-12 months in 78% and 73% of patients in the two groups, respectively. However atrial fibrillation recurred in 89% of Group I and developed as an apparently new arrhythmia in 13% of Group II.

Atrioventricular Reentrant Tachycardia in the Presence of Overt (WPW) or Concealed Kent Bundles

Atrial fibrillation is a common arrhythmia in patients with Kent bundles. In patients with the WPW syndrome atrial fibrillation is described in up to 30% of cases with recurrent palpitations [13, 14]. It has been suggested that in WPW patients atrial fibrillation is generally triggered by atrioventricular reentrant tachycardia [13-17]. In fact, almost all patients with paroxysmal atrial fibrillation also present with recurrent atrioventricular paroxysmal tachycardia. Faster rates of atrioventricular reentry appear to predispose to the development of atrial fibrillation [2, 3], but it is extremely common to observe degeneration of atrioventricular reentry into atrial fibrillation during electrophysiologic study in patients

with relatively slow atrioventricular reentry (150 beats per minute) [1]. A short refractory period of the Kent bundle is another factor predisposing to the development and maintenance of atrial fibrillation [3, 18]. Finally, intrinsic atrial vulnerability is probably a striking factor in patients with WPW who have no heart disease and present with clinical episodes of atrial fibrillation [17, 19]. In fact some authors [17, 18] described a greater atrial vulnerability and an easier initiation of atrial fibrillation by atrial stimulation in patients with WPW syndrome who have a history of atrial fibrillation. The hypothesis that atrioventricular reentrant tachycardia is the main trigger of atrial fibrillation in the WPW syndrome is confirmed by the observation that Kent bundle ablation is generally able to prevent both arrhythmias [2, 3, 7].

Some authors suggest that patients with concealed Kent bundles present with primary atrial vulnerability as well [20]. The incidence of atrial fibrillation in the latter patients is not well established but probably ranges between 10% and 20% [21, 22]. The diagnosis of tachycardia-induced atrial fibrillation in patients with concealed Kent bundles can be difficult, because in these patients the basal electrocardiogram is normal and it is not always possible to obtain an electrocardiogram during paroxysmal atrioventricular reentrant tachycardia. In fact, in many cases the paroxysmal atrioventricular tachycardia lasts only a few minutes and/or rapidly degenerates into sustained atrial fibrillation. Only when episodes are particularly frequent is it possible to record them by Holter monitoring or by transtelephonic transmission. The diagnosis must be suspected in patients which refer to regular paroxysmal palpitations for many years and who describe a modification of their symptoms owing to the occurrence of irregular palpitations. When suspected, the diagnosis can be reached by electrophysiologic study. Catheter ablation of the Kent bundle frequently eliminates all arrhythmias.

Atrioventricular Nodal Reentrant Tachycardia

About 10% of patients with atrioventricular nodal reentrant tachycardia also present with atrial fibrillation [21-23]. Some authors [24] suggest that, similarly to preexcitation syndromes, some patients with atrioventricular nodal reentrant tachycardia may present with a primary atrial vulnerability. In some cases the diagnosis of this form of tachycardia-induced tachycardia is difficult. In fact, as previously discussed for concealed Kent bundles, some patients have only brief (few minutes) episodes of paroxysmal supraventricular tachycardia and/or the latter rapidly degenerates into sustained atrial fibrillation. It follows that in some cases only atrial fibrillation is electrocardiographically documented, leading to an erroneous diagnosis of idiopathic atrial fibrillation. The diagnosis must be suspected when patients refer both regular and irregular palpitations. The diagnosis can be obtained by electrophysiologic study. Catheter ablation of the slow or fast pathway is able to eliminate both arrhythmias in subjects without structural heart abnormalities [8, 9]. In patients with structural heart abnormalities, atrial fibrillation can relapse [8] despite the cure of atrioventricular nodal tachy-

cardia. In the latter cases, however, antiarrhythmic drugs can reduce or abolish paroxysmal palpitations.

Clinical Implications of a Correct Identification of "Tachycardia-induced Atrial Fibrillation"

Atrial fibrillation is an arrhythmia that is frequent and difficult to cure. In fact, drug therapy is ineffective in preventing recurrences in over 40% of cases. Cath-eter ablation of its atrial substrate by multiple linear atrial lesions is currently experimental and cannot be extensively used. A small group of patients with atrial fibrillation also have other supraventricular arrhythmias. The latter can represent a casual association or they can be the main trigger of atrial fibrillation. The identification of patients with tachycardia-induced atrial fibrillation is of clinical interest because the ablation of the triggering arrhythmia can also cure atrial fibrillation. This is the case of focal rapid atrial tachycardia, of atrioventricular tachycardia related to an overt or concealed Kent bundle, and of atrioventricular nodal reentrant tachycardia. Atrial fibrillation can complicate the clinical course of the above mentioned arrhythmias in at least 10% of cases. The diagnosis of tachycardia-induced atrial fibrillation is sometimes difficult and requires an electrophysiologic study. It follows that it must be suspected in patients with recurrent episodes of atrial fibrillation referring to both regular and irregular palpitations especially when they have no structural heart abnormalities. In fact, in patients without heart disease the suppression of a rapid focal atrial tachycardia, of a Kent bundle or of the atrioventricular node slow or fast pathway can be curative. On the contrary, in patients who suffer from heart disease catheter ablation, while eliminating the regular reentrant arrhythmia, it is generally not able to influence the natural history of atrial fibrillation. In patients with atrial flutter the suppression of the arrhythmia seems to be ineffective in preventing atrial fibrillation even in the absence of evident structural abnormalities. This behavior probably depends on a concealed but diffused atrial disease.

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ATRIAL FIBRILLATION: CARDIOVERSION AND DRUG PROPHYLAXIS

Restoration of Sinus Rhythm: Pharmacological or Electrical?

M. Chimienti, S. Barbieri and G. Guazzotti

Atrial fibrillation (AF) is the most commonly occurring cardiac arrhythmia; nonetheless, management strategies for its control are far from satisfactory. Most patients experience palpitations, but dyspnea, lightheadedness and fatigue are not uncommon. In some patients even totally asymptomatic AF may be responsible for thromboembolic events, especially in the elderly and in patients with structural cardiac disease. Patients with high ventricular response during AF may develop heart failure and occasionally tachycardia-induced cardiomyopathy. Furthermore, AF has been demonstrated to be associated with decreased survival, regardless of the underlying heart disease [1]. For all these reasons, restoration of sinus rhythm is the ideal therapeutic intervention in the majority of cases; although a general management strategy can be established, a specific risk/benefit balance should be calculated for each individual patient.

Atrial Fibrillation: Aims of Treatment

Patients with AF may need different therapeutic approaches in relation to their clinical presentation. The aims of treatment are summarized as follows:

- *correction of the underlying disease*: a specific treatment should be provided first in order to control any possible etiologic factors that might be identified (hyperthyroidism, electrolyte imbalance, acidosis, etc.);
- *termination of sustained episodes*: this may be pursued by either pharmacological (intravenous or oral drugs) or electrical methods (transthoracic direct-current countershock is used most often, but internal low-energy cardioversion may be carried out in selected and particularly resistant patients). Characteristics, risks and benefits of the different therapeutic approaches to cardioversion of sustained episodes of AF are more extensively treated in this review;
- *prevention of recurrences*: a complete prevention is often difficult to reach with any antiarrhythmic agent; a reduction of frequency and duration of recurrences is usually considered a relatively satisfactory success;

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- *control of ventricular response*: in patients in whom any attempt of converting AF to sinus rhythm or preventing recurrences fails, therapy should aim at maintaining the ventricular rhythm at acceptable rate and regularity; this may be principally achieved with drugs that decrease AV nodal conduction and sometimes by means of ablation/modulation procedures and pacemaker implantation;
- *prevention of thromboembolic accidents*: in patients with prolonged recurrences, frequent paroxysms or permanent chronic AF, a specific anticoagulant or antiplatelet regimen should be instituted, according to specific well-established protocols.

Why to Convert Atrial Fibrillation?

In patients with sustained, not self-terminating accesses of AF, an attempt of converting to sinus rhythm is mandatory, unless there are particular reasons to believe that any attempt to restore and maintain sinus rhythm will be futile or hazardous. There are several reasons in favor of the restoration of sinus rhythm:

- *relief of symptoms*: even if some patients can be asymptomatic during AF, most patients complain of several symtoms, that may be troublesome (palpitations, fatigue) but sometimes may also be clinically dangerous (symptomatic hypotension, dyspnea, heart failure, angina, dizziness, syncope);
- *risk reduction*: it is well known that AF increases the incidence of thromboembolic events (stroke), and that it may precipitate uncontrollable angina (chest pain increases sympathetic tone which, in turn, may increase heart rate and oxygen consumption), syncopal attacks (due to abrupt heart rate acceleration and consequent cerebral-flow drop), heart failure (the so-called "rate-related cardiomyopathy" secondary to inappropriately rapid ventricular rates for long periods of time), ventricular tachyarrhythmias (favored by irregular and high rates, possible relative ischemia, autonomic imbalance, etc.) and occasionally death;
- *prevention of electrical remodeling*: clinical experience and recent experimental evidence [2,3] show that AF itself may cause electrical changes in the atria, thereby favoring the progression of paroxysmal to chronic AF ("atrial fibrillation begets atrial fibrillation"); that is why treatment should try to interrupt this vicious circle, by maintaining sinus rhythm as long as possible.

When to Convert Atrial Fibrillation?

As a general rule, AF should be converted *as soon as possible.* All patients should be given the chance to have their rhythm converted to sinus rhythm, independently of the presence of symptoms, unless the risks of the procedure (either pharmacological or electrical) outweigh the benefits of the possible results. Usually, an AF present for more than 1 year and the documentation of a conspicuous left atrial enlargement are considered negative prognostic factors that do not guarantee a high probability of success.

Where to Convert Atrial Fibrillation?

Both pharmacological and electrical cardioversion should be performed in an adequate hospital setting, under continuous electrocardiographic and vital-sign monitoring, with rapid access to resuscitation facilities. When oral antiarrhythmic drug loading is repeatedly effective during in-hospital administration without appearance of any adverse effects or complications, drug self-administration at home may be permitted in selected cases.

How to Convert Atrial Fibrillation?

In patients with new-onset (usually a few hours) and hemodynamically well-tolerated AF, without significant underlying heart disease, an immediate therapeutic intervention may be delayed, unless the patient is highly symptomatic, because spontaneous reversion is to be expected in at least half of the cases [4]; only drugs able to decrease atrial conduction through the AV node may be given, if needed, in order to relieve symptoms (digitalis, calcium antagonists, β-blockers or amiodarone may be helpful in this setting).

If the arrhythmia has been present for a longer period of time (but with reasonable certainty for less than three days) and is hemodynamically stable, an intravenous or oral drug therapy may be started without pretreatment with anticoagulants, since in this setting the risk of embolism is lower than that of hemorrhagic complications. Usually, it is preferable to make an attempt at pharmacologic conversion first, in order to understand how the arrhythmia is sensitive to a particular drug, with important prognostic implications: in fact, after the first episode nobody knows how many recurrences and how many hospitalizations will follow and how difficult prophylaxis will be in that particular patient (Table 1). During

Table 1. Pharmacological cardioversion

1. Main characteristics:
   - intravenous or oral drugs
   - hemodynamically and electrically stable patients
   - anticoagulation if needed
   - pharmacological heart rate control if needed
   - highly effective in recent-onset AF
   - time consuming

2. Benefits:
   - no need for anesthesia

3. Risks:
   - negative inotropic effects of most drugs
   - ventricular proarrhythmia

continuous electrocardiographic and vital-sign monitoring an antiarrhythmic agent is administered according to well-established protocols; the choice of the drug depends mostly on the preference and experience of the physician. Intravenous or oral flecainide has demonstrated to be the most effective and rapid drug in converting AF to sinus rhythm, with an acceptable incidence of side effects (e.g. hypotension) [4-8]. Propafenone is also frequently utilized either intravenously or orally, but the expected success rate is lower than that of flecainide, while the incidence of unwanted effects is the same [9-11]. Amiodarone is also utilized, particularly in unstable and ischemic patients with poor ventricular function, for its favorable slowing effect on ventricular rate and the lack of significant negative inotropic action: unfortunately, its efficacy is delayed and the success rate is only slightly higher than that of placebo even after 24 hours [4, 12-15]. Oral quinidine at increasing doses is highly effective in mid-term conversion, but prolongation of QT interval must be accurately monitored for the risk of ventricular tachyarrhythmias; moreover, a high incidence of side effects restricts the possibility of a large-scale use of this drug [5, 16]. Digitalis has long been given a prominent role in the rate control and conversion of AF, even if, due to its vagomimetic effect, it is expected to be profibrillatory; in fact, although AF may frequently convert to sinus rhyhm some hours after digitalis administration, the conversion rate parallels that of placebo [17].

In patients in whom AF has been sustained for more than a few days or its duration is uncertain, the current recommendation is to provide anticoagulant therapy since the risk of thrombus formation is particularly high [18]. Since anticoagulant treatment should be provided for at least 3 to 4 weeks, an attempt at pharmacologic conversion cannot be performed before one month from the onset of AF; because the pharmacological conversion rates fall dramatically when the duration of AF is prolonged, one should realize if a time-consuming pharmacological procedure is still worthwhile. In this clinical setting it is probably advisable to start with an electrical procedure without any further delay (Table 2). The

Table 2. DC shock cardioversion

1. Main characteristics:
   - hemodynamically and electrically unstable patients
   - anticoagulation if needed
   - pharmacological heart rate control if needed
   - may be utilized after drug failure
   - antiarrhythmic drugs may be associated (before or during the procedure)

2. Benefits:
   - highly effective even in long-lasting AF
   - relatively quick procedure
   - may be repeated immediately

3. Risks:
   - possible myocardial damage
   - dangers of anesthesia
   - ventricular tachyarrhythmias

same approach should be utilized in patients with recent-onset AF who are hemodynamically or electrically unstable. DC shock is considered a very effective therapeutic tool: the success rate is close to 100% when technically correct and performed by skillful hands. Moreover, it is a quick procedure and in case of failure it may be repeated safely at least three times in a few minutes. The risks of the procedure, that must be accurately evaluated, are the possible myocardial damage (a transient ST-segment elevation is frequently observed), the dangers connected to anesthesia, and the possible ventricular arrhythmias that may follow the defibrillating discharge [19-21].

In highly selected patients, when a pharmacological approach fails and an external DC shock also fails or is contraindicated, an attempt at internal cardioversion may be carried out. This technique is newborn and still performed on an experimental basis, but it is very promising, with a high success rate even in long-lasting AF and with a safe profile [22].

Clinical Implications

Comparison of the clinical effects of the two therapeutic strategies to restore sinus rhythm, the pharmacological and the electrical one, is difficult if not impossible: they both are effective and sufficiently safe. The indications to each procedure are slightly different, so the clinician should use them in a complementary fashion instead of in a conflictual one, in order to reach the maximum effect at the lowest cost, both in terms of risks for the patient and time saving for the clinician.

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Atrial Fibrillation: Which Drug to Prefer for Acute Cardioversion?

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The indisputed advantages of the pharmacological cardioversion of recent onset atrial fibrillation (good and at times high efficacy, action rapid and often during drug infusion, very good patient compliance, no need for hospitalization) have stimulated the interest of several authors to test both the efficacy of antiarrhythmic drugs and the possible preferential indications for each of them. In our opinion, there are three main factors that must be taken into consideration in choosing the kind of drug for atrial fibrillation (AF) cardioversion: 1) arrhythmia duration, 2) the clinical context in which it takes place, 3) ventricular function.

AF Duration

This represents by far the most important factor influencing the probability of sinus rhythm restoration. Furthermore, the choice of the kind of drug can also depend on this factor. In fact, we must take into account that most drugs used in the acute treatment of AF in the last 15 years (propafenone, flecainide, procainamide, amiodarone, sotalol, etc.), have generally been administered in patients whose AF duration was not longer than two weeks. For longer-lasting AF, we generally use drugs tested in the 1960s, like quinidine, or more recently, like amiodarone.

Clinical Context

Lone atrial fibrillation

This is the clinical situation in which class 1C antiarrhythmic agents may be most useful. Groups of patients affected by both lone AF and AF in the presence of different underlying heart diseases have been investigated, in several studies in which intravenous flecainide [1-5] and propafenone [5-9] have proved to be effective. It is not possible, however, to evaluate the effectiveness of drugs in the

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subgroups of patients separately, although in some studies in which the subgroups of patients affected by lone AF are dominant or can be easily distinguished from the remaining cases, the percentage of success ranges between 85% and 93% for flecainide [2, 3, 5] and between 57% and 87% for propafenone [3, 5, 8]. The present use of these drugs depends not only on their effectiveness, but also on the time till the sinus restoration (generally within 1 h and often during the drug infusion). In our opinion, such drugs must be preferred for their quick action, thanks to which in most cases the patient can return home. Intravenous amiodarone has also been frequently used in the treatment of AF [8, 10-16].

Concerning this drug, however, some important data must be taken into consideration. First of all, the number of patients studied from 1982 up to 1995 amounts to 183 only. Almost all studies [8, 10-14] except for two [15, 16] are not controlled. Furthermore, in the two controlled studies [15, 16] the percentage of success of amiodarone has resulted substantially similar to that of placebo in the 3rd and 8th hour. Also, most studies concerning propafenone and flecainide are not controlled, but in the controlled ones, in which the drug has been administered intravenously or per os [15-20], the percentage of success of flecainide in the 3rd hour was significantly higher than that of placebo [15-18]. In Capucci et al. [15, 18] this percentage was significantly higher in the 8th hour as well, while in Donovan et al. [16] it was similar to the placebo. A similar outcome was observed for propafenone in the 3rd and 8th hour [18, 20]. Therefore, in the pharmacological cardioversion of AF one must take into account that in a rather considerable percentage of cases the sinus rhythm restoration occurs spontaneously (percentages of restoration within the 3rd hour range between 18% and 27% and within the 8th hour range between 37% and 59%). Therefore, if the arrhythmia is well borne and it is not urgent at all to resolve it quickly, the patient can reasonably be kept under observation at least for 8-12 hours, since the sinus rhythm restoration can occur spontaneously.

Recently, the use of propafenone and flecainide in a single oral loading dose has been proposed. The aim of using this treatment is to allow the patient to follow the treatment at home, if it proves to be efficacious and safe in the hospital [15, 17, 18, 20-23]. In summary, up to now this procedure (propafenone, 600 mg and flecainide, 200 - 300 mg per os) has been tested in 354 patients, 51% of whom presented a lone AF, 34% only a slight associated hypertension, and 15% an underlying heart disease. The efficacy of such a procedure of administration is indisputable: percentages of conversion between 52% and 63% have been obtained within the first hour, between 52% and 82% within the 3rd hour, and 91% and 100% within the 8th hour with flecainide, and between 45% and 63% within the 3rd hour and 76% and 91% within the 8th hour with propafenone. It is interesting to observe that proarrhythmic effects, traditionally due to drugs, have occurred in the placebo group too. An atrial flutter with an A-V conduction ratio of 2:1 or 1:1 has been observed in between 7% and 11% of patients treated with propafenone or flecainide, but in between 5% and 8% of patients in the placebo group. Similar observations have been made for sinus pauses with percentages between 1.6% and 8.6% in patients treated with propafenone and flecainide, but

also between 4.5% and 5.7% in the placebo group. Mild congestive heart failure has been occasionally observed in patients with underlying heart disease. Only one case presented an irreversible pulmonary edema. In our opinion, this method of administration cannot be suggested yet as generalized praxis. It requires further evaluation and must be followed by physicians concerned with the problem.

WPW Syndrome

The incidence of AF in Wolff-Parkinson-White (WPW) syndrome is higher than in the normal population, and ventricular fibrillation may develop during an attack of AF if conduction through the accessory pathway is rapid [24]. Drugs like digoxin, verapamil and amiodarone are contraindicated because of the depressive action on nodal conduction which may speed up the ventricular response during AF and increase the risk of degeneration to ventricular fibrillation [24-28]. Flecainide and propafenone can be considered as the drugs of choice in the treatment of AF. Many studies have shown that in these patients both drugs determine the prolongation of the anterograde and retrograde refractory period of accessory pathway – both in patients with a long or a short refractory period – as well as the complete block of conduction, via the accessory pathway [29-36]. These drugs considerably slow down the ventricular response during AF with pre-excited ventricular response [29, 31, 34, 37, 38]. Thus, their effects are twofold: 1) restoration of sinus rhythm and 2) prolongation of pre-excited beat intervals or block of conduction via the accessory pathway with slowing down of the ventricular rate.

Bundle Branch Block or Multifascicular Block

There is a potential risk in patients with bundle branch block or multifascicular block of a complete paroxysmal atrioventricular block due to drugs which hardly depress the conduction through the His-Purkinje system. The H-V interval is actually prolonged by 1A class drugs such as procainamide [39] and 1C class drugs such as flecainide and propafenone [40, 41]. Amiodarone does not substantially modify the H-V interval, and in some studies it has been proved to be safe for patients with bundle branch blocks [42, 43]. Thus, in spite of limitations due to non-controlled studies, if we want to choose a pharmacological treatment for such patients, the safest drug is amiodarone.

Long-lasting AF in Patients with Left Ventricular Dysfunction

From a clinical point of view, this group represents the majority of patients. Sometimes, it is necessary to try a sinus rhythm restoration to utilize the atrial contribution of these patients. The general trend in this case consists in keeping AF and merely checking the heart rate. On the other hand, if a cardioversion attempt has to be made, amiodarone is likely to be the most suitable drug in these conditions. From the authors' review of the literature [44-48] the following data

come out: a total of 183 patients were tested, 170 of whom presented an underlying heart disease, also in NYHA III-IV functional class [47] lasting from 3 months to 75 months (on average), the sinus rhythm restoration occurred in 20% of the cases with the drug alone and in 51% with the drug associated with a direct current (DC) cardioversion, whereas other antiarrhythmic drugs had frequently failed. In spite of the uncertainty surrounding the real efficacy of amiodarone – since studies are not controlled – we are well aware that amiodarone at least does not reduce performance, as the majority of 1 class drugs do. From a series of studies it appears that amiodarone administered per os even at very high doses, for several days and even in patients with a serious left ventricular dysfunction, does not cause considerable hemodynamic variations [49-51]. A controlled study, the data of Deedwania, published recently [52], confirms this characteristic of amiodarone. In a subgroup of 103 patients with AF, dilated left ventricle, LVEF < 40%, and congestive heart failure, randomized through amiodarone per os or placebo, in an average follow-up of 4.5 years, the following was observed: 1) a probability of sinus rhythm restoration significantly higher in the amiodarone group (31% versus 8%, $p < 0.005$), and 2) a significantly higher survival rate in patients given amiodarone in association with conversion ($p < 0.05$). It is interesting to observe that neither the NYHA functional class, nor the etiology of congestive heart failure, nor the LVEF, nor the telediastolic diameter of the left ventricle and left atrium have been correlated with the probability of sinus rhythm restoration.

In conclusion, the knowledge of both the physiopathology of the different clinical conditions in which AF can occur and the hemodynamic and electrophysiologic effects of the various antiarrhythmic drugs must be used to indicate the most appropriate drug for restoring sinus rhythm.

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Drug Prevention of Paroxysmal Atrial Fibrillation, When and How?

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Paroxysmal Atrial Fibrillation: a Chronic Disease

Paroxysmal atrial fibrillation is *self-limiting* since – by definition [1] – attacks stop spontaneously, while only prolonged symptomatic episodes require drug intervention (Table 1). Despite being episodic and self-limiting, paroxysmal atrial fibrillation is a *chronic* disease: sooner or later after the first clinically significant attack most patients will experience a second one, even while using prophylactic antiarrhythmic drugs [2]. Therefore, drug intervention may at best reduce the number of attacks over time or postpone recurrences. Thus the primary aim of treatment is to improve quality of life rather than to simply suppress the arrhythmia. In this respect patient counseling is highly important. Patients should know that recurrences are a normal phenomenon even when using drugs, and that a breakthrough arrhythmia is not necessarily a sign of drug inefficacy. Consequently, a given drug should be replaced or non-pharmacologic treatment considered only if breakthrough arrhythmias or side effects are not tolerated.

Table 1. A possible classification of atrial fibrillation [modified after ref. 1]. This classification is based on the temporal pattern of atrial fibrillation and the spontaneous behavior as well as the response to pharmacologic or electrical cardioversion. Note that atrial fibrillation is a chronic disease irrespective of its temporal patterns

Type	Duration	Spontaneous conversion?	Conversion possible?
Paroxysmal	< 2-7 days, usually < 24 hrs	yes	on drugs
Persistent	> 2-7 days	no	electrical CV needed
Permanent	permanent	no	no

CV, cardioversion.

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Paroxysmal atrial fibrillation may turn into persistent atrial fibrillation [3]. This is due to progression of underlying heart disease but also relates to several arrhythmia related changes such as left atrial enlargement [4], progressive left ventricular dysfunction [5] and electrical remodeling [6]. After turning into persistent atrial fibrillation, treatment becomes more difficult and cardiovascular events increase. Again, counseling is important: given its tendency to become persistent, patients should have their paroxysmal atrial fibrillation terminated as soon as possible.

Precipitating Factors and Causes

The patient's history is too often neglected but may contain important precipitating factors. Triggers should be removed or avoided as much as possible before considering (non-)pharmacologic therapy. Among arrhythmia triggers are coffee, alcohol, fever and stress, but also aggravation of heart failure and ischemia. Additionally, specific stimuli have been described for vagal and adrenergic atrial fibrillation. Unfortunately questions regarding these items have to be asked for in a targeted manner since usually patients do not volunteer them to the clinician. Sometimes paroxysmal atrial fibrillation occurs in the setting of sick sinus syndrome. In those patients implantation of an electronic pacemaker may be inevitable to render attacks amenable to drug treatment.

Quality of Life

Quality of life is negatively affected by irregularity of the pulse, exercise intolerance, sequelae of thromboembolism and drug side effects. Loss of social contacts due to physical and emotional inability may further restrict quality of life [7,8]. His bundle ablation has been shown to improve quality of life dramatically [9,10]. There are no formal studies on the effects of drugs in this respect.

Antithrombotic Treatment

At present it is unknown whether antithrombotic treatment is specifically indicated in paroxysmal atrial fibrillation and if so who should receive it. Considering the frequent absence of underlying disease, most patients do not need oral anticoagulation. It is extremely unfortunate that the recently completed large scale trials [11] studied mixed bags of paroxysmal and chronic atrial fibrillation and are therefore only of little help in answering these questions.

Drug Prevention

In paroxysmal atrial fibrillation a significant cardiovascular cause is absent in over 50% of cases [12]. This is why prognosis is favorable and drugs well tolerated in many patients. Nevertheless, Vaughan Williams class Ia and III drugs may produce torsade des pointes even in "lone" atrial fibrillation, and chronic treatment with class Ia and Ic drugs should be avoided in case of significant ventricular disease (previous infarct, heart failure). It is questionable whether there still is a role for quinidine [13], especially in the elderly [14]. Obviously, it is of highest importance that proarrhythmia, heart failure, uncontrolled atrioventricular conduction and sick sinus syndrome be avoided when using prophylactic drugs.

The aim of antiarrhythmic drug therapy is to prolong the wavelength and reduce or eliminate precipitating arrhythmia mechanisms. Rather than complete suppression of atrial fibrillation, drugs may help to extend the interval between recurrences and shorten the attacks. Studies typically report drug effects in terms of arrhythmia free episode, the number of arrhythmia free patients after a limited period of follow-up (e.g. six months, or even less), or the relative risk to experience a recurrence compared to placebo. In their study, Anderson et al. showed that 300 mg flecainide lengthens the time to first recurrence from 3 at baseline to 15 days on the drug. Similarly the interepisode interval increased from 6 to 27 days [15]. In the UK Propafenone PSVT Study [16] propafenone reduced the risk of recurrences sixfold compared to placebo. In a direct comparison by Aliot et al. both agents performed similarly [17]. Two studies showed that quinidine was as effective as flecainide, but quinidine was less well tolerated [18,19]. Reimold et al. [20] could not find a difference between propafenone and sotalol, with 30% and 37% of the patients maintaining sinus rhythm for at least 12 months (*mixed bag* study of persistent and paroxysmal atrial fibrillation). Amiodarone is rather efficacious even after previous drug failure. It may be used as a first line agent in heart failure complicated by atrial fibrillation [21], but should be avoided in younger patients and those with pulmonary disease.

Vagal-induced atrial fibrillation should be treated with class Ia drugs since these agents have vagolytic properties. Flecainide may also be effective. By contrast, digitalis or β-blockade may provoke attacks. Adrenergic-dependent atrial fibrillation may best be treated with β-blockade or propafenone.

Future Perspectives

Paroxysmal atrial fibrillation is a *chronic* disease not only in terms of arrhythmia recurrences. Apart from a persistent risk of heart failure, antiarrhythmic and anticoagulant drugs constitute a continuous threat. At present it is unknown whether antiarrhythmic prophylaxis and anticoagulation, if needed, reduce morbidity or mortality compared to a simple rate control strategy. Possibly the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) may answer this question [22]. It compares primary acceptance of atrial fibrillation as

answer this question [22]. It compares primary acceptance of atrial fibrillation as the main rhythm (rate control plus anticoagulation) with a strategy aiming at maintaining sinus rhythm (antiarrhythmic drugs and anticoagulation). Patients qualify for this study if they have attacks lasting at least 6 hours, they should have had at least 1 episode in the last 6 months and the qualifying episode should have occurred in the past 6 weeks. Patients younger than 65 years may only be included if they have an increased thromboembolic risk. Considering these inclusion criteria, mainly *paroxysmal* atrial fibrillation will be included. It seems questionable whether in these patients accepting atrial fibrillation is satisfactory to the patient. On the other hand, Godtfredsen [3] has shown that paroxysmal atrial fibrillation tends to turn into chronic if episodes last relatively long and in these patients the AFFIRM question seems justified.

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Antiarrhythmic Drug Administration before Electrical Cardioversion of Atrial Fibrillation: Is It Useful to Prevent Early Arrhythmia Recurrence?

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Electrical Cardioversion and Risk of Atrial Fibrillation Recurrence

Electrical cardioversion may restore sinus rhythm in approximately 90% of patients with chronic atrial fibrillation [1]. The most relevant clinical problem after successful cardioversion is represented by the risk of recurrence which may occur either in a very early phase (first minutes after electrical shock), in an early phase (first 24 hours), in the days following the procedure or several weeks or months later.

The risk of recurrence without antiarrhythmic drugs prophylaxis is very high at long term follow-up: Lundstrom and Ryden [2] reported that only 30% remained in sinus rhythm off antiarrhythmic therapy at 3 months in a series of successfully cardioverted patients. These findings provide the rationale for long term prophylaxis with antiarrhythmic agents, although there is some concern about the risk-benefit ratio of these drugs [3].

The risk of atrial fibrillation recurrence is particularly high in the first minutes after successful cardioversion: Rossi and Lown [4] reported that 30% of the patients successfully cardioverted and not treated with antiarrhythmics had a recurrence within 1 minute. Figure 1 shows an example of a very early recurrence of atrial fibrillation after conventional external cardioversion. Even in the hours following cardioversion the risk of recurrence remains high: in the study of Van Gelder et al. [5] arrhythmia recurrence occurred between 0.5 and 24 hours in 10 patients, corresponding to 7% of the converted patients and to 17% of all the clinical failures.

In view of the substantial risk of atrial fibrillation recurrence in an early or very early phase after successful cardioversion, a brief course of antiarrhythmic drug therapy has been proposed, although few studies have analysed the risk-benefit ratio of this approach [4, 6-11].

Factors Conditioning the Risk of Early Recurrence

Many structural factors related to underlying heart disease, neurohormonal status, arrhythmia duration and patient age, may increase the risk of atrial fibrillation recurrence and several studies have assessed their influence on medium and

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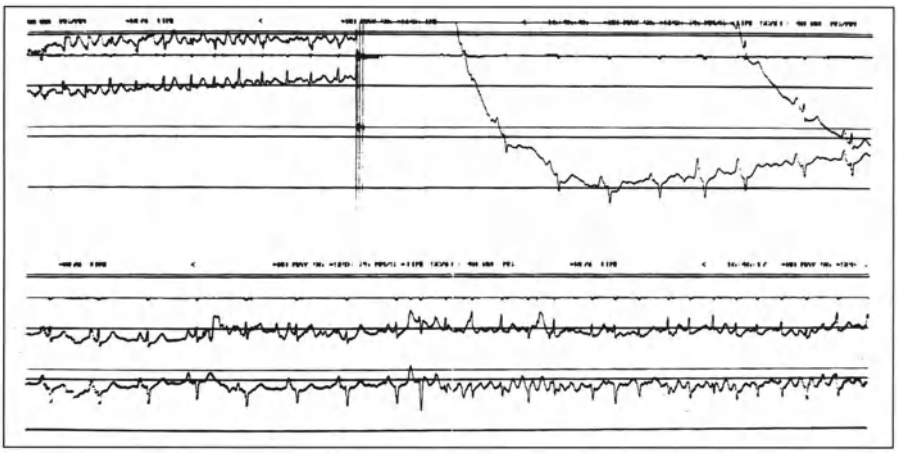

Fig. 1. Continous electrocardiographic tracing (leads D1 and D3) showing restoration of sinus rhythm by external transthoracic cardioversion with early recurrence of atrial fibrillation after few sinus beats

long-term recurrence. For early occurring recurrences electrophysiological factors may have a predominant role. An electrophysiological remodeling has been demonstrated by Wijffels et al. [12] in conscious goats in which repetitive induction of episodes of atrial fibrillation resulted in chronic atrial fibrillation after few days. The increase in duration of atrial fibrillation was accompanied by a marked shortening of the atrial effective refractory period with loss of the physiological rate adaptation of refractoriness. These changes persisted even after restoration of sinus rhythm and normalization was found only after a few days of stable sinus rhythm. If electrical remodeling is confirmed to occur also in humans, the finding that shortening of atrial refractoriness requires a few days to revert completely could explain the early recurrences seen after cardioversion [12].

Moreover, an interaction exists between the electrophysiological properties of the atrium and intra-atrial pressure. A condition of increased stretch of the atrial wall due to increased atrial pressure could shorten atrial refractoriness although controversial data have been reported [15-17]. After atrial fibrillation cardioversion, restoration of full mechanical activity may take 4 to 6 weeks, as documented by Doppler echocardiography [13, 14], thus determining persistent loss of electro-mechanical coupling, which favors persistence of increased atrial pressure and stretch of the atrial wall.

This hemodynamic-electrophysiological link may be involved in favoring atrial fibrillation recurrence after cardioversion in patients with underlying structural heart disease.

Moreover, atrial natriuretic factor, whose levels are increased in atrial fibrillation and progressively decrease after sinus rhythm resumption [17], can also enhance the risk of early arrhythmia recurrence, due to its ability to shorten atrial refractoriness [18].

In patients with congestive heart failure, adrenergic and neuro-hormonal activation may have a predominant role in increasing atrial arrhythmogenesis due either to reentry or to abnormal automaticity and triggered activity [19].

Rationale for Antiarrhythmic Drug Administration Before Electrical Cardioversion

The rationale for treating patients who are candidates for electrical cardioversion with antiarrhythmic drugs is based on:
- the possibility of obtaining conversion to sinus rhythm in some patients, thus avoiding the electrical procedure;
- the possibility of preventing early arrhythmia recurrence;
- the possibility of changing the pattern of atrial fibrillation, thus enhancing the possibility of obtaining cardioversion to sinus rhythm.

The potential detrimental effects are:
- the possibility of increasing the energy required for defibrillation, as demonstrated for ventricular defibrillation [20];
- the possibility of inducing proarrhythmic effects, like bradyarrhythmias or tachyarrhythmias immediately after cardioversion.

Because of this complex scenario a more precise assessment of the risk-benefit ratio of antiarrhythmics before electrical cardioversion can be achieved only through the analysis of controlled studies.

Antiarrhythmic Drugs Before Electrical Cardioversion: Clinical Results

Available data on the effects of antiarrhythmic drugs on the outcome of patients submitted to electrical cardioversion for atrial fibrillation were initially related to transthoracic cardioversion whereas, more recently, some studies were performed on subjects submitted to low energy internal cardioversion.

Quinidine has been the first drug studied for administration before electrical cardioversion. Two studies [4, 7] reported that treatment obtained sinus rhythm resumption in 12%-13% of the patients, thus eliminating the need for cardioversion. The ability to prevent early recurrences of atrial fibrillation by giving quinidine after cardioversion is not well defined, although Rossi and Lown [4] observed a non-significant trend in favor of quinidine (atrial fibrillation recurrence within 1 minute in 30% of placebo-treated patients versus 4% of quinidine patients). Atrial premature beats after the shock resulted to be decreased in quinidine-treated patients [4, 7]. Energy requirements for shock efficacy were reported to be lower in two studies [4, 7], and not significantly modified in another study [21].

Amiodarone, because of its particular pharmacokinetics, may create some different effects depending on the way of administration (intravenous or oral) and the length of oral treatment. In the study by Sagrista-Sauleda et al. [8] intra-

venous amiodarone obtained conversion to sinus rhythm in 12% of patients. Amioda-rone administration, either by long-standing oral treatment or short-term intravenous infusion, did not diminish the effectiveness of electrical shocks and the observed trend towards a reduction in energy requirement was not significant. Either intravenous amiodarone was associated with a higher incidence of post-shock bradyarrhythmias or intravenous and oral amiodarone determined a higher rate of ventricular premature beats compared to control [8].

Propafenone was tested by Bianconi et al. [9] in a placebo-controlled study involving 100 patients and comparing two different strategies: pretreatment with oral propafenone or propafenone treatment only after cardioversion. The drug obtained pharmacological cardioversion to sinus rhythm in 6% of the subjects. In the whole population propafenone did not exert any significant effect on the total energy required for cardioversion or on the success rate of the procedure. Indeed propafenone had differential effects on energy requirements for successful cardioversion: it significantly decreased DC shock energy in those patients (22% of the propafenone group) in whom atrial fibrillation was transformed into atrial flutter whereas energy requirements were increased compared to control if atrial fibrillation pattern didn't change. In this study propafenone significantly reduced arrhythmia recurrences occurring within 10 minutes (0% versus 17% in placebo-treated patients) and within 24 and 48 hours. After cardioversion the incidence of supraventricular ectopic beats was higher with placebo whereas sinus node dysfunction was more common with propafenone. During in-hospital stay propafenone was withdrawn in 7% of the patients because of its side effects.

Flecainide has been evaluated by Van Gelder et al. [10]. The drug was administered intravenously and although no differences were found in energy of the effective shocks, attempts with high energy shocks were more often required compared to placebo-treated patients.

More recently some studies were performed on patients submitted to low-energy internal atrial cardioversion, a procedure that in some patients can even be done without sedation [22].

Although different protocols were adopted, these studies were addressed to evaluate the effects of different agents on atrial defibrillation threshold and this kind of evaluation seems interesting even in the perspective of an internal atrial defibrillator. Preliminary data have shown reduction in defibrillating energies with intravenous sotalol [23], pretreatment with amiodarone [24] and intravenous flecainide [25].

Conclusions

Immediately after electrical cardioversion there is a high rate of atrial fibrillation recurrence, due to a complex electrophysiological remodeling which interacts with modulating factors, such as the autonomic nervous system.

The administration of class 1C and probably class 1A antiarrhythmic drugs has a favorable effect in reducing early arrhythmia recurrences which is counter-

balanced by the possibility of post-cardioversion bradyarrhythmias and by variable effects on defibrillation energy requirements. Indeed, at least for class 1C drugs, the possibility of reducing defibrillation threshold seems related to a pharmacological effect that is able to change the atrial fibrillation excitation pattern into a more organised arrhythmia, like a flutter. This finding however requires further confirmation with a more precise assessment of the risk-benefit ratio of each drug administered in different ways (intravenous or oral). In clinical practice an alternative approach to oral pretreatment with antiarrhythmic drugs should be considered, that is administering the drug intravenously immediately after cardioversion, thus avoiding potential unfavorable effects on atrial defibrillation threshold and on post-cardioversion bradyarrhythmias. In this view controlled studies analyzing the risk-benefit ratio of these different strategies are required.

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ATRIAL FIBRILLATION: ABLATION PROCEDURES

AV-Nodal Ablation versus AV-Nodal Modification for Control of Atrial Fibrillation

A.P. FITZPATRICK

In 1982, the first direct-current catheter-based interruption of the AV junction for medically-refractory atrial fibrillation in a human, was described [1]. Since that time, catheter ablation approaches have increased massively in number, complexity and technical capability. In spite of these momentous advances, atrial fibrillation is still commonly treated by AV junctional ablation and subsequent permanent pacing.

In 1994, Morady et al. described a novel approach to non-drug control of the ventricular rate response in patients with medically-refractory atrial fibrillation [2]. This involved radiofrequency modification of the AV junction in the mid-septal region close to the tricuspid annulus, at a site typically associated with the location of the AV nodal "slow pathway" in patients with electrophysiologically and anatomically dissociated dual AV nodal physiology. In patients treated in this fashion, however, there was no evidence of dual AV nodal physiology, and indeed, many patients so-treated were in atrial fibrillation, and therefore assessment of AV nodal function would be impractical. The technique took advantage of the fact that the "fast" anterior approaches to the AV node also have a relatively long refractory period, whilst the "slow" posterior approaches to the node have a long conduction time, but a relatively short refractory period. In this fashion modification of the posterior approaches would theoretically result in fast conduction of impulses via the normal anterior approaches, but longer recovery times before the node would conduct the next impulse. The net effect of this approach would therefore be to slow ventricular rate-response in atrial fibrillation, without the need for complete AV junctional disruption, saving the need for permanent pacing. Not surprisingly, this approach received a great deal of interest and excitement, and earned the name "catheter based digoxin".

In spite of the excitement generated, problems existed with adequate titration of the dose and location of radiofrequency application in the region of the posterior approaches to the node. Quite frequently inadvertent atrioventricular block was the end-point of such approaches, and patients were not ultimately spared a pacemaker. The technique required confirmation of effect with intravenous isoprenaline infusion, and in some cases the effect on ventricular rate-control was not long lasting. Such short lasting effects in slowing, or "stunning", AV nodal

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conduction are sometimes seen during AV nodal modification for AV nodal reentrant tachycardia, and when AV junctional ablation is the desired end-point. However, despite reservations about the possibility that AV block would result frequently from AV nodal modification attempts, and that the benefits seen during the acute phase would not be long lasting, Morady et al. recently published long-term follow-up data on 63 patients treated by a modification approach for control of ventricular rate-response, indicating a good long-term benefit [3].

Where modification is not attempted, the more traditional, though destructive approach of AV junctional ablation may be used. This invariably requires long-term pacing. The benefits to patients, however, may be considerable. Twidale et al. [1] prospectively studied total of 14 patients with drug refractory AF or atrial flutter with rate control provided by radiofrequency energy AV junction ablation and permanent ventricular pacing. A modest but significant increase in left ventricular ejection fraction was observed from 42% ± 3% during temporary ventricular pacing immediately prior to ablation to 47% ± 4% ($p < 0.05$) at 6 weeks follow-up at the same ventricular pacing rate. No significant change in treadmill exercise time was noted. As only 2 out of 14 patients had a baseline ejection fraction less than 40%, these findings may not reflect potential benefits in patients with more severely depressed systolic function.

Heinz et al. [5] prospectively studied control of rapid ventricular rates in AF using radiofrequency energy AV junction ablation and permanent ventricular pacing in 10 patients (9 with AF and 1 with atrial flutter) who had ventricular responses greater than 120 beats per minute for the majority of the day. Fractional shortening for the entire group improved significantly from 28% ± 9% within 1 day after ablation to 35% ± 8% ($p = 0.006$) at a mean of 49 days follow-up. Both studies were performed during ventricular pacing at similar rates. Subgroup analysis showed significant improvement in the 5 patients with baseline depressed fractional shortening, and a trend towards improvement which did not reach statistical significance in the 5 patients with normal baseline fractional shortening.

Brignole et al. [6] have prospectively studied rate control with radiofrequency energy AV junction ablation in drug refractory AF patients with resting average ventricular rates greater than 100 beats per minute. In a heterogeneous series of 23 patients with heart failure, NYHA class decreased significantly and exercise time increased significantly for the whole group. In the nine subjects with decreased left ventricular systolic function, echocardiogram assessment of fractional shortening increased significantly from 23% ± 5% to 31% ± 9% ($p = 0.003$). In the 13 subjects with normal baseline left ventricular systolic futnction, fractional shortening decreased significantly from 40% ± 5% to 36% ± 6% ($p = 0.05$). These findings lead the authors to view treatment of drug refractory AF patients as a balance between the benefits of rate control versus the possible deleterious hemodynamic effects of right ventricular pacing.

Because there is experimental and clinical evidence of improvement in left ventricular function after AV junction (AVJ) ablation, this would be expected to translate into improved functional capacity, a reduction in consumption of health

care and possibly an improved prognosis. A number of studies has addressed these issues in variable depth, and generally, these found an improvement. One study [7] attempted to address patient well-being and activity status, access to health care and morbidity and mortality after AVJ ablation. One hundred and seven consecutive patients underwent radiofrequency AV junctional ablation and permanent pacing for paroxysmal or established medically refractory atrial fibrillation at the University of California, San Francisco. After 2.3 ± 1.2 years, all patients who remained had a formal assessment of quality-of-life (scored as 1 = poor, to 5 = excellent), limitation of various daily activities (1 = very limited, to 3 = not limited), and Health Care consumption before and after the procedure. Doctor visits, emergency room and hospital admissions, pacemaker follow-up visits, number of anti-arrhythmic drug trials and anticoagulation, new stroke, heart failure episode or death, and maintenance of a dual-chamber pacing mode, were noted before and after the procedure.

Ninety patients were alive and gave information, of whom 55 were female, with a mean age 60 ± 16 years, after a mean follow-up of 2.3 ± 1.2 years. The mean left ventricular ejection fraction (LVEF) was 51% ± 11%. Seventeen patients out of the 107 in the series had died. Fifty-four patients had chronic atrial fibrillation at the time of ablation, and 46 had paroxysmal episodes. Quality-of-life index was improved significantly from 1.9 ± 1.2 to 3.6 ± 1.1, ($p < 0.001$). Overall, activities of daily living became significantly easier, with improvement in the score from 2 ± 0.4 to 2.4 ± 0.3 ($p < 0.001$). With pacemaker follow-up visits (3.6 ± 4 per patient per year) included, patients visited the doctor significantly less frequently each year after treatment, (5.06 ± 7 visits), than before, (10 ± 13 visits, $p < 0.03$). Annual emergency room attendances, (3.1 ± 8 vs 0.2 ± 0.62, $p < 0.03$), and hospital admissions, (2.8 ± 6.8 vs 0.17 ± 0.54, $p < 0.03$) fell significantly. Concurrent or serial antiarrhythmic drug trials prior to ablation were 6.2 ± 4 per patient, and these fell significantly to 0.46 ± 1.5 during follow-up, ($p < 0.001$). Congestive heart failure episodes occurred in 19 patients prior to, and in 8 patients after treatment.

In both established and paroxysmal AF quality of life improved. In patients with established AF (EAF), quality of life after treatment rose from 1.8 ± 1.14 to 3.5 ± 1.1, ($p < 0.0001$), and in patients with paroxysmal AF (PAF), from 2.1 ± 1.3 to 3.7 ± 1.1, ($p < 0.0001$). Patients' specific activities of daily living became significantly easier, in PAF, (1.9 ± 0.6 to 2.39 ± 0.5 ($p < 0.001$). In PAF activities of daily living were not significantly improved. These findings were consistent with expected activity impact for patients with intermittent symptoms, who were predominantly in atrial fibrillation. Consumption of health care resources in patients with established and paroxysmal AF was markedly reduced by ablation and pacing. Hospital admissions either direct or via the emergency room fell from 3.3 ± 8.2 to 0.13 ± 0.49, ($p < 0.03$), in EAF, and from 2.27 ± 4.1 to 0.2 ± 0.6, ($p < 0.005$) in PAF. Accident and emergency room attendances fell significantly, from 3.4 ± 9.8 to 0.16 ± 0.65 per year, ($p < 0.03$), in EAF, and from 2.7 ± 5.3 to 0.25 ± 0.56 per year in PAF, ($p < 0.005$). Outpatient doctor visits, with pacemaker follow-up attendances included (3.36 ± 4.1 per year), fell to 5.2 ± 7.9 from 11 ± 16.7, per year ($p < 0.03$), in EAF, and to 4.8 ± 5.1 visits from 8 ± 5.5 visits, ($p < 0.03$), in PAF, who had 3.3 ± 48.7 pacemaker follow-up vis-

its per year. Antiarrhythmic drugs used fell significantly from 6.12 ± 4.4 prior to ablation to 0.43 ± 1.8 ($p < 0.0001$), during follow-up in EAF, and from 6.3 ± 3.5 prior to ablation to 0.5 ± 0.8 during follow-up in PAF ($p < 0.0001$).

Significant events recorded were congestive heart failure episodes clearly documented in 12 patients prior to treatment, and in 4 patients afterward, and 8 strokes prior to treatment and 2 afterward in EAF, and congestive heart failure episodes documented in 7 patients prior to treatment, and in 4 patients afterward with 4 strokes prior to treatment and 1 stroke during follow-up, in PAF. From this study, it was concluded that there was evidence that AVJ ablation and pacing was beneficial in terms of quality of life and health care costs, whether AF was established or not.

In spite of these impressive benefits, many physicians are reluctant to render patients pacemaker dependent, even if their dependency upon the pacemaker is relative, and there is usually a satisfactory underlying rhythm. At present it is unclear whether patients who undergo AV junctional modification have such improvements, and as yet there has been no randomised controlled comparison of the two techniques. Provided AV nodal modification could reliably result in adequate rate control in all cases, then it is only the regularity, versus irregularity of the ventricular rhythm that might impair function.

It is known that atrial fibrillation at moderate heart rates causes negative long-term effects on systolic function, and it is reasonable to suspect that some portion of the negative effects may be indirectly related to the hemodynamic effects of an irregular heart rate. These may be related to activation of pressure receptors within the cardiovascular system. As early as 1915 Einthoven and Kortweg recognized that the amplitude of a given pulse wave was related to the duration of the preceding R-R interval [8]. This effect was first shown to be related to the effect of diastolic filling on contractile force (Frank-Starling mechanism) [9, 10]. It was later shown that this effect also occurs in isolated, perfused hearts and in isolated heart muscle strips in which the preload is held constant [11, 12]. In an isolated heart model, it was later shown that there is not only a strong positive correlation between contractility and the length of the immediately preceding R-R interval but also a smaller negative correlation between contractility and the length of the second to tenth preceding R-R intervals [13]. A study in a dog model found that loss of atrial function and irregular ventricular rate both contribute to a reduction in total cardiac output during atrial fibrillation [14]. Finally, it has been shown that patients with atrial fibrillation and depressed left ventricular function suffer from a larger beat-to-beat variation in stroke volume at rest (13% ± 8%) than do AF patients with normal ventricular function (7% ± 4%) [15].

At present direct evidence that an irregular ventricular rhythm, albeit appropriate in rate for a given demand for activity, is less beneficial than an appropriate rate in a regular rhythm, in humans, is lacking. Such information is difficult to obtain, but would help provide guidance for physicians contemplating a catheter-based approach to ventricular rate control in patients with atrial fibrillation.

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AV Junction Modification for Atrial Fibrillation: Which End Points?

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Controlling ventricular rate in patients with intermittent or chronic atrial fibrillation (AF), in whom it is not possible to maintain sinus rhythm through drug therapy, is often a problem. Control of ventricular rate is necessary because of invalidating palpitations and/or occurrence of hemodynamic impairment [1].

For this reason, as a primary therapeutic choice some drugs are employed which have a chronotropic action on AV node, such as digoxin [2], β-blocking agents [3], calcium channel antagonists [4] etc.

Sometimes drug control of ventricular rate is unsatisfactory due to both the ineffectiveness of drug therapy and the onset of intolerance, or side effects such as depression in cardiac output or proarrhythmic effect [5]. However, even when satisfactory results in basal conditions are achieved, drug control on ventricular rate often decreases during physical effort [6].

Recently new non-drug based therapy choices have been introduced such as AV junction ablation [7] or modulation [8].

However, even if it is easy to perform and highly successful, AV junction ablation presents some limitations:

1) It provokes anatomic damage with irreversible total AV block preventing the patients from successfully using new therapeutic findings.
2) It makes the implantation of a life-long pacemaker necessary.

Some authors, through the observation of the electrophysiologic modifications of the AV junction induced during radiofrequency ablation (RF) of atrioventricular nodal reentrant tachycardia (AVNRT) suggested modulation as an alternative to AV junction ablation. The purpose of this technique was to reduce ventricular response while avoiding the patient pacemaker implantation and life-long dependancy.

The first attempts of AV junction modulation were performed by Duckeck [9] who performed modulation with an anterior approach and a technique similar to the one used for the fast pathway ablation in AVNRT patients [10].

The results of this study were discouraging due to the high percentage of inadvertent AV block during procedure (28% of patients undergoing RF modulation) and follow-up (54% of patients with effective modulation including 4 in whom modulation was obtained through DC shock) and also because of poor

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clinical effectiveness in follow-up (32%). Moreover, in 36% of successfully modulated patients a life-long pacemaker implantation was necessary.

A new development in AV node modulation was made by other authors (Fleck [11], Williamson [8]) on the basis of observations of a new approach to AVNRT ablation. They noticed that by applying RF to the middle or posterior septum of the right atrium in the middle or lower region of triangle of Kock, proximal to coronary sinus, the nodal slow pathway disappeared while the effective refractory period (ERP) of AV node increased and the Wenckebach point (WP) decreased. For this reason they suggested that a similar approach could control AV conduction, while at the same time avoiding advanced AV block and subsequent pacemaker implantation. This hypothesis has been supported by Krainer [12] and Blanck [13] who observed that a selective elimination of the slow pathway reduces ventricular rate during AF.

Methods

The initial approach [9] to obtain AV node modulation consisted in applying RF while withdrawing the His bundle catheter until the distal electrode pair recorded a large atrial potential and a small but sharp His potential. The end point of this procedure was the lengthening of AH interval up to 50% of its baseline value or a lowering of a Wenckebach cycle length not exceeding 400 ms. In the clinical course during follow-up, modulation was considered effective if patients were symptom free and ventricular rate during AF did not exceed 120/min without further antiarrhythmic drug therapy or pacemaker implantation.

Successively AV junction modulation was performed by various authors in the slow pathway with different techniques. Feld [14] performed modulation in 10 patients, 8 of whom with cronic AF applying RF in midseptal area proximal to the tricuspid valve anulus with an atrioventricular ratio 1:1 to 1:2. Modulation was considered effective when a mean ventricular rate was reduced below 100/min. If the end point was not achieved, further applications were performed by shifting the catheter progressively more posteriorly up to the coronary sinus os. Effectiveness of the procedure was evaluated after administration of atropine i.v. when the highest ventricular response was not to exceed 120/min.

Williamson [8] and Brignole [15] performed AV node modulation in 19 and 20 patients respectively, by applying with an anatomical approach (dividing the atrium between coronary sinus and His bundle into three regions: anterior, medium, posterior) in the posterior region of interatrial septum. If unsuccessful the ablating catheter was progressively positioned towards the anterior region. Williamson performed modulation in patients with AF, and Brignole in patients with sinus rhythm. Brignole's end point was a reduction of average AF rate lower or equal to 80/min or lower or equal to 120/min during isoproterenol infusion.

Della Bella [16] performed modulation in 14 patients, 6 of them with sinus rhythm, 6 with atrial flutter or atrial tachycardia, and 2 with AF. He used an electrophysiological approach: for patients with sinus rhythm he employed the search

for the potential as described by Jackman [17] to selectively ablate the slow pathway in patients with AVNRT and RF was applied in the low posterior region of interatrial septum slightly anterior to the coronary sinus os.

Induction of junctional rhythm with fast retroconduction was considered as a criteria for efficacy. In patients with atrial flutter or atrial tachycardia the same area was mapped searching an atrial rapid potential to show the possible posterior site of application at the base of the triangle of Kock. In 2 patients with atrial flutter, modulation was performed with an anatomical approach anterior to the coronary sinus os 1 cm - 1.5 cm below His bundle where the largest atrial activity could be recorded. An initial increase followed by a sustained lowering of ventricular rate after the application was considered an indication for slow pathway ablation. End point was the lowering of WP < 120/min.

More recently, Chen et al. [18] have evaluated modulation in 50 patients with paroxysmal AF, comparing RF application on the slow pathway in 2 groups of patients (with or without atrioventricular nodal dual pathway). These authors divided each of the 3 regions of interatrial septum between His bundle and coronary sinus os (anterior, medium, posterior) into 2 subregions (three for the posterior region including coronary sinus os). They applied RF to Group 1 patients (absence of AV nodal dual pathway) with AF, under isoproterenol infusion, from the posterior region up to the midregion in case no reduction of mean AF rate to 120/min or 75% was obtained. In Group 2 (presence of AV nodal dual pathway) they applied RF in sinus rhythm with the purpose of selectively eliminating the slow pathway. End point was the same as in Group 1. Once the AF was induced, if average rate was lower than expected, a second modulation with Group 1 protocol was performed.

If the procedure was unsuccessful, AV junction ablation was performed in both groups and life-long pacemaker was implanted.

As to our experience we performed AV junction modulation with RF in 11 patients (7 female, 4 male) mean age 65 ± 9 range 56-71 with heart disease (2 hypertension, 5 dilated cardiomyopathy, 3 valve disease, 1 mitral valve prolapse), (8 with chronic AF, 2 with paroxysmal AF and 1 with atrial tachycardia). All patients reported poorly tolerated palpitations. Maximum AF frequency recorded by Holter monitoring ranged from 140 to 210/min. If modulation was unsuccessful, all patients should have undergone junctional ablation and pacemaker implantation. The modulation technique consisted in performing RF with an anatomical approach starting from the posterior region of interatrial septum opposite the coronary sinus os and progressively going up the midregion 1-1.5 cm below the His bundle if no modification of AF mean rate lower than 100/min was achieved. In 2 sinus rhythm cases, ablation of slow pathway was selectively searched by applying an electrophysiological and anatomical approach and searching for the potential described by Jackman at the base of the Kock triangle. Ablation was successful when WP was lowered < 120/min. If unsuccessful, the catheter was shifted to a progressively anterior position and application of RF was performed anatomically. If still unsuccessful, junctional ablation was performed.

Results

In the study by Williamson AV junction modulation was achieved in 89% (17/19) of patients; in one patient an inadvertent AV block was obtained, and in another, since RF was unsuccessful, an AV block was deliberately provoked. The number of RF applications for modulation was 11 (from 3 to 27). Three patients with effective modulation had a total AV block within 3 days, so RF was considered effective in 74% (14/19). In the 8-month follow-up only one patient relapsed in the symptoms. Another patient died suddenly during sleep 5 months later. In order to understand these data correctly, it must be pointed out that patients had chronic AF and most of them had heart disease.

In patients with chronic AF, electrophysiological modification induced by RF could not be evaluated, and in patients with heart disease the results could not be of use for patients without heart disease, or with mild heart disease.

In the report by Brignole modulation was successful only in 25% (5/20). This unsatisfactory result, however, is probably due to the adopted criteria of effectiveness (mean AF rate < 80/min or 120/min during isoproterenol infusion). On the whole, a successful result was achieved in 50% (10/20). In 3 patients (15%) an inadvertent total AV block was obtained. It is important to consider that in the follow-up (ranging from 3 to 15 months) one of the patients with effective modulation still referred invalidating symptoms as he had a mean AF rate of 70/min. For this reason he underwent AV junction ablation and life-long pacemaker implantation. Another one had a second-degree AV block requiring pacemaker implantation as well.

In the study made by Feld, effective modulation was achieved in 70% of patients by applying RF during a mean of 17 applications (range 2-34); 2 patients had inadvertent total AV block. During follow-up (14 ± 8 months) all successfully modulated patients were symptom-free; only one patient had a relapse of high frequency AF controlled through drug therapy.

Della Bella obtained a successful modulation in 87% of patients, a mean of 11 ± 4 applications. No patients had an inadvertent AV block. In two patients with RF ineffectiveness a total AV block was provoked and subsequently a pacemaker was implanted. During follow-up (mean 5.8 months, range 2-18 months) three patients had a recurrence of palpitations also during low frequency AF. Before RF, these patients had presented with syncope and pulmonary edema.

Chen obtained a successful modulation in 85% (34/40) of patients without a behavior of atrioventricular nodal dual pathway (Group 1) and in 60% (6/10) of patients with atrioventricular nodal dual pathway (Group 2).

In Group 1 RF was ineffective in 4 patients and provoked a total AV block in 2 patients. In 8 patients with effective modulation transient AV block was obtained, one of them later developed an AV block 2:1 with pacemaker implantation. Short-term efficacy was therefore of 82.5% (33/40). It can be pointed out as in this group there exists a close inverse relationship between mean rate of AF and increase of AH interval of Wenckebach cycle and effective refractory period of AV node. During follow-up (14 ± 8 months) no AV blocks appeared and on the whole, after a new modulation with RF in 3 out 4 unsuccessful cases, a success of

90% (36/40) was achieved. It is relevant to observe that in 4 unsuccessful patients of Group 2 there existed a peculiar behavior of basal AV node refractoriness with small differences between fast and slow pathways.

During follow-up, Group 2 patients with successful modulation did not have recurrence of symptoms. Patients with unsuccessful modulation who still reported symptoms underwent a second successful procedure performed with the technique of Group 1. Thus all Group 2 patients were asymptomatic after successful modification of the AV junction, without an antiarrhythmic drug, after elimination of slow pathway or further modification of the AV junction during a follow-up period of 15 ± 7 months.

In our experience modulation was effective during the procedure in 45% (5/11) patients. In three patients a transient total AV block was present, which disappeared completely after few minutes, therefore modulation was effective. Short-term success was achieved in 73% (8/11) patients. In two patients, one in sinus rhythm and the other with chronic AF, RF was ineffective since it failed the end point. The patients with AF underwent AV junction ablation and pacemaker implantation after procedure. Patient in sinus rhythm underwent junctional ablation and pacemaker VVIR implantation after 5 months and inefficacy of drug therapy in controlling ventricular rate. During follow-up (mean 3 months; range 1-31 months) no AV block was documented. Two patients (the one with AT and the one with AF) still referred palpitations even if mean ventricular rate was lower than 100/min. They underwent AV junction ablation and life-long pacemaker implantation with disappearance of symptoms.

Which End Point

The anatomical structure of AV junction is well known [19]. It is made up of a roughly triangular region called triangle of Kock. The AV node is to be found inside this region with the compact AV node proximal to the apex of the triangle relating to the tendon of Todaro, the central fibrous body and the tricuspid valve septal leaflet. Around the compact AV node there exists a transition zone with two inputs:

1) The anterior input, near the apex of the triangle of Kock
2) The posterior input, near the coronary sinus ostium.

Less known is the correct function of AV junction. The nodal dual pathway behavior in patients without AVNRT suggested the hypothesis that the existence of two access pathways (fast and slow pathway) to AV junction could be the physiology of the normal heart [20]. This behavior is absent when one of the two pathways is poorly developed or the electrophysiological properties of both are similar (same refractoriness) [12, 13].

During AF several factors contribute to determine the electrophysiological properties of AV node. They include concealed conduction, impulse sommation, atrial impulse irregularity, electrotonic modulations, local reentries, nodal cells automatic activity [21]. However the high ventricular response seems to be

dependant on the conductive capacities of AV node and in particular AV node EPR, AV node functional refractory period and shortest atrial pacing cycle length associated with 1:1 conduction [22].

Modulation through anterior approach on the fast pathway also results in damage to a compact AV node with lengthening of AH interval and a large number of inadvertent AV blocks during both application and follow-up [9]. After slow pathway ablation in patients with AVNRT an increase of ERP and WP of AV node can often be observed. In such cases the mean rate of induced AF shows a significant reduction before and after ablation [12, 13]. This type of approach seems to be preferable because RF is applied far from the compact AV node. However some points must be considered. The slow pathway ablation is likely to be effective in controlling AF mean rate, and consequently the symptoms, when there is a relevant difference of refractoriness between the two pathways with long ERP of fast pathway. In the other cases slow pathway ablation may be insufficient to control frequency. This happens particularly in patients with ERP or short WP of the pathways or absence of behavior of nodal dual pathway and EPR and short WP of AV node. In fact, applications were often repeated with progressively anterior shifting of the ablating catheter in the transition zone proximal to compact AV node.

Actually, in all studies where ablation is performed with posterior approach inadvertent AV blocks were observed. To obtain the expected end points (mean AF rate lower to basal 100/min or 120/min during isoproterenol infusion or WP lower to 140-120/min) a larger number of applications of RF and lesion enlargement involving midseptal zone are often necessary. It may be that, in such cases it is possible that not only the slow pathway but also the perinodal atrium, the transition zone and part of compact AV node are involved. Actually, in some patients the AH interval after RF is lengthened.

In patients where RF is performed in AF and therefore a prevailing anatomical approach is used, it is difficult to find a target so that neither a correct electrophysiological end point can be evaluated or lesions be graded.

Moreover, during follow-up some patients with controlled mean rate still report symptoms, since modulation is not able to eliminate irregularities in RR cycle [23]. For this reason it is difficult to single out these patients in whom modulation is effective. In patients with paroxysmal AF or in patients with heart disease and/or heart failure, there are not enough evaluations during physical effort when modulation is effective. Moreover a complete evaluation of the methodology is not possible yet because no adequate case histories and follow-up are available to correctly evaluate late AV blocks or symptomatic recurrences.

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Heart Failure Patients with Atrial Fibrillation: How Important Is It to Regularize Ventricular Rhythm?

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Introduction

Atrial fibrillation is the arrhythmia which is most frequently encountered in clinical practice and has a particularly high incidence in the elderly and in patients with organic heart disease. The classical treatment of this arrhythmia involves restoration of sinus rhythm, control of the ventricular rate and prevention of thromboembolic events. Recently, however, there has been a systematic evaluation of the probable hemodynamic and clinical benefit of regularizing the ventricular rhythm in patients with chronic atrial fibrillation in whom the restoration of sinus rhythm is deemed to be impossible.

It is well known that, in patients with chronic atrial fibrillation, apart from the loss of the atrial contribution to left ventricular filling, the continuous variations in the cardiac cycle also play a significant role in the reduced cardiac performance [1-3]. Furthermore, most of these patients have an inappropriate chronotropic response during exercise testing [4]. Recent clinical studies based on these observations have shown that regularisation of the ventricular rhythm, through ablation of the atrioventricular junction and implantation of a permanent VVIR pacemaker [5-7], leads to an increase in both cardiac output and exercise capacity, with a consequent improvement in the patient's quality of life, especially in the case of patients with compromised left ventricular function. This technique has so far been used in cases where the ventricular response could not be controlled with drugs or in cases of tachycardiomyopathy [8-12]. However, the recognition of the importance of the regularisation of the ventricular rhythm is likely to lead to the application of the method to patients with chronic atrial fibrillation and normal ventricular response.

Data from Experimental and Clinical Studies

Although the negative effect of an irregular ventricular rhythm on cardiac performance was proved long ago, mainly by experimental animal studies [3] but

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also by clinical studies in humans [1, 2], only recently there has 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. [3] reported their findings concerning the effects of an abnormal ventricular rhythm on cardiac output in dogs with complete atrioventricular 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 R-R 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. [6] were the first to examine the hemodynamic effect of regular and irregular ventricular pacing at identical average heart rates in patients with atrial fibrillation and complete atrioventricular block. They studied 11 patients with atrial fibrillation and mean ejection fraction 0.46 ± 0.11. After radiofrequency ablation of the atrioventricular 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. [5], in a recent prospective study, examined the impact on ventricular function and quality of life of atrioventricular 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-hour Holter recording. Ten of the 14 patients had structural heart disease (9 ischemic cardiomyopathy, 1 dilated cardiomyopathy) and none were taking antiarrhythmic medication. The ejection fraction and fractional shortening were measured echocardiographically before ablation and pacemaker implantation, and again one month and 12 months afterwards. At the same time 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 one 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 one month ($p < 0.001$) and the change was still 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 one month ($p < 0.001$) and remained stable over time. The authors concluded that a chronic irregular heart rate alone could produce an overall reduction in cardiac function that can be reversed by atrioventricular 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 [7], the authors reported that, in patients with chronic atrial fibrillation, discontinuation of "effective" therapy for rate control (β-blockers, Ca^{++} antagonists, digoxin) followed by atrioventricular 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 VO_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 establishing the importance of the restoration of the patients' chronotropy during exercise. This study involved 10 patients, aged 71 ± 5 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 atrioventricular junction and implantation of a permanent VVIR pacemaker. One day before and one month 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 35 ± 9% before to 42 ± 7% after the procedure ($p < 0.01$). The ergospirometric parameters also improved significantly after the atrioventricular junctional ablation. Oxygen consumption increased from 15.6 ± 0.8 to 17.8 ± 0.9 ml/kg/min ($p < 0.01$) at peak exercise and from 12.3 ± 0.7 to 14.9 ± 1 ml/kg/min ($p < 0.01$) 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, our patients all had heart failure and were not taking any β-blockers or Ca^{++} antagonists before the ablation. Furthermore, their exercise tolerance was assessed by cardiopulmonary stress testing with breath-by-breath analysis of respiratory gases, whereas it is not clear from the study by Natale et al. what the functional status of the patients was or how the the VO_2 measurements were obtained.

Pathophysiological Mechanisms to Explain the Reduced Cardiac Performance Associated with an Irregular Rhythm

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 [13]. It is therefore likely that the reduction in ejection fraction which is observed in very short cardiac cycles (short R-R 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 [14]. 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 turn, causes venous and arterial dilation 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 [2]. It is probable that abrupt changes in cycle length have a direct effect on myocardial contractility. Also, short R-R 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 hemodynamics [3].

At this point, it should be noted that a high percentage of patients with chronic atrial fibrillation show disturbances of chronotropy during exercise [4]. Ablation of the atrioventricular 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 to improve exercise capacity as well. However, it is not known whether the increase in exercise capacity we observed after atrioventricular 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.

Procedure-related Side Effects

Even though the findings of existing studies demonstrate that regularisation of the ventricular rhythm has a beneficial effect on the left ventricular function and quality of life of patients with chronic atrial fibrillation, some consideration must be given to the procedure by which this regularisation may be accomplished, that is, atrioventricular junction ablation and artificial pacing.

Although the radiofrequency catheter technique is today used almost universally for atrioventricular junctional ablation and has minimal side effects, a very small percentage of cases of sudden cardiac death may be associated with the procedure. On the other hand, it is well known that the abnormal ventricular sequence resulting from right ventricular apical pacing has a negative inotropic effect [15] and experimental studies have shown that this kind of pacing, when applied chronically, could be related to structural myocardial abnormalities [16]. Finally, it must be borne in mind that, following this procedure, most patients

remain pacemaker dependent and their life thus depends on the reliability of their pacemakers and pacing leads.

Questions Which Remain to Be Answered

Although regularisation of the ventricular rhythm by ablation of the atrioventricular junction seems to be an attractive therapeutic option, there are still a lot of questions which must be answered. Studies so far have followed patients for up to one year and the longer term effects need to be investigated, including whether the technique leads to an improvement in prognosis and a reduction in mortality. Secondly, the majority of patients in these studies had left ventricular dysfunction and it is not known whether other categories of patients could also benefit from the same treatment. Finally, it should be determined whether biventricular or septal pacing might be superior to pacing through the apex of the right ventricle.

Conclusions

It is certain that an irregular cardiac rhythm contributes materially to a reduction in cardiac performance in patients with chronic atrial fibrillation. On the other hand, regularisation of the ventricular rhythm by catheter ablation of the atrioventricular junction and right ventricular pacing is a relatively simple technique with little risk to the patient. The findings of the first clinical studies, which mainly concern patients with compromised left ventricular function and heart failure, are encouraging. However, before the method can become established as a basic treatment for these patients larger studies, with longer follow-up periods are needed, as well as studies which address not only cardiac performance and quality of life, but also patient mortality.

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Catheter Ablation of Atrial Fibrillation: Where Are We Now and Where Are We Going?

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Atrial fibrillation (AF), the most common supraventricular arrhythmia, [1] is also one of the few remaining challenges for curative catheter ablation techniques. Though AF can be cured by extensive surgical atriotomies placed to interrupt all potential re-entry circuits without interfering grossly with conduction of a sinus impulse, these procedures have attendant limitations.

Electrophysiology of Atrial Fibrillation

In 1964, Gordon Moe described the multiple wavelet hypothesis [1] based upon a computer model and proposed that the following factors – size and mass of the tissue, conduction velocity as well as refractory periods – all modulated the ability to sustain atrial fibrillation. The probability of sustenance was proportional to the number of simultaneous wavelets. Later, experimental data from Allessie et al. provided evidence of the re-entrant nature of this arrhythmia, with the estimation that only 4 to 6 simultaneous wavelets were sufficient to maintain AF in their model [2]. Intraoperative mapping studies from Cox's group confirmed the fleeting nature of wavelets both in time and location, precluding the use of mapping to guide ablative surgical therapy [3].

In contrast, however, spatial disparities of complex electrical activity have been reported recently in both atria during AF. Li et al. reported a disorganization of atrial electrograms on the posterior wall in both atria ("type III AF") which reorganized anteriorly towards a type I AF [4] while Jaïs et al. found that trabeculated regions in the right atrium exhibited temporally less frequent complex electrograms in comparison to the smooth walled region extending till the crista terminalis. In particular, electrograms recorded from the majority of the left atrium were complex except near the appendage – again a trabeculated region (Fig. 1).

Shah et al. explored the electrical activity of great veins derived from atrial muscle fibers in the venous walls. A spike like activity recorded from the superior vena cava was dissociated in 14 patients and followed the right atrial activity in one out of 15 during AF [6]. In contrast, activity in the pulmonary veins (notably

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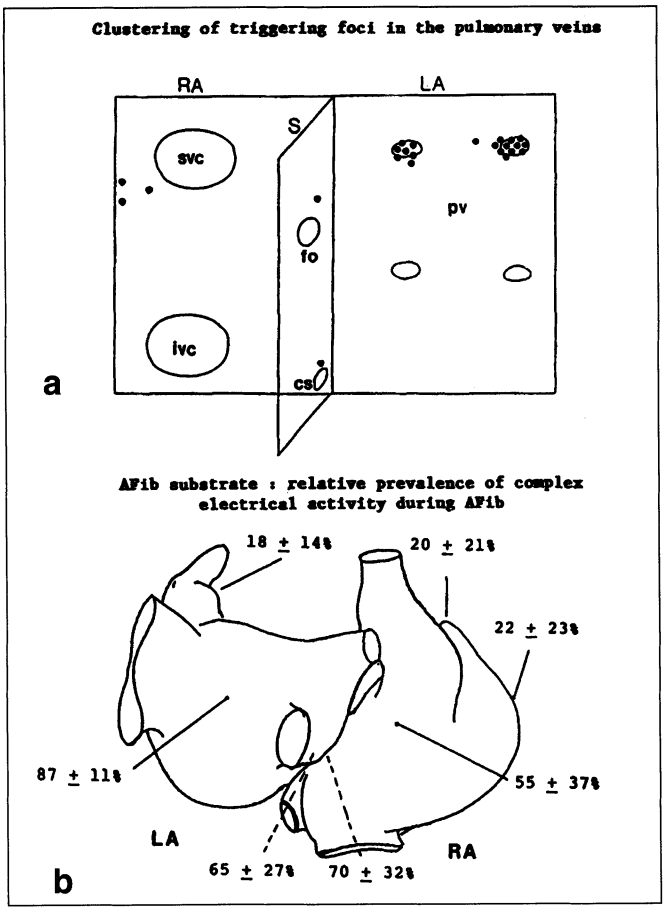

Fig. 1a, b. a A diagrammatic representation of the distribution of tachycardia foci in both atria. RA, right atrium; LA, left atrium; S, interatrial septum; SVC, superior vena cava; IVC; inferior vena cava; FO, fossa ovalis; CS, coronary sinus; PV, pulmonary vein. Note the prominent clustering around the left superior pulmonary vein. **b** Schematic diagram of both atria in the posterior view. The duration of complex activity (either continuous electrograms or FF intervals < 100 ms) assessed over 60 seconds is expressed as a percentage (± SD)

the superior ones) could be recorded up to 5 cm inside and could track the left atrial activity at a high rate thus indicating a better coupled interface with the LA.

Experimental Studies of Substrate Ablation

Most experimental studies have been performed in dogs with the limitation of the small size of the atria rendering induction of fibrillation more difficult and more importantly, making termination easier (i.e. with smaller lesions) - and therefore hampering extrapolation to the clinical context. Linear anatomically

based atrial lesions mainly have been shown to reduce the inducibility and duration of atrial fibrillation with success rates varying from 57% to 100%. Data from these studies suggest a possible role of the particular AF model in determining the efficacy of ablation targeted on a specific atrium. Ablation in the right atrium seems sufficient in either normal dogs or those with sterile pericarditis while ablation in the left atrium seems to be required in the rapid pacing and mitral regurgitation models [7]. Some results support the concept of using electrophysiologic data to guide atrial ablation (in contrast to the surgical strategy employed for the Maze procedure) as indicated by successes in targeting preferential regions of disorganization during AF [4, 8] or Bachman's bundle in the sterile pericarditis model. One relatively consistently described feature has been the "proarrhythmic" effects of discontinuous lesions and lesions in certain locations resulting in the induction of "new" atrial flutters.

Despite recent developments of different animal models of AF, there is no currently available in vivo model with a reproducible and spontaneous initiation of AF to allow study of triggering events. Nevertheless, foci of ectopic activity are considered either rare or occurring as solitary (non repetitive) events [2].

Clinical Studies

Results of Ablation Using Linear Lesions

Two case reports in 1994 demonstrated the feasibility of catheter ablation of AF in humans. Lesions restricted to the right atrium were successful for a patient with paroxysmal AF [11] using a multiple electrode catheter, whereas in the other report, a catheter based biatrial Maze procedure was performed in a patient with chronic AF [12].

The efficacy of ablation limited to the right atrium (RA) was subsequently assessed in 45 patients with daily paroxysmal AF [13]. Three groups of 15 patients each underwent increasingly complex lesion patterns in the right atrium. Ablation led to stable sinus rhythm during the procedure in 18 patients (40%) but non inducibility of AF using burst pacing was achieved in only 5 patients (11%). Final success rates with all three types of lesion patterns were similar– 13% without drug to 40% in combination with antiarrhythmic drug therapy (Fig. 2). No factor predictive of success using right atrial lines was recognized [13]. In view of these unimpressive success rates, the combination of a single right septal line with a simplified rectangular ablation schema was implemented in the left atrium with significantly improved results. The length of lines is minimized by joining fixed anatomical structures, except in the roof to avoid isolation of the posterior left atrium (Fig. 2). In a series of 32 patients, stable sinus rhythm was obtained in 29 patients and sustained AF was rendered non inducible in 24 (75%) at the end of the ablation session. Two ablation sessions were usually performed because most patients developed left atrial flutters a few days after the first session. When restudied, these patients did not have evidence of a conduction block across the

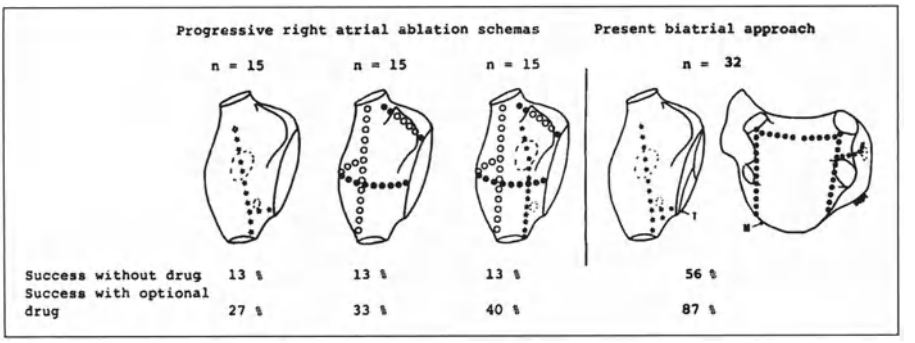

Fig. 2. Results of AF ablation in 69 patients: 45 patients only ablated in the right atrium and the initial 32 patients ablated using a biatrial approach. The creation of ablation lines is minimized by the use of barriers between structures of fixed anatomic block: superior to inferior vena cava via the fossa ovalis and isthmus ablation in the right atrium; both superior pulmonary veins to mitral annulus via the inferior veins

ablation lines (wide split potentials) in contrast to the immediate post ablation study. New energy applications were required to fill in the gaps and produce continuous and transmural lesions in order to interrupt flutters. The success rate was 87% but half of the patients still required adjuvant antiarrhythmic drug therapy (Fig. 2). The failures manifested mainly as recurrences of left atrial flutter.

Ching Man et al. [14] have also recently performed right atrial ablation in 12 patients with paroxysmal AF and the results are largely concordant with only 3 patients improved.

In a series of 34 patients with chronic AF, Swartz et al. [12] achieved a success rate of more than 80% with a progressively modified biatrial ablation schema with most patients being free of drug therapy. The linear applications were repeated several times to ensure the achievement of a conduction block. The procedures were prolonged and performed under general anesthesia and two patients developed an embolic cerebrovascular accident.

Focal Mechanisms

In contrast to the studies summarized above, a small and uncommon group of patients have been described who have the surface ECG features of atrial fibrillation produced by a very fast and irregular "focal" atrial tachycardia [15]. These patients are young and without structural heart disease. Depending on the focus rate, the ECG tracings exhibit AF or monomorphic atrial tachycardia or extrasystoles. The arrhythmia can be eliminated by local ablation – frequently in or near the ostia of great veins (Fig. 3).

Similarly in patients undergoing linear ablation for paroxysmal atrial fibrillation, the organization of atrial activity shortened or prevented episodes of AF allowing the unmasking of foci of extrasystolic activity which were triggers of episodes of AF before ablation. This is as yet an unreported finding and these foci

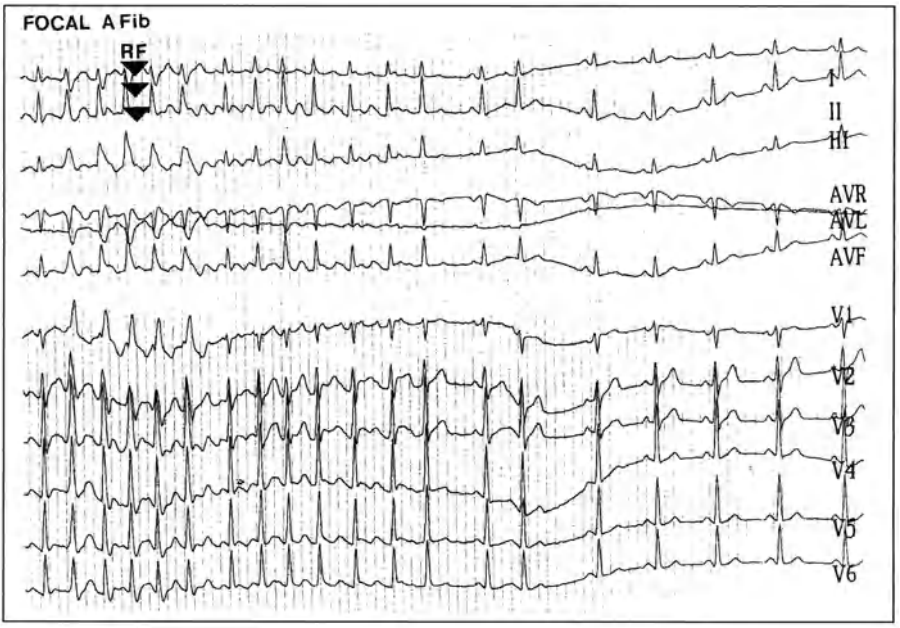

Fig. 3. Interruption of a focal atrial fibrillation during RF delivery. The focus originated from the right inferior pulmonary vein

manifest as isolated runs of extrasystoles or trigger bouts of AF. They are detected in at least one third of patients and originate again in or near the ostia of pulmonary veins (Fig. 1). Therefore, the left atrium appears to be both the most vulnerable substrate as well as the main feeder of triggers for AF (Fig. 1). The recognition and ablation of such foci associated to linear ablation is strongly predictive of a successful clinical outcome.

Safety Profile and Complications

Ablation in the right atrium may inadvertently involve the sinus node complex or the AV node. Such injury can be suspected earlier in sinus rhythm rather than during AF (because of an automatic rhythm or bradycardia) and therefore minimized by stopping RF delivery immediately. While the clinical data to date has indicated the relative safety of quite extensive ablation in the right atrium, the same cannot be said of left atrial ablation which is the main target for AF ablation. Strict anticoagulation (PTT $\approx$ 2-3 times the control value) and temperature controlled RF output (50°C-55°C) are mandatory in order to prevent embolic events; nevertheless, despite such precautions, strokes have occurred. On the other hand, the risks of manipulating stiff catheters within thin-walled atria are always present, and accordingly hemopericardium/tamponade was a potential complication which occurred in 3 patients in our series. The organization of atrial activity by linear ablation may result in "new" atrial arrhythmias or render

existing arrhythmias more frequent or more prolonged. This is presently the main obstacle to wider application of AF catheter ablation – e.g. to patients with disabling but infrequent episodes of arrhythmia. These new re-entrant atrial tachycardias, account in great measure for repeat or prolonged sessions in the electrophysiologic laboratory and in our experience are due to persistent gaps in the ablation lines chiefly because of the lack of suitable linear lesion making catheters.

Catheter Technologies to Create Linear Ablation

Two main approaches to endocardial catheter ablation of AF are being pursued: either the catheter drag technique with or without a guiding sheath, or the use of multielectrode catheters. Whatever the technique, the following steps are required to create linear lesion: (1) positioning catheter to desired locations, (2) ensuring adequate tissue contact all along the electrode surfaces, (3) delivering enough energy (with temperature control) to create lesion continuity and transmurality and (4) checking linear conduction block.

Some authors have suggested the possibility of assessing placement, tissue contact and lesion size using intracardiac echo guidance [10]. Also the in vivo assessment of the achieved lesions in terms of continuity and transmurality has involved correlation with electrogram changes (amplitude and dv/dt), pacing thresholds and altered activation sequences as well as altered echo characteristics. We found that the simple recording of electrograms along the line after ablation (with orthogonal spontaneous/paced atrial activation) is reliable in predicting linear block on the presence of double potential separated by isoelectric interval. A gap on the line is indicated (Fig. 4) by a local single or triple continuous electrogram straddling the adjacent double potential interval [13, 16, 17].

Technical means of achieving linear transmural continuous lesions intended to modify the atrial substrate with maintained safety standards are being explored. Different configurations of multiple ring electrodes, coils, ribbons and balloons or different sources of energy are under investigation – some with additional features such as phased or simultaneous multielectrode energy delivery.

A number of techniques include an irrigation system that cools the distal tip to minimize the risk of coagulum both on the electrode and endocardium, whilst still allowing the delivery of higher powers. We assessed the efficacy and safety of a dragging technique with high power delivered through an irrigated tip catheter in 10 anesthetized animals (4 dogs, 6 sheep). RF current was applied during sinus rhythm to create a continuous line using a 4 mm tip (Sprinklr, Medtronic Inc.) ablation catheter. A *single passage* was performed point by point along a predetermined course (50 W at each point with 4 incremental RF durations). The catheter was withdrawn a small distance under fluoroscopy after each application in order to ensure lesion continuity. The following results were obtained: ten lines were performed in the right atrium and 6 in the left atrium after transeptal catheterization. A mean of 10 ± 3 RF applications lasting 20 s (4 lines), 40 s (6), 60 s (3), 90 s (3) was delivered. Most lesions were transmural in the free wall with

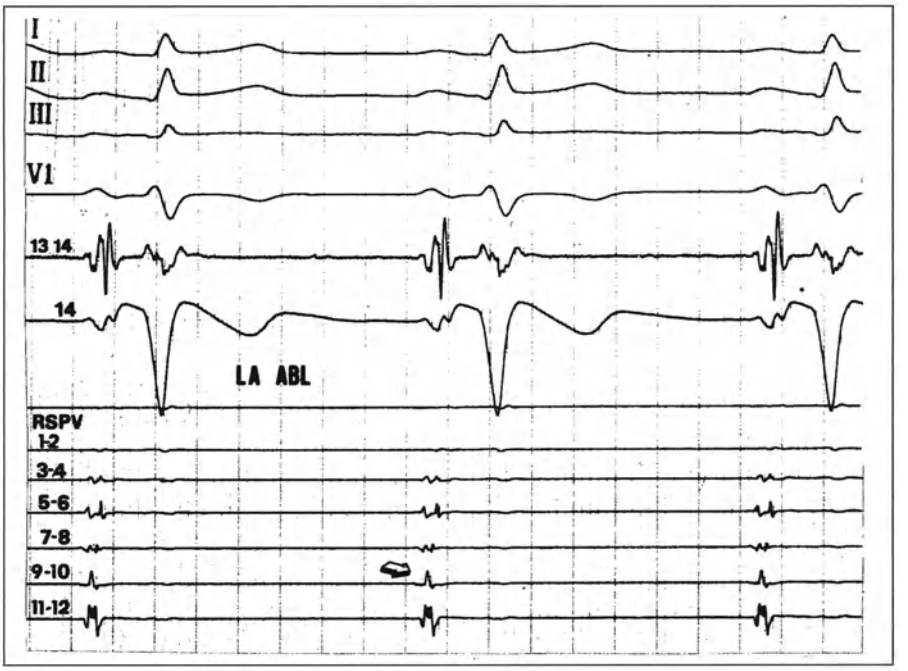

Fig. 4. Electrograms recorded from the left atrium (LA) along the line between the right superior pulmonary vein (RSPV) and the mitral annulus (bipole 13-14 and unipolar electrogram 14) after ablation. Double potentials are recorded during sinus rhythm at five bipoles; however a single electrogram (*arrow*) at the bipole 9-10 indicates a gap in the line

little endocardial alteration. One septal lesion extended non transmurally into the ascending aorta. No line was fully continuous and the lesions varied from multiple discrete punctate ones to large and discontinuous linear segments (up to 3 cm). Four pops (3%) were recorded (catheter entrapped), all after 40 s or more of RF application. No coagulum was found except in 3 trabeculated sites (2%). Three endocardial craters were noted only at the sites where pops occurred. Acute macroscopic examination of the heart showed there was no hemopericardium attributable to RF.

Therefore, high RF energies delivered through an irrigated 4 mm tip catheter are relatively safe on acute evaluation with a low incidence of coagulum formation. However, a single drag line is unable to create a linear lesion and several passages seem to be required to create a continuous transmural line.

Conclusion

Curative catheter ablation of AF is feasible and successful; particularly when a focal mechanism for AF is identified or when linear ablations are performed in the left atrium. The success rate reaches 87% in patients with paroxysmal AF

using a biatrial ablation schema. Arrhythmogenic foci play a significant role in human AF. They manifest as extrasystoles which can be mapped and ablated. The procedures intended to modify the atrial substrate are prolonged because it is difficult with current technology to consistently achieve a linear conduction block. The challenge remains to perfect this technique before envisaging wider application.

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ATRIAL FIBRILLATION: INTERNAL DEFIBRILLATION

Restricted or Expanded Indications for Low-Energy Internal Cardioversion?

M. Santini, C. Pandozi, G. Gentilucci and M. Villani

Atrial fibrillation is a very common and potentially dangerous cardiac arrhythmia [1-4]. A 5-fold embolic risk in the non-rheumatic atrial fibrillation and 18-fold risk in the rheumatic group has been ascertained [5] and full anticoagulation is frequently recommended in patients with atrial fibrillation [6-8]. Furthermore the loss of atrial contraction can cause a significant hemodynamic deterioration [9, 10]. Restoration of sinus rhythm seems therefore to be advisable.

In patients with atrial fibrillation, sinus rhythm can be restored by direct-current external cardioversion or by means of antiarrhythmic drugs given intravenously or orally [11]. High energy internal cardioversion has also been used in patients refractory to external atrial defibrillation [12, 13].

More recently, low-energy internal cardioversion has been developed and proposed as an alternative to transthoracic cardioversion [14-16] in patients with either paroxysmal or persistent atrial fibrillation. In this paper we report our experience with low-energy internal cardioversion in patients with persistent atrial fibrillation. The analysis of our results may help to select the indications for the procedure in patients with atrial fibrillation.

Methods

Sixty-four patients affected by persistent atrial fibrillation, who were candidates for transthoracic cardioversion or who had already been unsuccessfully submitted to transthoracic cardioversion, were included in the study.

All the subjects were submitted to full oral anticoagulation during the last three weeks.

Oral anticoagulants were discontinued three days before the procedure and were generally replaced with heparin that was stopped 6 hours before and restarted 6 hours after the procedure. Oral anticoagulation was restarted after the cardioversion and was continued at least for the following 30 days. Heparin infusion was stopped completely when therapeutic INR values (2.5-3) were again

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achieved. The minimum INR safe value, checked immediately before the invasive procedure, was considered to be 1.5.

Three intracavitary temporary leads were used in each patient. Two 6F custom-made large-active surface area catheters (Elecath Inc., Rahway, NJ, USA) were used for the shock and one USCI tetrapolar lead (Bard-USCI Inc., MA, USA) for ventricular synchronization. The first Elecath lead (cathode) was positioned, under fluoroscopic control, in the distal part of the coronary sinus in order to embrace as much as possible of the left atrium. In 5 patients, because of the impossibility to cannulate the coronary sinus, one Elecath lead was positioned in the left pulmonary artery. The second Elecath lead (anode) was positioned in the high right atrium paying attention to keep the electrodes in contact with the atrial wall. The quadripolar lead was positioned in the right ventricular apex for ventricular synchronization (Fig. 1).

The coronary sinus (or pulmonary artery) catheter was inserted by the femoral approach in 58 patients and by the subclavian in 6, while the femoral approach was always utilized for the ventricular and atrial leads. All the catheters were connected to a Teletronics Guardian implantable defibrillator. The defibrillator was used manually and not automatically.

A truncated, biphasic (3ms+3ms), exponential waveform was used [17, 18].

In 49 patients (group 1), beginning from 50-volts the voltage was increased progressively by 50 volt steps until the restoration of the sinus rhythm was obtained. All shocks were separated by an interval of at least one minute. Impedance, voltage, and both total and delivered energy of each shock were automatically measured by the device.

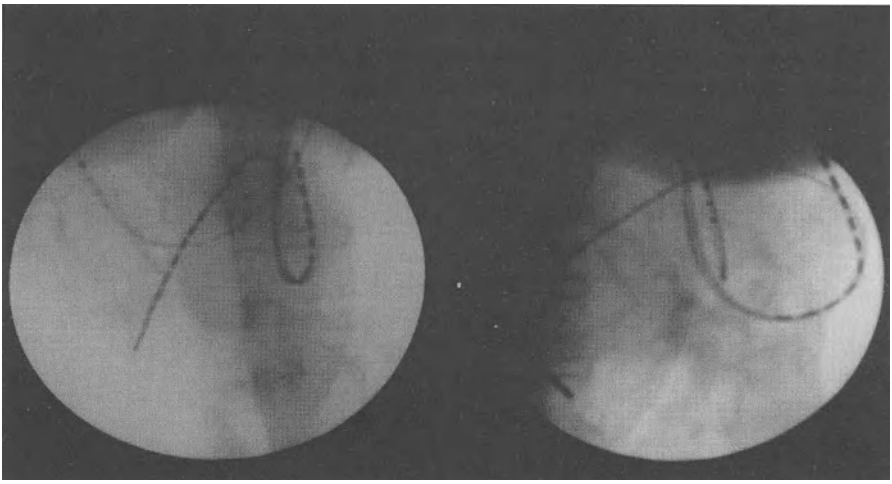

Fig. 1. Catheter positions in the 30° right (*right side*) and left (*left side*) anterior oblique views before a low-energy endocavitary shock. The two decapolar large active surface catheters are positioned in the coronary sinus and in the right lateral atrial wall, respectively. The tetrapolar USCI catheter positioned in the right ventricular apex is used for R-wave synchronization

In 15 patients (group 2) a single shock of energy approximating the ADT was given. (350 V, 7.7 J); a second 400 V (9.9 J) shock was given if sinus rhythm was not restored.

Continuous ECG recording was performed during the procedure. All the shocks were delivered synchronized on the R wave. The shock was considered successful if atrial fibrillation stopped either immediately or within 30 seconds.

After each shock the patients were asked to grade the degree of discomfort they felt, giving a score from 1 to 5 (1=not felt; 2=felt without discomfort; 3=mild discomfort; 4=moderate discomfort; 5=severe discomfort). In the first five cases sedation (diazepam 5 mg i.v.) was given routinely, immediately before the sequence of shocks. In the other cases the drug was administered only if necessary.

In all the patients an ECG was recorded every 6 hours for three days after the procedure. Patients were seen at 1, 2, 3 and 4 weeks after the procedure for ECG and physical examination. After this period they were seen every month. Patients were asked to come to the hospital for an additional control as often as symptoms recurred.

Results

Sixty-four patients were submitted to low-energy internal cardioversion. Their mean age was 63.1±11.0 years (range 40-82 years), 40 of them were male, the mean body weight was 77.2±13.3 Kg, the mean height was 169.3±9.0 cm and body surface area was 1.8±0.3 m^2. Four patients had lone atrial fibrillation. The atrial fibrillation duration, calculated from the time of diagnosis, ranged from 11 to 2920 days (mean 262.4±473.3 days, median 90 days); 51% patients had already had a previous episode of atrial fibrillation.

The left atrium transverse diameter ranged from 32.1 up to 68.0 mm with a mean of 47.2±6.4 mm. In 12 patients a previous attempt to restore sinus rhythm by transthoracic cardioversion had failed. In none of the patients examined and included in the study were auricular thrombi or spontaneous echocontrast observed by transesophageal Echo performed the day before the procedure.

The protocol was completed for all 64 patients. To 12 of them a mild sedation (diazepam 5 mg i.v.) was administered.

Sinus rhythm was restored in all the patients during the defibrillation procedure.

All the shocks were properly synchronized and no ventricular arrhythmia was induced by the atrial shocks in any of the patients.

No other complication occurred and creatine-phosphokinase rise was never observed.

In the 49 patients submitted to the step-up protocol (group 1) the mean shock voltage and energy necessary to restore sinus rhythm were 352.0±80.3 volts and 8.2±3.4 joules respectively, while the average impedance was 51.0±11.9 ohms. The mean discomfort score for the successful shock was 3.4±0.8.

In the patients submitted to the single shock procedure (group 2) sinus rhythm restoration was obtained with the first 350 V shock in 2 out of 15 (80%)

patients, while the remaining 3 patients required the second 400 V shock. The mean discomfort score was 2.4 in group 2 ($p<0.05$ versus group 1).

Follow-Up

The mean follow-up period was 182.5±50.7 days (range 45-290 days). All patients were treated with antiarrhythmic drugs after the intracardiac cardioversion.

Fourty-three percent of the patients had atrial fibrillation recurrence during the follow-up period; 71% of them in the first week after the cardioversion and the remaining 29% during the first month. Atrial fibrillation did not recur in any of the patients after the first month of follow-up.

Discussion and Conclusions

Transthoracic cardioversion is painful and therefore necessitates general anesthesia [1] which could be avoided if lower shock energies could be used. Our results demonstrate that persistent, long lasting, atrial fibrillation can be easily converted to sinus rhythm by a low-energy shock administered inside the heart without general anesthesia and without any evident dangerous effect for patients' safety. In fact, in our study all the delivered shocks were properly synchronized to R-waves and no ventricular tachycardia was induced [9].

The pain sensation referred by the patients is an important issue related to the procedure. Although Diazepam was used routinely in the first 5 patients, altogether only 12 of our patients required a mild sedation during the procedure in order to reduce their discomfort; moreover in none of them were we obliged to stop the protocol because of the patient's intolerance. Furthermore we have to consider that the discomfort created by the procedure performed according to the research step up protocol (Group 1) which required multiple shocks in order to define the atrial defibrillation threshold, is greater than that caused by one single and efficient shock. In fact in the 15 patients undergoing the single-shock procedure the discomfort score was significantly lower.

We think that, when complicated and time-consuming research protocols come to an end, intracavitary low-energy cardioversion should be performed very simply without anesthesia, giving just one or two shocks at most of a given energy level which is likely to be successful. Moreover, further modifications of the shock waveform [20] could lower the atrial defibrillation threshold and consequently reduce patient discomfort and the need for sedation.

In relation to the specific issue of indications to low-energy endocavitary cardioversion, at the moment they remain restricted. Low-energy endocavitary cardioversion should be considered the treatment of choice for all patients with persistent atrial fibrillation resistant to transthoracic shock, and for those in whom general anesthesia is contraindicated or hazardous. Low-energy internal cardioversion also represents the treatment of first choice in patients with atrial fib-

rillation induced during electrophysiological studies or ablation procedures, when a catheter is generally still positioned in the coronary sinus. Furthermore, we think that, at least in the centers having a high experience with the procedure, intracardiac low-energy cardioversion could also be proposed as the treatment of choice in patients with a low success rate with external cardioversion (obese patients, patients with lung disease). In the future the indications could probably be expanded if the procedure becomes more simple; this result can be obtained in the following ways:

- using one single lead with two or three separate electrodes in the pulmonary artery (shock delivering), in the right ventricle (R-wave synchronization) and in the right atrium (shock delivering).
- using one single lead positioned in the right atrium without fluoroscopy and confirming the correct position of the lead by transthoracic echocardiography. The shock could be delivered between the large active surface area atrial lead and an external patch, using the surface ECG for shock synchronization.

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Internal Atrial Defibrillation: What Are the Effects on Mechanical Function?

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Background

Atrial fibrillation (AF) represents the most common sustained arrhythmia that occurs in 0.3%-6% of the adult population and increasingly with age, and is therefore considered a large burden to the health care system because of direct and indirect costs due to morbidity and mortality rate [1-3]. The principal consequence of AF is the loss of organized atrial contractions that may have important hemodynamic effects on cardiac output expecially in those patients with underlying heart disease in whom the risk of stroke has increased five-fold [4]. Established methods for converting AF to sinus rhythm include treatment with antiarrhythmic drugs and application of external high energy shocks. Success rates ranging from 40% to 70% have been described with antiarrhythmic therapy [5]. The reported success rate for external cardioversion ranges from 61% to 90% [6, 7]. On the other hand, it is well known that electrical cardioversion may be complicated by cerebral, systemic and pulmonary embolic events in 0.6%-7% of patients undergoing the procedure [8, 9]. Thromboembolism after cardioversion has been attributed to the dislodgement of preformed thrombus from the left atrium with the resumption of sinus rhythm and atrial contraction [9, 10]. In the attempt to further reduce the prevalence of thromboembolic complications after electrical cardioversion, transesophageal echocardiography (TEE) has been proposed as a method of screening patients for left atrial thrombus before the external cardioversion. This tool has showed higher values of sensitivity and accuracy in comparison with transthoracic echocardiography (TTE) in this specific field [11, 12].

TEE in Evaluation of Left Atrial Mechanical Function after Cardioversion

TEE with pulsed-wave Doppler has been utilized for characterizing pattern of left atrial appendage (LAA) function during AF and after restoring sinus rhythm [13, 14]. Some studies have demonstrated a significant decrease in the peak Doppler velocities immediately after successful electrical cardioversion, implying

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reduced left atrial mechanical function [14, 15]. Other observations suggest that the most significant decrease in LA function results from conversion to sinus rhythm itself [15, 16]. It has been demonstrated that direct current countershock can give an "atrial stunning" characterized by a reduced left atrial contribution in ventricular filling [15], by an increasing of spontaneous echo-contrast or smoke, defined as dynamic intracavitary echoes with a characteristic swirling pattern [15], and by reduced of left auricolar Doppler velocities [16]. These findings suggest that stunned LAA function after cardioversion may produce a thrombogenic milieu with a direct consequence of higher risk of systemic embolization after cardioversion [15]. Electrically induced myocardial tissue damage occurs with electrical cardioversion, which is believed to be proportionate to the quantity of energy delivered and which may lead to decreased left ventricular contractility as reported by some [17, 18]. On the other hand, there are experimental studies on dogs that show an impairment of global heart function after repeated defibrillation with energies greater than 50 Joules applied directly to the heart [19]. In our previous experience with intraoperative TEE during implantation of implantable cardioverter-defibrillator (ICD) we did not find any significant impairment of left ventricular function, even in those patients with severe left ventricular dysfunction, probably because we used delivered energy lower than 34 Joules [20]. Several studies have also demonstrated that a great influence on the time of complete recovery of left atrial mechanical function is due to the duration of AF before cardioversion [14-16]. The time of recovery, or rather, a delayed return of atrial mechanical function following electrical cardioversion, seems to be strongly linked with higher thromboembolic risk [15].

Internal Atrial Defibrillation

Recently the internal atrial defibrillation (IAD) has been introduced in clinical practice because, in contrast with external cardioversion, the use of lower energies may avoid the stunning of the left atrium and left appendage and allow recovery of these structures earlier than after external cardioversion. The first results on the left atrial function 24 hours after IAD showed that left atrial appendage had depressed contractility with an increasing spontaneous echo-contrast (SEC) and thromboembolic risk [21, 22]. However it also demonstrated that the LAA completely recovers mechanical function within 1 week after IAD which is earlier than what happens with external countershock (3-4 weeks). Moreover it has well been established that IAD can be proposed with high probability of success in those patients in whom external cardioversion has failed [23].

Aim of the Study

In order to verify the safety, the efficacy, and especially to study the direct effect of IAD with lower energy on atrial mechanical function in those patients with AF

resistent to conventional external cardioversion, we have investigated patients undergoing IAD with transthoracic echocardiography one day before and one day and one week after, analyzing all conventional parameters. In addition transesophageal echocardiography was performed just before and during internal cardioversion.

Study Population and Methods

From January to May 1997 we submitted 11 patients, 7 males and 4 females, mean age 60 ± 9 years (range 40-72 yrs), with a mean weight of 79 ± 17 Kg to IAD, since some attempts with external cardioversion had failed. The mean period of duration of AF turned out to be 4.4 ± 3 min. All patients were anticoagulated with INR value in therapeutical range, and 9/11 patients (82%) were treated with antiarrhythmic drugs, 8 with amiodarone in and only one with sotalol. Four patients (pts) exhibited hypertensive heart disease, 3 patients valvular disease (2 pts mitral stenosis and 1 pt mitral regurgitation), 2 patients congestive cardiomyopathy and 2 patients had lone atrial fibrillation (Table 1). Written informed consent was obtained from all patients.

Three intracavitary temporary leads were used in each patient: one catheter was positioned in the distal part of coronary sinus, to embrace the left atrium as much possible, the second in the high right atrium and the third lead was positioned in the right ventricular apex. The defibrillator manually delivered a truncated-biphasic exponential wave, beginning from 50 V with progressive increments of 50 V until restoration of the sinus rhythm was obtained.

TTE was performed in all patients the day before and the day after the IAD as well as one and three months later: all conventional M-Mode, 2D and Doppler transmitral and transtricuspidal flows parameters were analyzed in accordance with the recommendations of the American Society of Echocardiography (ASE) [21].

TEE was performed with a 5 MHz multiplane transducer after induction of general anesthesia with propofol (1-2 mg/Kg intravenous) and all patients were previously intubated.

With TEE we investigated the heart function just before, during and just after intracardiac shock delivery: we evaluated 2D measurements of left and right atria, the percentage of variation of left appendage, EF of left ventricle and Doppler analysis of flow velocity in LAA, mitral and tricuspid valves.

Results

The IAD restored the sinus rhythm in 10/11 patients (91%) with a mean number of shocks of 3.7 ± 2.9 (range 1-7) and the mean value of effective delivered energy was 7.2 ± 2.9 (range 2.6-10.4) (Table 2). All 10 patients showed a recovery of atrial mechanical function just after IAD with a percentage mean value of atrial contribution in total mitral forward flow of 19.8% that reached the maximum value already 24 hours later (27.5%), increasing mildly after 1 week (29.7%).

Table 1. Patient characteristics

Pt No./ Gender	Age (yr)	Etiology	Duration of AF (months)	Antiarrhythmic Before IAD	EE (J)	Recurrence of AF
1/M	63	HHD-MP	3	No	5.7	5 days later
2/M	65	HHD-CC	1	Amiodar.	10	3 days later
3/M	60	CC	6	Amiodar.	ND	10 minutes later
4/M	40	APV	3	Amiodar.	10	< 5 days
5/F	69	MVD	> 12	Amiodar.	4	1 day
6/F	61	HHD	2	Amiodar.	3.8	no restoration SR
7/F	64	HHD	5	Amiodar.	0.4	no recurrence
8/F	68	MS	4	Amiodar.	2.6	> 4 days
9/M	44	LAF	6	Sotalol	2.6	no recurrence
10/M	66	MR	3	Amiodar.	5.2	no recurrence
11/M	72	HHD-CC	3	Amiodar.	5	1 week later
7M-4F*	Mean*** 60 ± 9		4.4 ± 3	10/11**	7.2 ± 2.9	No recurrence
	Range 40-72		(1-12)		(2.6-5.0)	in 3 pts

HHD, hypertensive heart disease; LAF, lone atrial fibrillation; APV, aortic prosthetic valve; CC, congestive cardiomiopathy; amiodar., amiodarone; MS, mitral stenosis; MVD, mitral valve disease; MP, mitral prolapse; MR, mitral regurgitation

Table 2. Electrical energy delivered

Pt No.	Weight (Kg)	EE (J)	N° of shocks	CE (J)	Mean Energy (J)
1	85	8	4	16.6	4.1 ± 2.6
2	83	10	4	26	6.5 ± 3.1
3	68	NR	7	95	13.6 ± 10
4	114	10	4	26	6.5 ± 3.1
5	95	10	3	18.2	6.0 ± 3.0
6	55	4	2	6.7	3.3 ± 0.9
7	60	2.6	1	2.6	2.6
8	63	3.8	2	2.5	2.5
9	87	5.7	3	12.1	4.0 ± 1.6
10	78	7.8	5	25.5	5.2 ± 1.4
11	86	10.4	6	26.3	4.3 ± 2.8
Mean	79 ± 17	7.2 ± 2.9	3.7 ± 1.7	23 ± 26	5.4 ± 3.2
Range	(55-114)	(2.6-10.4)	(1-7)	(2.5-95)	(2.5-13.6)

NR, non responder to IAD; CE, cumulative energy; EE, effective energy

The spontaneous echo-contrast (SEC) before IAD showed a mean value of 0.9 ± 0.5 increasing to 1.2 ± 0.6 just after IAD, at the limit of statistical significance (Table 3). The following behavior of increasing of SEC was clearly seen in 4 patients:

- One patient with congestive heart disease, a longer duration of AF and in whom the most frequent number of shocks (7) with the highest energy in absolute as well as in mean value (34 J; 13.6 ± 10 J) was delivered: in spite of this he was the only patient that did not restore sinus rhythm and an important observation was that the SEC augmented after the threshold of 15 J was delivered showing at the maximum shock a clear SEC in right atrium also.
- One patient with moderate mitral stenosis in whom the delivered energy efficacy was 10 J.
- One patient with a mild congestive cardiomyopathy for whom for restoring sinus rhythm a shock of 10 J was necessary.
- One patient with lone AF who did not show SEC before IAD and who just after the effective shock had an atrial prolonged standstill for almost 5 seconds (Fig. 1, 2).

The patients with recovery of sinus rhythm in whom it was sufficient to deliver lower energy showed the most complete recovery of atrial mechanical function, evaluated as percentage of end-diastolic contribution on the global transmitral (Fig. 3, 4) and transtricuspidal forward flow. Already 24 hours later the effective shock, and the mean value of the improvement in atrial contribution (A wave) after 1 week was of 50,4% (NS). The patient in whom the IAD did not restore the sinus rhythm showed the biggest left atrial size but above all the right atrial size. Also the patients who required the most frequent number of shocks showed a bigger right atrial size in comparison with the others ($p < 0.01$).

Table 3. Echocardiographic parameters

	LA			SEC	RA	
Pt No.	Diameter (cm)	Size (cm^2)	Area cm^2/m^2	Before ⟶ After	Size (cm^2)	Area cm^2/m^2
1	5.6	41	23	0 ⟶ 0	32	17
2	5.7	43	28	1+ ⟶ 1+	19	11
3	4.4	29	16	0 ⟶ 1+	23	12
4	4.9	36	18	1 ⟶ 1	21	10.5
5	5.2	35	19	1+ ⟶ 1+	29	18
6	5.3	39	21	1+ ⟶ 1+	24	16
7	4.9	36	18	2+ ⟶ 2+	26	15
8	4.6	33	19	1+ ⟶ 3+	28	19
9	5.1	39	24	1+ ⟶ 2+	27	20
10	4.6	36	18	0 ⟶ 0	23	12
11	4.7	38	20	1+ ⟶ 1+	21	13
Mean	5 ± 4	37 ± 3	21 ± 3.4	0.8 ± 0.5 ⟶ 1.2 ± 0.7	24.8 ± 4	15 ± 3.3
Range	(4.4-5.7)	(33-41)	(16-28)	(0-2) (0-3) (p = NS)	(19-32)	(10.5-20)

LA, left atrium; SEC, spontaneous echo-contrast; RA, right atrium

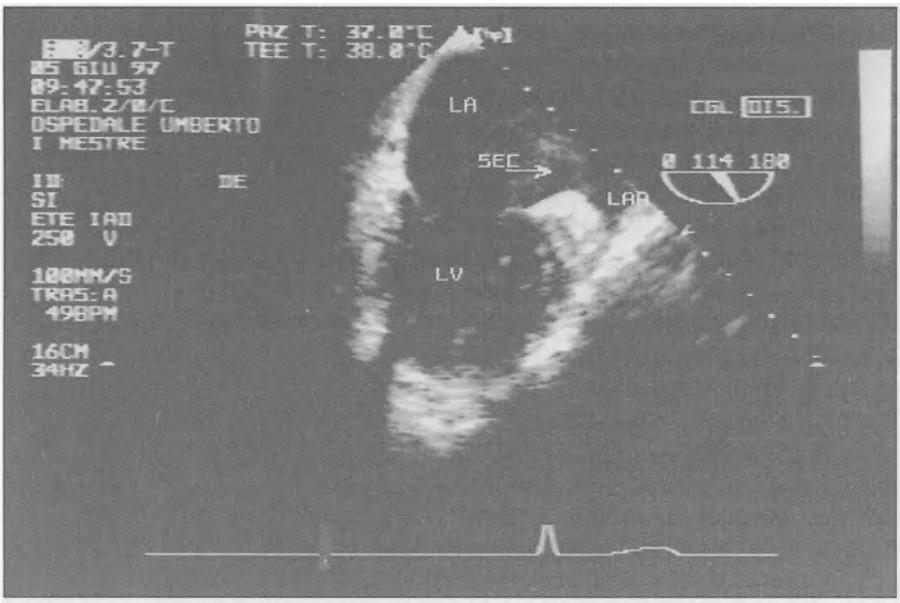

Fig. 1. Transesophageal echocardiographic approach of left atrium (*LA*), of left ventricle (*LV*) and of left atrial appendage (*LAA*): the spontaneous echocontrast (*SEC*) increased just after an effective shock with restoration of sinus rhythm is clearly visualized

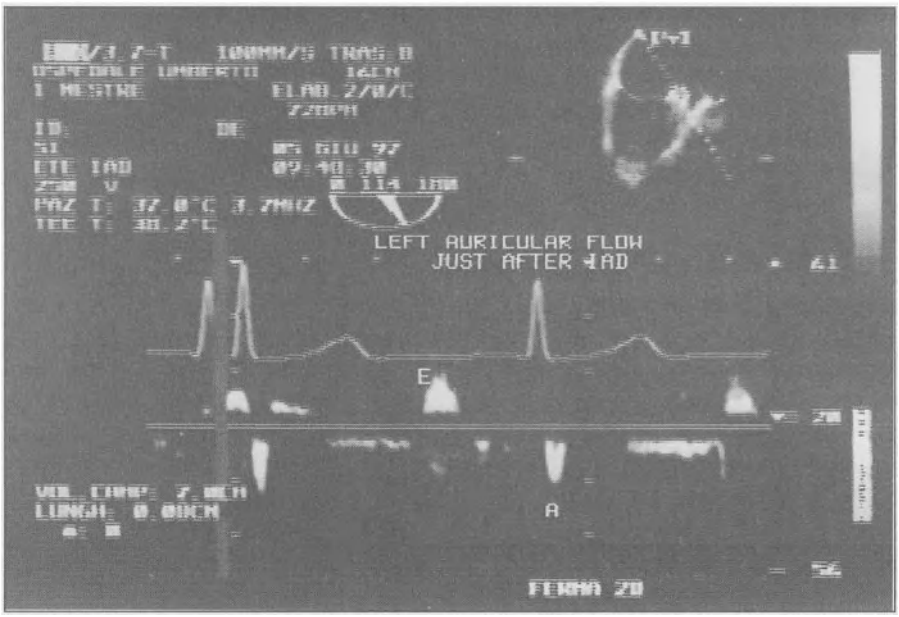

Fig. 2. Representative left atrial appendage pulsed Doppler flows illustrating the "stunning" phenomenon just after IAD: it is characterized by a low flow velocity and the presence of only the negative component of atrial contraction (*A*)

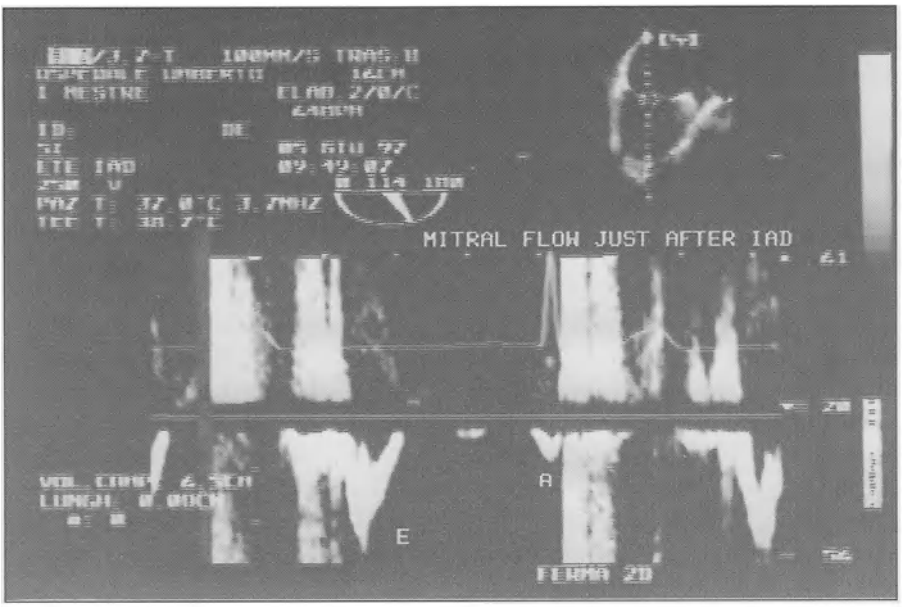

Fig. 3. Doppler analysis of mitral flow velocity recorded a few seconds after the restoration of sinus rhythm. The atrial stunning is expressed by the low velocity of forward flow during atrial contraction (*A*)

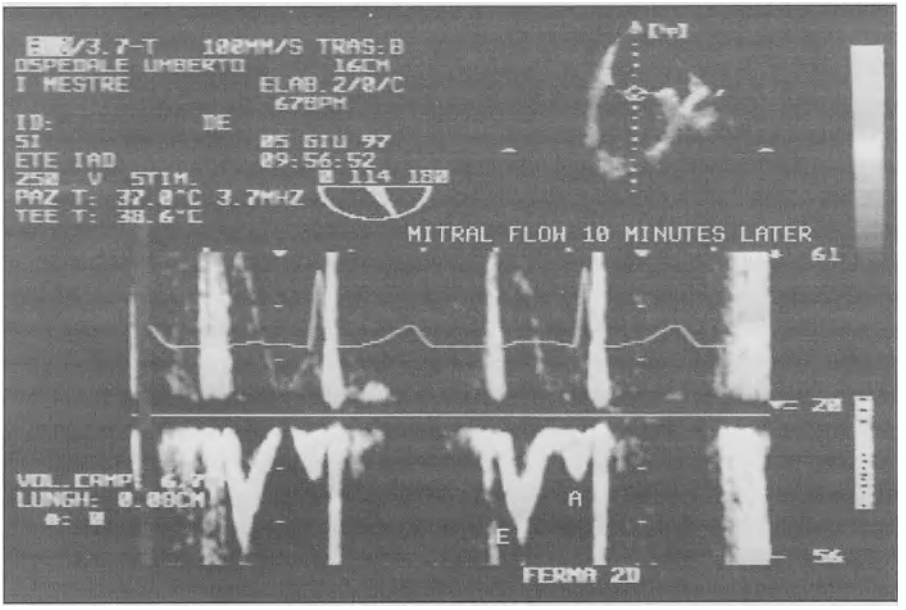

Fig. 4. Same Doppler evaluation as in Fig. 3, 10 minutes later: an increase of flow velocity during left atrial contraction as expression of a rapid recovery of atrial mechanical function after IAD is well visualized

Regarding the maintenance of sinus rhythm during our brief follow-up period (22 ± 12 days) we found:
- 2 pts had recurrence of AF within 2 days.
- 5 pts had recurrence of AF within 7 days.
- 3 pts maintained sinus rhythm after 1 week.

We observed no particular side effects or complications in all patients.

Discussion

As demonstrated by recent studies the efficacy of IAD for restoring sinus rhythm from AF is good and moreover this goal can be obtained by delivering low energy [3, 22, 23]. In our experience we have obtained optimal results in cardioversion efficacy with high percentage of patients that showed a promptly normalization of sinus rhythm after IAD: this is in accordance with the most recent observations [3, 22-24]. We found less increase of SEC just after IAD with the impression that this finding is the expression of several factors: in fact, the patients in whom we observed the new appearance or incremental degree of SEC had a history of a longer AF duration, a longer delay in the recovery of left auricular systolic function, and the biggest size of both atrial areas. Moreover in 2 patients it was clearly influenced by the intensity of delivered shocks and also by the duration time of electrical and mechanical atrial stunning after IAD. In our opinion a new parameter that can guide the IAD towards a good success, is represented by the accurate evaluation of right atrial size compared with the evaluation of only left atrial size: in fact the patients in whom IAD failed, or more attempts were necessary, showed the biggest values of right atrial size. Besides another important observation regards the recovery time necessary to have the maximum in atrial mechanical function: in all 6 patients in whom the maximum efficacy of the delivered energy was equal to or lower than 10 J we observed a complete recovery already 24 hours after IAD with a miniminal further increase within the following week. This is at variance with previous studies [3, 22, 23] that showed a progressive and significant increase of atrial function for one week after the shock. One possible explanation could be that the effective energy for restoring sinus rhythm in those experiences was higher than in our study. A similar conclusion gives more force to the concept that the degree of energy delivered can greatly influence thromboembolic complications. We considered this as a crucial finding for the adequate anticoagulation strategy to be employed in IAD in the future.

Conclusions

An impairment of the mechanical atrial function is also given by IAD but the recovery time of atrial mechanical function after IAD is certainly shorter than after external cardioversion.

The time of complete recovery is influence by several factors such as the duration time of AF before the IAD, the kind of heart disease, the size of both atria appendage and finally degree of delivered energy: our impression is that by using delivered energy lower than 10J one obtains a more rapid recovery of atrial mechanical function with a consequently reduced thromboembolic risk.

An important role in successful AF recovery in sinus rhythm is given by the right atrial size that is not usually estimated before cardioversion.

Globally thromboembolic risks are present but, with a more prompt recovery of mechanical and atrial function, they are reduced in comparison with external cardioversion. If our findings are confirmed in a larger number of cases, they can change the approach to AF cardioversion drastically considering the high success rate and the low side effects with internal atrial defibrillation.

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Implantable Atrial Defibrillator: Which Results and Indications?

W. JUNG AND B. LÜDERITZ

Rationale for an Implantable Atrial Defibrillator

Atrial fibrillation (AF) is a frequent and costly health care problem and represents the most common arrhythmia resulting in hospital admission. The overall prevalence of AF in the United States ranges from <1% in young, otherwise healthy individuals up to nearly 9% in elderly patients. AF may cause disabling symptoms and serious adverse effects such as impairment of cardiac function or thromboembolic events. Due to the limited efficacy of antiarrhythmic drugs for AF, several non-pharmacologic options have evolved including pacemaker therapy, transvenous catheter ablation techniques, surgical procedures, and treatment with an implantable atrial defibrillator (IAD). The high prevalence of AF and its clinical complications, the poor efficacy of medical therapy for preventing recurrences, and dissatisfaction with alternative modes of therapy stimulated interest in an IAD [1].

Internal Cardioversion for Atrial Fibrillation

The treatment of AF represents one of the therapeutic challenges of modern cardiology. One of the options for conversion of AF to sinus rhythm has been external cardioversion using energies in the range of 50 to 350 J. External electrical cardioversion/defibrillation has been a remarkably effective and safe method for termination of this arrhythmia. Originally introduced by Lown and et al. in 1962, it has been a well accepted mode of acute therapy [2]. However, this technique requires general anesthesia or heavy sedation and must be undertaken in the hospital environment. In addition, there is a potential risk of myocardial necrosis, ventricular tachyarrhythmias or thromboembolism. Internal atrial defibrillation has been evaluated as an alternative approach to the external technique for over two decades.

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Animal Studies

Previous animal work has demonstrated the feasibility of low-energy transcatheter countershock of AF. Mower et al. using two catheters, one in the right atrium (RA) and the other in the superior vena cava (SVC), have shown successful defibrillation with energies ranging from 0.05 to 3 J in acetylcholine-induced AF in dogs [3]. Dunbar et al. were able to terminate only 26% of AF episodes induced by talc pericarditis in dog [4]. Subsequent investigations from the same group did not demonstrate increasing efficacy with sequential shocks compared to single monophasic shocks utilizing a three electrode lead configuration [5]. In contrast, Kumagai et al. had an efficacy rate of 47% at energies of <0.5 J, 74% at 1 J and 100% at <5 J in the same model [6]. Powell et al. reported a lower success rate with biphasic shocks and a RA-apical left thoracic patch configuration in a large sheep model [7]. During 768 defibrillation attempts in 16 sheep, the percent of successful cardioversion increased in a dose-dependent manner, reaching a plateau at the average energy level of 5 J. Recently, Cooper et al. studied several different lead systems using single capacitor monophasic and biphasic shocks in the same model [8]. They found that the optimal lead systems for internal cardioversion of AF were those that had electrodes that encompassed as much of the fibrillating atrial tissue as possible and that did not create high potential gradients near the sinus or atrioventricular nodes. In this study, the right to left lead system using the distal coronary sinus (CS) as the left electrode and a 3/3-ms biphasic waveform resulted in low energy requirements for cardioversion of AF in sheep. Studies comparing shock electrode lengths demonstrated that 6 cm electrodes located in the CS and RA exhibited a trend toward lower defibrillation thresholds than 3 or 9 cm lengths did in the sheep model [9], while in the canine model 6 cm electrodes located in the right atrial appendage and CS produced significantly lower thresholds than 3 cm electrodes did [10].

Studies in Humans

Previous studies in humans have demonstrated that high energy (200-360 J) transcatheter atrial defibrillation is safe and effective when using standard electrophysiology catheters [11, 12]. A recent randomized study demonstrated that internal cardioversion using high energy shocks (200-300 J) was more effective than external cardioversion (300-360 J) in restoring sinus rhythm and was as safe as external cardioversion in patients with chronic AF [13]. However, reports of low energy endocardial defibrillation in humans are limited. An early feasibility study of low energy cardioversion for atrial arrhythmias did not yield successful results in patients with AF [14]. More recently, preliminary studies demonstrated the feasibility of low energy cardioversion in selected patients with recent onset as well as with chronic AF. Keane et al. reported that chronic atrial arrhythmias could be cardioverted efficiently in 15 out of 16 patients with a mean atrial defibrillation threshold of 6.7 ± 2.2 J [15]. Johnson et al. compared a 6-ms monophasic with a 3/3-ms biphasic truncated exponential waveform in 6 patients [16]. The biphasic

waveform required less total delivered energy (mean 2.5 ± 1.4 J) than the monophasic one (4.7 ± 3.1 J) for successful atrial defibrillation. Murgatroyd et al. attempted cardioversion in 22 patients with paroxysmal AF of short duration using a coronary sinus and right atrial electrode system and a 3/3-ms biphasic waveform [17]. Cardioversion was achieved in all 19 patients who completed the study, with a mean energy of 2.16 ± 1.02 J. In a recent study successful internal electrical defibrillation was achieved in 10 out of 14 patients with a mean duration of AF of 5.7 ± 5.4 months at a mean energy of 3.7 ± 1.7 J using a right to left electrode configuration [18]. In contrast, Kalman et al. used either a right sided electrode configuration or a three lead system for endocardial defibrillation in 5 patients with atrial flutter and in 4 patients with AF with a mean duration of 3.75 months [19]. Successful cardioversion was accomplished in all 5 patients with atrial flutter with energies of ≤ 10 J but in only one patient with AF at the 10 J level. This low success rate was probably due to the less optimal lead configuration used in this study.

In summary, low energy biatrial internal defibrillation has recently been shown to be an effective and safe means of restoring sinus rhythm in patients with both acute and chronic AF [20-25]. The electrode locations for minimum defibrillation threshold appears to be in the vector encompassing the RA and the CS (Fig. 1). In addition, biphasic shocks have been demonstrated to be superior to

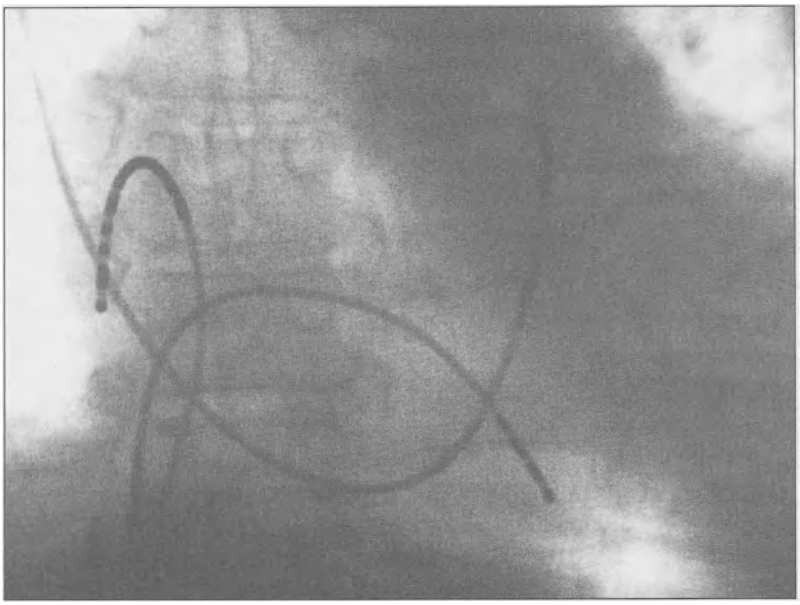

Fig. 1. Right anterior oblique view (30°) of catheter electrode configuration for atrial defibrillation in a patient with chronic AF. The 6-French decapolar catheters are positioned in the right atrium (anode) and in the coronary sinus (cathode). Biphasic shocks are delivered between these decapolar electrodes. A conventional quadripolar catheter is placed in the apex of the right ventricle for proper R wave synchronization

monophasic shocks. Ventricular proarrhythmia has not been reported in well synchronized low energy shocks when closely coupled to RR intervals and long-short cycles are avoided [25, 26]. Consequently, an IAD that promptly recognizes AF and restores sinus rhythm may be a valuable tool.

Implantable Atrial Defibrillator

The development of an implantable cardioverter-defibrillator for the management of ventricular tachyarrhythmias has stimulated investigation of a similar approach to AF [27]. Conversion of atrial arrhythmias has been attempted in patients with an implantable cardioverter-defibrillator using epicardial or non-thoracotomy lead configurations. High energy shocks applied via epicardial patches during AF were in no case successful in restoring sinus rhythm [28]. In a prospective and randomized study, Saksena et al. reported on the clinical efficacy and safety of atrial defibrillation using three current non-thoracotomy endocardial lead configurations: two right sided vectors, RV-RA and RV-SVC leads and one right to left vector, RA-left thoracic patch [29]. Atrial defibrillation thresholds in 21 patients with cardiac disease were lowest for the RV-SVC configuration. The mean defibrillation threshold in the best randomized lead configuration was 9.9 ± 7.7 J. All patients could be cardioverted by at least 20 J. [30]. Recently, Bardy et al. reported on the feasibility of atrial defibrillation in 10 patients using a unipolar, single lead right ventricular pectoral defibrillation system [31]. The atrial defibrillation threshold data were 8.3 ± 4.1 J using the active can system. AF remains a common post-shock arrhythmia with implantable ventricular defibrillators and may result in inappropriate ventricular shock delivery [32, 33]. Adding an atrial cardioversion system to the ventricular system would allow for better arrhythmia discrimination as well as provide more complete arrhythmia treatment coverage.

Description of the Metrix Implantable Atrial Defibrillator

The Metrix Model 3000 or 3020 (InControl, Redmond, WA, USA) IAD uses a pair of defibrillation leads to detect AF in the CS and RA [34]. Both are 7-French in diameter and the defibrillation coils are each 6 cm in length (Fig. 2). The RA lead has an active fixation in the RA. The CS lead has a natural spiral configuration for retention in the CS, and can be straightened with a stylet. A separate bipolar right ventricular lead is used for ventricular pacing and sensing. The device, with a weight of 79 g and a volume of 53 cc, is intended for implantation in the pectoral region like a conventional antibradycardiac pacemaker. The device can be programmed into one of four different operating modes: fully automatic, patient activated-mode, monitor mode, or pacing only mode. As AF is not life-threatening, the device is only intermittently active in detecting and treating AF, and this "sleep wake-up" cycle interval is programmable. A two staged AF detection algo-

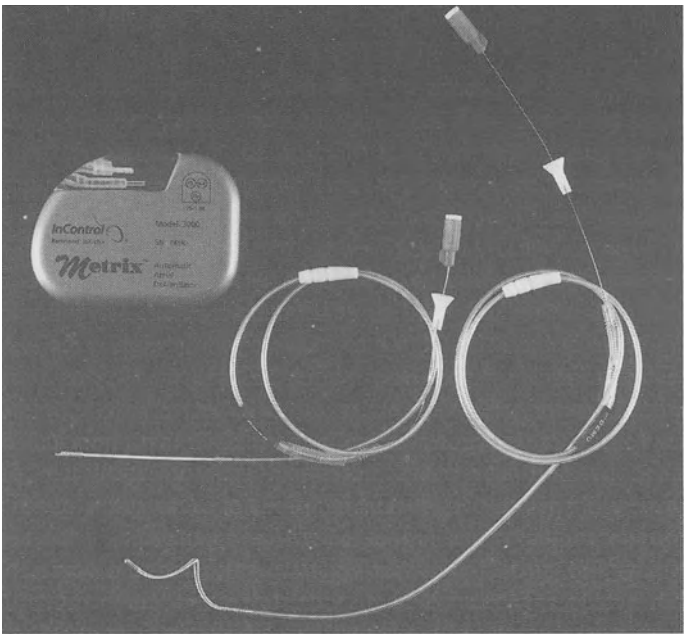

Fig. 2. The Metrix implantable atrial defibrillator and the atrial defibrillation leads. The device has a weight of 79 g and a volume of 53 cc, and is implanted in the pectoral region. The defibrillation coils for both the right atrium and the coronary sinus leads are each 6 cm long. The defibrillation lead for the right atrium has a non-retractable screw-in active fixation and the defibrillation lead for the coronary sinus has a preformed spiral shape at the end, designed to stabilize the lead in the coronary sinus

rithm is operative after automatic gain control [34]. The "quiet interval" analysis measures the duration of absence of atrial activity. This algorithm is highly specific for sinus rhythm thereby reducing the number of inappropriate therapies. Thereafter, the second test, the "baseline crossing" analysis is applied, an algorithm which is very specific for AF. The Metrix device uses a dual channel synchronization algorithm. This algorithm is designed to ensure that all shocks will be delivered only to correctly synchronized R-waves. Before synchronization is attempted, two electrograms are evaluated simultaneously in real time for integrity and data quality. Graded shock therapy is available for up to 8 shocks (2 at each level) for each episode of AF. Biphasic shocks are programmable in 20 V increments up to 300 V (about 3 J in the Model 3000 and 6 J in the Model 3020).

Indications for an Implantable Atrial Defibrillator

Patients with symptomatic recurrences of AF despite the use of antiarrhythmic drug therapy represent potential candidates for an IAD [35-37]. The number and duration of AF episodes should be taken into account in the indications. Patients

with frequent episodes must be excluded as candidates for implantation of an atrial defibrillator because of too frequent discharges, patient discomfort, and rapid battery depletion. Similarly, patients with episodes of short duration and spontaneous termination may not be good candidates. Selected patients with infrequent, symptomatic attacks of long-lasting episodes of AF despite antiarrhythmic drug therapy may benefit from an IAD.

Results with an Implantable Atrial Defibrillator

Initial clinical experience with a human IAD has been recently reported [34]. The device was implanted in 3 patients with drug refractory paroxysmal AF. The mean implant threshold (ED 50) was 195 V (1.8 J), and minimum voltages at conversion during follow-up assessments at 1, 3, and 6 months were 260 V (2.5 J), 250 V (2.3 J) and 300 V (3.0 J), respectively. Detection of AF was 100% specific and shocks were 100% synchronized, although only a proportion of synchronized R waves were considered suitable for shock delivery primarily because of closely coupled cycle lengths. Three patients had 9 spontaneous episodes of AF with 8 out of 9 (89%) successfully defibrillated by shocks of 260-300 V. Sedation was not used in 4 out of 9 (45%) episodes. Back-up ventricular pacing was initiated by the device in 6 out of 9 (67%) episodes. One patient had more frequent episodes of AF after lead placement, which subsided after a change in medication. There was no ventricular proarrhythmia observed. Initial clinical experience with an IAD indicates stable atrial defibrillation thresholds, appropriate R-wave synchronization markers, no shock induced ventricular proarrhythmia, and detection of AF with a specificity of 100% [34, 38, 39].

Results with the First Arrhythmia Management System for Patients with Ventricular and Supraventricular Tachyarrhythmias

On January 10, 1997, a 61-year-old woman suffering from both recurrent, drug refractory supraventricular and ventricular tachycardia was the first patient in the world to receive a multiprogrammable dual-chamber implantable defibrillator (model 7250, Arrhythmia Management Device, AMD, Medtronic Inc., Minneapolis, MN, USA) in our institution [40]. The device, with a weight of 93 g and a volume of 55 cc, was implanted in the left pectoral region and connected with transvenous defibrillation leads placed in the apex of the right ventricle (Model 6936) and in the appendage of the right atrium (Model 6943). This defibrillator offers a new tiered-therapy approach to patients suffering from supraventricular as well as from ventricular tachycardias. It combines atrial and ventricular detection and therapy modalities in a single unit and provides a new algorithm ("atrial rate stabilization") for prevention of atrial arrhythmias. A sophisticated dual-chamber detection algorithm is used to improve discrimination of

ventricular tachycardia from supraventricular tachycardia by applying pattern recognition methods based on different P-wave positions within RR sequences. The detection algorithm can be used to withhold inappropriate ventricular therapies for atrial tachycardias, atrial fibrillation, sinus tachycardia, 1:1 supraventricular tachycardias, or any combination of these. The first day after implantation of the new defibrillator, three sustained episodes of atrial fibrillation occurred which were all successfully treated by high frequency burst pacing, a new option, which allows painless termination of recent onset atrial tachycardias. None of these arrhythmias were inappropriately detected or treated as ventricular episodes.

Conclusions

At present, the chronic use of an IAD is a major challenge in the non-pharmacologic treatment of AF. Studies in animals as well as in humans have demonstrated the feasibility and safety of internal atrial defibrillation. The major issues which have to be addressed are the pain perception and the potential risk of inducing life-threatening ventricular arrhythmias during delivery of low energy atrial shocks. The available data show that ventricular proarrhythmia has not been observed in well synchronized low energy shocks when closely coupled to RR intervals and long-short cycles are avoided. A first step to this novel approach is a physician activated device. At the very beginning, the IAD should be restricted to highly selected patients with drug refractory, poorly tolerated, recurrent AF episodes. The extention of this therapy to wider subsets of patients should be dependent on the initial results with regard to clinical efficacy and safety as well as patient tolerance. Finally, cost-effectiveness as well as quality of life studies are needed to demonstrate the benefit of this specific therapy among other therapeutic strategies available for the management of AF [41-43]. An arrhythmia management system that combines both detection and treatment in the atrium as well as in the ventricle may represent an important milestone and a significant improvement in the management of patients with both supraventricular and ventricular tachyarrhythmias.

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The Implantable Atrial Defibrillator: Are All the Problems Solved?

S. Lévy

Atrial fibrillation (AF) is an extremely common arrhythmia seen in clinical practice, as shown by a number of epidemiologic studies. A significant number of patients either have recurrent attacks of atrial fibrillation despite pharmacological therapy, or are controlled, but complain of intolerable side effects. The atrial defibrillator (AID), a device capable of detecting and automatically terminating AF, may be an interesting non-pharmacological therapy of atrial fibrillation. Two devices are currently available for clinical evaluation: The Metrix system (In Control Redmond, USA) which is a stand-alone defibrillator, and the Medtronic 2030 which is a double-chamber defibrillator under evaluation solely in patients in whom a ventricular defibrillator is indicated, and who have paroxysmal atrial fibrillation. This presentation will focus on the Metrix system aimed at the tratment of patients whose major clinical problem is atrial fibrillation. This type of system has to deal with four issues: (1) the feasibility of atrial defibrillation, (2) the possible shock-related discomfort, (3) the safety of the device, and (4) the proper identification of patients who might benefit from the device. Several studies have shown that atrial defibrillation using low-energy shocks between two intracardiac catheters, in the coronary sinus and in the right atrium is feasible in patients with persistent spontaneous atrial fibrillation. As the minimum energy requirement in order to successfully terminate atrial fibrillation in 75% of patients averages 200-300 V (2-3 J), the conversion voltage needs to be above these values in order to have a satisfactory safety margin. Termination of atrial fibrillation with energy levels of less than 1 joule was found to be associated with little, if any discomfort. A good correlation was also found in our study between the level of discomfort and increasing voltage. The difference was statistically significant ($p < 0.02$) between 140 V and 220 V shocks and 220 V and 300 V shocks ($p < 0.01$). A marked inter-individual variation was noted. Therefore, this aspect should be tested before indicating the device in a given patient. Both in the XAD study and the Metrix study with the physician-activated device in more than 50 patients and more than 3000 shocks, no ventricular proarrhythmia was observed with synchronized shock. As shocks delivered following short (below 300 ms) RR intervals were associated with a low but definite risk of ventricular fibrillation, the shocks were delivered after an RR interval of 500 ms or longer.

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However this represent a limitation in patients with atrial fibrillation and rapid ventricular response. The importance of R wave synchronization is emphasized and requires a lead in the right ventricle. The device also uses 2 other leads, one in the right atrium and one in the coronary sinus, and lead dislodgement may be a potential complication. The indications of an atrial defibrillator have to be assessed carefully according to the currently available device and to our current understanding and knowledge of atrial fibrillation. Obviously, symptomatic patients in class III, i.e., patients who experience symptomatic episodies of AF despite the use of antiarrhythmic agents (sodium channel blockers and potassium channel blockers), represent potential candidates. The number and duration of episodes should be taken into account in the indications. Patients with frequent episodes (several episodes per day) must be excluded, as AID implantation may result in too frequent discharges, patient discomfort, and rapid battery depletion. Similarly, patients with episodes of short duration and spontaneous termination may not be good candidates. The severity of patient symptom(s) and arrhythmia tolerance must be taken into account. Selected patients with unfrequent attacks, fewer than one episode per 3-month period, may benefit from an AID, particularly those patients with long-lasting episodes of AF than require pharmacological or electrical reversion. It is not known whether there is an indication for an AID in patients with asymptomatic AF and a history of embolic complications. A selected group of patients with established atrial fibrillation may benefit from an AID e.g. patients who have undergone successful external cardioversion and who experienced recurrence after period of time ranging from 1 to 6 months. At this stage of evaluation of the efficacy as well as the safety of the device, it might be advisable to avoid implantation of an AID in patients with coronary artery disease associated with active ischemia or patients with depressed ventricular function. More clinical experience assessing the usefulness of currently available devices is needed and includes a patient-activated device preceded by a physician-activated device phase. As the technology progresses and experience is gained, indications will probably evolve. The perspective is a small device with a maximum of two leads capable of double-chamber sensing and pacing in order to prevent and terminate atrial fibrillation.

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ATRIAL FIBRILLATION: PREVENTION OF THROMBOEMBOLISM

Atrial Fibrillation and Thromboembolic Risk: Is It Safe to Cardiovert Acutely under Heparin?

M. Disertori[1] and A. Menotti[2]

Introduction

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and predisposes a person to significant increase of systemic embolism. The risk of systemic embolism, particularly cerebral embolism, is present when arrhythmia is chronic but is higher at the moment of cardioversion to sinus rhythm (SR), when the resumption of mechanical activity of atrium and left atrium appendage (LAA) can favor embolisation of thrombus.

Cardioversion of Atrial Fibrillation and Embolic Risk

Atrial fibrillation can be cardioverted pharmacologically, or electrically with external direct-current shock; (recently internal high- or low-energy transcatheter cardioversion has been introduced).

A decision about the kind of cardioversion is substantially empirical; usually pharmacological conversion is preferred in AF lasting a few days, while direct current cardioversion is used when more time has elapsed since the beginning of arrhythmia or pharmacological therapy has failed.

Cardioversion of AF is tied to a significant risk of embolism both after spontaneous, or induced (pharmacological or electrical) restoration of SR. The estimated incidence of thromboembolism varies in the studies between 0% and 7% [1]. Variability of the incidence of thromboembolic episodes depends on the heterogeneity of the patient population; particularly etiology and duration of AF, and presence, duration and intensity of anticoagulant therapy are different in the series.

Some conditions increase the embolic risk: rheumatic heart disease, past embolic event, cardiopathy (hypertension, coronary heart disease, cardiomyopathy), long lasting AF, heart failure, left atrium dimension, anulus calcification that can be evidenced by transthoracic echocardiography (TTE).

Since the 1950s numerous retrospective studies have postulated the efficacy

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of anticoagulant therapy in reducing embolic risk during cardioversion of atrial fibrillation.

The three most convincing studies, that confirm the utility of anticoagulant therapy in reducing embolic risk during cardioversion in patients with AF lasting more than 48 hours or at high embolic risk, were carried out by Bjerkelund and Orning in 1969 (the only prospective study), Weinberg and Mancini in 1989 and Arnold et al. in 1992 (Table 1).

Table 1. Utility of anticoagulant therapy during cardioversion of atrial fibrillation

Source	N° pts	N° (%) of embolic events	
		Anticoagulation	No anticoagulation
Bjerkelund and Orning 1969 [2]	437	2/228 (0.8%)	11/209 (5.3%)
Weinberg and Mancini 1989 [3]	79	0/51 (0%)	2/28 (7%)
Arnold et al. 1992 [4]	332	0/153 (0%)	6/179 (3.3%)
Total	848	2/432 (0.5%)	19/416 (4.6%)

The results of the study of Bjerkelund and Orning [2] were impressive particularly because the group receiving anticoagulation was more likely to have mitral stenosis, congestive heart failure, or prior embolic events and thus were at higher embolic risk. The other two studies were retrospective, but the same impressive results in favor of anticoagulant therapy were found.

These data form the basis for the guidelines published in 1992 by the American College of Chest Physicians for the prevention of the embolic risk in cardioversion of AF.

Table 2. Recommendations of ACCP in the cardioversion of atrial fibrillation

Atrial fibrillation < 3 days:
1) Cardioversion without anticoagulation
2) Anticoagulation in patients at high risk

Atrial fibrillation ≥ 3 days or unknown duration:
1) Anticoagulation with warfarin therapy for 3 weeks before cardioversion and for 4 weeks after cardioversion;

Emergency atrial fibrillation
1) Cardioversion without anticoagulation if duration < 3 days
2) Anticoagulation immediately (heparin) if high risk or ≥ 3 days

Target INR 2.0 to 3.0

What duration of AF requires anticoagulation before cardioversion has been controversial. It is believed that thrombus formation during AF takes one week

or more and that an AF of less than 3 days duration carries a low risk of thromboembolic events after cardioversion and requires no anticoagulation. This data is not confirmed by some studies: the study by Arnold et al. [4], where five out of the six embolic events occurred in patients whose AF was less than 1 week in duration and recently Stoddard et al. [6] have documented with transesophageal echocardiography (TEE) the presence of thrombus in 14% of patients with AF of less than 3 days duration (patients at high risk).

According to the ACCP guidelines, anticoagulant therapy for 3 weeks prior to cardioversion permits organization/adherence of eventual thrombus present at an atrial level, impeding dislodgement and formation of new thrombi. One study, involving 14 patients with AF (non rheumatic) and thrombus upon TEE, administered anticoagulant therapy (medium duration 5.8 ± 3.9 weeks), resulting in resolution of thrombus in 89% of cases [7]. This indicates that perhaps the benefits are tied to resolution of the thrombus rather than thrombus organization and adherence.

The continuation of warfarin therapy for 4 weeks after cardioversion is considered necessary because restored atrial activity can increase the risk of intracavitary thrombus dislodgement, but above all, as confirmed by echocardiographic studies, there is a delay in returned atrial and LAA mechanical function compared to electrical activity and this delay may last some weeks.

Recently TEE has shown that after cardioversion there is an appearance or accentuation of the spontaneous echocontrast (SEC), designating hematic stasis, marker of potential thrombus formation and increased risk of thromboembolus. Three studies [8-10] with TEE have in fact documented hemodynamic modifications that occur immediately after cardioversion and the risk of thromboembolic complications in patients where intracardiac thrombosis was excluded [9, 10]. Fatkin et al.'s work [9] with TEE during cardioversion revealed that the first few seconds after cardioversion brought about a significant rise in SEC, more pronounced in patients with long lasting AF. In this study of 56 patients undergoing cardioversion with a negative TEE for intra-atrial and LAA thrombosis, 4 episodes of embolus were documented.

A multicenter study [8] documented 17 embolic events after cardioversion out of 712 patients after TEE had excluded the presence of thrombi. It should be taken into account that no patients had received anticoagulant therapy to achieve therapeutic levels at the time of the embolic episodes, and in 14 cases the episodes occurred more than 24 hours after cardioversion.

The Role of Transesophageal Echocardiography in Identifying Thrombus and the Mechanisms of Its Formation

Evaluation of Atrial and Left Atrial Appendage Anatomy and Physiology

The advent of TEE has permitted the addition of new and important information in the evaluation of patients with AF. In fact the TEE guarantees better visualiza-

tion (compared with TTE) of the atria and in particular the LAA, where thrombus formation is more frequent [11]. The TEE has also allowed a better understanding of the SEC phenomenon which is characterized by a particular slow, spiraliform movement of the blood, that has been called "smoke" due to its resemblance to cigarette smoke. Remarkable is its frequency at atrial (and LAA) level in patients with AF and the incidence is particularly high in patients with rheumatic heart disease, valve prosthesis, left ventricular dysfunction and presence of atrial thrombosis.

Some studies have documented a close correlation between the presence of thrombi and SEC, both indicating an increased risk of thromboembolism [12-15]. It is to be noted that anticoagulant therapy reduces the risk of embolism in patients, but does not significantly alter the prevalence of SEC. This is probably because clotting factors inhibited by warfarin therapy are not necessary for the formation of SEC [16].

Another aspect of AF that could benefit from the use of TEE is the study of LAA function; in particular doppler flow filling/emptying and the emptying fraction of LAA. Numerous works have confirmed the relation between LAA peak flow, SEC, presence of LAA thrombus and embolic risk [12, 17, 18]. A reverse correlation between LAA morpho-functional parameters and duration of AF was revealed in the same studies. Other studies have demonstrated significant correlation between peak flow velocity in LAA and successful cardioversion or risk of relapse in patients with chronic AF [19-22].

As ACCP guidelines indicate, anticoagulant therapy is continued for 4 weeks after cardioversion due to the slowed resumption of atrial mechanical function which in itself is a potential cause of thrombus formation even after restoration of the SR [5]. Studies done with TEE have confirmed that following cardioversion, atrial and LAA function are not immediately resumed and often elevation of SEC is seen [9, 23], with a potential risk of thrombus formation and consequent systemic embolism as evidenced in already mentioned study by Black et al. [8]. Another contribution to understanding atrial function after cardioversion comes from Manning et al.'s studies [24, 25]. It was found that slowed resumption of mechanical function, evaluated with transmitral doppler flow, was proportionate to the duration of arrhythmia, lasting even up to 4 weeks in patients with AF for > 5 months. By confirming these data one could hypothesize a reduction of the length of anticoagulant therapy after cardioversion in patients with AF of recent onset.

Also evaluated with conflicting results, has been the impact of the type of cardioversion (direct-current or pharmacological) on atrial and LAA function: Manning et al. [26] evidenced a more rapid recovery of atrial mechanical function after pharmacological cardioversion than in patients cardioverted with DC shock. To be noted is that patients undergoing direct-current cardioversion were likely to be more compromised as pharmacological cardioversion (unsuccessful) had been tried first. This data is not confirmed in one study by Falcone et al. [27] which documents a significant worsening of LAA function after both direct-current and pharmacological cardioversion.

Accuracy of TEE in the Diagnosis of Atrial and Atrial Appendage Thrombosis

TEE proved significantly superior compared with TTE in the visualization of atrial and atrial appendage thrombi for both major proximity to the structure being examined as well as the capacity to visualize the atrial appendages, this not being possible with the TTE [11]. Compared with the "gold standard" of surgical examination it provided high sensitivity and detail in the location of thrombi. The diffuse use of biplane and multiplane probes together with the increased experience of operators has contributed to improving this method [28, 29].

Manning et al.'s study on 231 patients, published in the Annals of Internal Medicine [30], found that TEE compared to surgical evaluation, had a sensitivity of 100%, a specificity of 99%, an 86% positive predictive value, and a 100% negative predictive value in evidencing atrial and LAA thrombi.

Cardioversion of Atrial Fibrillation TEE Guided with and without Short-term Anticoagulant Therapy

In the past few years some researchers have proposed to cardiovert AF using TEE. This method has been carried out in many centers, utilizing diverse criteria in the selection of patients to be cardioverted and different therapeutic approaches in the use of anticoagulant therapy. Two principal options can be outlined:

A) Evaluation with TEE and cardioversion without anticoagulant therapy, or with therapy given only at the moment of cardioversion, excluding patients who present with atrial and/or LAA thrombi and significant SEC.
B) Evaluation with TEE in patients that have undergone short-term anticoagulant therapy with heparin, cardioversion and continuation of anticoagulant therapy with warfarin for 4 weeks, normally excluding only patients with thrombus.

The results of the studies published with these 2 options are presented in Tables 3 and 4.

A multicenter study guided by Black [8] must be added to these data. He documented 17 cases of systemic embolism out of 712 patients (2.4%). However, this study did not evidence the characteristics of the population nor the therapeutic approach of the various centers and therefore cannot be an indication (as the authors themselves affirm) when evaluating the incidence of embolic events in cardioversion guided by TEE associated with the use of anticoagulant therapy.

Though the amount of research is limited, it documents the safety of TEE-guided cardioversion of AF. Reliability is based on percentages of embolization similar to the studies with anticoagulant therapy 3 weeks before and 4 weeks after cardioversion as in option "A", and is particularly promising with option "B" which did not document embolic events. This heightened reliability, also confirmed by our survey, is probably due to exclusion of patients who have intra-atrial/appendage thrombus, more susceptible to embolization. Moreover the admin-

Table 3. Option A (CV TEE guided, without anticoagulant therapy)

Source	N° patients	N° embolic events
Grimm et al. 1992 [31]	9	0
Chan et al. 1992 [32]	18	0
Daniel et al. 1992 [33]	12	0
Orsinelli and Pearson 1993 [34]	15 (5 flutter)	0
Black et al. 1993 [35]	114 (36 flutter)	1
Fatkin et al. 1994 [9]	56	4
Antonielli et al. 1995 [36]	39	1
Stoddard et al. 1995 [37]	107	0
Total	370	6 (1.6%)

Table 4. Option B (CV TEE guided, with anticoagulant short-term therapy)

Source	N° patients	N° embolic events
Orsinelli and Pearson 1993 [34]	13	0
Klein et al. 1994 [38]	47	0
Stoddard et al. 1995 [37]	46	0
Manning et al. 1995 [39]	186	0
Menotti et al. 1997 [40]	26	0
Total	318	0 (0%)

istration of anticoagulant therapy permits the reduction of possible formation and dislodgement of thrombi during the post cardioversion period, reducing the risk of systemic embolism.

Patients with intracavitary thrombus must continue anticoagulant therapy for 6-8 weeks and undergo a repeat TEE to evaluate for an eventual cardioversion.

Short-term therapy is carried out with heparin I.V. (bolus followed by continuous infusion with a aPTT ratio value of between 2-2.5), initiating therapy upon TEE, rapidly attaining anticoagulation efficacy, administering simultaneously therapy with warfarin. The use of heparin I.V., is continued till the patients reaches therapeutic INR levels with warfarin therapy. This option is particularly indicated in patients admitted with first episode and/or cardiac symptomatology and are in need of a full investigation.

There are no data on the use of subcutaneous calcium heparin; it has been used in our department without complications in patients (medium-low risk) where warfarin therapy were contraindicated (random compliance).

Cardioversion TEE Guided with Short-term Anticoagulation: Potential Pros and Cons

Advantages may be summed up by the following:
- *Shorter duration of anticoagulant therapy*: reduction of therapy of at least 3 weeks leading to lower risk of hemorrage.
- *Acceleration of cardioversion*: some studies seem to indicate that early cardioversion increases the probability of the restoration of SR.
- *Low risk of embolism*: published studies indicate that TEE in association with short-term anticoagulant therapy has a very low risk of systemic embol-ism.
- *Selection of patients at higher risk of embolism*: evidence of atrial and/or appendage thrombus selects a population at higher risk; a more intensive therapy can be applied to reduce the risk of embolization.
- *Reduced recovery time.*

The TEE guided cardioversion is not immune to uncertainties:
- The absence of thrombus upon TEE does not exclude the possibility of formation and embolization of thrombus in the hours following cardioversion; it is for this reason that short-term anticoagulant therapy precardioversion and continuation for 4 weeks after seems more preventive against eventual embolic events.
- The method, that is operator dependent, may not evidence thrombi because of technical problems: a) thrombi below power of resolution of probe may have possibility of causing significant cerebral lesions; b) type of probe used (monoplane instead of biplane or multiplane; c) poor echogenicity of new thrombi that can have similar characteristics to that of blood and so pass undetected.

Not to be undervaluated are organizational problems with possible work overload on the echocardiographic department due to frequency of pathology.

Studies were done in the U.S.A. on the cost-effectiveness of TEE guided cardioversion with anticoagulation compared to conventional therapy; TEE guided cardioversion seems more cost-efficient [41, 42].

Open Problems

Some questions remain open regarding the indications of cardioversion of AF and atrial flutter. Firstly concerning the management of patients with AF for < 3 days. Stoddard et al.'s articles [6] published in 1995, evidenced the presence of thrombi in 14% of patients (at high risk) with AF of recent onset (< 3 days); it seems advisable, at least in patients with a medium-high risk of AF for < 3 days, to administer anticoagulant therapy for 3 weeks or cardiovert after TEE and short-term anticoagulation.

Another point which remains unclear is management in patients with atrial flutter considered at very low risk of embolism. In a recent publication by Mehta and Baruch [43], 3 episodes of systemic embolism were documented in 16 patients cardioverted for atrial flutter with previous negative TEE; the same authors had previously documented a significant diminished velocity of LAA

flow and increased SEC after cardioversion in patients with atrial flutter [44]. Also, it should not be overlooked that atrial flutter, in some cases, can be preceeded by AF, increasing the risk of embolism after cardioversion.

Conclusions

TEE has certainly permitted a better understanding of the thromboembolic problem in AF, and a detailed insight of the modifications that take place during cardioversion and the complex function of LAA. To say that cardioversion guided by TEE is more cost-effective but, above all, safer, we must await the results of the ACUTE study (Assessment of Cardioversion Utilizing Transesophageal Echocar-diography), which is a multicenter, random, prospective study. The result of the pilot study involving 123 patients [39] indicated safety and feasibility of the study with an apparently better cost/benefit ratio compared to conventional therapy.

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Prevention of Thromboembolism in Atrial Fibrillation: When Antiplatelet Agents and When Anticoagulants?

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Prevalence of Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia encountered in clinical practice.

The prevalence of AF increases dramatically with age and is slightly more common in men than in women. The prevalence of AF rises from < 0.05% in subjects 25 to 35 years old to 0.5% in the group 50 to 59 years and to 8.8% in the group aged 80 to 89 years. The overall prevalence of AF in the Framingham cohort was 2.2% in men and 1.7% in women [1].

AF is frequently a consequence of rheumatic valvular disease, but it is encountered much more often in association with hypertensive or coronary heart disease and in patients with congestive heart failure. Non-valvular AF (NVAF) represents 70% of all cases of AF. Finally the prevalence of AF not associated with any cardiac disease ("lone" AF) is approximately 10%.

Risk of Stroke

AF carries a high risk of systemic embolism, in particular stroke. This is true not only when AF is associated with valvular heart disease but also in patients with NVAF [1-9].

The principal mechanism for stroke in AF are emboli due to stasis-related left atrial thrombi (associated with enlarged atria, and thrombi in the left atrial appendage or atrial septal aneurysm), or stasis-related left ventricular thrombi (associated with left ventricular enlargement). Because of stasis of blood flow, activation of the coagulation system with fibrin formation predominates over platelet activation as the principal mechanism in the development of intracavitary thrombi. According to the pathogenetic mechanism anticoagulation seems the most appropriate prophylactic treatment [10].

Alternative mechanisms for stroke in patients with NVAF include structural abnormalities of the mitral valve (including myxomatous or thickened valvular

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leaflets or mitral annular calcification), coexisting atherosclerotic carotid artery disease (in approximately 25% of AF-associated strokes), or atherosclerotic plaques in the ascending aorta and proximal arch. In these conditions sources of emboli are represented by platelet-fibrin thrombi and therefore platelet inhibition may be effective [11].

The five recent randomized placebo-controlled clinical trials (12-16) assessing antithrombotic therapy as primary prevention in NVAF have shown that in patients with NVAF who are not anticoagulated the annual incidence of ischemic stroke ranges between 3.0% and 7.4 % (mean 4.5%) with a 2.5% incidence of disabling stroke; including also transient ischemic attacks (TIA) the incidence rises up to 7% and to > 7% when considering silent cerebral infarction detected by CT scan or MRI.

When acute ischemic stroke occurs in association with AF the cerebral infarct size is generally large and more than half of the victims are severely affected (the incidence of disabling or fatal strokes in the AFASAK and in the SPAF I studies was 64% and 44%, respectively).

An analysis of the SPAF study [17] subsequently confirmed by metanalysis of pooled data from the five randomized controlled trials [18] has shown that in the large population of patients with NVAF the risk of stroke is not homogeneous. Stratification of AF patients into those at high and low risk of thromboembolism is possible and warranted in order to plan optimal antithrombotic prophylaxis [19].

Clinical risk factors predictive of stroke include age (> 65 years), history of hypertension, prior stroke or TIA, recent heart failure and diabetes. Patients younger than 65 years who have none of these predictive factors (15% of all patients in the randomized clinical trials) have a low annual rate of stroke, approximately 1%, in the absence of any antithrombotic prophylaxis.

These results confirm a previous observation that patients with "lone" AF (defined also by the absence of hypertension and diabetes) younger than 60 years have a risk for stroke less than 0.5% per year [20].

Besides the clinical risk factors, a SPAF analysis has identified echocardiographic predictors of stroke [21]. They include left ventricular systolic dysfunction and left atrial enlargement. Transesophageal echocardiography provides further markers of embolic risk, i.e. left atrial and left atrial appendage thrombi, spontaneous echocontrast, and left atrial appendage dysfunction [22].

Primary and Secondary Prevention Studies

Anticoagulation with oral vitamin K antagonists such as warfarin is highly effective for preventing ischemic stroke in AF patients. Over the past few years five randomized clinical trials have investigated the safety and efficacy of warfarin for primary stroke prevention in patients with NVAF (Table 1).

Overall warfarin decreased the frequency of all strokes by 68% with an absolute annual reduction of 3.1% ($p < 0.001$), i.e. 31 strokes can be prevented per

Table 1. Primary prevention studies with warfarin in patients with NVAF

Study	No. of pts	Mean follow-up (yrs)	Target INR	Annual stroke reduction	Annual major bleeds
Warfarin vs placebo					
AFASAK [12]	1.007	1.2	2.8-4.2	- 58%	0.3%
SPAF [13]	1.330	1.3	2.0-4.5	- 67%	1.5%
BAATAF [14]	420	2.2	1.5-2.7	- 86%	0.9%
CAFA [15]	383	1.3	2.0-3.0	- 42%	1.5%
SPINAF [16]	525	1.8	1.4-2.8	- 79%	1.5%
Warfarin vs aspirin					
SPAF II [23]	1.100	2.7	2.0-4.5	≤ 75yrs - 10%[a]	1.7%
				> 75yrs - 9%[a]	4.2%
Adjusted dose warfarin vs low-intensity fixed-dose warfarin + aspirin					
SPAF III [28]	1.004[b]	1.1	2.0-3.0	- 62%	2.8%

NVAF, non-valvular atrial fibrillation; INR, international normalized ratio; AF, atrial fibrillation.
[a]cumulative endpoint of ischemic stroke + intracranial hemorrhage
[b]high risk patients with AF with at least one thromboembolic risk factor (congestive heart failure or left ventricular dysfunction, prior thromboembolism, hypertension, woman > 75 years).

1000 patients treated per year. Also the incidence of stroke with residual deficit was reduced by 68% with an absolute annual reduction of 1.4%.

The intensity of anticoagulation in the 5 trials varied consistently, the International Normalized Ratio (INR) ranging between 1.4 and 4.5. No correlation emerges between intensity of anticoagulation and consistency of reduction of stroke. Also low-intensity anticoagulation (INR ranges 1.5-2.8), as that adopted in BAATAF and SPINAF studies, confers substantial benefit.

The risk of bleeding in patients receiving warfarin in these studies was quite low. The annual frequency of major bleeding events was 1.3% in warfarin treated patients. In a more generalized outpatient population the risk of bleeding is probably greater. In elderly patients the risk of bleeding, mainly cerebral, appears to be higher. The rate for intracranial hemorrhage in patients > 75 years on warfarin was 1.8%/year in the SPAF II study [23]. In the other trials in which the intensity of anticoagulation was lower, also the risk of intracranial hemorrhage was significantly lower (mean 0.3%/year).

Secondary prevention of thromboembolism in patients with NVAF has been assessed in two studies, EAFT and SIFA. In the EAFT study [24] 1.007 NVAF patients with a recent TIA or minor ischemic stroke were randomized to open anticoagulation or double blind treatment with either 300 mg aspirin per day or placebo; patients with contraindications to anticoagulation were randomized to

receive aspirin or placebo. In these high risk patients warfarin was very effective, reducing the risk of stroke from 12% per year to 4% per year, while aspirin showed only a modest efficacy reducing that risk from 12% to 10% per year.

In the Italian SIFA study (Studio Italiano Fibrillazione Atriale) [25] the efficacy and safety of the antiplatelet drug indobufen, a reversible cyclooxygenase inhibitor (100-200 mg bid) has been compared with warfarin (INR 2.0-3.5) in patients with NVAF and a recent (≤ 14 days) TIA or stroke.

In this multicenter open trial 916 NVAF patients were randomized to anticoagulation or indobufen. At the end of treatment after 1 year follow-up the frequency of primary outcome events (non-fatal stroke, systemic embolism, non-fatal myocardial infarction or vascular death) was 10.6% and 9.0%, and of vascular death 6.7% and 6.2% in the indobufen and warfarin groups respectively, with no statistical difference between treatments. Major bleeding events (0.9%) were observed only on warfarin.

In comparison with the EAFT study, the efficacy of antiplatelet treatment was substantially higher.

The efficacy of aspirin for primary stroke prevention in AF patients is unclear and quite controversial. The effect of aspirin in doses between 75 and 325 mg/day has been assessed in 2 placebo-controlled studies of primary prevention (AFASAK, SPAF I). The AFASAK study observed a not statistically significant decrease in the frequency of strokes by 18%, while a statistically significant decrease of 44% was observed in the SPAF I study.

Possible explanations for the different efficacy of aspirin in these two studies include different dosages of aspirin (75 mg in AFASAK and 325 mg in SPAF I) and different age of treated patients (mean age 75 years in AFASAK and 67 in SPAF I).

Other possible explanations for this difference may be the higher prevalence of stasis-related thrombi in the AFASAK study patients, compared with SPAF, as suggested by the higher incidence of congestive heart failure (51% vs 19%). It is conceivable that aspirin does not prevent stasis related causes of stroke due to left atrial and possibly left ventricular thrombi in patients with enlarged left ventricle.

It is unlikely that different dosages of aspirin could account for different efficacy [26]. Several studies have demonstrated that also dosages of 30 mg/day are equally effective. As far as the age is concerned it is important to consider that a further analysis of SPAF has demonstrated that aspirin was ineffective in the subgroup of AF patients older than 75 years.

The differential effect of aspirin associated with age could be accounted for by differences in the effect of aspirin on platelets, different stroke mechanisms, or age related patient characteristics (e.g. intrinsic fibrinolitic activity or intra-atrial stasis of blood due to congestive heart failure) which might render the antithrombotic effect of aspirin inadequate.

A differential effect of aspirin according to stroke mechanism is another important issue. Platelet inhibitors and anticoagulants may influence cardioembolic and non-cardioembolic sources of stroke differently. Aspirin may have a greater prophylactic impact on non-cardioembolic mechanisms than on strokes of presumed cardioembolic origin in AF patients. In a SPAF secondary analysis strokes were categorized as cardioembolic or non-cardioembolic according to

clinical and neuroradiologic criteria (27). The preventive effect of aspirin therapy was different for cardioembolic relative to non-cardioembolic ischemic strokes ($p = 0.001$). Aspirin was associated with a risk reduction in non-cardioembolic strokes of 100% (95% CI, 60 to 100%; $p = 0.001$), but with a risk reduction of only 31% for cardioembolic strokes (95% CI, -35 to 65%; $p = 0.31$).

In the secondary prevention study EAFT aspirin had only a modest efficacy in preventing recurrence of stroke (-17%) in patients with NVAF and recent TIA or stroke. Combining the three placebo-controlled studies of primary (AFASAK, SPAF I) and secondary prevention (EAFT) overall the risk reduction with aspirin was only 25%.

A direct comparison of aspirin with warfarin has been made in 3 studies (AFASAK, SPAF II, EAFT). Aspirin resulted significantly less effective than warfarin (combined risk reduction was 47% by warfarin relative to aspirin) but associated with a substantially lower risk of bleeding. Recently the SPAF III [28], a study of fixed-dose mini-intensity warfarin (INR 1.2-1.5) in combination with aspirin (325 mg per day) was completed. This combination therapy was not found to be effective for primary stroke prevention in AF patients with risk factors when compared with dose-adjusted warfarin (INR 2.0-3.0). Moreover the incidence of major hemorrhage was not significantly different in the two treatment arms (2.4% per year with combination therapy vs 2.1% per year with adjusted-dose warfarin).

Treatment Recommendations

It is evident that adjusted-dose warfarin is much more effective than aspirin in decreasing the risk of stroke in AF patients. The majority of AF patients are over 65 years and have other risk factors for stroke. Their annual risk of stroke is therefore 5% or more and the decision to use oral anticoagulation is quite straightforward (Table 2).

Table 2. Guidelines for antithrombotic prophylaxis in patients with AF

Age < 65 years		
no risk factors ("lone" AF)	→	aspirin or no treatment
risk factors[a]	→	warfarin (INR 2.0-3.0)
Age 65-75 years		
no risk factors	→	warfarin (INR 2.0-3.0) or aspirin
risk factors	→	warfarin (INR 2.0-3.0)
Age > 75 years		
no risk factors	→	warfarin (INR 2.0-3.0)[b]
risk factors	→	warfarin (INR 2.0-3.0)[b]

AF, atrial fibrillation; INR, international normalized ratio; TIA, transient ischemic attack.
[a]risk factors include: previous TIA or stroke, hypertension, heart failure or left ventricular dysfunction, diabetes.
[b]keep anticoagulation at the lower end of the therapeutic range; consider INR 1.5-2.0 for older patients at higher hemorrhagic risk.

It is recommended that long-term oral anticoagulant therapy (INR 2.0 to 3.0) be strongly considered for all patients older than 65 years with AF and also for patients younger than 65 years who have any of the following risk factors: a previous TIA or stroke, hypertension, heart failure or left ventricular dysfunction, diabetes, clinical coronary artery disease, mitral stenosis, prosthetic heart valve or thyrotoxicosis.

In patients younger than 65 years with no risk factors for stroke ("lone" AF) either aspirin or no antithrombotic therapy is appropriate.

In patients between age 65 and 75 without risk factors aspirin can be an acceptable alternative to warfarin in patients who are poor candidates for oral anticoagulant therapy because of risk factors for bleeding.

In patients older than 75 years oral anticoagulation is recommended because of their high risk of stroke and inadequate protection by aspirin. However in the very elderly AF patients anticoagulation should be used with caution and carefully monitored because of the potential age-related increased risk of bleeding and in particular of intracranial hemorrhage. As the risk of bleeding is related to the intensity of anticoagulation, anticoagulant regimen at the lower end of the therapeutic range of INR 2.0 to 3.0 seems to be appropriate in these patients. An even lower intensity of anticoagulation between 1.5 and 2.0 of INR appears to confer an acceptable protection (80%-85% as effective) as recently demonstrated by the time-exposure analysis of data in the SPAF III study.

It appears reasonable to consider aspirin for those who are poor candidates for anticoagulation, patients with extracardiac causes of embolism (i.e. carotid artery disease, aortic plaques) and patients without gross echocardiographic abnormalities (i.e. atrial and left ventricle enlargement) favoring thrombi formation.

Bleeding is the most important complication of anticoagulant therapy. In particular conventional intensities of anticoagulation increase the risk of intracranial hemorrhage 7- to 10-fold. Therefore cerebral bleed is often a major clinical concern about anticoagulation in elderly patients for stroke prevention.

The key issue in using warfarin to prevent stroke and systemic embolism in AF patients is whether the benefit of therapy outweights the risk of bleeding in an individual patient [29]. Risk factors for bleeding during oral anticoagulant treatment include intensity of anticoagulation, advanced age, recent initiation of warfarin therapy and comorbid conditions.

In a recent prospective Italian collaborative study (ISCOAT) [30] the frequency of bleeding complications has been studied in outpatients treated routinely in anticoagulation clinics. The rate of fatal, major and minor bleeding events was quite low: 0.25, 1.1 and 6.2 per 100 patient-years of follow-up respectively. The rate was higher in older patients and during the first 90 days of treatment compared with later. The risk of bleeding was related to the intensity of anticoagulation, even if one fifth of the bleeding events occurs at INR < 2.0.The risk of bleeding complications in this study was much lower than those recorded in other previous observational and experimental studies. This means that oral anticoagulation has become safer in recent years especially if monitored by specialized anticoagulation clinics.

Safe anticoagulation requires monitoring with the INR that corrects for varying thromboplastin sensitivities. Studies of the optimal intensity of anticoagulant therapy provide information about the target for each of the indications for this therapy. In AF patients the risk of stroke increases at INR values below 2.0 [31], while the risk of hemorrhage increases at INR above 4.5 (EAFT).

Caution is required in elderly patients. They should be treated at a low target zone and anticoagulation intensity should be closely monitored to reduce periods of overdosing. Finally, older patients on anticoagulation need to be carefully followed so that conditions potentially interfering with oral anticoagulation can be monitored.

Conclusions

Because of epidemiologic considerations the impact of AF in clinical practice is extremely important not only for the cardiologist but also for the general practitioner. Among the therapeutic goals to consider for patients with AF, the prevention of thromboembolism comes first.

The indications for oral anticoagulant prophylaxis are expanding, particularly among older patients, and are now much less empirical than in the past. Warfarin prophylaxis not only substantially reduces embolic risk in AF, but has also an economic impact. The impact of aspirin is uncertain given current available data. At present time indications for aspirin are limited to AF patients with low thromboembolic risk or to those with high risk for anticoagulation.

Cost-effectiveness analyses have been performed in patients with NVAF incorporating costs of managing stroke, cost of warfarin prophylaxis and expenses of managing bleeds. Also these economic analyses support the recommendation for warfarin in patients who are at high or medium risk for stroke [32]. This strategy is cost-saving in high risk patients and cost-effective in medium risk patients with AF.

Besides general guidelines based on the results of clinical trials, the risk/benefit ratio for anticoagulation should be assessed by the cardiologist or primary care physician in the individual patient with AF.

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ATRIAL FLUTTER AND OTHER SUPRAVENTRICULAR TACHYARRHYTHMIAS

Inappropriate Sinus Tachycardia: Mechanism and Therapy

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Definition

Inappropriate sinus tachycardia (IST) is a chronic non-paroxysmal tachycardia arising from the sinus node, and is characterized by a sinus rate that is excessive with respect to the level of physical or psychological stress. Apart from early contributions given by Codvelle and Boucher [1] in 1939 and by Wising [2] in 1941, the first clinical report dedicated to this particular arrhythmia was published in 1979 by Bauernfeind et al. [3]. Although the concept of IST is obvious, there is no agreement on the quantitative criteria required for the diagnosis. This has resulted in substantial differences between published series of patients: for example all Bauernfeind's patients had resting sinus rate > 100 [3], whereas 5 out of 6 patients reported by Morillo et al. [4] had normal resting heart rate even though reflecting an exaggerated rate response to physical activity.

Clinical Presentation

Inappropriate sinus tachycardia is far more common in females than in males, with a 5:1 ratio, and has been mainly observed in young adults, with an average age of about 30 years [5]. Symptoms include palpitations, dizziness, presyncope or, more rarely, syncope. Physical examination is normal, as well as chest X-ray, echocardiogram and laboratory tests; in particular urinary cathecholamines have been shown to be normal.

Diagnosis

The diagnosis of IST requires not only the presence of an excessive sinus rate, but also the exclusion of known conditions that are commonly associated with sinus tachycardia such as hyperthyroidism, fever, pheochromocytoma, pulmonary dis-

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ease, heart failure, chronic infection, systemic disease, malignancy or drugs affecting the heart rate (thyroid hormones, β-adrenergic agonists, theophylline, xantines, alcohol, tobacco, etc.) [5].

The electrocardiogram is normal, apart from the increased heart rate, and the P waves are typical of sinus origin, being positive in leads I, II and aVF. Sinus tachycardia is evident at rest, and an excessive and disproportionate heart rate increase occurs as a consequence of even minimal efforts. This is clearly revealed by Holter monitoring, that also elucidates the non-paroxysmal character of sinus tachycardia. Typically in IST the heart rate in not fixed, being higher during the day than during the night, and the increase in rate is not abrupt, but progressive [5].

Effort test results in exaggerated chronotropic response, and usually patients attain the maximal heart rate at a very low workload.

Inappropriate sinus tachycardia should be distinguished from: (1) normal or "physiologic" sinus tachycardia; (2) sinus node reentry tachycardia; (3) atrial tachycardia arising from a region close to the sinus node [5]. It should be emphasized that clinical and electrophysiological features make the distinction between IST and sinus node reentry tachycardia relatively easy, whereas differentiation of atrial tachycardia from IST is often impossible. This is because the electrocardiographic pattern of an atrial tachycardia arising from a region close to the sinus node is identical to that of (physiologic or inappropriate) sinus tachycardia, and even invasive studies do not provide clues for the distinction, unless atrial tachycardia is due to a reentry mechanism, revealed by the ability to initiate and interrupt the arrhythmia by means of programmed atrial stimulation. Moreover, a moderate variability in P wave morphology, such as a slightly different P wave axis and configuration during tachycardia, in comparison to normal sinus rhythm, does not automatically suggest that tachycardia originates outside the sinus node. This is because the sinus node is a very large and poorly defined structure, made of countless pacemakers: any shift of the dominant pacemaker *within* the node may, thus, be associated with small P wave changes that do not necessarily express pacemaker migration *outside* the node. Using atrial activation maps obtained from patients undergoing cardiac surgery for WPW syndrome, Boineau et al. [6, 7] demonstrated that the right atrial pacemaker region may correspond to a zone of 7.5 x 1.5 cm, namely longer and larger than the usually anatomically defined sinus node. In this respect it becomes meaningless to distinguish between "sinus" rhythm and "ectopic" atrial rhythm on the basis of P wave configuration.

The electrophysiological study in IST patients shows a normal high-to-low right atrial activation, indistinguishable from that of sinus rhythm, and normal electrophysiological parameters. Tachycardia cannot be initiated by electrical stimulation [8].

It is worth noting that some patients with IST (5 out of 7 patients in Bauernfeind's series) are erroneously diagnosed as having paroxysmal supraventricular tachycardia, and receive treatment with antiarrhythmic drugs [3].

Mechanisms

Inappropriate sinus tachycardia may theoretically result from enhanced sinus node automaticity or from autonomic nervous system imbalance, consisting in either increased sympathetic tone or lowered vagal tone [5]. It is not clear whether one single mechanism is responsible for all patients presenting with the "syndrome" of IST, or whether substantially different mechanisms are involved in different patients. To assess the role of these hypothetical mechanisms in determining IST, the following investigations have been performed: (1) determination of the intrinsic heart rate (IHR), (2) evaluation of the response to isoproterenol, propranolol or atropine administration, (3) study of the heart rate variability, (4) study of the baroreflex response to vasopressor drugs, and (5) study of cardiovagal reflex activity.

The IHR after autonomic blockade (propranolol plus atropine) has been determined by Bauernfeind [3], who observed an abnormal value in only 1 out of 7 patients, while in Morillo's series [4] the IHR was increased in all 6 patients. In Lee et al.'s study [8] the average IHR of IST patients was significantly higher than the expected value (118.6 ± 8.6 versus 97.7 ± 1.7; $p < 0.01$); IHR, however, was within the normal range in 5 out of 11 patients in whom this parameter was measured. These conflicting data concerning IHR suggest that enhanced sinus node intrinsic automaticity is not the only basic mechanism responsible for IST.

The response to propranolol and to atropine allowed Bauernfeind [3] to separate his patients into 2 groups, since 2 patients had a marked decrease in heart rate following propranolol (a normalization of sinus rate following the drug), and relevant rate increase after atropine, while 5 patients showed only relatively small sinus rate variations after propranol or atropine. These latter patients were believed to have their IST explained by insufficient resting vagal influence, whereas in the former ones an excessive sympathetic influence was estimated to be responsible for IST. β-adrenergic hypersensitivity has also been observed by Morillo et al. [4]: in their study the isoproterenol dose necessary to achieve an increase in heart rate of 25 beats was markedly lower in IST patients than in controls (0.29 ± 0.10 μg versus 1.27 ± 0.4 μg; $p < 0.001$).

The heart rate variability (HRV) in frequency domain has been studied by Morillo et al. [4], who determined the LF/HF ratio and did not find any difference between IST patients and sex- and age-matched healthy volunteers. In contrast, Sgarbossa et al. [9] calculated the HRV in time domain in 6 IST patients and 6 control patients, observing a markedly reduced HRV in IST patients.

The baroceptor sensitivity has been studied in IST patients by Bauernfeind et al. [3]; in response to phenylephrine, 2 patients (the ones reflecting an exaggerated sensitivity to propranolol) manifested a greater than normal cardiac slowing, while the other 5 patients, in whom both propranolol and atropine were scarcely effective, showed only a minimal cardiac slowing. These data confirmed the author's point of view that in some patients IST was the result of excessive β-adrenergic tone, revealed by high baroceptor sensitivity, whereas in other subjects IST depends upon reduced vagal drive, demonstrated by scarce response to

atropine and reduced baroreflex sensitivity. It is worth noting that in 2 patients manifesting a scarce vagal influence on the sinus node, revealed by a minimal change in rate following phenilephrine, the drug resulted in second degree type 1 A-V block. This suggested that there was a normal baroceptor vagal reflex, expressed by normal efferent influence on the A-V node; the deficient sinus node reflex response in these patients has been attributed to selective cholinergic insensitivity of the sinus node, or to a reduced number of cholinergic receptors in the sinus node area [3].

The cardiovagal reflex has been evaluated in Morillo's study [4] by means of the "cold face test", consisting in application of cold pads (0° C) on the ophthalmic branches of the trigeminal nerves. Abnormality of the reflex was evident in all IST patients, as demonstrated by a significantly minor heart rate decrease with respect to normal subjects (6.3 ± 2.1% versus 24 ± 8.5%; $p < 0.001$).

Analysis of available data shows that no unique mechanism is responsible for IST, but both enhanced sinus node automaticity and autonomic imbalance are involved in various ways in different patients. Inappropriate sinus tachycardia, therefore, should not be considered as a single entity, but as a spectrum of diseases whose common denominator is an excessive resting sinus rate and/or an exaggerated chronotropic response to effort.

Post-Ablation Inappropriate Sinus Tachycardia

A peculiar form of IST has been observed in patients submitted to catheter ablation for A-V junctional reentrant tachycardia [10], and also in patients with parahissian accessory pathways treated by radiofrequency ablation [11]. This phenomenon has been observed only when the anterior or "fast pathway" approach was used for ablation of A-V junctional reentrant tachycardia. Although the origin of this type of IST is still debated, it has been suggested that tachycardia is due to disruption of efferent vagal fibers that enroute to the sinus node through the atrioventricular region. The same explanation may be applied to IST following catheter ablation of parahissian accessory pathways, since in this procedure radiofrequency energy is applied to the anterior region of Koch's triangle, in such a way that lesion of vagal fibers may ensue, resulting in reduced vagal tone [10, 11].

Treatment

Patients with IST require treatment because of their symptoms. Theoretically, asymptomatic patients with IST could be treated in order to avoid a possible tachycardia-mediated left ventricular dysfunction; such a situation, however, has not been reported up to now, so that treatment is entirely aimed at symptom relief.

Drug treatment is mainly based on β-blockers or verapamil; administration of β-blockers had a favorable effect in 5 out of 6 of Morillo's [4] patients, whereas it was totally unsatisfactory in Waspe's patient [12] and in Lee's study [8]. A new

investigational drug, zatebradine, that acts as an inhibitor of hyperpolarization activated current (I_f), results in significant sinus rate reduction in animals [13], and has been well tolerated by healthy volunteers [14]. This drug might be used in the future in IST patients, but it is not currently available.

Alternative therapeutical strategies include surgery and catheter ablation. Subtotal right atrial exclusion has been reported in 1984 by Yee et al. [15] as a possible solution in patients with refractory IST; the results of operation were favorable, but nowadays a surgical approach appears unnecessary in these patients, provided that catheter ablation is associated with a good success rate.

The catheter technique has been initially used either for radiofrequency A-V nodal ablation, or for chemical ablation of the sinus node [16]. The latter approach is no longer used, both because of possible complications and the widespread diffusion of the radiofrequency technique. Ablation of the A-V junction is not an optimal solution for IST, since it requires permanent pacemaker implantation. Moreover, if after A-V node ablation a dual-chamber pacemaker is inserted, the problem of excessive sinus rate will still be present, since ventricular tracking by atrial impulses will once more result in tachycardia, unless a "Wenckebach" mechanism is used in order to avoid 1:1 A-V synchronization. It is worth noting that in Lee et al.'s study [8] 3 out of 16 patients treated with sinus node ablation for IST had previously undergone A-V nodal ablation followed by permanent dual-chamber pacemaker implantation: in these patients interruption of A-V conduction did not result in satisfactory symptomatic relief.

The feasibility of radiofrequency ablation of the sinus node was first suggested by laboratory experiments. Laser coagulation of the sinus node region has been performed in open-chest dogs, targeting the lesion on the basis of earliest atrial activation [17]. The procedure resulted in permanent sinus rate lowering without excessive bradycardia and without significant sinus pauses. Further laboratory investigation proved that it was possible in dogs to achieve sinus node modification by catheter application of radiofrequency energy [18]; the intrinsic heart rate was reduced by 31%, as well as the maximal response to isoproterenol, the maximal heart rate and the average heart rate. The first case of catheter ablation of the sinus node for treatment of IST was reported by Waspe et al [12]: a 38-year-old female with typical drug-refractory highly symptomatic IST underwent electrophysiological study. Radiofrequency energy was applied in the sinus node area, selecting the target for ablation on the basis of the earliest local activation; 6 radiofrequency energy pulses resulted in permanent sinus rate reduction, with total symptomatic relief.

The largest series of IST patients treated with radiofrequency catheter ablation has been reported by Lee et al. [8], who used 2 different procedures, defined as "Total sinus node ablation" (4 patients) and "Sinus node modification" (12 patients). The end point was a heart rate reduction of > 50% for total sinus node ablation, and a reduction of > 25% for sinus node modification. Radiofrequency energy was applied along the crista terminalis, starting from its most superior aspect, and giving further energy pulses to progressive inferior sites until the targeted result was achieved. In the last 8 patients submitted to the procedure,

radiofrequency energy application was guided by intracardiac echocardiography; this resulted in a better recognition of the crista terminalis with respect to the fluoroscopy-guided procedure, and ultimately in a more precise and systematic approach to the sinus node, reflected in the reduction of the pulse numbers and diminished fluoroscopy time. The results of total sinus node ablation are relatively unsatisfactory, since the extensive node damage was followed by slow A-V junctional escape rhythm, and 2 of 4 patients required pacemaker implantation for prolonged pauses. Sinus node modification, in contrast, was followed by disappearance of IST and did not require a pacemaker; only 2 out of 12 patients had recurrences.

Conclusion

Inappropriate sinus tachycardia is a relatively rare arrhythmia characterized by excessive resting heart rate and/or disproportionate sinus rate increase as a consequence of mild effort. More than one mechanism may account for IST, including enhanced sinus node automaticity, β-adrenergic hyperactivity, and reduced vagal drive to the sinus node. In this sense IST may be regarded as the common manifestation of different disorders, namely as a "syndrome" rather than as a single disease. The clinical diagnosis is easy on the basis of standard ECG, Holter monitoring and effort test. Secondary causes of sinus tachycardia must be ruled out before diagnosing IST. Prognosis of patients with IST is poorly known; treatment should be undertaken only for symptomatic relief. β-blockers or verapamil are suitable for the treatment of IST; in patients unresponsive to drugs, catheter ablation of the sinus node should be recommended. Although the experience with catheter ablation in patients with IST is limited, this technique appears very promising, and clearly preferable to ablation of the A-V junction or surgical isolation of the right atrium.

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What Is the Relationship between Atrial Fibrillation and Flutter in Man?

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Introduction

In typical human counterclockwise or clockwise atrial flutter, the barriers of the right atrial reentrant circuit are reasonably well established, and curative ablation with a high rate of success is available for this arrhythmia [1-7]. Atrial fibrillation has long been described as a disorganized or random phenomenon [8]. Recent studies, however, found evidence that the activation during atrial fibrillation is not entirely random [9], suggesting similarities among these common arrhythmias. In an animal model, the conversion of atrial fibrillation into atrial flutter and back has been shown to occur spontaneously [10]. In humans, however, the conversion of one arrhythmia into the other has not been extensively analyzed, although recent studies found evidence that especially atrial fibrillation may spontaneously convert into atrial flutter [11, 12]. Thus, in the present article, we will review the role of atrial anatomy for the relationship between atrial fibrillation and atrial flutter and its consequences for diagnosis and treatment.

Animal Models of Atrial Flutter and Fibrillation

Recent reliable animal models of atrial flutter demonstrated the necessity of barriers in order to maintain atrial flutter. Sustained stable reentry without any degeneration into atrial fibrillation occurred either around an Y-shape lesion in the trabeculated right atrium [13], a crush lesion [14], or around a ligated crista terminalis [15]. In the canine model of sterile pericarditis not involving artificial obstacles, multielectrode mapping in the open chest state [16] demonstrated that the onset of atrial flutter is preceded by a short period of atrial fibrillation. Using the same model [10], the aforementioned group performed multisite mapping of the conversion of atrial flutter to atrial fibrillation and atrial fibrillation to atrial flutter. It was shown that the continuous lengthening of a line of functional block along the right atrial free wall was critical for the maintenance of stable atrial

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flutter, whereas after adenosine-induced shortening of refractory periods, the rhythm reverted back into atrial fibrillation.

Atrial Flutter and Fibrillation in Man

For human typical clockwise or counterclockwise atrial flutter, recent careful activation and entrainment mapping studies have defined the tricuspid annulus as the anterior barrier during atrial flutter [1]. Likewise, using intracardiac echocardiography, the crista terminalis and eustachian ridge have been shown to form a posterior barrier of the flutter circuit [2]. During typical counterclockwise atrial flutter, the trabeculated right atrium - anterior to the crista terminalis and Eustachian ridge - is activated superior to inferior, and the smooth-walled right atrium - posterior to the crista terminalis and eustachian ridge - is activated inferior to superior.

Little is known, however, about the mechanism and significance of the conversion of atrial fibrillation to atrial flutter and vice versa. Watson and Josephson [17] described a brief period of irregular atrial activity in one or more intracardiac leads in most of the patients with inducible atrial flutter during programmed atrial stimulation. Using single intracardiac recording, Waldo and Cooper [11] recently reported that a transitional rhythm, usually atrial fibrillation, precedes the spontaneous onset of atrial flutter in patients following open heart surgery. They noted that atrial fibrillation often slowed and became more regular in cycle length prior to conversion to atrial flutter. Inadvertently induced atrial fibrillation spontaneously organizing into atrial flutter is occasionally observed during invasive electrophysiologic evaluation. We systematically analyzed atrial fibrillation organizing into typical atrial flutter in patients undergoing multisite recording during electrophysiologic study for atrial flutter [12].

Spontaneous Conversion of Atrial Fibrillation to Flutter in Man

From our consecutive series of patients undergoing electrophysiologic evaluation of typical atrial flutter, atrial fibrillation lasting longer than 15 seconds and converting spontaneously into typical atrial flutter prior to attempted catheter ablation occurred in 10 patients (2 women and 8 men, mean age 66 ± 6 years). Eight of the 10 patients had no structural heart disease with echocardiographically normal left ventricular function. One patient had idiopathic cardiomyopathy with moderately reduced left ventricular function (ejection fraction 45%), and one patient had coronary artery disease with a history of myocardial infarction, bypass surgery and compromised left ventricular function (ejection fraction 25%). In 7 patients, all antiarrhythmic drugs, with the exception of digoxin, were stopped at least 24 hours before the study. Three patients were receiving chronic amiodarone treatment.

For mapping the right atrium, a 7F, 20-pole catheter (Cordis-Webster) with

alternating 2 and 10 mm interelectrode distance (2 mm interpolar distance) was situated in the trabeculated portion of the right atrium, as previously described [1]. Furthermore, a multielectrode catheter was placed in the coronary sinus via the right internal jugular vein. Bipolar intracardiac electrograms filtered between 30 and 500 Hz were recorded and stored digitally on a Cardiolab system (Prucka Engineering) simultaneously with the 12-lead surface electrocardiogram. Calculation of atrial fibrillation cycle length was performed on the Cardiolab system using digital calipers. Twenty-five cycles of atrial fibrillation in two different bipoles along the trabeculated right atrium were measured in every episode of conversion of atrial fibrillation to atrial flutter: (a) 5 seconds after onset of atrial fibrillation, (b) just prior to a more organized pattern of atrial fibrillation (see definitions below), and (c) during the period of a more organized pattern of atrial fibrillation immediately prior to conversion to typical atrial flutter.

The macroreentrant circuit and the surface and endocardial appearance of typical counterclockwise and clockwise *atrial flutter* have been well defined [1-3]. *Atrial fibrillation* was defined as a rapid atrial rhythm (rate > 260 beats per minute) characterized by a variability of the beat-to-beat cycle length, morphology, and/or amplitude of recorded bipolar atrial electrograms. *Organized atrial fibrillation* was considered present if discrete atrial complexes, separated by an isoelectric baseline, were seen during 3 or more cycles over at least 3 cm along the right atrial free wall. *Disorganized atrial fibrillation* was considered present if atrial electrograms failed to demonstrate discrete complexes or isoelectric intervals over at least 3 cm along the right atrial free wall.

In 10 patients, a total of 17 episodes (range 1-4) of atrial fibrillation organizing into typical atrial flutter were observed. Atrial fibrillation converted into typical counterclockwise atrial flutter in 14 episodes and into typical clockwise atrial flutter in 3 episodes. Specific attempts to induce atrial fibrillation were not made. However, atrial fibrillation was induced by rapid pacing during atrial flutter entrainment in 7 episodes, by low energy internal cardioversion of atrial flutter in order to restore sinus rhythm in 6 episodes, by rapid pacing during sinus rhythm in order to induce atrial flutter in 2 episodes, and the onset was spontaneous in 2 episodes.

Prior to conversion of atrial fibrillation to atrial flutter, a characteristic sequence of events was present in all 17 episodes (Fig. 1). First, a significant increase in atrial fibrillation cycle length was found, from 146 ± 26 ms 5 seconds after onset of atrial fibrillation, to 165 ± 28 ms immediately prior to the occurrence of a more organized pattern of atrial fibrillation. Secondly, a long, electrically silent period along the trabeculated right atrium with a mean duration of 264 ms in all 17 episodes was noted. Afterwards, organized atrial fibrillation was present on the right atrial free wall, with a mean duration of 11 cycles. Before typical atrial flutter with a mean cycle length of 242 ms became established, another activation delay was present, significantly longer than the preceding organized atrial fibrillation and the subsequent typical atrial flutter. During the whole period of organized atrial fibrillation preceding atrial flutter, distinct potentials on the coronary sinus catheter were present in all 17 episodes, although the atrial

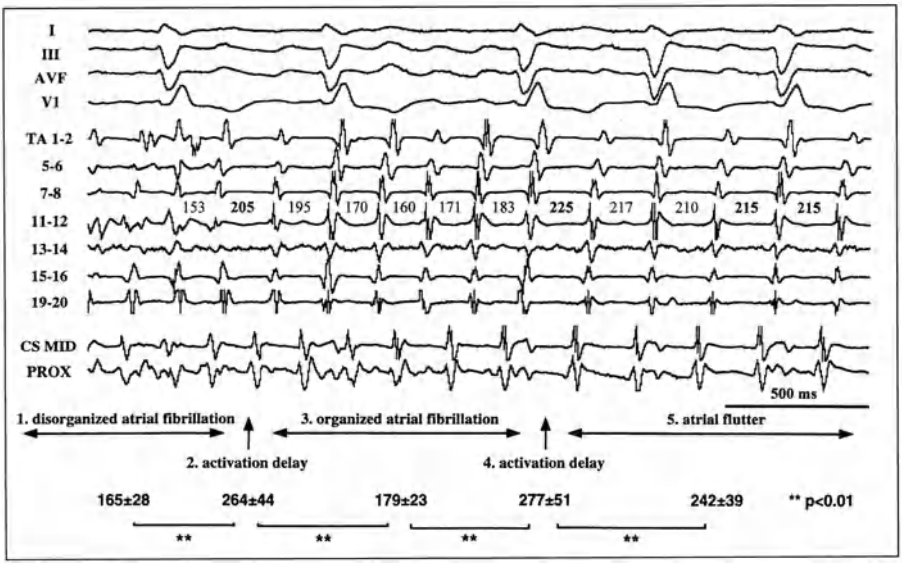

Fig. 1. A characteristic sequence of events in the conversion of atrial fibrillation to typical counterclockwise atrial flutter. First, disorganized atrial fibrillation is present. Then, a sudden activation delay occurs, such that the right atrial free wall is not activated for 205 ms (bipole TA 11-12). A period of 5 cycles of organized atrial fibrillation follows, with an activation sequence characteristic for typical counterclockwise atrial flutter. After another activation delay of 225 ms, typical stable counterclockwise atrial flutter with a cycle length of 215 ms resumes. Note the recording in the coronary sinus, showing distinct atrial depolarizations even during disorganized atrial fibrillation, although a stable 1:1 relation of the coronary sinus atrial signal preceding the activation sequence along the trabeculated right atrium does not occur until the onset of typical atrial flutter. I, III, AVF, V1 = 4 surface electrocardiogram leads; TA 1-2 - TA 19-20 = bipolar recordings along the tricuspid annulus, TA 1-2 being low lateral right atrium and TA 19-20 being high trabeculated right atrium; CS mid, prox = middle and proximal coronary sinus catheter recordings, respectively; numbers = cycle length intervals in ms; numbers on the bottom = mean cycle length intervals for all 17 episodes

coronary sinus signal was not synchronized to the activation sequence on the right atrial free wall. With the onset of typical atrial flutter, however, a stable 1:1 relation between the activation sequence along the trabeculated right atrium and the atrial activation recorded in the coronary sinus was established.

Although several limitations have to be considered, such as the absence of septal and true left atrial recordings, we speculate that the increase in atrial fibrillation cycle length prior to organized atrial fibrillation is due to a coalescence or annihilation of wavelets. Organized atrial fibrillation may represent an unstable right atrial wave, as the coronary sinus activation was not synchronous to the right free wall activation. Higher density recordings will be necessary to characterize the precise activation during organized atrial fibrillation. We further hypothesize that the crucial event for the onset of atrial flutter is the synchronization of the right and left atrium. In all our studied 17 episodes, atrial flutter

became established when the coronary sinus activation was synchronous to the right free wall activation.

Atypical Atrial Flutter

Compared to typical counterclockwise and clockwise atrial flutter, where the anatomic barriers have been well defined, less is known about true atypical atrial flutter, a frequent laboratory arrhythmia with unknown clinical relevance. Kalman et al. [18] have shown that the distinction between typical counterclockwise or clockwise flutter and atypical atrial flutter can be readily made from a combined evaluation including activation and entrainment mapping. In 20 patients, induced atypical flutter showed a heterogenous ECG morphology even in individual patients, a cycle length shorter than that of clockwise flutter, and no consistent concealed entrainment. Furthermore, the clinical presenting arrhythmia predominantly was either counterclockwise or clockwise atrial flutter, and only 2 patients had true atypical flutter exclusively. Another feature which clearly separated episodes of atypical and typical atrial flutter was the frequent transition from and to atrial fibrillation. In the absence of high density mapping and consistent entrainment, circuit and barriers of atypical atrial flutter have yet to be defined. Interestingly enough, however, 35% of patients with induced atypical atrial flutter developed atrial fibrillation during the follow-up period.

The Role of Atrial Anatomy

Recent activation and entrainment mapping suggests that patients with typical clinical and induced atrial flutter demonstrate a complete line of block along the entire length of the crista terminalis and the Eustachian ridge [2]. The crista terminalis has been shown to have poor transverse coupling even in normal subjects [19], and an exaggeration of this normal anisotropy can therefore provide the structural substrate for typical atrial flutter. Brief episodes of atrial fibrillation are assumed to precede the onset of atrial flutter, but as soon as typical atrial flutter becomes established, the reversion back into atrial fibrillation is unlikely. This is also in keeping with the clinical observation that atrial flutter is a remarkably stable arrhythmia, which may occasionally be present for many years once it is initiated. Likewise, Stambler et al. [20] noted that adenosine administration during type I atrial flutter did not cause degeneration into atrial fibrillation in 41 patients. In contrast, adenosine has been reported to consistently cause degeneration of atrial flutter into atrial fibrillation in the canine model [10]. One possible explanation for the disparity noted in adenosine's effect in the canine model and in man is that the line of block along the crista terminalis and Eustachian valve [2,3] may be fixed in patients susceptible to typical atrial flutter, and is therefore not affected by the adenosine-induced shortening of the refractory period. In true atypical atrial flutter [18], on the other hand, the anatomical barriers are not

well defined, and the frequent reversion from and to atrial fibrillation may suggest a functional component in addition to incomplete anatomic obstacles.

Clinical Implications

Whereas predominant typical atrial flutter can be cured by radiofrequency catheter ablation with a high rate of success and a low rate of complications [4, 5], few and controversial data are available for patients with both atrial flutter and atrial fibrillation. Movsowitz et al. [21] found that catheter ablation of atrial flutter was not proarrhythmic with respect to the occurrence of atrial fibrillation, and Katritsis et al. [22] reported a decrease in the incidence of atrial fibrillation in a small number of patients following typical atrial flutter ablation. Philippon et al. [23], however, reported the late occurrence of atrial fibrillation after successful atrial flutter ablation in 27% of patients without a prior history of atrial fibrillation, and Kalman et al. [18] found that atrial fibrillation occurred in 35% of patients with clinical typical atrial flutter and induced true atypical flutter. However, it may be possible that such patients have had brief or asymptomatic periods of unmonitored atrial fibrillation prior to ablation. Thus, patients with the requisite anatomic substrate for typical atrial flutter may only present with clinical flutter if they also have some tendency for atrial fibrillation. When the substrate for atrial flutter is removed by severing the subeustachian corridor, patients may alternatively present with atrial fibrillation, since fibrillation can no longer stabilize into flutter. Until long-term follow-up in a larger series of patients is available, one should be aware that atrial flutter ablation might exchange the clinical presentation of one arrhythmia for another.

Conclusions

In patients with typical atrial flutter, anatomic barriers and obstacles have been shown to be crucial for the maintenance of the flutter circuit. Short periods of atrial fibrillation are assumed to precede the onset of atrial flutter, and crista terminalis and tricuspid annulus might form a funnel which facilitates the spontaneous conversion from atrial fibrillation to flutter in man. Except for electrophysiologically induced true atypical atrial flutter, where the flutter circuit has not yet been well defined, these anatomic barriers make either the spontaneous or pharmacologically induced reversion back into atrial fibrillation very unlikely.

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Physiology of AV Junction: What Have We Learnt from Radiofrequency Ablation?

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The atrioventricular (AV) junction is a rather complex structure involved in the genesis of the atrioventricular junctional reentrant tachycardia (AVJRT), which is the most frequent supraventricular arrhythmia. The advent of radiofrequency (RF) catheter ablation, that has been developed in the recent years, has provided a new therapeutic tool for the radical cure of this arrhythmia. In the meantime the more precise and extensive mapping of the septal region has provided new insight in the physiology and anatomy of the AV junction. This has led to questioning of some previously accepted concepts on its electrophysiology, and rekindled the interest of anatomists and experimental and clinical electrophysiologists, particularly in relation to the mechanism of reentry in humans.

Most of the knowledge on AV node physiology was acquired at the beginning of the century and came from the studies by Mines [1]. Although many cellular and anatomical studies on AV node electrophysiology and anatomy have been performed since Mines' studies in 1913, it was only sixty years later that Denes [2] and Rosen [3] described the electrophysiologic phenomenon of dual AV nodal conduction in humans. Using the techniques of intracardiac recordings and programmed electrical stimulation, in patients with AVJRT, they demonstrated the typical pattern of the dual AV nodal pathways.

Their data suggested that the AV conduction system was longitudinally dissociated into two functionally discrete pathways. One pathway (the β or fast pathway) had a rapid conduction and a relatively long refractory period in the anterograde direction. The other pathway (the α or slow pathway) had a relatively slow conduction and a shorter refractory period than the fast pathway. These pathways have been considered to be the substrate for the reentrant circuit of AVJRT also in humans where during the common type of AVJRT, anterograde conduction occurs via the slow pathway and retrograde conduction via the fast pathway. Although the exact site of the reentry and the tissues involved in the reentrant circuit were not demonstrated, it was generally accepted, until a few years ago, that the reentrant circuit was wholly intranodal and that common pathways of AV nodal tissue were present above and below the reentrant circuit. Using this model, however, it was difficult to understand and explain the results of surgical ablation [4] at first, and catheter ablation more recently [5-10]. In fact,

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in 1985 Ross [4] showed that it was possible to cure the AVJRT with a surgical dissection or criolesion of the atrium, near the AV node, without affecting the normal AV conduction, thus suggesting that part of the reentrant circuit is outside the AV node and also includes atrial fibers.

In fact, at the beginning of the 1990s some questions about AV node physiology were still unresolved, such as: is the dual AV node pathway solely a pathological finding or is it present also in normal subjects? Is the dual AV node pathway a functional or an anatomic separation? Where exactly is the reentrant circuit localized? Is it completely inside the AV node or is part of the atrium also involved? Is the left atrium also involved? Are only two pathways present or in some patients may there be more? Most of these questions has been clarified thanks to the advent of catheter ablation.

In the past the presence of the longitudinal dissociation of the AV node was demonstrated only in few (15%-35%) normal subjects without evidence of AVJRT. However, more recently this percentage has grown to more than 80% of cases [11, 12], suggesting that the dual AV node physiology is a common finding in the general population. Hazlit [12], from the Oklahoma group, studying WPW patients during heavy sedation in 1993, found the presence of dual AV node pathways, either anterograde or retrograde, in 82% of cases. These differences can be explained considering the influence of the autonomic tone on the fast and slow pathways. In an awake patient the adrenergic tone shortens the refractory period of the fast pathway, thus hiding the conduction over the slow pathway. On the other hand, in heavily sedated patients this is not the case and the conduction over the slow pathway may become evident.

The exact site of the reentrant circuit sustaining the AVJRT has been more discussed in the last years. Sung [13] was the first to demonstrate in humans that the fast and slow AV node pathways have anatomically distinct atrial insertions during retrograde conduction in patients with dual AV node pathway physiology. The retrograde atrial exit of the fast AV node pathway (characterized by a short VA interval) was located in the anterior part of the septum, near the His bundle recording site, while the retrograde atrial exit of the slow pathway (characterized by a long VA interval) was located in the posterior part of the septum, near the coronary sinus os, inferior or posterior to the exit of the fast pathway.

This was confirmed first by the surgical studies [4] and then by catheter ablation studies initially of the fast and then of the slow pathway. Considering the fact that in common forms of AVJRT, retrograde conduction is through the fast pathway localized in the anterior part of the septum, the first attempts at catheter ablation were performed in this zone [5, 6] demonstrating that it was possible to modify the reentrant circuit preserving the conduction through the AV node. These papers showed that a selective catheter ablation of the fast pathway with DC shock was possible in about 80%-90% of patients, and then similar or better results were obtained using RF current. However, the fast pathway is located very close to the compact AV node and the His bundle, consequently the risk of complete AV block was relatively high (2%-10%) considering that AVJRT is generally a well tolerated and not life-threatening arrhythmia.

A further demonstration that part of the reentrant circuit is extranodal, involving the perinodal atrium, was provided by the possibility of curing the AVJRT with the selective ablation of the slow pathway through the delivery of RF energy in the posterior part of the septum, far from the compact AV node. Nowadays slow pathway ablation is generally preferred due to the lower risk of AV block; however, the fact that the prevention of recurrences of AVJRT is possible by ablating either the fast or the slow pathway in two very different places, far from each other, is another demonstration that the two structures are anatomically separated and a broad area of atrial tissue is comprised between them.

Three different approaches for slow pathway ablation in AVJRT were proposed. The anatomical approach was proposed by Jazayery [7] and was characterized by a stepwise movement of the catheter from the posterior zone of Koch's triangle to the midseptal and anteroseptal zone, using only the recording of a small AV ratio as an endocardial guide.

In the same period two other approaches were proposed; one by Haissaguerre and us [8, 9] and the second by Jackman [10], both using endocardial potentials to guide application of RF energy. These two potentials are often considered similar and this creates some confusion. However they are different not only morphologically but also in the sites where they are recorded and in their electrophysiologic behavior and significance.

The potential described by Jackman [10] is sharp and it is the latest atrial electrogram following a low amplitude atrial electrogram, during sinus rhythm while, during atypical AVJRT, the sequence is inverted and the sharp potential precedes the atrial electrogram. It can be recorded around the coronary sinus os, sometimes above it, sometimes inside it, but usually below it.

The potential described by Haïssaguerre and us [8, 9] is generally recorded at the mid or posterior septum, anterior to the coronary sinus, but not inside or posterior to it. Usually the site of a more vivid slow potential is projected at two thirds anterior one third posterior of the area between the His bundle and the coronary sinus os.

Although the morphology of the slow potential may be different in the various patients, it can be identified based on its electrophysiologic behavior. In fact, it is characterized by the progressive reduction in amplitude until it disappears with atrial incremental pacing.

The two potentials can be recorded simultaneously in the same patient in the posterior part of the septum and often, near the coronary sinus, an overlapping zone is present where both potentials can be recorded. This overlap zone has been well demonstrated by McGuire [14] through high resolution mapping of Koch's triangle using sixty electrodes during open heart surgery in humans with AVJRT.

The origin and the significance of these two potentials is not completely clear and some investigations on them have been performed by some experimental electrophysiologists. Some hypotheses have been suggested. One by Racker [15, 16] who, using isolated canine heart preparation, suggested the presence of an atrionodal bundle, forming a sino-ventricular conduction system with anterior and pos-

terior AV nodal inputs. The posterior is formed by medial and lateral internodal bundle converging in the proximal AV bundle. At the level of the proximal AV bundle it was also possible to record a slow potential, which she called "P potential". In her paper published in 1993 [16], she proposed that the slow potential recorded in humans may represent the activation of the proximal atrio-ventricular bundle recorded in dogs, while the sharp potential may be the expression of the lateral atrionodal bundle lying in the low posterior septum. However a recent study [11] showed that the concept of insulated atrionodal tracts has no morphologic basis in humans.

A different explanation was proposed by de Bakker [17]. He showed that it was possible to record a slow potential between the atrium and the ventricle in the midseptal zone in human and in pig hearts and stated that slow potentials arise from transitional cells and have action potentials similar to nodal cells.

In a more recent paper McGuire [18] showed it was possible to record potentials like the slow potential in the mid of the septum and posterior zones, while potentials like the sharp potential were recorded more posteriorly. Intracellular recordings in the area where slow potentials were recorded showed an activation potential similar to that recorded in the AV nodal cells. On the contrary, intracellular recordings in the zone where the sharp potentials were recorded showed an activation potential similar to that recorded in common atrial fibers. He explained the different significance of the two potentials by suggesting that the slow potential is due to a band of nodal-type cells close to the tricuspid annulus, and it is not part of the compact AV node. They may represent the substrate of the slow AV nodal pathway; on the contrary the sharp potential may be a far field signal caused by asynchronous activation of muscle bundles above and below the coronary sinus os.

Independently of their meaning, the use of slow or sharp potentials as markers for slow pathway ablation, in clinical practice, makes it possible to obtain a high success rate with a selective lesion in the region of the slow pathway, without affecting the compact AV node, with few RF pulses and a very low risk of complete AV block.

In the past few years the existence of more than two pathways has been postulated based on the fact that besides the two classical, well known slow-fast and fast-slow forms of AVJRT, a third type has been described, called slow-slow and, using two pathways both with slow conduction in the anterograde and retrograde limb of the circuit. In this type of tachycardia AH and HA intervals are similar and both long, while the activation sequence shows the earliest retrograde atrial activation near the coronary sinus os in the region where the slow pathway is generally ablated. This demonstrates that at least in some patients more than two pathways may be present.

Although many years have elapsed since the first works on physiology of the AV junction, several questions are still unresolved and a wide space remains for further studies.

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What Is the Clinical Significance of Ventricular Repolarization Abnormalities during Supraventricular Tachyarrhythmias?

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Tachycardia-Related T Wave Changes

T wave changes can be classified as either primary or secondary. Primary T wave changes have been defined as the result of uniform or nonuniform changes in action potential duration in the absence of changes in the sequence of activation. Secondary T wave changes have been defined as reflecting changes in the sequence of repolarization that result solely from changes in the sequence of activation, without any abormalities in the duration and shape of action potentials [1-3]. However, Chatterjee et al. [4] and Rosenbaum et al. [5] demonstrated that prolonged alteration in the sequence of activation caused by ventricular pacing not only caused secondary T wave changes during the period of pacing, but that conspicuous T wave changes persisted for a long time after pacing was terminated and a normal supraventricular activation pattern had resumed. In other affections, such as intermittent left bundle branch block, ventricular tachycardia, or ventricular preexitation transient T wave alterations can be present. These alterations persist after normalization of ventricular activation and, for the most part, in the absence of known myocardial disease that would allow these T wave changes to be classified as primary. This finding has been interpreted as "memory", that is the heart adjusts its repolarization to an altered activation sequence and retains the adapted state long after the activation sequence in normalized. However, the basic electrophysiological mechanism of "cardiac memory" is controversial.

A role for the ventricular gradient between epicardium and endocardium has been suggested [3]. A number of investigators provided evidence that the ventricular gradient was independent of the activation sequence and related to intrinsic properties of the myocardium occurring during repolarization [6-9]. Later, other investigators suggested that the sequence of activation may alter the ventricular gradient [10-16] and that regional differences in action potential duration might be secondary to the activation sequence. If the depolarization time is longer, a secondary effect may outweigh the electrotonic modulation and produce a discordant QRST relationship. Therefore, the activation sequence may

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electrotonically modulate the order of ventricular repolarization and create its own ventricular gradient. This mechanism could explain T wave changes which occur after the reversal of abnormal depolarization sequences such as those noted after an intermittent bundle branch block, temporary right ventricular pacing or an intermittent Wolff-Parkinson-White syndrome.

Therefore, the mechanism of electrotonic modulation alone cannot be responsible for the slowly developing and persistent effects on repolarization. Other possible mechanisms have been suggested, such as ischemia, local tissue injury induced by electrical stimulation, autonomic reflex alteration [17] or damage to the afferent or efferent cardiac nerves [18]. Del Balzo et al. [19] hypothesized that a likely mechanism for the slow modulation of repolarization and its prolonged retention might be searched for in some form of conditioning of a cellular or molecular structure of the myocardium. To test this hypothesis the authors investigated the effects of lidocaine, a local anesthetic that accelerates repolarization, and the effects of 4-aminopyridine, an agent whose major effect is to block the transient outward potassium current I_{to}. The authors evidenced that in the open-chest anesthetized dog model lidocaine does not modify the changes in the T wave occurring during normal conduction after a period of right ventricular pacing, but 4-aminopyridine effectively abolished the T wave changes. Thus the conditioning by cardiac pacing of channels carrying I_{to} may account, at least in part, for the phenomenon of cardiac memory. In other words, T wave changes may reflect the effect of an electrical field on channel structure or function rather than a pathological condition.

ST Tachycardia-Related Alterations

Besides T wave alterations occurring after a period of abnormal ventricular depolarization, an abnormal repolarization can also be observed during paroxysmal supraventricular tachycardia. In fact, during this arrhythmia a marked ST segment depression has been described, sometimes associated with chest discomfort, simulating angina pectoris. Nelson et al. [20] investigated this repolarization abnormality; the main findings reported were the following: (a) some degree of ST segment depression was present in about 100% of the 25 patients during reentrant supraventricular tachycardia induced by programmed stimulation, (b) ST segment depression during supraventricular tachycardia does not appear to be associated with myocardial ischemia because the myocardial lactate extraction remained unchanged from baseline in 88% of the patients, (c) the mean ST segment score (calculated by summing the amount of ST depression in each lead) measured during AV nodal reentrant tachycardia did not differ significantly from the ST segment score measured during tachycardia retrogradely involving an AV bypass tract, and (d) the presence of chest discomfort in 64% of the patients did not correlate with the mean ST segment score, nor with the tachycardia cycle length, the arterial pressure or the lactate extraction.

The lack of a role for myocardial ischemia in the genesis of ST segment

depression during paroxysmal supraventricular tachycardia has been confirmed by Petsas et al. [21] who demonstrated that ST segment depression observed in 16 patients during episodes of paroxysmal supraventricular tachycardia cannot be reproduced during exercise testing in the vast majority of cases.

Present Study

The purpose of the present study was to systematically investigate (1) the ST segment depression during spontaneous paroxysmal supraventricular tachycardia and (2) ST-T alterations during sinus rhythm, after the interruption of the arrhythmia.

We prospectively investigated 81 patients admitted to our Division of Cardiology for paroxysmal supraventricular tachycardia. The inclusion criteria were the following: (1) paroxysmal supraventricular tachycardia with narrow QRS complexes due to AV nodal reentry or reentry involving a concealed AV bypass tract, (2) absence of ventricular pre-excitation during sinus rhythm, (3) documentation of a previous standard electrocardiogram (ECG) performed during sinus rhythm.

The following variables were analyzed: heart rate and ST-T segment alterations during tachycardia, heart rate and ST-T segment alterations after sinus rhythm had restored and in subsequent ECGs. A 12-lead ECG was performed during tachycardia, one minute after normal sinus rhythm had restored and every 6 hours thereafter untill normal repolarization appeared.

The examinations required to define the presence and the type of underlying heart disease in each patient were carried out.

Patients

The mean age of these 81 patients was 56 years (range 8 to 84 years); 61 were female. Sixty-six patients had no history or clinical evidence of underlying heart disease and 15 showed organic heart disease (5 hypertensive heart disease, 4 ischemic, 3 valvular heart disease, 1 congenital heart disease, not well defined cardiac enlargement in 2 patients).

At the admission to the hospital, 24 patients were taking antiarrhythmic drugs. In 38 patients conversion to sinus rhythm was obtained with vagal maneuvers, in 10 with verapamil infusion, in 5 with amiodarone, in 6 with propafenone, in 3 with ATP and in 9 with atrial pacing. In 10 patients conversion to sinus rhythm occurred spontaneously just after the hospital admission.

The data were analyzed utilizing the Mann Whitney test for two independent samples, and correlation coefficient for 2 tailed significance.

ECG Findings

The supraventricular tachycardia appeared related to AV nodal reentry in 73 patients and to concealed bypass tract in 8 [22]. The tachycardia duration was

172 ± 216 min (range from 3 min to 16 hours) and the heart rate was 173 ± 26 beats/min (range from 100 to 230 beats/min).

ST Alterations during Tachycardia

A ST segment depression ≥ 1 mm in one or more leads was present in 55 patients (68%). With regard to ventricular repolarization localization in these 55 patients, the ST segment was depressed in one or more of the inferior leads (II, III, aVF) in 36 patients (65%), in the lateral leads (I, aVL, V_5, V_6) in 40 patients (73%), in one or more of the anteroseptal leads (V_1-V_4) in 49 patients (89%). The amount of the maximum ST segment depression was 2 ± 1 mm (range from 1 to 5 mm). Age, heart rate during tachycardia and prevalence of organic heart disease did not significantly differ between patients with and without ST segment depression. Tachycardia duration was significantly longer in patients without ST segment depression (Table 1).

Table 1. Comparison of clinical and electrocardiographic variables between patients with and without ST segment depression during supraventricular reentrant tachycardia (T)

	Patients with ST segment depression (55 pts)	Patients without ST segment depression (24 pts)	*p* value
Age (years)	57 ± 18	54 ± 13	NS
Heart rate during T (beats/min)	176 ± 21	167 ± 32	NS
T duration (min)	140 ± 179	278 ± 290	0.05
Heart disease (pts)	13	2	NS

NS, not significant

Comparing patients with organic heart disease to those without underlying heart disease, the former were older (65 ± 16 vs 54 ± 16 yrs, $p = 0.01$) and showed a more marked ST segment depression (2.6 ± 1 vs 1.8 ± 1 mm, $p = 0.02$). In both groups the heart rate during the tachycardia showed an indirect correlation with age ($r = -0.34$, $p = 0.005$) but it did not correlate with the amount of the ST segment depression.

ST-T Alterations after Interruption of the Tachycardia

A complete follow-up, with ECGs recorded every 6 hours until normalization of repolarization was possible in 61 patients. Thirty-six out of these did not show

any ST-T segment alteration, whereas 25 (41%) showed negative T waves (not present in the previous standard ECG recorded during sinus rhythm before the tachycardia access). Twenty of these patients had ST depression during tachycardia (Table 2).

Table 2. Comparison of clinical and electrocardiographic variables between patients with and without ST-T alterations after sinus rhythm had been restored. T = supraventricular reentrant thachycardia

	Patients with ST-T alterations (25 pts)	Patients without ST-T alterations (36 pts)	*p* value
Age (years)	56 ± 17	59 ± 17	NS
Heart disease (pts)	5	8	NS
Heart rate during T (beats/min)	172 ± 20	177 ± 27	NS
T duration (min)	128 ± 121	174 ± 234	NS
ST depression during T (mm)	1.7 ± 1	1.6 ± 1	NS

NS, not significant

The mean duration of ST-T abnormalities was 70 ± 73 hours (range 6 hours to 14 days), these 25 patients did not differ from the 36 without ventricular repolarization alterations as regard to age, heart rate and duration of the tachycardia, and the amount of ST segment depression during the tachyarrhythmia. The post-tachycardia repolarization abnormalities were slightly more frequent in the patients with organic heart disease than in those without underlying heart disease (46% vs 32%).

Repolarization abnormalites normalized within 6 hours in one patient, within 24 hours in 7 patients (28%), within 48 hours in 15 (60%), within 72 hours in 20 (80%), in the remaining 5 patients the alterations persisted for 4-14 days (Figures 1-3).

Conclusions

It has been reported that ST depression is a very common finding during paroxysmal supraventricular reentrant tachycardia. The present study is the first examining ST segment alterations during spontaneous access of reentrant tachycardia. It has been previously demonstrated that this finding is not related to

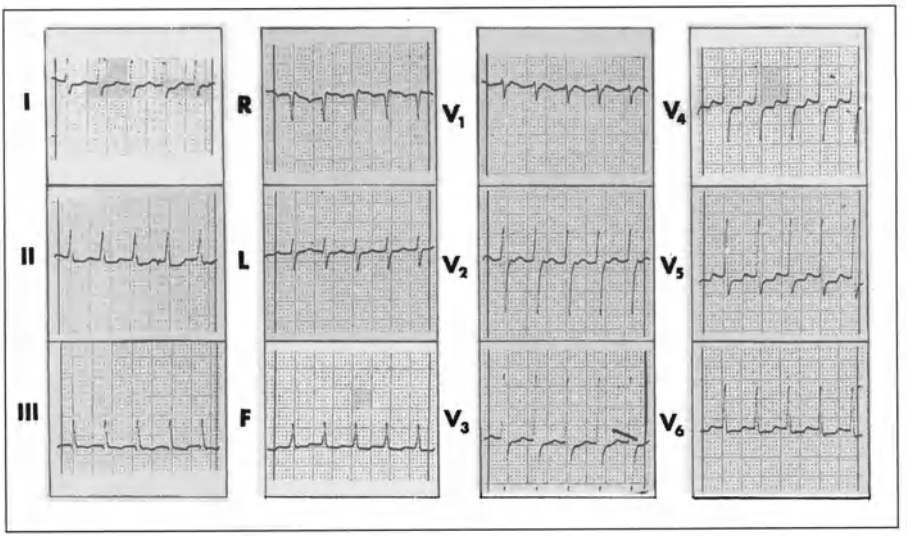

Fig. 1. Patient MA, 46 years old, without apparent organic heart disease. During tachycardia an ST segment depression is present in the anteroseptal leads

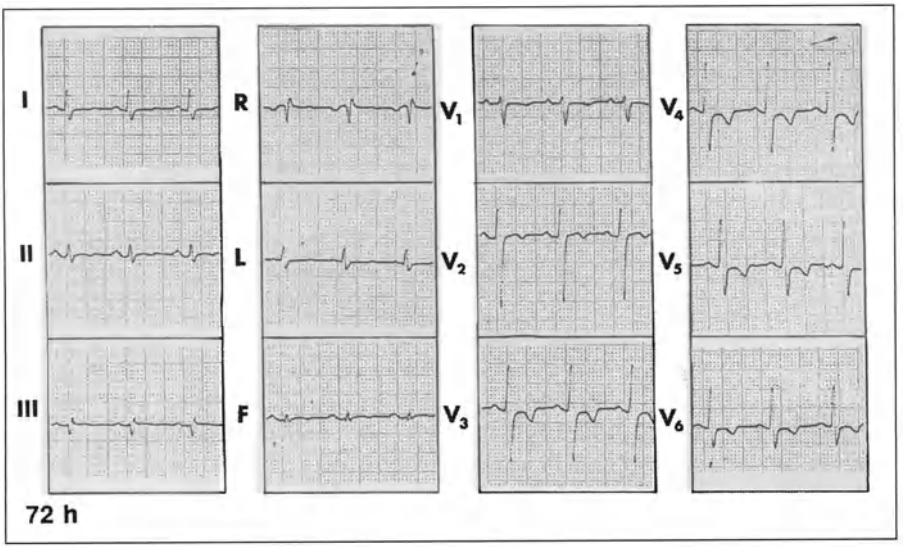

Fig. 2. Same patient as in Figure 1. At the end of tachycardia negative T waves progressively appeared. After 72 hours negative T waves were present in the anteroseptal, lateral and inferior leads

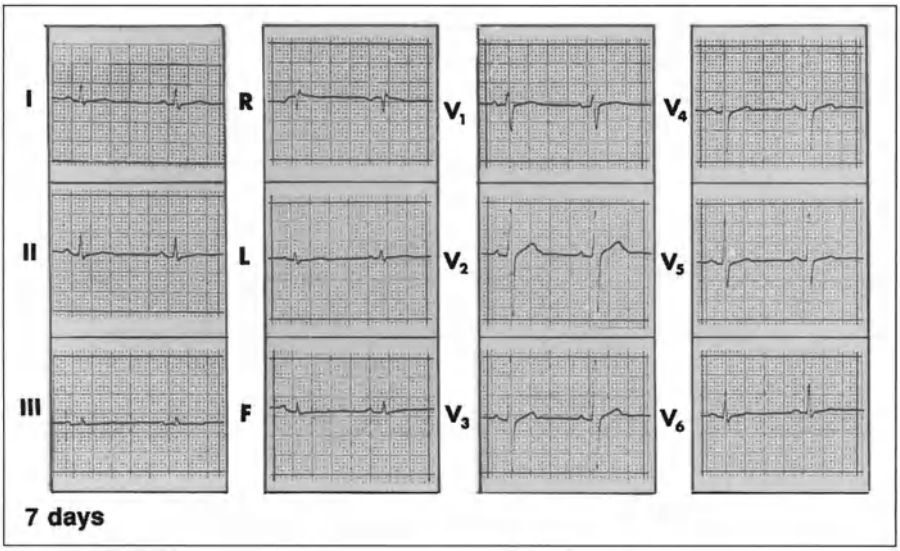

Fig. 3. A complete normalization of repolarization appeared only after 7 days. In this patient a successive exercise test, myocardial scintigraphy and coronary angiography failed to demonstrate the presence of ischemic disease

ischemic heart disease [21, 22]. We found an ST depression during tachycardia in about 70% of patients. This alteration can be present in all the ECG leads, especially in the anteroseptal ones and does not appear to be related to age, heart rate during tachycardia, tachycardia duration and presence of heart disease. The etiology of these abnormalities remains unknown; very likely ionic currents alterations, secondary to the high rate, play a major role.

Up to now ventricular repolarization alterations after tachycardia interruption have not been investigated. We have found negative T waves in about 40% of patients. The post-tachycardia repolarization abnormalities do not appear to be related to age, heart rate during tachycardia, tachycardia duration or presence of organic heart disease. The findings offered by effort scintigraphy and coronary angiography in the patients with long-lasting negative T waves are normal. Therefore the etiology of post-tachycardia repolarization abnormalities remains unknown, as well, but our results suggest that these alterations are not relevant from the clinical point of view.

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Prolonged or Failed Attempts at RF Ablation of Accessory Pathways: What Are the Causes?

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In 1997 almost the entire population with arrhythmias related to the presence of an anomalous AV pathway (AP) is treated successfully by radiofrequency catheter ablation (RF-CA) without excessive difficulty, but in some cases a very prolonged procedure or a second session or both are required to obtain a successful outcome [1].

In this report we analyze the reasons for these findings in a large group of consecutive patients with APs undergoing RF-CA at the Laboratory of Electrophysiology of the University of Pavia over the past few years.

Population

In this review we report the results obtained by our group at the I Medical School of the University of Pavia between January 1991 and December 1996. In this series of 670 patients, the first 100 patients treated until October 1992 were excluded from the study because they were considered to be part of the learning curve of the main operators.

We considered as the procedure time (PT) the entire duration of the electrophysiologic study (pre- and post- RF-CA EPS), including the time required to insert catheters, to obtain electrophysiologic measurements during sinus rhythm and during tachycardia, to manage atrial fibrillation, etc. and not only the time required for mapping and for RF-CA itself.

In cases with more than one mechanism of tachycardia (i.e. more than one AP, nodal + AP reentry, etc.), the entire amount of time required to achieve the final success was considered. The reason for this choice is that we considered every individual consecutive patient and not the single AP.

If the PT required to ablate an AP exceeded the sum of the mean duration required in our laboratory to treat patients with APs plus the value of the SD (138 ± 52 min), it was considered as a lengthy procedure. No procedure was longer than 300 min because this was the upper limit permitted in our laboratory for

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administrative reasons (regarding physicians, nurses, technicians, etc.). According to this criteria, 98/570 patients where considered in this study. Sixty-eight patients of this study were males and 30 females and their mean age was 33 ± 16 years (range 4-70). Five had an Ebstein anomaly, one a dextrocardia, one a congenitally corrected transposition of the great vessels and one a hypertrophic cardiomyopathy. In 47/98 patients, a single but very long procedure was carried out (PT 205 ± 34 min), in 37/98 patients a first failed attempt (PT 245 ± 55 min) required a second one (PT 152 ± 56 min) to reach a successful outcome and finally in 14/98 patients after the first (PT 239 ± 54 min) and the second attempt (PT 192 ± 68 min), a third one (PT 123 ± 63 min) was necessary.

Among these 98/570 patients, the first 74/320 (23%) patients were treated by RF-CA until June 1995 without temperature control mode, while in the last 24/350 (7%) cases, treated between July 1995 and December 1996, the energy delivery was guided by temperature monitoring.

All the patients (pts) who experienced a second RF-CA for pre-excitation recurrence, were excluded. On the other hand, in this analysis we included 8/570 cases (1.4%), in whom, after unsuccessful RF-CA performed in our Institute, the final success was obtained by cryosurgery (3 pts), by drugs (4 pts) or by RF-CA performed in another Institution (1 pt).

Electrophysiologic Procedure (Pre-EPS + Mapping + RF-CA + Post-EPS etc.)

The EPS and the RF-CA were performed in every patient in the same session. After the insertion of 3 catheters (two 6F diagnostic, multipolar catheters and one 7F ablator catheter) utilized both for recording and for electrical stimulation, a standard EPS was carried out. Mapping and CA were performed using the same ablator catheter (Mansfield EP, Webster-Cordis, Medtronic and EP Technologies). Recordings and analysis during the procedure were made by Bard or Mennen devices. RF energy was delivered by a Medtronic source (using catheters with a thermocouple) and EPT (using catheters with a thermistor). ACAC or EPT devices for RF delivery were used in the initial group of patients in whom the RF-CA was performed without temperature control.

For the ablation of left-sided APs, a transseptal approach was used as the first choice technique. Among the 48 cases with a left-sided AP considered in this analysis, in five patients it was necessary to switch to the transaortic one. The inferior vena cava approach was used for septal and right-sided AP. Among the 50 cases with septal or right-sided AP considered in this study, in six patients it was necessary to switch from the inferior to the superior vena cava in order to enhance catheter stability.

Study Protocol

The analysis reported here was performed retrospectively. The majority of the patients (38/42), who had previously undergone one or multiple failed attempts in another hospital, were excluded since according to our point of view, their RF-CA procedures did not present particular difficulties. However, the remaining 4 patients who underwent prolonged or multiple RF-CA procedures at our Institution were considered in this study.

The different causes of lengthy or failed RF-CA procedure are reported in the following list:

1) Problems related to catheter manipulation
2) Mechanical temporary ablation
3) Inaccurate localization of APs
4) Epicardial APs
5) Unusual APs
6) Very complex APs
7) Iterative atrial fibrillation
8) Associated abnormalities
9) Multiple problems

All the 98 patients were assigned to one of these groups or more, according to the problem(s) encountered during the ablation sessions.

Results and Discussion

- Single and multiple Aps: 17 patients (17%) of this study had two APs and in 4/17 a third AP was also present. The prevalence is different from the one in the overall group of 570 consecutive patients treated in our laboratory (11%).
- Latent and manifest Walff Parkinson White (WPW): among the 98 patients, 81% showed ventricular pre-excitation, while the remaining 19% had a concealed AP. Also the prevalence of concealed AP was slightly different from the one in the entire population (17%).
- Location of APs: we learned from our previous experience of surgical ablation in WPW syndrome, the use of the clock hours scheme to map and to define the location of APs. In left anterior oblique projection, we considered the mitral and tricuspid rings as two different clocks; six o'clock corresponds to the posterior limit, while 12 o'clock to the anterior one. The location of the APs was classified according to the site of successful RF-CA, as shown in Table 1 (5 on right side, 5 on left side and 1 septal).

Problems Related to Catheter Manipulation (40/98; 41%)

Out of all factors conditioning the final success during RF-CA, the most relevant was related to the stability of the catheter, that is the inability of the operators to firmly position the mapping-ablator catheter at the ideal target site. This was the case in 40 of these patients. In 23 cases, the PT of a single RF-CA was very pro-

Table 1. Location of the AP in cases with prolonged or failed ablation attempt. (98 patients had 115 APs)

Septal	3
R - Antero-medial	6
R - Anterior	5
R - Lateral	10
R - Posterior	-
R - Postero-medial	30
L - Postero-medial	15
L - Posterior	3
L - Lateral	35
L - Antero-lateral	5
L - Anterior	3

R, right; L, left

longed, while in 17 patients two attempts were necessary. The majority of these cases had APs located in the lateral regions of the AV rings both right and left. Catheter stability was reached in many of these cases by using EPT catheters rather than Mansfield, Webster-Cordis or Medtronic catheters that are the first choice catheters used for ablation in our center like in many others.

In two cases with a lateral right-sided accessory pathway, the success was achieved by using 60 cm guiding sheath (Daig Corp.). To enhance catheter stability in another 6 patients with a right free-wall AP, the success was reached by switching from the inferior to the superior vena cava approach.

Mechanical Temporary Ablation (5/98; 5%)

This situation is often closely related to the excessive manipulation of catheters, but in some cases there is a propensity to a traumatic lesion related to some particular localization of the AP, placed endocardially. This finding was observed in 5 cases.

A temporary mechanical ablation was induced several times in two cases with parahissian APs before the definitive RF-CA. A traumatic lesion is also frequent in cases with the so-called Mahaim fibers and we observed this condition in two cases. According to our experience, traumatic lesion of this arrhythmogenic substrate results in methodologic problems and it can be seldom considered as a useful tool in localizing the accessory connection.

In the remaining patient, who had a left free-wall AP, the first session of RF-CA was interrupted because of a prolonged catheter-induced mechanical lesion.

Inaccurate Localization of APs (8/98; 8%)

What we learned during our experience with surgical ablation performed in 180 cases treated in the Eighties was very helpful in the initial part of the learning curve of RF-CA, when one of the limitations to final success was related to inaccurate localization of APs. For example, an oblique course of some APs, specially in the region of the crux cordis, can be responsible for the difficulties in the precise localization of a postero-medial AP during mapping. In this area, the ventric-

ular insertion is far from the atrial insertion of the AP: the former is placed at the pyramidal body of the left ventricle, which can be reached from the left side (in our case with transseptal catheterization) and the latter at the right side, which can be ablated from the orifice of the coronary sinus. For this reason, in these cases (4 in this population) we firstly approach the right side and then completed the RF-CA from the left side via the atrial approach.

It is possible to find an oblique orientation also in patients with APs placed in the left free-wall (2 cases) or at the right side of the heart (1 case).

Epicardial APs (29/98; 30%)

Epicardial location of an AP was observed in cases with accessory AV connections placed in the left free-wall or in the postero-medial region. In the cases with left free-wall APs and multiple unsuccessful procedures, we prefer cryosurgical ablation to avoid RF energy applications in the distal part of the coronary sinus. In this series, three patients were surgically treated after unsuccessful attempts of RF-CA from the endocardium.

In the crux cordis, epicardial location of several components of an accessory AV connection is not infrequent and it is anatomically related to the orifices of the coronary sinus and/or the middle cardiac vein. This was the finding in 17 of the cases considered here. In every case, it was possible to demonstrate anomalous components placed both at the left and at the right side.

In 3 cases, postero-medial multicomponent epicardial APs were ablated only by using close-circuit irrigated catheter (Cardiac Pathways) to enhance the depth of the lesion, after a conventional unsuccessful RF-CA.

Unusual APs (6/98; 6%)

In six patients, the unusual ventricular insertion of the APs was the reason for a very long procedure. Four of them exhibited a right lateral AP with decremental atrio-fascicular Mahaim-like fibers and the very distal insertion into the right ventricle was the reason for the abnormal finding. In one patient with hypertrophic cardiomyopathy and bilateral APs, both appendages inserted directly to the ventricular epicardium, far from the AV rings. In one patient without manifest WPW a very unconventional ventricular insertion was reached from inside the aortic root at the level of the non-coronary cusp.

Complex APs (29/98; 30%)

A very important complexity of the AP was the reason for a prolonged attempt of RF-CA in 29/98 patients. The most frequent finding during these situations was a very broad but not necessarily epicardial AP. The prevalence of such a finding is increased in this series with the respect to the overall population, in whom complex APs were observed in 4% of the cases. In many of these patients, we could not identify the anatomical basis for the complexity; in some of them the pro-

longed PT was presumably related not only to a very broad insertion but also to either catheter manipulation and/or inaccurate mapping.

Iterative Atrial Fibrillation (5/98; 5%)

More than one third of patients with manifest WPW undergoing RF-CA showed one or more episodes of atrial fibrillation during EPS, mapping and/or RF-CA itself, but only in 10/570 (1.8%) cases was it necessary to perform the procedure during this arrhythmia because of its iterative nature. In five of them the presence of a very high rate rendered the RF-CA very difficult and prolonged.

Associated Abnormalities (8/98; 8%)

In 8 cases, the presence of an associated congenital abnormality, rendered the ablation attempt(s) very complex. Such a problem was related to the presence of an Ebstein anomaly in 4 patients, dextrocardia in 1, congenitally corrected transposition of the great vessels in 1 and bilateral hypertrophic cardiomyopathy in 1 (in this case other problems were associated as well).

Multiple Problems

It appears from our data that in about one third of the patients, multiple problems had to be faced during a RF-CA procedure.

Conclusions

Today, very prolonged or failed attempts at RF-CA of APs are very rare. In our experience, this increased success rate seems to be related to the temperature control at the interface between the tip of the catheter and the myocardium during energy application. A variety of reasons (catheter manipulation and instability, mechanical temporary ablation, inaccurate localization of APs, epicardial insertion of APs, unusual APs, very broad APs, iterative or permanent atrial fibrillation, associated anatomical abnormalities and finally different problems combined together) which are listed in the present paper can be responsible for prolonged or failed ablation attempts; each problem asks for a specific solution. The knowledge and of possible problems the prompt understanding that one of these variables is conditioning the ablation procedure may be helpful in difficult cases.

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SUDDEN DEATH RISK STRATIFICATION AFTER ACUTE MYOCARDIAL INFARCTION

What Is the Clinical and Prognostic Significance of Atrioventricular and Intraventricular Conduction Defects?

E. Piccolo and G. Zuin

In dealing with these electrocardiographic questions, we cannot leave aside the classical notions developed during the pre-thrombolytic era, since these will always constitute, as much as possible, the premise and the point of reference for the various analyses that we will develop. Moreover, we will attempt to deal separately with the incidence of the various conduction defects and their diagnostic and prognostic significance. In addition, our assessment of prognostic significance will be subdivided in order to deal separately with the period of hospitalization and the post-discharge period up to a year after the onset of infarction.

Atrioventricular Blocks (AVB)

In AMI, first-degree AVB, Mobitz 1 and complete AVB (AVB III) are more frequent in inferior AMI, and show an incidence of < 15%, < 10% and 5%-15% respectively [1]. Their origin is nearly always suprahisian, i.e. nodal. Mobitz 2, on the other hand, is more frequent in anterior AMI, is of infrahisian origin and is fairly rare (< 1%) [1]. In a study of 250 first infarctions, Opolksi et al. in 1986 [2] found AVB I in 1%, and AVB II or III in 18%. Constans et al. [3] report an overall incidence of AVB of 7.7% and a 4.1% incidence of AVB III (2.4% in anterior AMI and 5.7% in inferior AMI).

The above data refer to the pre-thrombolytic period, during which attempts were also made to draw up a risk score for the appearance of AVB III by analyzing the ECGs of AMI patients. This risk is low (1.2%) when conduction defects do not appear in the ECG during the acute phase; it increases to 7.8% if RBBB appears, to 25% in the presence of bifascicular block (including LBBB) and to 36.4% when AVB I or II is associated to bifascicular block [4].

It was also observed that Mobitz 1 constitutes 90% of cases of AVB II, is nearly always transient, disappearing within the first 72 hours, is often intermittent and rarely progresses to AVB III. By contrast, Mobitz 2, which is of subhisian origin, is accompanied by a wide QRS complex and often progresses to AVB III [1].

Studies carried out after the advent of thrombolysis show a 5.3% overall inci-

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dence of AVB III, which is higher in inferior AMI (10.4%) than in anterior AMI (2.0%) [5]. This is the same incidence as was seen in the previous studies and reveals no significant difference between thrombolysis-treated patients and controls (5.0% vs 5.7%) [6, 7]. There is, however, a lower incidence of AVB III in non-Q AMI (2.0%) [8] than in all the other cases (5.7%), and in inferior AMI without elevated ST in V4R (2%), which is indicative of extension to the RV, when compared with inferior AMI with elevated ST in V4R (9%) [9].

AVB I and Mobitz 1 do not influence prognosis. AVB III in inferior AMI almost always results from AVB I-II, and the accompanying 15% mortality rate doubles if there is RV involvement. In anterior AMI, AVB III is of sudden onset or stems from Mobitz 2; it is associated with extensive infarcts and has a very high mortality rate (70%-80%) [1].

In Constans' study [3], which dates from the pre-thrombolytic period, all conduction disorders, whether A-V or ventricular, were included in the assessment of mortality. In the acute phase (first 3 weeks) of anterior AMI, mortality rates were 32% and 22%, respectively, in the presence and absence of conduction disorders. In inferior AMI, however, there was no significant difference (11% vs 10%). In the late phase (24-78 months) of anterior AMI, the respective mortality rates were 40% and 20%, while in inferior AMI mortality was again unchanged (30% vs 30%). While this study confirms that mortality is lower in inferior AMI than in anterior AMI, it does not enable us to distinguish between the risk engendered by A-V blocks and that engendered by ventricular blocks. Consequently, the mortality reported by Constans [3] in anterior AMI with AVB III is lower than that reported in the other studies, and no prognostic difference emerges between inferior AMIs with and without AVB III.

The large-scale trials carried out on thrombolytic therapy not only enabled the influence of this treatment on mortality to be evaluated, but also yielded data on a very large number of patients, therefore providing better statistical significance. The GISSI study [5], which assessed mortality in the acute phase (first 15 days following the onset of pain) in patients with or without AVB III, recorded mortality rates of 21.1% and 8.1% respectively ($p = 0.001$) for the whole population; in patients with inferior infarction, the values were 12.8% and 4.5% ($p = 0.001$), while for anterior infarction the rates were 58.5% and 12.3% ($p = 0.0001$). The six-month mortality rate proved to be low and was not significantly different in patients with AVB III (4.0%) and those without (3.5%). The GUSTO study [10] considered AVB II and III together (mortality 8.5%) and recorded a significant difference between patients treated with t-PA + heparin (7.3%) and those treated with SK + heparin (9.1%). The ISIS-4 study [11] reported a 3.8% incidence of AVB II and III, which was significantly higher ($2p = 0.001$) in patients treated with ACE-inhibitors (4.1%) than in controls (3.5%) right from the first days of treatment.

The results of these large-scale studies seem to show that mortality in the acute phase of all types of AMI complicated by AVB III is lower than previously reported, though the clear-cut difference between anterior and inferior localizations is maintained. During the subsequent follow-up, mortality declines and

shows no significant difference between the two types of infarction. It is difficult to interpret the results of the GUSTO and ISIS studies with regard to the roles of the different thrombolytic agents and ACE-inhibitors.

Another interesting study was carried out by Mavric at al. [12], who evaluated the prognostic significance of AVB III in inferior AMI with or without RV involvement. From their analysis of the various hemodynamic, electrocardiographic and laboratory parameters, these authors conclude that in inferior AMI:

1. AVB III only has prognostic significance if there is RV involvement (mortality 41% vs 14% without RV involvement);
2. there is no significant difference in mortality between patients with and without RV involvement when AVB III is absent (14% vs 11%);
3. the high rate of mortality among patients with inferior AMI involving the RV and with AVB III seems to be the result of the greater magnitude of the infarction, though the influence of RV dysfunction and A-V dissociation cannot be ruled out.

There are two further studies which deal with the question of inferior AMI with or without RV involvement. Zehender et al. [9] examined 200 cases, 107 (54%) with elevated ST in V4R and 93 (46%) without; AVB III was present in 18 (16.8%) of the first group but only in 4 (4.3%) of the second. Mortality, cardiogenic shock and pacemaker implantation were also much more frequent in patients with RV involvement. Among 116 consecutive cases of inferior AMI, Bassan et al. [13] observed 23 cases of AVB (6 AVB II, 17 AVB III) and 27 cases of RV involvement. On analyzing the clinical and hemodynamic data, they concluded that:

1. in inferior AMI with RV involvement, AVB is for to five times more frequent (48%) than in isolated inferior AMI (11%);
2. RV involvement via the Bezold-Jarisch reflex is probably responsible for many AVBs in inferior AMI;
3. the hypotension commonly observed in these patients with AVB is often due to RV dysfunction and to increased vagal tone, rather than to insufficiency of the LV;
4. late AVB (linked to ischemia) is responsible for the higher mortality rate during hospitalization among patients with inferior AMI complicated by AVB.

These results and their interpretation seem to corroborate those of Mavric et al. [12], who maintained that prognosis is fundamentally linked to AVB associated to RV involvement, rather than to RV involvement *per se*.

Another much-debated question regarding inferior AMI is that of the appearance of depressed ST on the anterior leads. Peterson et al. [14] reassessed the thrombolysis-treated patients from the GUSTO-1 study by dividing them into four groups (without ST depression, with ST depression from V1 to V3, from V4 to V6, and from V1 to V6). These authors found that AVB II-III was significantly more frequent ($p < 0.05$) in the group with ST depression from V1 to V6. In these patients, moreover, 30-day and 1-year mortality was higher and cardiac insufficiency, cardiogenic shock and the appearance of VT and/or VF were more frequent.

Finally, regarding the need for cardiac pacemaker implantation in patients

with AVB during AMI, we should mention the "final report" of three comparative studies which considered both pre-thrombolytic and post-thrombolytic results, the latter also prospectively. No significant difference was observed with regard to definitive pacemaker implantation in the various groups, while the incidence of temporary implantation proved to be significantly lower in the thrombolysis-treated patients with inferior AMI than in the non-thrombolysis-treated (p = 0.008) [15].

Bundle Branch Blocks or Ventricular Activation Delays

In the days before thrombolysis, overall incidences of 5% to 10% (about 50% pre-existing) were reported for these conduction disorders: RBBB 2%, LBBB 5%, AFB 3%-5%, PFB 1%-2%, bifascicular B 4.9%. Opolski et al. [2] found: RBBB 2.8%, LBBB 3.6%, AFB 2.8%, and bifascicular B 4.4%. Constans et al. [3] reported lower values of BBB (2.1%), of which LBBB was only 0.2%.

The multicenter study carried out by Hindman et al. [16] examined almost 500 cases of AMI with BBB (anterior AMI 63%, inferior 18%, undetermined 18%, lateral 1%), subdivided into the following types: LBBB 38%, RBBB 11% bifascicular B 44% and alternating B 6%.

The GISSI study [6], the first large-scale trial on thrombolysis in AMI, reveals a 5.6% incidence of BBB, with no significant difference between thrombolysis-treated patients and controls. The ISIS-2 study [17] reports a very similar incidence of BBB (6%). It is interesting that the studies which followed (GISSI-2 [7] and ISIS-3 [18]) report BBB percentages that are lower (2.8% and 4.1%) by 50% and 30% respectively.

While it is difficult to compare present-day statistics with those of the past, that is to say before the advent of thrombolysis, we believe that, in the light of studies on large populations, such as those on thrombolysis, the incidence of BBB is closer to 5% than to the 10% reported in the earlier studies. Moreover, thrombolysis does not appear to modify this incidence, which is already *per se* very low and regards an event that either arises early or pre-exists. As far as the prognostic significance of BBBs is concerned, it has long been accepted that all ventricular activation delays, except anterior fascicular block, increase both early and late mortality. In addition, all those delays that involve at least two conduction pathways (LBBB, bifascicular B or trifascicular B) also engender a high risk of AVB III [1].

Left ventricular delays also facilitate cardiac insufficiency, especially if the AMI is anterior and is associated to advanced AVB. The one-year mortality rate is higher in LBBB or intermittent block (33%) than in RBBB or bifascicular B (23%) or left monofascicular B (15%). In this last case, mortality is similar to that seen in cases without delays (14%) [16].

Hauer et al. [19] followed up a group of 42 patients with anterior AMI complicated by BBB. In the first six weeks, 24 died of cardiogenic shock or myocardial rupture. Of the 18 survivors (11 with bifascicular B, 6 with RBBB and 1 with LBBB), 7 suffered potentially lethal complications, but almost all (17 patients)

were long-term survivors. The authors therefore conclude that the critical period in anterior AMI with BBB is represented by the first six weeks. While these data refer to the pre-thrombolytic period, they are nevertheless useful in outlining the features of the clinical problem.

The FTT study [20] analyzed almost 60 000 patients involved in the various thrombolytic trials. This study revealed that patients with BBB, like those with elevated ST, in the early phases of AMI, regardless of age, sex, arterial blood pressure, heart rate, diabetes and previous history of infarction, derive the greater benefit from thrombolytic treatment the earlier it is administered. Indeed, in the 45 000 patients with elevated ST or BBB, a 30/1000 reduction in mortality was observed among patients treated within the first 6 hours, 20/1000 for those treated between 7 and 12 hours, and 10/1000 for those starting treatment after 13 to 18 hours. Moreover, mortality between day 1 and day 35 in patients with BBB proved to be 18.7% among thrombolysis-treated and 23.6% among controls [20].

A specific evaluation of LBBB as a risk factor in AMI emerges from a study by Laji et al. [21] involving 817 patients in whom initial ECG showed elevated ST in 89.4% (82.2% with Q wave), no ST elevation in 8.2% (41.8% with Q wave) and LBBB in 2.4%. In comparison with patients with or without elevated ST, the LBBB group was characterized by a higher rate of mortality in hospital (40% vs 14% and 3% respectively), a lower rate of event-free survival (31% vs 72.9% and 85.6%), a higher rate of cardiac insufficiency (60% vs 29.5% and 13.4%), and also a higher incidence of previous infarctions (75% vs 23% and 37.3%).

Clearly then, even after thrombolytic therapy, patients with BBB, and in particular with LBBB, are subject to significantly higher rates of mortality and cardiovascular complications involving both damage to the pump and destruction of the conductive system.

ECG Diagnosis of AMI in the Presence of Ventricular Delays

It should first be said that the only ventricular activation delay capable of completely masking an infarction even in the acute phase is left ventricular bifascicular delay, i.e. LBBB. In such cases, the inversion of the initial septal activation and the frequent presence of a certain degree of secondary-type elevation of the ST in V1 and V2 deprive the ECG of its diagnostic specificity with regard to AMI. The other types of ventricular activation delay can only partly mask an AMI. A right ventricular delay, i.e. RBBB, involves only the medial-terminal part of the ventricular activation; consequently, it does not prevent the appearance of the pathological Q wave, a phenomenon which concerns the initial and post-initial phase. A superior left delay, i.e. anterior fascicular block or left anterior hemiblock, can partially modify the initial vectors and therefore create a certain diagnostic difficulty in ascertaining or excluding a necrosis. Finally, an inferior left delay, i.e. posterior fascicular block or left posterior hemiblock, may mask or reduce the signs of an inferior necrosis.

The ECG criteria for diagnosing a myocardial infarction in the presence of

LBBB were proposed in the 1950s and 1960s. Over the years, they were subsequently reassessed and modified on the basis of numerous case studies.

The main criteria are as follows:

1. the presence of an abnormal Q wave in D1, aVL or V6 (sensitivity 31%, specificity 91%);
2. the Cabrera-Friedland sign: notching on the ascending branch of S in V2, V3, V4 (sensitivity 27%-47%, specificity 87%);
3. Chapman's sign: notching on the ascending branch of R in D1, aVL, V5 or V6 (sensitivity 21%, specificity 91%);
4. Sodi Pallares's sign: RS in V6 (sensitivity 8%, specificity 91%);
5. elevated ST consensual with QRS in V5-V6, D3-aVF (sensitivity 54%, specificity 97% during AMI).

Other signs, such as positive T in V6, elevated R in V1-V2 or left axial deviation, have proved to be less useful on account of their lower sensitivity and specificity.

The question of the difficulties involved in diagnosing an infarction in the presence of LBBB received scant attention for many years, until a more pressing need arose to administer thrombolytic treatment to a larger number of patients, especially those capable of reaching the coronary care unit within six hours from the onset of symptoms.

The MILIS study in Boston [22], which was already in progress when thrombolytic treatment was introduced, assigned a specificity of 90%-100% and a predictive value of 85%-100% for the diagnosis of previous or acute infarction to the following criteria: Q wave in at least two of the leads D1, aVL, V5, V6; R decreasing from V1 to V4; notching in the ascending branch of S in at least two of the leads V3, V4, V5; primary alterations of ST and T (consensual with the QRS) in at least two contiguous leads.

Angioplasty is able to provoke ischemia during inflation of the balloon. It can therefore be used under epicardiac and thoracic ECG monitoring to reproduce those ischemic alterations which enable the clinical alterations to be better evaluated. This has also been done in the presence of LBBB and has confirmed that the shift in ST is a valid criterion, though with the following specifications: elevated ST in the inferior leads is indicative of ischemia both when it is consensual and when it is opposite to the QRS, while in the lateral leads (D1, aVL, V5, V6) it is indicative only if consensual with the QRS; regarding the anterior locations (V1-V3), elevated ST is indicative of ischemia only when it exceeds 8 mm [23].

These studies mark a shift in the attention of researchers from what may be called stable modifications of the QRS, which are indicative of necrosis, to unstable modifications due to ischemia, still in the presence of LBBB. The reason for this new approach stems from the need to recognize an infarctional ischemia early in order to undertake thrombolytic therapy or revascularization. It was in this context that Sgarbossa et al. [24, 25] carried out their research on 131 patients with AMI plus LBBB from the GUSTO-1 study. The three ECG criteria which showed an independent value in the diagnosis of AMI were:

1) ST elevation $\geq$ 1 mm consensual with the QRS (sensitivity 73%, specificity 92%);

2) ST depression ≥ 1 mm in V1, V2 or V3 (sensitivity 25%, specificity 96%);
3) ST elevation ≥ 5 mm opposed to the QRS (sensitivity 31%, specificity 92%).

When the specificity of these criteria was evaluated on a scale from 0 to 5, a score of 5 was obtained for the first, 3 for the second and 2 for the third.

When these same criteria are applied to patients on ventricular pacing from the right ventricle, fairly similar values of sensitivity and specificity are found [25].

In conclusion, those studies aimed at the early recognition of AMI in the presence of spontaneous or pacemaker-induced LBBB enable the following considerations to be made:

1. ST alterations are of greater utility than QRS alterations in the early diagnosis of AMI in the presence of LBBB;
2. false positives are rare and do not constitute a great problem in the case of inappropriate thrombolytic treatment;
3. since patients with LBBB plus AMI present either proximal involvement of the anterior descending branch (especially when LBBB and AMI arise together) or serious damage of the left ventricle, they could gain greater benefit than other patients from thrombolytic therapy or early revascularization.

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What Is the Usefulness of Ventricular Premature Beats and Ventricular Late Potentials in the Thrombolytic Era?

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Risk evaluation in survivors of a myocardial infarction after the widespread application of thrombolysis has been submitted to extensive reassessment. In particular the prevalence of ventricular arrhythmias and late potentials and their prognostic significance allow a reappraisal of their impact on mortality.

Ventricular Arrhythmias

In the pre-thrombolytic era the prevalence of ventricular arrhythmias (PVBs) has been reported as 86% of patients in the Multicenter Postinfarction Research Group (MPIP) [1] and as 84% in the Placebo Group of the BHAT study [2]. Nonsustained ventricular tachycardias were reported as 19.5% by Cats et al. [3], 8.6%-11.6% by Bigger [4] and 11.3% in the MPIP Study [1]. The occurrence of frequent PVBs (> 10 per hour) was 22.1% for MPIP [1], 14.6% for MILIS [5] and 12.9% for BHAT [2].

In the thrombolytic era Maggioni et al. [6] reported a reduced prevalence of ventricular arrhythmias (64%), of nonsustained ventricular tachycardias (6.8 %) and of patients with more than 10 PVBs/hour (19.7%). Théroux et al. [7] also found a statistically significant lower PVB frequency in patients receiving streptokinase compared to those not submitted to thrombolysis (21 ± 64 vs 40 ± 123 per hour). In contrast Zimmermann et al. [8] found no difference in the rate of polymorphic PVBs, presence of couplets or runs of nonsustained ventricular tachycardias in patients with or without thrombolysis. In addition they did not find a correlation between the patency of infarct related artery and the frequency of PVBs. Pedretti et al. [9] did not find significant differences in PVB frequency or in the proportion of patients with various Lown grades between patients submitted or not submitted to thrombolysis.

Dorian et al. [10] observed a similar PVB frequency in patients submitted to thrombolysis with t-PA or to placebo. Patients with ST depression had greater PVB frequency than those without, while ejection fraction correlated negatively with PVB frequency. These authors demonstrated with multivariate analysis that

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low ejection fraction and presence of ST depression were the only independent predictors of PVB frequency, while thrombolysis was ineffective on PVBs. These data confirm previous results published by Camacho et al. [11] who demonstrated a correlation between silent ischemia and ventricular arrhythmias in post-myocardial infarction patients.

In the study by Marino et al. [12], in patients with acute myocardial infarction (AMI) and submitted to thrombolytic therapy, the number of PVBs per hour was found to depend in a linear, inverse fashion on the residual ventricular ejection fraction, and was independent of the occurrence of reperfusion in the acute phase of infarction. Thus patency of the infarct-related vessel could contribute to reducing post-AMI ventricular arrhythmias by reducing infarct size, which would minimize pump damage. Early reperfusion could reduce areas in which mechanical stress develops and reduce the risk of arrhythmias in patients with increased left ventricular volumes and decreased pump performance.

In conclusion, at the moment there are no conclusive data regarding the effect of thrombolysis on ventricular arrhythmias in post-AMI patients. Early reports showed favorable effects which were not confirmed by subsequent studies. In particular, it seems that only a low ejection fraction and the persistence of myocardial ischemia, demonstrated by coexistence of ST segment depression, are the only independent predictors of PVB frequency.

Late Potentials

Several studies have shown that signal averaged electrocardiography provides important prognostic information in identifying patients who subsequently develop arrhythmic events and sudden death after AMI [13-16]. The presence of late potentials (LP) prior to discharge in survivors of AMI has a good negative predictive accuracy (between 81% and 98%) for developing ventricular tachycardia or sudden death while positive predictive accuracy is very low (8%-48%) [17]. Since LP are rarely influenced by drugs, any intervention leading to their suppression or reduction is expected to reduce the risk of ventricular tachycardia and sudden death in post-AMI patients. It has clearly been demonstrated in many reports that there is a lower prevalence of LP in thrombolytic drug treated patients (range: 5%-24%) compared to those who were treated with conventional therapy (18%-43%) [8, 9, 17-21].

Only in the study by Turitto et al. [22] was no difference found between the two groups. This discrepancy could be explained by the use of 25 Hz high pass filtering in this study, the use of a different thrombolytic agent and by a longer delay between onset of symptoms and thrombolysis.

The mechanism by which thrombolysis reduces the prevalence of LP is unclear. Thrombolysis therapy may reduce ischemia in the border zone of the infarct, change the electrophysiologic properties of surviving cells, influence the remodeling process after AMI [23] and may facilitate local hemorrhage [24]. In many studies the reduction of LP after thrombolysis was demonstrated to be

independent of global left ventricular function and ejection fraction and the favorable effect of treatment was correlated to patency of the infarct-related artery [8, 9, 18].

In the study by Maki et al. [25], the prevalence of LP was directly correlated with the delay between the onset of symptoms and primary PTCA (Table 1).

Table 1. Relationship between frequency of late potentials (LP) and delay between onset of symptoms and PTCA (adapted from [25])

Delay (hours)	LP (%)
< 4	8
4-6	12
6-8	24
8-10	33
> 10	43

In the study by Zimmermann et al. [8], a lower incidence of LP was correlated with a patent infarct-related artery (13% vs 26%). Similar data were reported by Pedretti et al. [9] and Breithardt et al. [26]. Since multivariate analysis showed that the patency or occlusion of the infarct-related coronary artery was the only independent predictor of LP, the occlusion of the infarct-related coronary artery seems to be the most important cause of late potentials independently of the global left ventricular function [8, 9-18]. Late potentials are one of the specific markers of occlusion of the infarct-correlated coronary artery and their detection in a post-AMI patient is a predictor for survival [27].

Regarding the influence of late reperfusion on LP there are no conclusive data. From the report by Vatterott et al. [28], Pedretti et al. [9] and Théroux et al. [7], it can be hypothesized that a late reperfusion has a beneficial effect on LP. Since thrombolysis has deeply modified the evolution of AMI, doubts have been raised about whether LP are still a marker for developing ventricular arrhythmias and sudden death in patients treated with thrombolysis. In the group of 99 patients reported by Pedretti et al. [9] and treated with thrombolysis, LP significantly correlated to late arrhythmic events.

In conclusion, patients with AMI and treated with thrombolysis show a reduced prevalence of LP when compared to patients treated with conventional therapy. Also in the thrombolytic era, LP maintain their characteristic of being a marker for developing ventricular tachycardia and sudden death. In particular, since LP are correlated with the patency of the infarct-linked coronary artery, their detection has great prognostic significance given that an occluded infarct-related coronary artery is crucial from the prognostic point of view.

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What Is the Predictive Value of Heart Rate Variability and Baroreflex Sensitivity?

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In the last two decades several experimental and clinical studies have pointed out the prognostic value of autonomic function in heart disease. Two main techniques have been employed: (1) assessment of tonic control by the analysis of heart rate variability (HRV), (2) assessment of reflex autonomic responses, in particular baroreflexes. In the present chapter, those studies that were critical in the development of the prognostic role of these autonomic tests will be reviewed. Since most of the available information relates to coronary artery disease, data which will be reported here concern patients surviving a recent myocardial infarction. Finally, a large prospective international multicenter trial and its preliminary results will be discussed. This study was specifically designed to provide a definitive answer about the prognostic power of HRV and baroreceptor reflex sensitivity (BRS) after myocardial infarction.

Heart Rate Variability

The first evidence on the clinical relevance of beat-to-beat heart rate variability (HRV) comes from Wolf et al. [1]. In 1978 they recorded a 60-s ECG strip in 176 patients admitted to coronary care unit because of an acute myocardial infarction. The variance of 30 consecutive RR intervals was used as a measure of HRV. This index, that in such a short time measures primarily respiratory sinus arrhythmia, was dichotomized at a value of 1,000 ms^2 (standard deviation – SD – 31.6 ms). Of 176 patients, 103 (59%) had RR variance $\geq$ 1,000 ms^2 and 73 (41%) had RR variance $<$ 1,000 ms^2. The authors showed that patients with low HRV were more likely to have anterior myocardial infarction and poor hemodynamic status. Moreover, the relative risk of in-hospital death was 3.8 in patients with RR variance $<$ 1,000 ms^2 compared to patients without (15.5% vs 4.1%). The significant association be-tween short-term prognosis and RR variance was maintained after adjustment for heart rate and infarct location; other risk predictors, i.e. left ventricular function, ventricular arrhythmias and myocardial ischemia, were not considered.

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Using 24-hour Holter recordings, Myers et al. [2] analyzed differences in time and frequency domain measures of HRV among 3 groups of 6 subjects each, as follows: (1) normal subjects, (2) patients with heart disease and non-sustained ventricular arrhythmias but who did not have inducible ventricular tachycardia at programmed stimulation, (3) patients with resuscitated ventricular fibrillation. Results showed that time (number of RR interval increases > 50 ms [NN50+]) and frequency domain (high-frequency [HF] power spectral component [0.35 to 0.50 Hz and 0.15 to 0.35 Hz bands]) measures were associated with occurrence of non-fatal cardiac arrest. Despite the fact that the association between HF component of HRV, which reflect respiratory sinus arrhythmia, has not been confirmed in studies where mortality was the endpoint, this study was important in calling attention to the prognostic significance of the average power spectral values recorded over the course of a day by a 24-hour ECG monitoring.

In 1987 Kleiger et al. [3] reported results of the HRV substudy in a multicenter trial aimed to assess the natural history of myocardial infarction (the Multicenter Post-Myocardial Infarction Program [MPIP]). Of 820 patients who had Holter ECG recordings performed 11 ± 3 days after infarction, 808 had tapes suitable for HRV analysis. During the follow-up period 127 deaths occurred. A strong association between the SD of the normal RR intervals (SDNN) and all-cause mortality after myocardial infarction was found; 15.5% of the patients had a SDNN < 50 ms and this subgroup had a mortality rate of 34.4% compared to 12.3% for patients with SDNN ≥ 50 ms. All-cause mortality relative risk of patients with SDNN < 50 ms was 2.8 compared to patients with SDNN ≥ 50 ms and 5.3 compared to patients with SDNN ≥ 100 ms. Patients with depressed SDNN were more likely to be older and with low left ventricular function. However, after adjustment for other risk predictors (age, NYHA functional class, rales in coronary care unit, left ventricular ejection fraction, and ventricular arrhythmias) SDNN was still significantly related to 4-year all-cause mortality.

To understand the contribution of autonomic nervous activity to the prediction of all-cause and cause-specific (cardiac and arrhythmic) death and to evaluate the prognostic power of different time domain measures of HRV, in two different studies Bigger et al. [4, 5] reanalyzed 24-hour ECG recordings from 715 patients enrolled in the MPIP. During the follow-up period 119 deaths occurred, of these 88 were cardiac and 68 arrhythmic. Each time and frequency domain measure of HRV had a significant and at least a moderately strong univariate association with all cause, cardiac and arrhythmic mortality. However, after adjustment in a Cox regression model for several covariates (age, NYHA functional class, rales in coronary care unit, left ventricular ejection fraction, and ventricular arrhythmias), ultra low and very low frequency (LF) power were still strongly and significantly associated with death [4]. It is interesting to note that very LF power was more strongly associated to arrhythmic death than to other death modalities, before and after covariate adjustment. Among time-domain measures of HRV, SDNN index (i.e. the mean of the SDs of all normal RR intervals for all 5-minute segments of a 24-hour ECG recording), and SDANN index (i.e. the SD of the average normal RR intervals for all 5-minute segments of a 24-hour ECG recording), were still signifi-

cantly associated with mortality after adjustment with covariates. Specifically, patients with a SDANN index < 40 ms had a relative risk of death of 3.8. In one of these two papers, Bigger et al. [5] also studied the correlations between the most commonly used time and frequency domain measures of HRV. Among time and frequency domain variables three clusters were found: (1) SDNN, SDANN index, total power, and ultra LF power, (2) very LF power, LF power, and SDNN index, and (3) HF power, root of mean square successive difference (RMSSD), and proportion of differences in normal RR intervals > 50 ms. Therefore Bigger et al. showed that slow cyclic variability was a stronger predictor of death in postinfarction patients than HF variability.

The above mentioned studies were important milestones in underlining the clinical usefulness of HRV analysis in coronary artery disease. However, these reports referred to populations who suffered from a myocardial infarction before an extensive use of thrombolytic agents and ACE-inhibitors. Two studies apply to current practice: they analyze the prognostic power of a new time domain measure of beat-to-beat variability, i.e. the HRV index, in patients treated in part with thrombolysis (48% and 54%, respectively) [6, 7]. This index, which is dominated by ultra LF cyclic variability, was derived from the frequency distribution of normal RR intervals in a 24-hour ECG recording (the baseline width of triangular interpolation). Holter monitoring tapes were recorded 6 to 7 days after the infarction in the first study [6], and 21 ± 6 days in the second [7]. Late arrhythmic events, i.e. sudden death or sustained non-fatal ventricular tachyarrhythmias, were used as major end-points during the follow-up period. Farrell et al. [6] reported that of 416 patients 24 had an arrhythmic event, Pedretti et al. [7] found that of 303 patients 19 had sudden death or non-fatal malignant ventricular arrhythmias. In both studies, HRV index was significantly lower in patients with arrhythmic events; a low HRV index, i.e. < 20 U and ≤ 29 U, respectively, showed sensitivity from 89% to 92%, specificity from 68% to 77%, positive predictive value from 15% to 17%, and negative predictive value from 77% to 99%. In both studies, HRV was a significant predictor of arrhythmic events in postinfarction patients, independently of the most widely used non-invasive markers of arrhythmic risk: left ventricular ejection fraction, ventricular late potentials and ventricular arrhythmias on Holter monitoring. Moreover, a combined use of HRV and other risk markers identified subgroups of patients with a high risk of subsequent arrhythmic events with good sensitivity and specificity. Farrell et al. [6] showed that ventricular late potentials and depressed HRV index identified patients with subsequent arrhythmic events with a sensitivity of 58%, specificity of 93%, positive predictive value of 33%, and negative predictive value of 93%. Pedretti et al. [7] found that 2 or more variables among low left ventricular ejection fraction, prolonged filtered QRS complex duration on signal-averaged ECG, and depressed HRV, identified patients with subsequent arrhythmic events with a sensitivity of 83%, specificity of 83%, positive predictive value of 25%, and negative predictive value of 99%.

The clinical relevance of HRV as a prognostic marker in the thrombolytic era is further supported by two recent papers which addressed the association

between mortality and HRV in two large multicenter studies, the GISSI-2 and the GUSTO-I [8, 9]. Both studies showed a significant relationship between mortality and HRV measures, even after adjustment with covariates in the multivariate analysis. Zuanetti et al. [8] analyzed 24-hour ECG recordings obtained at discharge in 567 patients treated with recombinant tissue-type plasminogen activator or streptokinase. Three time-domain indexes of HRV were computed: SDNN, RMSSD and NN50+. During the 1000 days of follow-up, 52 patients died, 44 of cardiovascular causes. All measures of HRV were significant independent predictors of total mortality with the following relative risks: NN50+, 3.5; SDNN, 3.0; and RMSSD, 2.8. Advanced age, previous myocardial infarction, Killip class at entry, and use of digitalis were also independent predictors of total mortality; similar data were obtained for cardiovascular mortality. In the GUSTO-I substudy, Singh et al. [9] analyzed HRV in 203 patients, 10 of whom died within the 30th day after the infarction. The authors found that a low LF to HF ratio two days after the infarction was significantly lower in patients who died. When the Cox proportional hazards model was used, the LF to HF ratio had prognostic value independently of ejection fraction, anterior wall myocardial infarction and TIMI grade. A LF to HF ratio ≤ 1.2 had optimal sensitivity of 88%, specificity of 64%, and negative predictive value of 99% for 30-day all-cause mortality. Unfortunately, in this study the power in the ultra and very LF bands was not available, therefore data from Singh et al. may not be compared with results of Bigger et al. However, Singh et al.'s [9] results stimulated interest about the possible use of another frequency domain measure of HRV to predict short-term mortality in thrombolytic-treated patients.

All these studies showed that HRV, as other non-invasive techniques, may be useful to predict short and long-term mortality and electrical instability in patients recovering from a recent myocardial infarction. This clinical application is supported by recently published statements of a Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [10]. However, very few studies have focused on identifying patients with a high risk of specifically arrhythmic or non-arrhythmic death or on distinguishing between arrhythmic and non-arrhythmic death. This topic is of great clinical importance, because these patients may benefit from different modes of treatment [11]. Hartikainen et al. [11] in a recent paper studied 575 patients who were followed-up for 2 years. The aim of the study was to evaluate the relation between HRV, ventricular arrhythmias on Holter monitoring, signal-averaged ECG, left ventricular function and the mechanism of cardiac death in survivors of acute myocardial infarction. The relative risks for arrhythmic or nonarrhythmic death were 7.5 and 8.5 for HRV < 20 U, 2.6 and 2.0 for ventricular late potentials, 2.5 and 8.2 for ventricular ectopic beat frequency >10 per hour, 2.9 and 1.9 for runs of ventricular tachycardia, 1.8 and 6.1 for left ventricular ejection fraction $<$ 40%. A combination of risk factors identified patient groups in which a majority of deaths were either arrhythmic or non-arrhythmic. The study showed that arrhythmic death was associated predominantly with depressed HRV and ventricular tachycardia runs, and non-arrhythmic death with low ejection fraction, ventricular ectopic beats and depressed HRV. Once again, this study supports the

hypothesis that HRV has some specificity for predicting arrhythmic events and sudden death.

The predictive value of HRV has almost exclusively derived from data analyzed from 24-hour Holter recordings; unfortunately, the technical difficulties limit the assessment of HRV from ambulatory 24-hour Holter recordings. Short-term recordings are obviously more practical and cheap in the clinical application of HRV assessment. However few studies addressed a detailed comparison of the predictive values between short- and long-term HRV. In two recent studies, Fei et al. [12] and Adamson et al. [13] found a significant correlation in both time and frequency domain measures between short- and long-term recordings. Bigger et al. [14] reported that spectral HRV from short-term recordings randomly selected from 24-hour Holter ECG strongly predicts postinfarction mortality. However, the predictive power of short-term HRV (positive predictive value up to 31%) seems to be lower than that of long term HRV (positive predictive value up to 41%). Fei et al. [12] analyzed the predictive value of short-term HRV for 1-year total cardiac mortality in 700 consecutive patients after myocardial infarction. All patients underwent 24-hour Holter monitoring 5 to 8 days after myocardial infarction. Short-term HRV was computed as the SDNN from a 5-minute stationary period selected from 24-hour Holter ECG recordings. Long-term HRV was computed as an HRV index over the entire 24 hours. As found by Bigger et al., the positive predictive value of SDNN for 1-year mortality (13% to 18%) was lower than the HRV index (17% to 43%) over a range of sensitivity of 25% to 75%. However, assessment of HRV index in $\geq$ 35% of the patients, preselected by the lowest short-term SDNN, was able to achieve predictive power similar to that of HRV index assessed in all the patients. These data suggest that lower predischarge short-term HRV is associated with increased 1-year total cardiac mortality in patients after myocardial infarction [12]. Thus, analysis of long-term HRV can safely be limited to patients preselected by depressed short-term HRV measures [12]. This approach may provide a cost-effective method of risk stratification.

Baroreceptor Reflex Sensitivity

Several methods are available to measure baroreceptor reflex sensitivity (BRS). However, in most clinically relevant experimental studies and subsequent clinical papers, BRS was evaluated by correlating the blood pressure rise induced by bolus injections of phenylephrine with the consequent beat-to-beat RR interval lengthening, according to the method first described in the 1960s by the Oxford group [15]. BRS was first shown to predict life-threatening ventricular arrhythmias in a conscious canine model [16]. In this model, exercise, which provides a physiologic increase of sympathetic activity, is combined with acute inferior myocardial ischemia in the presence of a healed anterior wall myocardial infarction [17]. During acute ischemia, about half of the dogs develop ventricular fibrillation (susceptible dogs) and the other half do not have malignant arrhythmias (resistant dogs). An important characteristic of this model is the very high repro-

ducibility (90% to 95%) of the outcome, i.e. ventricular fibrillation in susceptible, and survival in resistant, dogs [18]. From the study of this animal model two points of high clinical relevance emerged: (1) BRS was significantly lower after myocardial infarction compared to the preinfarction condition, (2) BRS was significantly lower in susceptible dogs when compared to resistant ones (9.1 ± 6 vs 17.7 ± 6.5 ms/mmHg) [19]. In this large population of 192 dogs with a prior myocardial infarction, the risk of ventricular fibrillation increased from 20%, for dogs with BRS > 15 ms/mmHg, to 91%, for animals with BRS < 9 ms/mmHg [19]. These data provided the experimental background for subsequent clinical studies.

The first clinical study examining the possible prognostic value of BRS in patients having survived a recent myocardial infarction was published in 1988 by La Rovere et al. [20]. In this study BRS was measured using the phenylephrine method in 78 patients 1 month after their first infarction. Patients were followed-up for 2 years and 7 cardiac deaths, 4 of them sudden, were reported. BRS was markedly lower in the 7 patients who died compared to the 71 survivors (2.4 ± 1.5 vs 8.2 ± 4.8 ms/mmHg). Interestingly, patients with BRS < 3 ms/mmHg had a cardiac mortality rate of 50% compared with a 3% mortality rate of patients with BRS ≥ 3 ms/mmHg. Two other important points emerged from this study: (1) there was no correlation between BRS and left ventricular ejection fraction (r = 0.07), (2) among patients with reduced left ventricular function, the prediction of mortality was enhanced by the analysis of BRS: for patients with a left ventricular ejection fraction < 50% mortality increased from 10% (2 of 20) to 50% (3 of 6) if BRS was also < 3 ms/mmHg.

Three subsequent studies provided additional support for the data of La Rovere et al. In 68 patients at day 7-10 after myocardial infarction, Farrell et al. [21] analyzed the relationship between autonomic tone and markers of arrhythmic propensity including programmed ventricular stimulation. In those patients in whom sustained monomorphic ventricular tachycardia was induced, BRS was significantly ($p = 0.001$) reduced (1.8 ± 1.5 vs 7.8 ± 4.5 ms/mmHg) as were HRV ($p = 0.007$) and left ventricular ejection fraction ($p = 0.022$). Among all analyzed markers (including HRV, ventricular late potentials, left ventricular ejection fraction) depressed BRS had the strongest association with the induction of sustained monomorphic ventricular tachycardia (relative risk of 36.28). Moreover, 5 major arrhythmic events occurred during the follow-up period, all of which were correctly identified by a markedly depressed BRS (< 3 ms/mmHg) and inducibility of sustained arrhythmias at electrophysiologic testing. Similar results were found by Pedretti et al. [22] who studied 41 patients at day 15 to 21 after myocardial infarction to evaluate the relationship between BRS and inducibility of sustained monomorphic ventricular tachycardia at electrophysiologic study. Eight patients had positive programmed stimulation, and 7 of them (87%) also had a BRS < 3 ms/mmHg; conversely, of 33 patients without inducible sustained ventricular tachycardia only 3 (9%) had a markedly depressed BRS ($p < 0.01$). Patients were followed-up for 10 ± 3 months and 5 of them developed a late major arrhythmic event. All of these (100%) had inducibility of sustained monomorphic ventricular tachycardia and BRS < 3 ms/mmHg. At multivariate

analysis BRS had the strongest relation with both inducibility of sustained monomorphic ventricular tachycardia, and occurrence of arrhythmic events during the follow-up. Farrell et al. [23] extended their first observation in a second paper which included data on 122 patients with a 1-year follow-up after myocardial infarction. During this period 13 deaths and 10 arrhythmic events occurred: BRS had a relative risk for an arrhythmic event of 23 and it was highest when compared to both HRV and left ventricular ejection fraction.

Therefore, both BRS and HRV appear to be significantly related to occurrence of lethal and life-threatening ventricular arrhythmias after myocardial infarction. Since both tests analyze cardiac autonomic activity, an additional question may be the following: do they provide the same kind of information? A study of Bigger et al. [24] has already shown that this is not the case. A significant relationship exists between BRS and HRV, however the correlation is weak suggesting that in most patients one measure is not able to predict carefully the other. Therefore, BRS and HRV are not redundant measures of cardiac vagal activity. This is not unexpected because HRV quantifies cardiac vagal tone while BRS measures cardiac vagal reflex activity.

Autonomic Tone and Reflexes After Myocardial Infarction (ATRAMI) Study

The papers presented above suggested that assessment of autonomic nervous system may have important implication in prognostic evaluation of patients with coronary artery disease. To provide a definitive answer about the value of different autonomic tests it was necessary to design a specific clinical study. A large multicenter trial, ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) involved over 20 centers in Europe, Asia and North America and investigated the predictive value of HRV, BRS and their combination following myocardial infarction [25].

The study has completed enrolment and results of preliminary analyses have been recently presented. Although a complete and appropriate analysis of the trial will be possible only after publication of extended results, preliminary reports are very encouraging. La Rovere et al. [26] reported cardiac mortality data of 1294 patients below age 80 enrolled in 25 centers and followed-up for 21 ± 8 months. There were 49 cardiac deaths: BRS, HRV (measured as SDNN on 24-hour Holter monitoring), left ventricular ejection fraction and ventricular ectopic beats were significantly different between deceased patients and survivors. At univariate analysis BRS < 3 ms/mmHg and SDNN < 70 ms were significant predictors of mortality: relative risks were 4.7 and 5.6, respectively. The association with mortality still remained significant after adjustment for left ventricular ejection fraction in a Cox model. The combination of impaired BRS or SDNN with low (< 35%) left ventricular ejection fraction increased the relative risks to 13.3 and to 8.3, respectively; positive predictive values of depressed BRS and impaired SDNN increased from 7.8% to 17.6% and from 10.7% to 14.2%. Similar results were found when the relationship between autonomic function and arrhythmic

events was evaluated. ATRAMI investigators [27] reported that during the follow-up period an arrhythmic event (including arrhythmic death, resuscitated cardiac arrest due to ventricular fibrillation and sustained ventricular tachycardia) occurred in 35 patients. Impaired BRS, SDNN and left ventricular ejection fraction < 35% were all significant independent predictors of an arrhythmic event at multivariate analysis, while ventricular ectopic beats > 10/h were not. The relative risks of impaired BRS and SDNN were 2.5 and 2.9, respectively. Combined with low left ventricular ejection fraction the relative risks increased to 9.28 and 3.76, respectively.

Preliminary data presented above support the prognostic power of markers of vagal reflexes and tone after myocardial infarction. Moreover, they show that the combination of BRS or HRV with low left ventricular ejection fraction is a very powerful predictor of cardiac mortality or life-threatening ventricular arrhythmias in myocardial infarction survivors.

Conclusions

Papers above show that assessment of tonic and reflex autonomic control of the heart is feasible and may provide useful prognostic information in patients with coronary artery disease, particularly in those surviving a recent myocardial infarction. Combination of autonomic tests with other techniques substantially improves the positive predictive accuracy for cardiac and arrhythmic mortality over a clinically important range of sensitivity. Moreover, data suggest that autonomic markers have some specificity for predicting arrhythmic events and sudden death. This may be a critical point for the future clinical application of autonomic assessment after myocardial infarction. As reported in a recent "position paper" of the American College of Physicians [28], advances of treatment can affect risk stratification. The proper use of new medications or interventions whose efficacy is specific for a given subset of patients will require that these patients be identified. Autonomic tests could play a critical role in stratification of patients at high risk of arrhythmic death who can receive the maximum benefit from antiarrhythmic interventions.

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Clinical Usefulness of QT Prolongation, QT Dispersion and T-Wave Alternans

X. Viñolas, A. Cabrera and A. Bayés de Luna

Introduction

The prognosis of postmyocardial infarction patients depends especially upon the interaction between ischemia, left ventricular dysfunction and electrical instability. Repolarization parameters (QT interval, QT dispersion and T-wave alternans analysis) are used for noninvasive evaluation of patients prone to ventricular arrhythmias after myocardial infarction. The publication of the results of the MADIT trial makes the development of new techniques for noninvasive risk stratification of arrhythmias even more important, because one of the major limitations to extrapolation of the results in daily clinical practice is the need for an invasive electrophysiological (EP) test to stratify the patients.

QT Prolongation, Dynamics of QT Interval and Prognosis in Ischemic Heart Disease

The relationship between the duration of the QT interval and the presence of malignant ventricular arrhythmias has its maximum expression in the congenital long QT syndrome. Interest in the QT interval also derives from observations that excessive prolongation of the QT interval with group I drugs is associated in some cases with proarrhythmia. In contrast, prolongation of the QT interval by amiodarone, within limits that have not been well established, is considered a good parameter of the drug's effectiveness. All these findings have awakened interest in the relationship between QT and ventricular arrhythmia or sudden cardiac death in heart disease patients especially in post-MI patients.

The QT interval is a simple measurement on the surface ECG so the possibility of finding a relation between this measurement and the presence of malignant ventricular arrhythmias could be very important. However, measurement of the QT interval always has limitations. It is a simple measurement of cardiac repolarization, which is an extremely complex process that is influenced by many factors: presence or absence of underlying organic heart disease, the autonomic ner-

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vous system, circulating catecholamines, electrolytes, drugs (cardiac and noncardiac) and others. Moreover, the QT interval varies with heart rate, being shorter in shorter cycles, an effect that usually is corrected by the Bazett formula [1], which somewhat distorts the results that occur primarily at the upper and lower limits of heart rate.

QT Interval in Surface ECG and Prognosis

As we have already mentioned, it would be very interesting to find a relation between the value of QT (and/or QTc) on the surface ECG and the risk of sudden death or ventricular arrhythmias. Some studies have been conducted [2-9] but the results are discordant. Some of them found that a QT prolongation is an independent factor of prognosis and others did not find this relation.

These discordant results can be due to the important limitations of a single 12-lead surface ECG in evaluating QT interval. First of all, a single measure of QTc simply reflects the state of the autonomic nervous system at a precise moment, and, as we will see later, QT and QTc show a dynamic behaviour with changes over a 24-hour period. Thus a patient with a borderline QT at one moment during the day can show prolongation some hours later. Another factor to be kept in mind is that QT varies with heart rate, and for this reason we must make some kind of correction using different formulas, none of which are exact. Furthermore, heart rate is not the only factor that changes QT; for instance, at the same heart rate isoproterenol infusion shortens the QT interval. Likewise, in patients with VVI pacemakers with a fixed heart rate, the QT interval becomes shorter with exercise. This indicates that the QT interval is influenced by a number of factors, many of them dependent on the autonomic nervous system.

Advantages of the Study of Dynamicity

Therefore, the study of the dynamic behavior and circadian rhythm of the QT interval seems to be more important than a single measurement of QT because the latter reflects multiple interactions. Another important aspect of the study of the dynamics of QT prolongation is that the circadian variations in the QT interval examined in relation to the circadian rhythm of malignant ventricular arrhythmias or sudden death may clarify some of the triggering mechanisms of sudden death.

QT Dynamicity in Postinfarction Patients

In order to test the possible value of dynamic QT behavior in post-MI patients, we first analyzed the value of QT variations in the Holter tapes of postinfarction patients with and without malignant ventricular arrhythmias [10]. At first, manual measurement of the QTc intervals was done by selecting several beats per hour. We found no differences in mean QTc value between postinfarction patients with and without malignant ventricular arrhythmias. However, patients

with malignant ventricular arrhythmias during follow-up had QTc peaks > 500 ms more frequently than patients without these arrhythmic complications. Manual measurement is very time consuming and therefore not applicable to large series of patients. Another limitation is that manual measurement does not provide information about the transient subtle changes of QT, because it only analyzes some beats per hour.

Due to these limitations we developed an algorithm for automatic measurement of QT interval in Holter tapes [11]. The mathematical algorithm for automatic measurement of the QT interval has been described in detail elsewhere [11]. The next step was to validate the algorithm. This was done by comparing the results obtained from manual measurements by two cardiologists on recordings printed at 25 mm/s with the results obtained by automatic analysis [11]. An analysis was made of 650 beats on 18 different tapes. The mean error between the manual and automatic measurements was 2.4 ± 17 ms and 2 ± 14 ms and the difference between the manual measurement by the two experts was 1.9 ± 10 ms. Therefore, the differences between automatic and manual measurements were similar to those of manual measurements by two experts. Although mean differences are small the high standard deviation reflects the observer variability of measurements. This validated the use of this method for analysis of larger patient groups and, above all, the analysis of all QT values, which cannot be done manually. Automatic measurement is the only valid means of evaluating transitory changes in the value of QT intervals, and thus analysing "peaks" of QT.

Using this algorithm [12], we recently published the results of automatic measurement. We studied two groups of postinfarction patients (with and without malignant ventricular arrhythmias) in a case control study. The clinical characteristics are summarized in Table 1. There were no significant differences in the clinical characteristics of the two groups of patients. It is important to emphasize

Table 1. Clinical characteristics of postmyocardial infarction patients with and without life-threatening arrhythmias

	Group I[a] ($n = 14$)	Group II[b] ($n = 28$)	p value
Sex (M/F)	12/2	25/3	NS
Age (years)	59 ± 13	57 ± 10	NS
Anterior MI	9 (64%)	16 (57%)	NS
LV ejection fraction (%)	40 ± 6	44 ± 8	NS
LV ejection fraction < 40%	6 (42%)	13 (46%)	NS
Angina	3 (21%)	7 (25%)	NS
Diabetes Mellitus	3 (21%)	8 (28%)	NS
Hypertension	8 (57%)	15 (53%)	NS

MI, myocardial infarction; NS, not significant
[a]Postmyocardial infarction patients with secondary life-threatening arrhythmia
[b]Postmyocardial infarction patients without life-threatening arrhythmias

that we analyzed the results based on a QT interval reaching the end of the T wave. Other authors use a QT interval ending at the peak of the T wave (peak QT) because it is considered simpler and more stable. However, with use of peak QT values part of the information gets lost because QT may be prolonged exclusively at the expense of the terminal parts of the T wave. Later, the QT interval was corrected using the Bazett formula [1], which is simple and used in spite of its limitations. Other formulas could have been used but none of these is accepted universally and all have limitations so we used the most widely accepted correction method. Data from the various QTc intervals could be represented as a trend that allowed exact assessment of the behavior of the QTc interval throughout the day in a practical form.

We analyzed mean QTc values, "peaks" of QTc (QTc values above a certain value), and clusters (groups of peak QT values lasting more that 1 min). The mean QTc interval was longer in patients with malignant ventricular arrhythmias than in patients without these arrhythmias: 425 ± 20 ms vs 408 ± 19 ms (Table 2).

Table 2. Automatic QTc analysis in the three studied groups

Groups	Group I[a] ($n = 14$)	Group II[b] ($n = 28$)	Group III[c] ($n = 10$)	p value I vs II	p value I vs III
Total of beats automatically analysed	682,960	1,276,498	563,910	NS	NS
Global QTc	425 ± 15	408 ± 19	402 ± 20	< 0.005	< 0.001
Total number of peaks of QTc > 500 ms	11,114 (1.62%)	823 (0.06%)	0 (0%)	< 0.005	< 0.005
Patients with peaks of QTc > 500 ms	7 (50%)	2 (7%)	none	< 0.005	< 0.03
Patients with clusters of peaks of QTc > 500 ms	4 (28%)	none	none	< 0.02	< 0.02

[a]Postmyocardial infarction patients who presented a secondary life-threatening arrhythmia
[b]Postmyocardial infarction patients who did non present life-threatening arrhythmias
[c]Healthy subjects

The behavior of the QT interval in relation to time of day is shown in Figure 1. The data in Figure 1 confirm the tendency toward longer QTc values from 11 p.m. to 11 a.m. than from 11 a.m. to 11 p.m.(430 ± 18 ms vs 425 ± 19 ms). These differences were not statistically significant, perhaps because of the small sample size, but they suggested a trend and concurred with findings in healthy subjects.

QT Peaks. QT peaks were analyzed for different cut-off points: > 440, > 460, > 480, and > 500 ms. Statistically significant differences were found only when

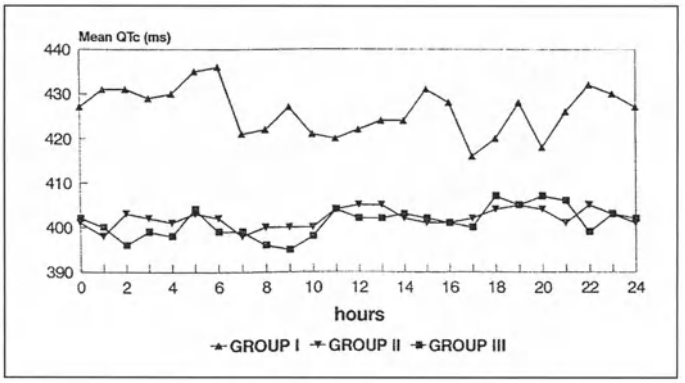

Fig. 1. Plot of the mean hourly QTc interval of the postmyocardial infarction patients with (Group I, ▲) and without (Group II, ▼) life-threatening ventricular arrhythmias and healthy subjects (Group III, ■). Note that patients who developed life-threatening ventricular arrhythmias presented a longer QTc over 24 h than postmyocardial infarction patients who did not present with life-threatening arrhythmias

the group of patients with interval values above 500 ms were analysed (Table 3). Fifty percent of the postinfarction patients who had malignant ventricular arrhythmias had QT values over 500 ms as compared with only 7% (2 of 28) of postinfarction patients who did not have malignant ventricular arrhythmias. None of the healthy subjects analyzed had peak QTc over 500 ms. When we examined the presence of clusters, we found that none of the postinfarction patients without malignant ventricular arrhythmias had clusters but 28% of the postinfarction patients with malignant ventricular arrhythmias did (Table 2). When the number of beats with QTc > 500 ms was analyzed, postinfarction patients with malignant ventricular arrhythmias had long QTc in 1.62% of beats compared with only 0.06% of beats in postinfarction patients without malignant ventricular arrhythmia.

Circadian Rhythm of Peaks. QTc peaks > 500 ms exhibited a circadian rhythm, the percentage of QT peaks per hour being higher between 11 p.m. and 11 a.m. than during the rest of the day. This finding coincides with hourly mean QTc values, which were longer during the same hours of the day. The QTc clusters also

Table 3. Patients with peaks of QTc lengthening measured automatically in Holter recordings according to a determinated cut-off of QTc value

Peaks of QTc interval (ms)	Group I[a] ($n = 14$)	Group II[b] ($n = 28$)	p value
> 500	14 (100%)	20 (71%)	NS
> 460	10 (71%)	14 (50%)	NS
> 480	7 (50%)	8 (28%)	NS
> 500	7 (50%)	2 (7%)	< 0.005

[a]Postmyocardial infarction patients who presented a secondary life-threatening arrhythmia
[b]Postmyocardial infarction patients who did not present life-threatening arrhythmias

demonstrated circadian behavior, with a higher incidence between 11 p.m. and 11 a.m. If we analyze the total duration of QTc clusters, which also occurred at a periods in which patients are at "higher risk", QTc duration was longer in the same hours. The mean duration of clusters from 11 p.m. to 11 a.m., was 10.60 ± 9.64 min, and from 11 a.m. to 11 p.m. it was 2.85 ± 1.95 min. However, this behavior does not indicate whether the QT interval was a triggering factor in malignant ventricular arrhythmias or only an accompanying event.

The behavior of the QT/QTc interval varied throughout the day in postinfarction patients with malignant ventricular arrhythmias: there was a longer mean QTc/h, a larger number of QTc values > 500 ms in absolute terms and as a percentage of beats, and more frequent and prolonged QTc clusters in the period between 11 p.m. and 11 a.m.

Algra et al. [13] recently published the report of a study in which QTc interval was analyzed automatically on Holter tapes. Here, prolongation of the QTc interval to more than 440 ms doubled the patients' risk of sudden death. Moreover, the presence of a short QTc interval (< 400 ms) was also predictive of arrhythmic complications during follow-up. However, Algra's study is not entirely comparable to ours because only 50% of their very heterogeneous group of patients were postinfarction and many of them were taking drugs that can modify QT interval. The rate of occurrence of sudden death and malignant ventricular arrhythmias is greater between 6 a.m. and noon. Although this fact may show a link between these two factors, it does not demonstrate a cause-effect relationship. Prolongation of the QT interval may only be a marker of malignant ventricular arrhythmias but not a trigger. Although some isolated cases have been described, we have been unable to confirm in our review, that a sudden prolongation of QTc is the triggering mechanism of sudden death and not only a manifestation of an underlying mechanism.

As noted, the QT interval is influenced by sympathetic/parasympathetic tone. The QT and the RR interval also varies with sympathetic or parasympathetic stimulation. Variations in the QT interval may coincide with disturbances in the autonomic nervous system that may trigger malignant ventricular arrhythmias.

Conclusions

1. There are different algorithms that have been validated so we now have the possibility to measure automatically the QT interval (QT,RT, JT, QT apex, etc) corrected by heart rate.
2. Although these algorithms have some limitations their usefulness for studying the dynamic behavior of QT and stratify risk in postinfarction patients has already been proved.
3. Nevertheless it is necessary to compare these different algorithms in different subset of patients before arriving at a final statement, and in large scale trials in order to find their definitive clinical value in risk stratification, and to standardize the different measures.

QT Dispersion

Day et al. in 1990 [14] introduced the concept of QT dispersion measured in 12-lead ECG recordings. The dispersion of QT interval was defined as the difference of maximum and minimum QT interval measured. The hypothesis is that QT dispersion reflects a heterogeneity of repolarization, that is differences in recovery times through different zones of the heart. Since it is a very simple measure it has attracted considerable interest and has been applied to different subsets of patients: normal, post-myocardial infarction, long QT syndrome, diabetics, etc. We will limit our presentation to the possible clinical value and its limitations, especially in the risk stratification of postinfarction patients.

Regarding the prognostic value of QT dispersion studies reporting the usefulness [15-19] or not [20-22] of its measure in different subset of patients has been reported. This implies that no definitive answer regarding its clinical application can be provided at present. This is surely due to some problems with the technique. The first question we should try to answer is if QT interval dispersion in surface ECG really reflects a heterogeneous repolarization recovery. Using monophasic action potential recording, evidence exists that QT can reflect the action potential duration (thus also repolarization duration). A further step has been to consider then that QT dispersion should reflect the dispersion of repolarization times through myocardium [23, 24]. Theoretically this can be true but some limitations of the technique still exist.

Several methodological problems are still not solved, and the measurements are not standardized. The accuracy of the QT interval depends essentially on the accuracy of QT measurements. It has been demonstrated that variability of QT interval measurements from standard ECG is around 10 to 20 ms depending on the methodology used (digitized ECG or manual measurement), paper speed (error decreases when higher speeds are used), number of leads, etc. Obviously if single lead QT measurement has a certain inter- and intra-observer variability, this variability will be reflected in the QT dispersion measurement. Kautzner et al. [25] nicely demonstrated the low inter-observer and day to day reproducibility of QT dispersion measurements (differences higher than 20%). This is an important limitation in order to find clinical applications, because this high variability makes the definition of cut-off values difficult. Probably the "best" method in order to reduce the observer variability is to use a paper speed of 50mm/sec, calibrated at 2 cm/mv and a mean of 3 to 5 beats [26].

Several measurements are possible, and not one is yet standardised. QT dispersion can be reflected as range, standard deviation, QT dispersion corrected by the leads measured, etc. Some authors present QT dispersion and others correct the measure with heart rate (QTc dispersion). The Bazett formula is quite useful for correcting QT values in the range of 60-100 bpm, thus for the usual values in surface ECG recording. The main concern with QTc dispersion is that although it is well demonstrated that the QT value is strongly related to heart rate, the relation of QT dispersion to heart rate is only a non-tested hypothesis. If QTc dispersion is used, the heart rate at the time of recording should probably be quoted.

It is well known that sometimes the end of the T wave is not easily seen. In some studies the leads where QT cannot be measured are excluded and then a "corrected QT dispersion" depending on the leads measured is presented. Although this can seem logical, errors can be introduced using this system, because QT dispersion can be underestimated.

Some studies uses simultaneous 12-lead ECG recordings. This is probably the best method, but several others use 3-channel ECG recording. In this case, the non-simultaneous recording can also introduce some measurement errors.

Sometimes, the beginning of QRS is not easy to determine specially when small q wave is present. As the T wave end is also sometimes difficult to define precisely, some authors replace QT interval measurement with the RT apex interval measurement. In stable conditions it is true that the correlation between RT apex and QT interval is strong, and it is also true that this simplifies the method, but we can lose some important physiological information. The terminal part of T corresponds to the phase III action potential. We know that early after depolarizations are seen in this phase [27]. Thus arrhythmogenic information can be lost.

All these technical problems could explain the very different results reported in the literature. Normal values are not yet established. The average normal value was less or equal to 40 ms in several studies [15, 16, 19, 28-37] but other studies showed a dispersion greater than 40 ms in the same population [38-43]. In the later studies QT dispersion is as high as 50 and 70 ms [43]. These highly variable normal values are a limitation in the practical application of QT dispersion, because a cut-off value is difficult to define. A cut-off value of QT dispersion greater than 65 ms separates patients at risk quite well from normal subjects. The mean value of QT dispersion is usually higher in patients with arrhythmic events after a myocardial infarction than in normal subjects or in healthy subjects, but the overlap is too high at the present time. The sensitivity and specificity of abnormal QT dispersion is difficult to assess in the absence of a standardized methodology, and this explains why we can find studies that confirm and deny the prognostic value of a QT dispersion > 65 ms. The committee for proprietary medicinal products is indicating at present that a QT dispersion > 100 ms after any intervention (drug) or an increase of 100% of baseline value should be considered as pathological, and should raise concern about the potential risk of torsade de pointe [26].

Another very important question to be answered is whether QT dispersion represents a unique or a redundant prognostic marker for ventricular arrhythmias. The lack of large, well-designed studies with logistic regression analysis makes it possible to confirm if QT dispersion is an independent marker compared to left ventricular ejection fraction, late potentials, heart rate variability, etc.

T-Wave Alternans

Measurement of T-wave alternans is another promising non-invasive way to disclose cardiac electrical instability and heterogeneity in ventricular repolarization

to predict life-threatening ventricular arrhythmias. Formerly, T-wave alternans was considered as a qualitative rather than a quantitative variable, as its recognition was based on the visual inspection of the ECG. However at present, methods for evaluating this phenomenon at the microvolt level make it possible to quantify the phenomenon and to use it as a continuous variable, identifying its presence in subjects where, in the surface ECG, the phenomenon is visually undetected [44]. T-wave alternans, a distinctive concept [45], has been defined as changes in T wave without changes in P wave or QRS complex. More recently, T-wave alternans has been considered more precisely to be the variability of the T wave of the electrocardiogram ECG in terms of beat-to-beat shifts in amplitude, polarity and duration of the wave; this concept therefore implies a temporal dispersion. Although electrical alternans is occasionally visible, it usually requires high amplification to be detected since the ECG signal is obtained from amplified, digitized leads. Some authors have found that in surface ECG, the V5 is best lead to detect this phenomenon [46] while others use orthogonal X, Y, Z [19].

The analysis of T-wave alternans is more complex than the QT dispersion. It has been performed either in the time or the frequency domain. Up to now there has been a lack of a standardized procedure for the assessment of the T-wave alternans. Methods applied at present include the Fast Fourier Transformation (FFT) of the ECG signal assuming that the T-wave is a low frequency sinusoidal wave of fixed [47-49] or variable [46, 50, 51] amplitude and phase. Other authors employ methods of high frequency sampling (1 KHz) of the orthogonal ECG, calculating the amplitude of the T-wave on a beat-to-beat fashion; the amplitude of T-wave in each lead is obtained and from these values a specific T-wave alternans dimensional index is derived [52]. Mathematical difficulties with FFT applications include the measurement of signals under non-stationary conditions as usually occur during mental or physical stress, or the activation of internal neurohumoral triggers. Nevertheless, Verrier et al. [53] have found that their method (complex demodulation) is more transient tolerant. As a consequence of the absence of a standardized method, T-wave alternans is currently expressed in different units as microvolts, microvolts.ms or adimensional units.

The accumulated evidence indicates that T-wave alternans is dependent on local ischemic transmembrane alterations at the compromised ischemic area rather than on impairment of the activation [54]. A substrate of the repolarization alternans has been obtained in intracellular recordings of transmembrane action potentials, where alternations in the repolarization phases 2 or 3 of the action potential are observed with minimal or no alterations in phase 0. Delayed recovery of the calcium inward current, the transient potassium outward current and different intracellular calcium handling have been proposed as electrophysiological mechanisms at the cell membrane level.

Several reports indicate that visible T-wave alternans appears during attacks of variant angina [55-58], but the impact of T-wave alternans in the clinical setting has been evaluated in several types of designs as the provocation of ischemic episodes in humans and experimental animals and testing the magnitude of T-wave alternans. Nearing et al. [51] correlated the amplitude of T-wave alternans

with the sum of episodes of ventricular tachycardia (VT) and fibrillation (VF) both in human (during angioplasty) and dogs (during coronary occlusions) and found a high and significant correlation between these variables (but not ST segment) either during occlusion or reperfusion. From these experiments it was possible to reveal that T-wave alternans were only recorded in the epicardial compromised areas but not in the normal zones. This means that this phenomenon shows a spatial dispersion. From these results it was possible to predict the appearance of VT or VF with a sensitivity of 78% and a specificity of 86% (Fig. 2).

The most important clinical report at this time has been made by Rosenbaum et al. [48]. In their study of 83 patients submitted to atrial pacing, they were able to provoke ventricular arrhythmias in 39% of the group. They found that ST-T

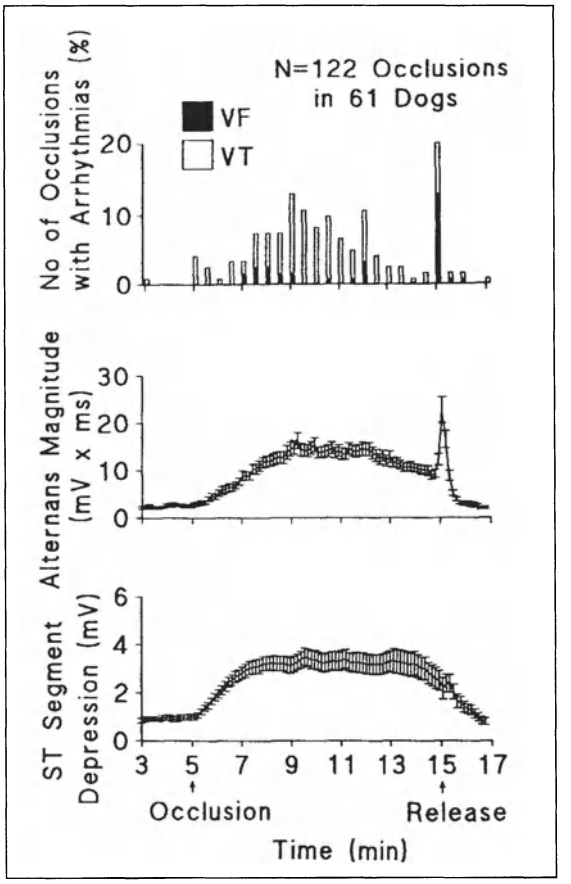

Fig. 2. Simultaneous time course of spontaneous ventricular fibrillation (VF) and tachycardia (VT), T-wave alternans, and ST segment depression occurring 10 minutes of left anterior descending coronary artery occlusion and reperfusion in 61 anesthetized dogs monitored with a left ventricular (LV) ECG catheter. Two occlusion release sequences were performed in each dog. Incidence of spontaneous VT and VF was summed for each 30 s period. T-wave alternans and ST segment changes were summed for each 10 ms interval

alternans predicted ventricular arrhythmic episodes with 81% sensitivity and 84% specificity, figures resembling those of Nearing et al. [52]. In a prospective study, a Kaplan-Meier life-table analysis showed that 20 months later, actuarial survival of T-wave alternans patients without arrhythmias was 19%, significantly lower than those without T-wave alternans (94%) (Fig. 3). This seems to indicate a good correlation between findings of EP study and T-wave alternans. At present no large scale prospective trial results are available in order to know its real clinical prognostic value.

It has also been shown that long QT syndrome patients with T-wave alternans are at higher risk of arrhythmic events [58].

In conclusion, in agreement with what has been recently pointed out by others [59], despite the existing clinical and experimental evidence indicating that T-wave alternans measurement could be an important tool for evaluating patients at risk of malignant arrhythmias, several limitations need to be removed before a reliable predictive value of the method can be established; they are mainly related to the methods applied in the clinical setting, including the most suitable ECG leads and the selection of the most adequate mathematical models before frontiers of normality can be instituted.

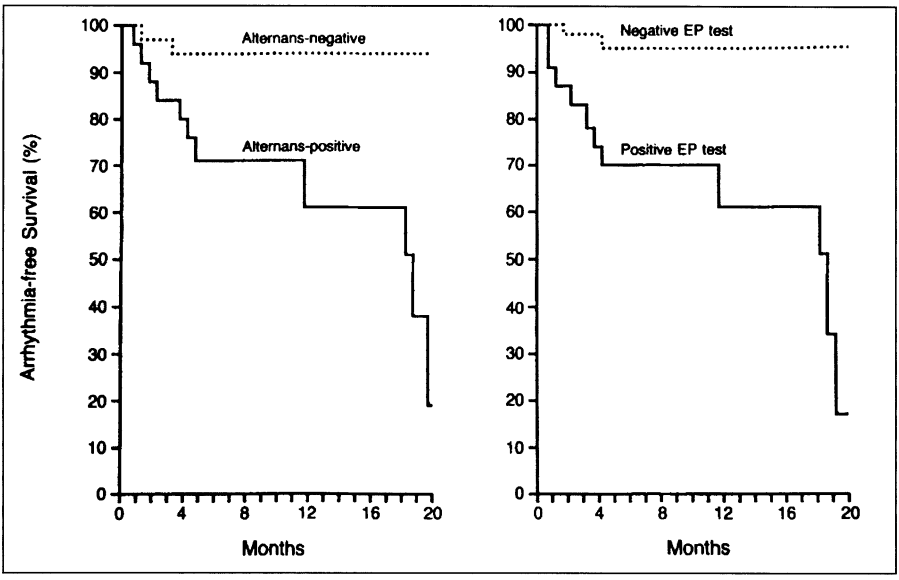

Fig. 3. T-wave alternans and EP study result and survival during follow-up Rosembaum et al [51]. Note the close correlation between the survival curves of T-wave alternans and results of EP study

Conclusions

Analysis of repolarization parameters gives us important clinical information. Several clinical studies have shown differences between normal subjects and patients with different cardiac diseases. But none of them has yet passed the rigorous test of sensitivity, specificity and prognostic value, especially the value as an independent prognostic test in comparison with other already established parameters.

A standardization of the three techniques is needed, and afterwards large trials comparing their prognostic value should be carried out before a definitive answer can be given.

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Risk Stratification after Acute Myocardial Infarction: What Is the Usefulness of Programmed Ventricular Stimulation ?

M. Zoni-Berisso and D. Silvestri

In the first year following acute myocardial infarction (AMI), sudden death, generally due to ventricular tachyarrhythmias [1, 2], and spontaneous sustained ventricular tachycardia (SVT) occur in 3%-5% of patients discharged from the hospital. In addition, in this setting, sudden death represents approximately one half of all cardiac deaths [3-5]. Therefore, it is evident that an early and accurate identification of patients at risk of such arrhythmic events is highly desirable. This capability would allow therapeutic intervention to be limited to selected patients only.

In the past, numerous noninvasive procedures have been utilized singly or in combination to predict sudden death and life-threatening ventricular arrhythmias in post-AMI patients. Unfortunately, their predictive accuracy cannot be considered quite satisfactory because of lack in sensitivity or specificity [3-8]. More recently, programmed ventricular stimulation has shown to be an interesting and promising technique in the risk stratification for arrhythmic events. This is due to its ability to induce ventricular tachyarrhythmias of potential predictive value [9-16]. The rationale underlying the use of programmed ventricular stimulation as an indicator of prognosis after AMI is the following: 1) in the border zone of the infarction scar, anatomical reentrant circuits may develop as a consequence of the presence of areas of unidirectional block and slow conduction; 2) spontaneous ventricular ectopic beats, if appropriately sited and timed, may induce sustained reentrant ventricular tachyarrhythmias; 3) in the presence of a reentrant circuit, programmed ventricular stimulation may initiate sustained arrhythmias; 4) inducible ventricular tachyarrhythmias might be an accurate indicator of prognosis.

In the present review the prognostic value of inducible ventricular arrhythmias in post-AMI patients, and the indications and timings of programmed ventricular stimulation are discussed.

Programmed Ventricular Stimulation: Prognostic Value

In previous years, a large set of clinical studies has been performed to assess: 1) whether inducible ventricular arrhythmias are actually of clinical importance, and 2) which inducible arrhythmia is the best indicator of adverse prognosis.

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Contrasting results were obtained. In a first series of 5 studies [17-21] performed on a relatively small number of patients ($n = 405$), programmed ventricular stimulation failed to show any usefulness in the identification of patients at risk of late arrhythmic events. However, in these studies, the assessment was performed generally on patients with uncomplicated infarction, with left ventricular ejection fraction > 40% and low frequency of spontaneous ventricular arrhythmias on 24-hour electrocardiographic recording. In addition, in the majority of cases, the electrophysiologic study was performed utilizing no more than 2 extrastimuli, applied at only 1 site (apex) of the right ventricle (Table 1). This means that the study population represents a particular subgroup of postinfarction patients with

Table 1. Studies in which programmed ventricular stimulation failed to show any usefulness in the risk stratification: characteristics of the patients submitted to the electrophysiologic study, stimulation protocols

		Stimulation protocols		LVEF %		Spontaneous ventricular arrhythmias	
	n Pts	*n* Extra Stimuli	*n* Sites	Pts Ind	Pts Nonind	Pts Ind	Pts Nonind
Roy et al. [17]	150	2	1	45 ± 12	46 ± 12	4 ± 10 VPD/h	2.5 ± 6 VPD/h
Marchlinski et al. [19]	46	2	1	50 ± 13	42 ± 13	Lown 4 70%	Lown 4 25%
Bhandari et al. [20]	75	2	3	47 ± 15	48 ± 11		
Gonzalez et al. [21]	84	2	1			Lown ≥ 3 45%	Lown ≥ 3 20%
Santarelli et al. [18]	50	2	2	45 ± 10		Lown 4 23%	Lown 4 33%

n, number; Pts, patients; LVEF, left ventricular ejection fraction; Ind, induced; Nonind, noninduced; VPD, ventricular premature depolarization

a very low risk of future arrhythmic events, and that the study protocols utilized were not aggressive enough to achieve significant results. In fact, in such patients the frequency of late arrhythmic events was lower (0%-3%) than that generally observed on the whole of post-AMI patients (3%-5%), and the frequency of inducible sustained ventricular tachycardias was only 11%-20% in comparison with 19%-42% observed in other studies where 3 extrastimuli were utilized [10-12, 14-20]. In contrast with these results, a second larger group of investigations showed a significant association between some forms of inducible arrhythmias and late arrhythmic events. Among such studies, 2 further subgroups can be identified. The first consisting of 4 investigations [9-12], performed on 1922 non-

selected patients, characterized by a relatively high frequency of spontaneous complex ventricular arrhythmias (see Table 3), and by a relatively high frequency of moderate to severe left ventricular dysfunction (left ventricular ejection fraction ≤ 40% approximately in one third of cases) (Table 2). The second consists of

Table 2. Studies performed on nonselected patients: stimulation protocols, relation between inducible arrhythmias and late arrhythmic events

	n Pts	n Extr Stim	Site	Arrh	*p*	Sen %	Sp %	PPV %
Bourke et al. [9]*	1209	2(4)	2	MSVT > 230ms	< 0.001	19(53)	98(93)	30(17)
Cripps et al. [10]	75	3	2	MSVT	< 0.002	100	97	75
Iesaka et al. [11]	146	3	2	MSVT	< 0.02	82	84	29
Brembilla-Perrot et al. [12]	492	3	2	MSVT > 230ms	< 0.001	21	83	21

Pts, patients; ExtrStim, extrastimuli; Sen, sensitivity; Sp, specificity; PPV, positive predictive value; MSVT, monomorphic sustained ventricular tachycardia; * in brackets are shown sensitivity, specificity and positive predictive value when up to 4 extrastimuli were delivered at the apex of the right ventricle

7 investigations [13-16, 22-24] performed on 450 patients, all preselected on the basis of clinical and laboratory noninvasive variables indicative either of adverse prognosis or arrhythmic events (Table 3). In these studies, programmed ventricular stimulation was performed utilizing at least 2 extrastimuli (maximum 4, in 1 study only), preceded by drive trains of 8 extrastimuli at 2 or 3 different cycle lengths, delivered generally at 2 sites of the right ventricle (apex and outflow tract). When considering all the 11 above mentioned studies in a common pool, it appears that: 1) monomorphic SVT is the only inducible arrhythmia of prognostic importance, 2) monomorphic SVT at cycle length > 230 ms is the strongest independent predictor of arrhythmic events, and 3) monomorphic SVT shows the highest positive predictive value when the electrophysiologic study is performed on preselected patients. More specifically, such arrhythmia is inducible approximately in 12% of patients (range 6.5%-42%) and allows the identification of subjects at risk with 50%-100% sensitivity, 75%-98% specificity, and 21%-75% positive predictive value [9-16, 24].

Although the results of the above mentioned studies are not easily comparable because of marked differences in patient enrolment criteria, stimulation protocols, timings of electrophysiologic studies and follow-up durations, there is clear evidence that programmed ventricular stimulation, performed just before hospital discharge, can be considered the best single procedure to predict late arrhythmic events after AMI (Table 4). This is true either the stimulation protocol includes the erogation of 3 extrastimuli preceded by 2 drive cycle lengths ero-

Table 3. Studies performed on selected patients: criteria of selection, stimulation protocols, arrhythmias of prognostic importance

	n Pts	Criteria of selection	Extr Stim	Site	Arrhythmia progn imp	*p*	Sen %	Sp %	PPV %
Waspe et al. [13]	50	AV Block II-III; BBB; HF	3	2	nsVT SVT	< 0.001	100	76	41
Breithardt et al. [22]	59	VLP	2	1	> 4 VPD	< 0.01	100	73	33
Bhandari et al. [16]	53	HF; Angina; nsVT	3	2	SVT	< 0.03	62	89	50
Zoni-Berisso et al. [14]	103	VLP; LVEF ≤ 40%; Compl VA	2	2	MSVT > 230 ms	< 0.001	55	99	67
Hamer et al. [23]	70	HF; BBB; AV Block II III; VT; VF	2	2	> 5 VPD	< 0.05	80	75	33
Pedretti et al. [15]	47	VLP; LVEF ≤ 40%; Compl VA	3	1	MSVT > 230 ms	< 0.001	81	97	65
Farrell et al. [24]*	68	BRS; HRV	3	1	MSVT > 230 ms	< 0.001			

Abbreviations – See Tables 1 and 2; Progn Imp, prognosic importance; nsVT, nonsustained ventricular tachycardia; Compl VA, complex ventricular arrhythmias (VPD > 10/h, couplets of VPD, nsVT); BBB, bundle branch block; VLP, ventricular late potentials; HF, heart failure; VF, ventricular fibrillation; VT, ventricular tachycardia, BRS, baroreflex sensitivity; HRV, heart rate variability.
* This investigation was performed to assess the relation between BRS, HRV and electrophysiologic study results

Table 4. Sensitivity, specificity and positive predictive value of noninvasive variables significantly related to sudden death and spontaneous sustained ventricular tachycardia

Variables	Pts Pos %	Sen %	Sp %	PPV %
LVEF ≤ 40%	25-45	45-80	55-75	9-24
VLP	30-50	60-85	65-80	8-29
Compl VA	30-60	50-80	42-85	6-23
HRV	27-35	90	77-98	15-17
BRS < 3 ms/mmHg		80	91	44
SMVT	**7-42**	**50-100**	**75-98**	**21-75**
LVEF < 40% + VLP	20-30	25-80	60-90	10-30
LVEF < 40% + Compl VA	10-30	35-75	45-90	15-30
LVEF < 40% + HRV		40	90	22
VLP + LVEF < 40% + Compl VA	3-15	25-50	50-95	45-55
VLP and/or LVEF < 40% and/or Compl VA	50-90	100	50-55	10-15
VLP and/or Killip ≥ 2 and/or VPD ≥ 30/h	40	100	58	12

Abbreviations – See Tables 1, 2 and 3; Pts Pos, positive patients
Data from [3-9, 22, 24, 31]

gated at 2 sites of the right ventricle (maximal sensitivity achievable), or 2 extrastimuli at 2 sites of the right ventricle (maximal specificity achievable), or 3 extrastimuli erogated only at the apex of the right ventricle (compromise between high sensitivity and specificity) [9-16, 22-24] (Tables 2 and 3).

Programmed Ventricular Stimulation: Feasibility, Indications, Timings

The experience accumulated in the past few years on a relatively large series of post-AMI patients (more than 3000 published cases) has clearly shown that programmed ventricular stimulation is a test feasible in the majority of coronary care units, and not overloaded by severe complications. This on condition that it is performed by well-trained teams, in laboratories equiped adequately for cardiorespiratory resuscitation, and, in particular, if the criteria of exclusion are strictly observed. These include the presence of congestive heart failure or

myocardial ischemia resistant to adequate medical therapy, recurrent episodes of sustained ventricular tachyarrhythmias after the first 48 hours of AMI, significant associated noncardiac diseases, electrolyte or metabolic imbalance, intraventricular thrombosis at risk of embolization. In the presence of the last two complications, it is mandatory to postpone the electrophysiologic study [9, 10, 14, 17, 19, 25].

If no controversy exists at present on the usefulness, feasibility and safety of programmed stimulation after AMI, uncertainty still persists on its optimum timing and on the most appropriate indications to achieve the best cost-benefit ratio. With regard to the first question, recently some investigators have shown that the later in the postinfarction period, the lower myocardial electrical instability, and that the later the time of ventricular tachycardia induction the better the prediction of late arrhythmic events [26-28]. Consequently, Nogami et al. suggested that programmed stimulation be performed at least 1 month after AMI [27]. Unfortunately, these experiences are too small to draw definitive conclusions. Therefore, at present, we suggest to continue to perform programmed stimulation just before hospital discharge.

With regard to the second question, some preliminary clinical and ethical considerations are needed. Although programmed ventricular stimulation has been shown to be the best single procedure in predicting post-AMI arrhythmic events [3-11], it cannot be considered an ideal screening test for large number of patients. In fact, because of its invasive nature, the significant psychological consequences determined by the utilization of DC shock in those patients who experience inducible ventricular tachyarrhythmias, and its evident uselessness in those patients clearly known to be at extremely low risk of future arrhythmic events, it should be reserved only to subgroups of post-AMI patients previously identified at risk on the basis of clinical and laboratory noninvasive variables [9, 29, 30]. Unfortunately, as recently outlined by Dhingra [29] and by our group [3], all the variables utilized or only suggested to be utilized(either singly or in combination) for patient preselection appear to be inadequate for this purpose since they allow the identification of risk patient subgroups with a predictive sensitivity ranging from 65% to 80% only [3-8, 22, 31] (Table 4). This means that more than one fourth of those post-AMI patients who will develop late arrhythmic events are excluded, *a priori*, from programmed ventricular stimulation assessment. In our opinion, the ideal noninvasive selection procedure should allow the identification of patients at risk with maximal predictive sensitivity. On this regard, we and other investigators have shown that the presence of at least 1 of the following conditions: 1) left ventricular ejection fraction $\leq 40\%$, 2) ventricular late potentials, and 3) spontaneous complex ventricular arrhythmias on 24-hour electrocardiographic recording, allows the identification of a subgroup of patients at risk (approximately 40% of the entire population) with a predictive sensitivity near to 100% [3, 6-8]. This modality of patient preselection has been utilized recently in two studies with encouraging results. In these studies, at the end of the "two-level" risk stratification procedure, inducible monomorphic SVT at cycle length > 230 ms predicted sudden death and spontaneous SVT with a sensitivity, specificity and positive predictive value of 55% and 80%, 97% and

98%, 65% and 67%, respectively [14, 15]. Such findings represent the best results in the field of the risk stratification after AMI.

Conclusion

On the basis of the above mentioned data, it appears that programmed ventricular stimulation performed just before hospital discharge is a useful procedure to predict sudden death and spontaneous SVT occurring after AMI. However, to achieve the best cost-benefit ratio, the electrophysiologic study must be reserved only to patient subgroups preselected by means of noninvasive clinical and laboratory parameters. Nonivasive preselection should allow the identification of patients at risk with maximal predictive sensitivity. The most appropriate stimulation protocol must include the erogation of triple extrastimuli at 2 drive cycles, at least at the apex of the right ventricle. Under these conditions, the induction of monomorphic SVT allows the identification of a small subgroup of patients (less than one fifth) with a very high likelihood of developing future arrhythmic events (more than 50%). Unfortunately, there are two significant limitations to the above mentioned "two-level" risk stratification strategy: 1) the number of patients to submit to the electrophysiologic study is still too large; 2) the predictive sensitivity of programmed stimulation results is relatively low. To improve the effectiveness of the entire procedure, further efforts are necessary to identify more appropriate noninvasive preselection criteria and more sensitive stimulation protocols.

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PREVENTION OF SUDDEN DEATH IN POST-MI PATIENTS

After CAMIAT and EMIAT What is the Role for Amiodarone in the Prevention of Sudden Death

Y.G. Yap and A.J. Camm

Introduction

Despite the tremendous strides in its diagnosis and management over the 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 everyday–over 170 000 people every year [1]. The majority of deaths following an acute myocardial infarction (AMI) occur in the first year, with a mortality rate ranging from between 5% to 15% [2, 3]. The major cause of death in the first year after acute myocardial infarction is sudden death, usually due to ventricular arrhythmias [4, 5]. While the definition of sudden death is still under much debate [6] it is recognised that the majority of these events, although not exclusively, begin as ventricular tachycardia which quickly degenerates into ventricular fibrillation, in the absence of either acute infarction or significant ischaemia [7, 8].

Recognition of the relatively high rate of arrhythmic death has prompted the search for an effective prophylactic antiarrhythmic drug for the prevention of arrhythmias following an AMI. Apart from β-blockers [9-11] and angiotensin converting enzyme inhibitor [12], no other agent has been conclusively shown to reduce mortality. Indeed, several recent randomised clinical trials showed that some antiarrhythmic agents increased the mortality instead. Both the CAST and SWORD studies demonstrated that the prophylactic use of class I agents (encanide, flecainide or moricizine) and class III agent (d-sotalol) increased the mortality in postinfarction patients [13-15]. This has raised doubt whether pharmacologic agents can reduce arrhythmic death. Amiodarone, however, is a unique antiarrhythmic agent which has proven to be effective in the treatment of sustained, life-threatening ventricular arrhythmias [16, 17]. Several small- and large-scale trials, most notably the CAMIAT and EMIAT, were conducted to evaluate the potential benefit of amiodarone in the prevention of arrhythmias using either ventricular premature depolarisation (VPD) or left ventricular dysfunction as a surrogate marker of arrhythmias in patients following an AMI [18-24]. In this chapter, we will discuss the role of amiodarone in the prevention of arrhythmic and sudden deaths in light of these recently published trials.

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Mechanism of Antiarrhythmic Action of Amiodarone

Traditionally, antiarrhythmic drugs are classified into groups presumed to have common mechanisms of action on arrhythmias. The classification most widely used is the Singh and Vaughan Williams classification [31, 32]. According to this classification, antiarrhythmic drugs are divided into 4 main classes:
Class I: sodium channel blockers
Class II: sympatholytic drugs
Class III: agents that prolong action potential duration
Class IV: calcium antagonists.

Amiodarone is a complex molecule in that it uniquely possesses pharmacological properties from all 4 antiarrhythmic classes [25].

Class I effect:

Depression of ventricular conduction results in slowing of ventricular tachycardia rendering it haemodynamically less challenging. Another property common to class I agents is the ability to suppress VPD and amiodarone has exhibited a high efficacy in suppressing VPD.

Class II effect:

Sympatholytic effects may lead to sinus node and atrioventricular node suppression. Such sympathetic antagonism can be attributed to potential mechanisms such as reduction in β-adrenoceptor numbers, calcium channel antagonism and interactions with thyroid hormone. It is likely that these class II effects may also exert some protection against sudden death following acute myocardial infarction.

Class III effect:

Prolongation of action potential duration by amiodarone can prevent both reentrant atrial and ventricular arrhythmias.

Class IV effect:

Calcium channel antagonistic action is responsible for a substantial portion of the ability of amiodarone to inhibit atrioventricular node conduction and may also reduce arrhythmogenesis (e.g. torsades de pointes) caused by early afterdepolarisation.

Results of CAMIAT and EMIAT Trials

In CAMIAT, the aim of the studies was to assess the effect of amiodarone on the risk of resuscitated ventricular fibrillation or arrhythmic death among survivors of myocardial infarction with ≥ 10 ventricular premature depolarisations (VPDs)/hour or ≥ 1 episode of ventricular tachycardia (VT). Patients were randomised to amiodarone (606) or placebo (596) with a mean loading dose of 776 mg reducing to 208 mg/day on amiodarone and 294 mg/day on placebo at 12 months. Patients were followed-up for up to 2 years. The primary end point of the study, a composite of resuscitated ventricular fibrillation (VF) and arrhythmic death on the basis of an efficacy end point was reduced by 48.5% with amiodarone.

As for the secondary endpoints, amiodarone showed favourable trends in the reduction of arrhythmic death (32.6%), cardiac mortality (27.4%) and all-cause mortality (21.2%) though they did not reach any statistical significance [18].

In EMIAT, the aim was to assess whether amiodarone reduced all-cause mortality (primary endpoint) and cardiac mortality and arrhythmic death (secondary endpoints) in survivors of myocardial infarction with a left ventricular ejection fraction (LVEF) ≤ 40%. Patients were randomised to treatment with amiodarone 800 mg/day, or matching placebo, for 14 days, followed by amiodarone 400 mg/day for 14 weeks and 200 mg/day for the remainder of the study. There were 743 patients for each arm. The patients were followed-up for up to 2 years. The results showed that the primary end point of total mortality did not differ between the 2 groups, nor did the cardiac mortality. However, in the amiodarone group, there was a 35% reduction in the risk of arrhythmic death [19].

Essentially, both CAMIAT and EMIAT showed that amiodarone, when used prophylactically in postmyocardial infarction patients with ≥ 10 VPDs/hour or one episode of VT, or LVEF ≤ 40%, reduced the risk of arrhythmic death. There was no reduction in total mortality. However, controversies have arisen from these trials since their publication. There was a high proportion of withdrawal in the amiodarone-group patients compared with placebo in both trials (36.4% vs 25.5% in CAMIAT, 38.5% vs 21.4% in EMIAT). Most of the withdrawals were due to drug-induced hypothyroidism. Furthermore, EMIAT showed a 33% increase in the non-arrhythmic cardiac death, which offset the 35% reduction in the arrhythmic death. Although this excess might have been resulted from chance or from the imbalance in significant prognostic factors between the groups, there has been concern that it could have been directly caused by amiodarone [26]. As it happened, fatal reinfarction contributed most to this non-arrhythmic cardiac death in the amiodarone group. There were, however, three deaths due to pulmonary fibrosis, presumably a direct consequence of treatment with amiodarone.

Both CAMIAT and EMIAT showed that there was an important synergistic interaction between amiodarone and β-blockers in the reduction of mortality. In EMIAT, there were fewer cardiac deaths among amiodarone-treated patients who were receiving concomitant β-blockers than among those who were not. Similarly, of those patients who received β-blockers, there was a substantial reduction in the cardiac and arrhythmic mortality among those who were also given amiodarone. In CAMIAT, the reduction in the rate of primary outcome cluster (i.e. resuscitated VF and arrhythmic death) among amiodarone-treated patients was even greater in those patients who were also taking β-blocker than in those who were not (relative risk reduction of 87%).

Both CAMIAT and EMIAT represented the largest trials to date examining the prophylactic use of amiodarone in postmyocardial infarction patients. Despite this, both trials were underpowered to detect a modest reduction in the total mortality. As a result, this has prompted the principal investigators of the amiodarone trials to collaborate and carry out a systematic meta-analysis on all relevant randomised trials to specifically examine whether the apparent beneficial effect of amiodarone on arrhythmic death could translate into a beneficial effect

on total mortality, or conversely, whether the adverse effect of non-arrhythmic death might offset the decrease in arrhythmic death (Amiodarone Trials Meta-analysis Investigators, unpublished data).

Meta-analysis of the Randomised Trials on the Effect of Prophylactic Amiodarone on Mortality

In this meta-analysis, patient data from 13 randomised controlled trials (including CAMIAT and EMIAT) of prophylactic amiodarone in patients with recent myocardial infarction (MI)(8 trials) or congestive heart failure (CHF)(5 trials) were pooled. Nine trials were double-blind placebo-controlled and 4 compared amiodarone with usual care. A total of 6553 patients were randomised (78% post-MI and 22% CHF). The results showed that sudden death or arrhythmic death in high risk patients (i.e. recent MI or CHF) was reduced by 29%, with this translating into an overall reduction of 13% in all-cause mortality when amiodarone was used prophylactically. The effect on non-arrhythmic death was neutral. There was no difference in the treatment effect between post-MI and CHF studies.

Role of Amiodarone in the Prevention of Sudden Death

The results from this meta-analysis appears to strengthen the role of amiodarone as a prophylactic agent in suppressing arrhythmic deaths as well as reducing all-cause mortality in high risk patients (i.e. those with poor LVEF or frequent VPD) in survivors of AMI. Although amiodarone is not recommended for systematic prophylactic use in survivors of AMI, these findings appear to advocate early amiodarone treatment in high risk patients with poor LVEF or ventricular arrhythmias after infarction. Use of low dose amiodarone will prevent one death for every 43 postmyocardial infarction treated for 2 years.

The beneficial effect observed with low dose amiodarone treatment in the first year after infarction continues for several years following discontinuation [27]. However, the question of optimal duration of amiodarone therapy following infarction is unresolved and this will be a useful line of future investigation [28]. The BASIS study suggested that treatment could be discontinued after 1 year without loss of the antiarrhythmic benefit which had been seen during the active treatment phase of this post-AMI trial [27].

Unlike class I antiarrhythmics and d-sotalol, amiodarone appeared to be safe and did not show any pro-arrhythmic effect. Adverse experiences attributable to low dose amiodarone that resulted in discontinuation of treatment occurred at a low rate. From the meta-analysis, only about a third of amiodarone discontinuation was due to adverse effects during the two year duration of treatment, which would suggest a possibly much lower rate of discontinuation in clinical practice. Hypothyroidism is the commonest adverse effect.

An unexpected finding from both CAMIAT and EMIAT is the protection con-

ferred by amiodarone in patients receiving concomitant β-blockers. The mechanism of the protection is unknown. It may be attributed to its non-competitive adrenergic blockade action. Alternatively, it may be that the patients selected for treatment with β-blocker are intrinsically not sensitive to the beneficial effect of amiodarone. This reviews the possibility of a greater potential benefit of using a combination therapy with amiodarone and other drugs (e.g. β-blocker or angiotensin converting enzyme inhibitors) in the reduction of arrhythmic, sudden or cardiac mortality among postmyocardial infarction patients. A randomised control trial will be needed to explore such a potential.

Finally, can the results from these amiodarone trials be extrapolated to other subgroups of patients at risk of ventricular arrhythmias such as patients with hypertrophic cardiomyopathy or dilated cardiomyopathy? Previous studies demonstrated similar differences in favour of amiodarone in patients with hypertrophic cardiomyopathy [29]. Likewise, amiodarone has also been shown to suppress ventricular arrhythmias in 70% of patients with idiopathic cardiomyopathy [30]. The potential of amiodarone on these at risk groups may need to be confirmed with separate prospective randomised controlled trials. However, not every small subgroup can be realistically tested and it is probably appropriate to extrapolate the results of the meta-analysis to other aetiological groups at high risk of sudden death due to ventricular arrhythmias. In patients with chronic heart failure, however, the meta-analysis has already indicated amiodarone has the same survival benefit in this subgroup of patients as post-myocardial infarction patients. The benefit is even greater in patients with symptomatic heart failure (NYHA III-IV) where 1 death will be prevented for every 13 of these patients treated for 2 years with amiodarone.

In conclusion, after CAMIAT and EMIAT, the role of amiodarone in the prevention of sudden death has only just begun.

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Beta-blockers Prevent Sudden Death: so Why Is Their Use Limited after Myocardial Infarction?

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Introduction

There is overwhelming evidence that in the post myocardial infarction (MI) setting β-blockers (BB) are of benefit (in terms of safety and efficacy): they reduce recurrent MI, sudden death (SD) mortality, total mortality especially in patients with depressed ventricular function [1-14].

With regard to the treatment of this clinical setting and the appropriate use of antiarrhythmic agents (AA) it seems important to remember what an International Consensus Committee stated in 1994 [15]:

"The most important antiarrhythmic drug attributes an AA should show are:
- 1 no increased post-MI mortality risk;
- 2 low cardiac adverse effects;
- 3 documented long-term safety;
- 4 low proarrhythmic incidence;
- 5 low organ toxicity;

aside from BB no single agent demonstrated all of these. Sufficient post-MI trial data show a decrease in mortality only with BB (the beneficial effect may be more than just antiarrhythmic). Some limited data on amiodarone appear promising."

It also seems crucial to repeat the recently published ACC-AHA Guidelines for the Management of Patients With Acute Myocardial Infarction [16]. Among the recommendations for the long-term management of a specific Class I intervention (conditions for which there is evidence and/or general agreement that the treatment is beneficial, useful and effective) it states:

"All but low risk patients without a clear contraindication to β adrenoceptor blockers therapy should be treated.Treatment should begin within a few days of the event (if not initiated acutely) and continue indefinitely".

In order to try to give a reply to the question of the title it seems reasonable to review some data about this problem in advance.

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Overview of the Results of Prophylactic Therapy with Beta-blockers on Mortality in Patients with Post-MI Ischemic Heart Disease

Many studies show evidence of the benefits of the BB in the secondary prevention after MI. In particular the Norwegian Multicenter Study Group Trial (with timolol, 1981) [1], the Beta-Blockers Heart Attack Trial (with propranolol, 1982) [2], and the Goteborg Metoprolol Trial (with metoprolol, 1984) [3] demonstrated a significant reduction in total mortality (from 20% to 30%). Sudden death (SD) mortality is also successfully diminished in this setting: in the analysis of Olson (pooled results from five clinical trials with metoprolol) the reduction of total mortality depends primarily on the reduction of SD [8].

It seems reasonable to present and make some comments on the largest study of metanalysis published up to now. Teo et al. [13] in 1993 investigated the effects of prophylactic therapy with AA in patients with MI. The mortality rate from 138 trials (98 000 patients) was combined by the Yusuf-Peto adaptation of the Mantel-Haentzel method. In patients allocated to the treatment with Class I AA there were 660 deaths among 11 712 patients who received active drug and 571 deaths in 11 517 control patients (51 trials: odds ratio = 1.14, 95% C.I. 1.01-1.28; $p = .03$). In patients allocated to receive a Class IV AA there were 982 deaths among 10 154 patients who received active treatment and 949 deaths in 10 188 control patients (24 trials: odds ratio = 1.04, 95% C.I. 0.95-1.14; $p = .41$). In patients allocated to receive amiodarone (Class III AA) 77 out of 778 patients died compared with 101 deaths in 779 control patients (9 trials: odds ratio = 0.71, 95% C.I. 0.51-0.97; $p = .03$).

These data indicate that routine use of Class I AA is associated with increased mortality, the use of Ca-Channel blockers is unpromising or might be harmful, limited data on amiodarone appear promising (this is confirmed by more recent studies and by the metanalysis of Cairns et al., [17]). Conversely the review of the systematic analysis concerning the data of the controlled trials (55) that evaluated Class II AA evidenced a dramatic reduction of mortality. There were 1464 patients who died in the group of 26 973 patients randomized to BB and 1727 in 26 295 controls (odds ratio = 0.81, 95% C.I. 0.75-0.87; $p = .00001$).

The beneficial effects of BB (reduction of the risk of death = 19%) are extremely convincing and conclusively demonstrated. Moreover a very important retrospective study [18] searched the CAST results for evidence of mortality and morbidity reduction in patients receiving optional BB therapy. The authors studied 2611 patients of the CAST I and II enrollment (population with an ejection fraction $\leq$ 40%) and analyzed survival curves for the patients (27%) in BB therapy. Significantly fewer all-cause deaths in patients receiving BB (> 75% of the patients taking BB at baseline were still receiving therapy at 1-year follow-up examination) were found (approximately 1/3 less mortality, $p = .036$). Multivariate analysis showed BB therapy to be a significant independent factor related to a decreased risk of arrhythmic death and increased freedom from congestive heart failure. The reduction in death rate is more evident in the initial 6 months but with continued efficacy later. This study confirms previous knowledge (analysis from BHAT-1993 [2], from BB Pooling Project-1988 [6], from APSI-1990 [7]) of better results of BB

in highest mortality risk cohort of patients, based on findings of recurrent ischemia, arrhythmias, congestive heart failure. There is, in addition, evidence of a "anti-proarrhythmic" effects of the "CAST" drugs [18].

Other authors found significantly better effects of BB in specific subgroups: in diabetics [19], in older patients (60-74 years, reduction of mortality of 40% versus 28% in younger patients) [20], in non Q wave MI [21], in patients without anterograde flow in the infarct artery [22].

Mechanisms of Action of Beta-blockers

The β-adrenergic inhibition exerts complementary effects which are extremely complex and not fully understood. Cardiac arrhythmias, especially in post-MI ischemic heart disease, involve multiple mechanisms and only a multifocal approach appears logical and not harmful today.

Several factors account for the prophylactic efficacy of BB, which we will try to summarize.

1. The electrophysiologic benefits derive from the multiple mechanisms of antiarrhythmic action of these drugs.
   - Primary antifibrillatory mechanism (through a relation with serum potassium?) and prolongation of ventricular effective refractory period.
   - Increase in parasympathetic tone. The enhanced vagal activity seems to be due to a direct effect in the CNS and is a typical clue of lipophilic BB which can penetrate into the brain. The lipophilicity of propranolol, timolol and metoprolol could explain the decreased risk of SD.
   - Attenuation of heterogeneicity associated with regional denervated areas of ischemic and necrotic myocardium and autonomic supersensitivity.
   - Blocking of the increased cardiac catecholamine spillover (typical of patients with cardiac heart failure).
   - Anti-proarrhythmic effects.
   - Moderate suppression of premature ventricular beats.
   - Bradycardic-induced decreased dispersion of refractoriness and rate-dependent fractionation of conduction.
2. The anti-ischemic effects of BB are well demonstrated and explained by the reduction of oxygen demand (through a negative chronotropic and inotropic effect).
3. Other cardioprotective effects.

Among these we can remember: decrease of Ca^{2+} uptake in atherosclerotic plaque, decrease of platelet aggregation mediated by catecholamines, increased synthesis of prostacyclines, decrease of thrombotic risk through an action on fibrinogen.

It is quite obvious that the pharmacologic regimen of BB does not act directly on arrhythmias but has nevertheless a substantial effect by continuously modulating the arrhythmogenic influences on the substrate (ischemic and/or necrotic myocardium) and decreasing ischemic burden (General Law → Ischemia + High

Sympathetic Activity = initiation and perpetuation of fast, unstable ventricular arrhythmias).

These data have led to a shift in the search of the AA of the future: blunting of sympathetic stimulation is considered an integral component of a new antiarrhythmic drug or regimen [23].

Physician's Biases in Not Prescribing Beta-blocker Therapy in Post-MI Ischemic Heart Disease

The problem is of course conspicuous (only 25% of the patients are allocated to BB) and multifactorial.

In the following pages we will consider the possible causes of the biases and will make some comments on this behavior and on the possible solutions.

- Beta blockade is associated with many side effects (moderate and serious) which are more likely to occur after longer exposure and are a concern for patients and physicians. Among these one finds: sinus bradycardia, asthma or bronchospasm, hypotension, fatigue, mental depression, sexual interferences, Raynaud's phenomenon. Moreover indirect effects (potential atherogenic changes in lipid metabolism) and above all the belief that BB are detrimental to patients with decreased left ventricular function strongly affected prescription.

If one considers recent studies it seems obvious that lipidic alterations have no clinical relevance (on the contrary BB contrast development of atherosclerosis) and it is clear and conclusively accepted that the worse the post-MI status of the patient is (highest mortality risk for ischemia, arrhythmias, left ventricular dysfunction) the better the benefit in terms of survival and decreased morbidity.

The rate of withdrawal of BB is considerably high (up to 30%) [14]. It is important to reassure the clinicians and the referring cardiologists that one has to choose the "right" BB and the "right" dosage of the drug for the individual patient and that the benefit of long-term treatment largely outweighs the cost.

- The questions of major importance which BB should be used and how long BB therapy should be maintained seem to remain unanswered (and lead to "low compliance" by the patient and his referring cardiologist or general practitioner).

Recent studies support the view that it is safest to stick to BB with documented efficacy and follow-up (propranolol, metoprolol, nadolol, atenolol, timolol) and to maintain the treatment indefinitely [1-10].

- The traditional arrhythmia suppression hypothesis, which formed the basis for an enormous number of clinical trials with various AA, largely affected clinical practice but only recently has been abandoned. After the disasters of trials such as CAST I and II [24] and SWORD [25] (excess of mortality in patients receiving moricizine, encainide, flecainide, d-sotalol) not only was there a reevaluation of the practice of prescribing prophylactic antiarrhythmic drug therapy with the currently available agents, but

(importantly) there was also a shift from the traditional end point of arrhythmia suppression (Holter) and/or arrhythmia induction (Electrophysiologic Study), and the search for the presence of other markers of electrical instability such as the presence of late potentials, and the evidence of low vagal and high sympathetic activity (depressed baroreflex sensitivity, reduced heart rate variability). The concept that decreasing heart rate and ischemia, and reducing sympathetic activity, is a more promising approach to the prevention of SD than suppressing ambient arrhythmias recorded on ECG or Holter monitoring, will take some years to be universally accepted.

- Concern in the field of post-MI arrhythmias is generally much more influenced by large-scale clinical trials which demonstrated a negative and very harmful effect (CAST [24], SWORD [25]) than by studies which clearly delineate a positive effect of a drug. In this field, the "climate of reevaluation" of a consolidated hypothesis has a strong impact on prescribing behaviors: in Italy the GISSI studies clearly evidenced the rapid transfer of the trial results to routine clinical practice [26]. There is a significant decreasing trend from the early 1980s to the early 1990s in the use of AA in the post-MI setting :

amiodarone	8.6 %	$\longrightarrow$	4%	$p<0.001$
mexiletine	3.1 %	$\longrightarrow$	1.1%	$p<0.001$
propafenone	1.8%	$\longrightarrow$	0.5%	$p<0.001$
flecainide	0.7%	$\longrightarrow$	0.1%	$p<0.001$
others	1.1%	$\longrightarrow$	0.2%	$p<0.001$.

- In Italian physicians there is a relevant "cultural dependency" on North American and English studies that report, up to now, usage of BB in 20%-30% of post-MI patients (CAMIAT, SAVE, SOLVD, MADIT) [27-29] whereas in Europe and Scandinavia the prevalence of optional BB therapy is 50%-70%.
- Last but not least, there is nevertheless conclusive evidence that also in Italy the trend for the use of BB is significantly and continuously increasing. According to GISSI 1 (1983-1985, 12 000 patients), GISSI 2 (1988-1989, 12 490 patients), GISSI 3 (1991-1993, 19 394 patients) the prescription of BB at follow-up increased from 10% (GISSI 1) to 32% (GISSI 3) whereas in the same time the prescription of Ca-antagonists decreased from 58% to 20%, nitrates from 32% to15%, inotropic agents from 23% to 8%, and diuretics from 25% to 15% [30].

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Prevention of Sudden Death in Post-MI Patients: What Is the Role of Non-Antiarrhythmic Drugs?

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Ventricular arrhythmias have a relevant prognostic significance, particularly when associated with myocardial infarction, ischemic heart disease or congestive heart failure. Unfortunately, very effective antiarrhythmic drugs failed to improve prognosis as shown by the CAST studies. Moreover, their use has been limited by several hazardous side effects such as negative inotropic action and serious proarrhythmia. Furthermore, in ischemic heart disease, the electrophysiological mechanisms responsible for ventricular arrhythmias are complex (reentry, abnormal automaticity, delayed after-depolarization), variable and often interdependent. Besides, concomitant factors as sympathetic hypertone, hypokalemia and acidosis play a crucial role. Thus, clinical indications for antiarrhythmic therapy are still controversial and it could be reasonable to consider, when approaching ventricular arrhythmias, the treatment of concomitant factors and the use of drugs such as fibrinolytic agents, β-blockers and ACE inhibitors, that are not traditionally considered as antiarrhythmic agents.

Triggering Factors

Acute myocardial infarction (AMI) is a clinical condition characterized by increased neurohormonal activation (high levels of adrenergic tone, renin-angiotensin system activation). Thus, findings of hypokalemia and hypomagnesemia, that are strongly related with ventricular arrhythmias are common [1]. Data from the MRFIT trial showed that the number of premature ventricular complexes (PVC) increases by about 28% for any reduction of kalemia of 1 mEq/l [1]. In AMI, hypokalemia and potentially fatal ventricular arrhythmias, like sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) are closely associated (in patients suffering AMI, the risk of VT is 5 times more frequent when serum potassium is below 3.9 mEq/l [2]).

Besides, the effectiveness of antiarrhythmic drugs may be dramatically reduced in hypokalemic patients. On the other hand, the favorable effect of β-blockers on VF in AMI may come out not only from their antiadrenergic action,

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but also from the reduction of the hypokalemia induced by the activation of β-2 receptors.

Fibrinolytic Agents

Large randomised trials have demonstrated that fibrinolytic therapy can reduce mortality in patients with AMI by about 18% [3]. This beneficial effect is attributed to a reduction of the myocardial damage and to the recanalisation of the occluded infarct-related artery (IRA) [4]. Furthermore, reperfusion therapy has well established antiarrhythmic effects: first, reperfusion may reduce the incidence of arrhythmias through a limitation of peri-infarctual ischemia, moreover a patent IRA can improve the electrical stability through a favorable effect on ventricular remodeling. On the other hand, reperfusion can frequently elicit ventricular arrhythmias, secondary to intracellular calcium overload, oxygen-derived free radicals and free fatty acids toxicity. The final result is a beneficial effect on ventricular arrhythmias. In fact, although the meta-analysis [5] of the major clinical trials did not demonstrate a reduction of VF in the first 24 hours after AMI, ventricular arrythmias dramatically decreased in the later hospital phase. These data have been confirmed by the GISSI-2 study [6], where a 20% reduction in the later in-hospital VF of patients treated with fibrinolytic agents has been showed.

In conclusion, there is no doubt that early intravenous thrombolytic therapy reduces ventricular arrhythmias, both during the acute phase and the later hospitalization, and improves electrical stability. The benefit is probably the result of the patency of the infarct-related artery that, limiting ventricular dilatation and preventing left ventricular aneurysm, obviates the development of electrophysiological alterations that can predispose to arrhythmias.

β-Blockers

Augmented sympathetic drive is one of the most typical pathophysiological alterations in AMI. It is related to the occurrence of serious arrhythmias and results in an increased myocardial oxygen consumption and ischemia. Furthermore, other structural abnormalities like ventricular hypertrophy and/or dilatation, ischemia, hypokalemia, etc., may work as predisposing factors to potentially lethal ventricular arrhythmias.

The beneficial anti-ischemic and cardioprotective effects of β-blockers in this setting are well known. In addition they have a mild antiarrhythmic effect that is due to the antagonism of catecholamines. Experimental and clinical studies supported a powerful antifibrillatory action as opposed to a weak positive effect on PVC and other stable ventricular arrhythmias [7]. The cause of these different effects is probably a consequence of the distinct mechanisms of initiation of PVC and stable monomorphic ventricular tachyarrhythmias compared to that of electrically unstable ventricular tachyarrhythmias. Thus, β-blockers seem to be much

more effective in suppressing "unstable" than "stable" ventricular arrhythmias [7]. In fact, β-blockers appear to be particularly effective in controlling factors predisposing to electrical instability, like myocardial ischemia, high cardiac sympathetic tone and decreased vagal tone. The role of β-blockers in increasing the threshold for VF has been clearly demonstrated by the reduced incidence of VF in the early phase of AMI. Selective β-2 blockers showed better results than β-1 agents, probably due to their effect on the balance between intra- and extracellular potassium. The overview [8] of 28 randomized trials indicates that early intervention with β-blockers (intravenous or oral) in AMI reduces the risk of reinfarction, sudden death and lethal ventricular arrhythmias by 15%-20%. These encouraging results with the early use of β-blockers may be even better after long-term administration.

β-blocker therapy has also been intensively investigated for secondary prevention following AMI. The beneficial effects of β-blockers after AMI are extremely convincing: broad trials with different agents (propanolol, metoprolol, timolol) have demonstrated that these drugs improve survival and also reduce the incidence of sudden death. The meta-analysis [9] of 5 different long-term metoprolol trials confirmed that the reduction in total mortality was primarily related to a 40% reduction in the incidence of sudden death. The benefit was mainly observed in the high risk subjects (low ejection fraction, warning arrhythmias on Holter).

β-blockers may also be safely used in patients taking other antiarrhythmic drugs: a retrospective analysis of the CAST study [10] showed that those patients treated with β-blockers were less likely to have sudden death or non-fatal cardiac arrest than those receiving only an antiarrhythmic drug. These data suggest that β-blockers prevented the adverse effects of antiarrhythmic drugs observed in the CAST study and may indeed have an effective "anti-proarrhythmic" action. More recently the CASH study [11] revealed that metoprolol, propafenone and amiodarone were less effective than implantable defibrillators in preventing sudden death in survivors of cardiac arrest, but when the long-term follow-up was assessed, mortality among the different groups was not statistically different.

Angiotensin Converting Enzyme (ACE) Inhibitors

ACE inhibitor drugs have extended their first indication for the treatment of hypertension to that of congestive heart failure, AMI and chronic ischemic heart disease. These agents inhibit the conversion of circulating angiotensin 1 to the powerful vasoconstrictor angiotensin 2. Therefore ACE inhibition leads to peripheral vasodilatation and beneficially acts on the complex and compensatory neurohormonal changes (activation of the renin-angiotensin-aldosterone axis, heightened noradrenaline release, inactivation of the breakdown of bradykinins) that follow these clinical conditions. The electrophysiological effects of ACE inhibitors are a consequence of their antagonism to the detrimental effects of angiotensin 2 on autonomic nervous system, of their mild β-blocking properties

and of the decrease of the parasympathetic tone. Furthermore, ACE inhibitors have been reported to improve the balance of electrolytes through a reduction of hypokalemia. Last, but not least, ACE inhibitors have a powerful hemodynamic effect and they might reverse hypertrophy and decrease left ventricle chamber size, both determinant factors in the genesis of arrhythmias. Experimental studies clearly demonstrated a strong association between myocardial cells stretching and ventricular arrhythmias, and these findings suggest that drugs effective in reducing parietal tension may have an antiarrhythmic action [12]. Thus, it is still questionable how much the hemodynamic improvement may affect the electrophysiological properties of ACE inhibitors. In conclusion, the electrophysiological effects of ACE inhibitors are a consequence of many intricate factors such as hemodynamic effects, electrolyte stabilisation, regression of left ventricular hypertrophy and β-blockers action [13].

In the clinical setting, ACE inhibitors have been reported to have a beneficial effect in reducing arrhythmias in patients with acute AMI. The CATS study [14] revealed that early administration of captopril in patients treated with fibrinolytic agents for anterior AMI, significantly reduces the incidence of sustained ventricular arrhythmias and accelerated idioventricular rhythm, probably through the limitation of the reperfusion damage. A similar effect on the reduction of ventricular arrhythmias and sudden death, by early ACE inhibition with zofenopril, has been reported in the SMILE trial [15]. These beneficial antiarrhythmic properties of ACE inhibitors confirm the critical role of the activation of the renin-angiotensin-aldosterone axis and of the enhanced adrenergic drive in the genesis of ventricular arrhythmias. Moreover, ACE inhibitors may also have a promising electrophysiological role in chronic congestive heart failure (CHF), since the presence of left ventricular dilatation, hypertrophy and fibrosis may be predisposing factors for arrhythmias. In 1987 the CONSENSUS study [16] clearly indicated that treatment with enalapril reduces the risk of death by 31% in patients with CHF after a 1 year follow-up. The reduction in mortality was mainly due to a substantial decrease in death from progressive heart failure rather than an effect on sudden death. In subsequent studies, the mortality benefits of ACE inhibitors have been confirmed, but until VHeFT-II there was nothing to suggest an ACE inhibitor effect on sudden death. In the VHeFT-II trial [17], enalapril demonstrated a favorable trend toward less arrhythmic death, especially in patients with relatively preserved left ventricular ejection fraction. These data support the hypothesis that if myocardial stretch were one of the mechanisms involved in the genesis of arrhythmias, they would be more readily modified before widespread fibrosis had become established. In the SAVE trial [18] a reduction in sudden death and incidence of arrhythmias was observed among patients survivors of AMI treated with captopril, while data from the SOLVD study did not seem as favorable [19]. In the Hy-C trial [20] a very impressive 75% reduction in sudden death (7% captopril vs 28% hydralazine) was observed in patients with NYHA class III-IV CHF treated with captopril. Recently, the TRACE trial [21] demonstrated that the early administration of trandolapril in patients with AMI and echocardiographic signs of left ventricular systolic dysfunction significantly

reduces cardiovascular mortality, mainly through a reduction in sudden death. Similarly, the AIRE investigators [22] found that ramipril reduced overall mortality by 27% in patients with clinical evidence of heart failure after AMI, with a 30% reduction of sudden death. In this trial the decrease in sudden death might reflect the prevention of progression of left ventricular failure more than the reduction of arrhythmic death.

However, further support for an antiarrhythmic effect of ACE inhibitors comes from analysis of Holter recordings in CHF subjects. Captopril can reduce the frequency of PVC [23] and in the VHeFT-II trial [17], patients treated with enalapril had fewer VT than their counterparts. It is noteworthy that the enalapril associated 27% reduction of VT at one year, was paralleled by a 51% reduction in sudden death. Thus, the antiarrhythmic role of ACE inhibition, although still speculative, seems to be promising.

Conclusions

Conventional treatment of AMI with vasodilators, anti-ischemic and fibrinolytic agents can not be a definitive substitute for individualized antiarrhythmic therapy. Nevertheless, unsatisfactory results from the CAST and the SWORD trials prompted a careful reevaluation of antiarrhythmic drugs post-AMI. Therefore, in the clinical practice it could be useful to consider the potential electrophysiological effects of other drugs that are not traditionally seen as antiarrhythmic. Hence, in post-AMI subjects it is important to prevent and correct any electrolyte imbalance (especially hypokalemia and hypomagnesemia in high-risk patients), to preserve the jeopardized myocardium as much as possible with fibrinolytic agents, and to extend the use of β-blockers and ACE inhibitors that may antagonize the complex and even proarrhythmic outcome of the neurohormonal activation in a positive way.

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How to Treat High-Risk Post Myocardial Infarction Patients Based on MADIT and Other Recent Trials

S. Saksena and I. Giorgberidze

Noninvasive tests for risk assessment and empiric selection of drug therapy have long been used in managing high-risk patients after myocardial infarction. Risk stratification using ventricular function is effective in predicting overall survival but less valuable with respect to defining sudden cardiac death risk [1, 2]. Newer approaches such as heart rate variability, while promising, are yet to be widely evaluated in clinical practice [3]. Empiric drug therapy is less attractive. Therapy with class 3 antiarrhythmic agents after myocardial infarction in high risk patients has been abandoned due to unfavorable clinical studies. Only β-blocking agents remain of proven benefit; but patient acceptance, compliance and tolerance are problematic. Less than 50% of patients actually receive such agents in clinical trials. In patients with depressed ventricular function, better acceptance exists for angiotensin-converting enzyme inhibitors [3]. Yet, in a meta-analysis of all ACE inhibitor trials, Garg and Yusuf noted the incidence of sudden death was unaltered [4]. In the CHF-STAT study, there was 19% incidence of sudden death at two years in the placebo arm despite such therapy [5]. Addition of amiodarone has conferred no improvement [5-7]. In the same trial, it was 15% in patients randomized to amiodarone at two years. In fact, after myocardial infarction, prophylactic amiodarone may or may not have shown arrhythmic death reduction but did not improve overall survival [8]. This suggests, yet again, that only the mode of death was altered. Based on these unsuccessful strategies, it has been suggested that risk stratification and treatment by whatever method chosen, noninvasive or invasive and pharmacologic or nonpharmacologic respectively, will fail to establish a reasonable balance between patients submitted to the screening, evaluation and treatment algorithm and the additional mortality benefit conferred by the strategy [9].

The MADIT Strategy

Before accepting this premise, we can recognize two central issues. Firstly, can we reliably identify patients at high risk of sudden death without excessive additional

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screening? Initially, we need to select a high risk population by noninvasive screening based on prospective criteria and subsequently, enrich the risk in this population by using laboratory tests for risk stratification. MADIT proposed a combination of noninvasive criteria for screening and invasive testing for stratification [10]. Two or more nonsustained ventricular tachycardia (VT) runs have been shown to have a modest sensitivity (42%) but a high specificity (> 90%) for sudden death risk [11]. Combining this with ventricular dysfunction of moderate to high degree adds the strong predictive capability of left ventricular ejection fraction to increase the mortality risk. In the heart failure population, each of these variables was an independent and major predictor of mortality [12].

The use of electrophysiologic testing after myocardial infarction to identify patients at risk for arrhythmic events has been widely debated since its introduction [13]. Interestingly, much of the testing performed in these early, inconsistent studies occurred in the acute or subacute period after infarction. More recently, electrophysiologic testing in the chronic infarction period in patients with ventricular dysfunction has revealed more concordant results. Iesaka et al. noted a high arrhythmic event rate in a population with myocardial infarction of > 30 days duration and inducible sustained monomorphic VT. This was particularly true in patients with an ejection fraction < 40% and approximated 30% at one year of follow-up [14]. The same group noted that induced arrhythmia varied based on the time interval after myocardial infarction. However, it has been argued that risk stratification including routine electrophysiologic testing after myocardial infarction requires routine testing of many more patients than lives saved, with the best ratios being estimated at 30:1 [9].

Such commentary does not address a significant body of literature that suggests that patients with nonsustained VT and left ventricular dysfunction can have more favorable ratios. Wilber et al. reported a 50% mortality in coronary patients with inducible sustained VT at two years with a screened population to arrhythmic death ratio of approximately 13:1 [15]. In progressing from class 1 to class 2 and 3 heart failure, SOLVD patients encountered a marked increase in total annual mortality from 4% to 8% and 30% respectively with one half being arrhythmic death. Class 2 and 3 patients who comprised the MADIT cohort can be anticipated to have an annual sudden death risk of 12% to 15%.

Nonsuppressible arrhythmia after type 1 drug challenge in the MADIT population was a further effort to enhance risk event rates in the study and the success of the MADIT strategy can be judged from the need for implantable cardioverter-defibrillator (ICD) therapy [16]. Thirty-nine percent of patients had shocks for tachyarrhythmias classified as VT/ventricular fibrillation (VF) based on clinical parameters within one year in the defibrillator arm with 60% doing so at two years. Shocks may, of course, occur for rhythms other than VT/VF and stored electrogram data may be critical in this regard. It is estimated 0% to 21% of patients with ICDs have shocks only due to cardiac rhythms other than VT/VF. Thus, even discounting the MADIT data by such a figure, shock event rates in MADIT patients are clearly consistent with the VT/VF event rates seen in prior studies on chronic infarction patients with ventricular dysfunction stratified by electrophysiologic studies [14].

Selecting Therapy: The Increasing Role of ICD

In the MADIT data, sudden death was minimized in the defibrillator arm and this accounted for the survival benefit. A small difference in non-sudden cardiac death seen in the two groups was not critical to the outcome. Another issue raised is whether the events shocked would result in patient death or even serious symptoms. MADIT devices were largely first and second generation ICDs with long charge and detection times. Most VT/VF episodes of >15 seconds duration become sustained though a few may not do so [17]. Whether this intervention of shock therapy aborted a mortal event is best answered by the marked (approximately 77 %) relative reduction in sudden death events in the defibrillator arm of the MADIT study.

Another potential concern with recommending ICD use as primary therapy is that the defibrillator arm of MADIT has shown better outcome due to a proarrhythmic process in the comparison drug therapy arm [18]. In the conventional therapy arm, the average annual mortality over five years was 15%. The SOLVD study showed an annual mortality estimated at 30% for class 3 heart failure patients and 8% for class 2 heart failure. Reviewing the balance of class 1, 2 and 3 patients in MADIT, this would give an estimated annual mortality of 14% for the conventional therapy group, not distinguishable from the observed data in MADIT.

Finally, our comments on ICD benefits are consistent with the results of studies in patients with serious symptomatic ventricular arrhythmias including the recently released results of randomized trials (the Netherlands cooperative study, CASH, and recently AVID). All of these trials prematurely terminated one or all arms of the study. In all these trials, the defibillator recipients have had a uniformly superior survival outcome to one or more of the drug treated patients including those on amiodarone therapy [19-21]. In the AVID study, the relative risk reduction was 28% to 35% over the first three years.

Prospective Application of the MADIT Strategy

What is the denominator for the patients entering MADIT and what happened to those who did not enter the study? Our group, concurrently with entering patients in the MADIT study, conducted a prospective six-year study of all (n = 111) coronary patients with nonsustained VT and minimal, moderate and severe left ventricular dysfunction seen by our service [22]. Fifty-seven (51%) patients had potential minimal arrhythmia related symtpoms. In this project, all patients underwent ambulatory ECG monitoring, assessment of ventricular function, signal-averaged electrocardiography, and electrophysiologic testing. Inducible sustained VT was elicited in 35% of all patients with only one of four being drug suppressed at type 1 drug testing. Based on available data, this would predict at least 23% two-year mortality for the entire screened population [15, 23]. Our data also suggest significant enrichment, with at least doubling of sudden death risk

by electrophysiologic testing in the inducible VT population with screened patients to lives saved ratio of 8:1.

Sudden death was eliminated in the inducible patients by ICD or guided drug therapy with a similar overall survival to the noninducible group, despite a somewhat poorer clinical disease profile. However, in the noninducible group, a significant incidence of sudden death occurred in the subgroup (17% of all patients) with advanced left ventricular dysfunction. This risk is estimated at 30% over five years. These patients received class 3 (largely amiodarone) therapy [24]. The overall concomitant survival of this group is under 65%.

The benefits of ICD therapy in these high risk coronary patients with and without inducible VT can be inferred from our study and the MADIT data. There is <5% risk of sudden death with a 70% survival in ICD recipients at five years. Additional benefit may accrue if cardioverter-defibrillators are used in the high risk subgroup of patients with no inducible VT instead of class 3 drugs. There are presently limited data suggesting a proarrhythmic effect of amiodarone accounting for this sudden death risk. It would seem unlikely that this could account for the majority of the observed sudden death in this cohort. Even if 50% of the risk is due to tachyarrhythmia as suggested by others, [25] this would increase the overall population at risk for sudden death by at least 28%.

ICD therapy can be used in patients with inducible VT as well as patients with severe left ventricular dysfunction and no inducible VT. This combination constituted 24% of our study population with nonsustained VT and coronary disease. Assuming that a cardioverter-defibrillator affords 90% protection against sudden death at five years and a 1% implant mortality risk (implant and proarrhythmia), testing of 100 patients could potentially save 16 additional lives as compared to conventional drug therapy. Presence of more than one myocardial infarction and diabetes mellitus were shown in a multivariate analysis of MADIT data to predict further increased hazard ratios (2.5 to 10:1) for tachyarrhythmic events and ICD shock delivery [16]. Thus, it is conceivable that such clinical parameters can further refine the population admitted to invasive testing and this could improve the yield ratios for invasive testing beyond 8:1. It is also clearly conceivable that future studies could evolve noninvasive indices that would provide similar yields to invasive studies [3]. This hypothesis is clearly now suitable for testing in prospective clinical studies. Nevertheless, the basic strategy for the immediate future in addressing the enormous problem of sudden cardiac death, remains to identify the patient at risk for arrhythmic death without limiting the benefit by other competing mortalities. In this regard, advanced class 3 heart failure may need further stratification for nonarrhythmic mortality risk [26].

Conclusions

The present exercise illustrates the new directions in screening, stratification and therapy of patients with nonsustained VT that may evolve with the MADIT strategy and further prospective trials. It may well be that noninvasive criteria for

screening and stratification will be supplemented by invasive testing in select subgroups. Maximal antiarrhythmic protection, currently afforded only by ICD devices but hopefully matched in the future by other therapeutic options, can help to hasten the demise of the contention that antiarrhythmic interventions alter the mode of death without prolonging patient survival. In any case, management of coronary patients with nonsustained VT has been irrevocably changed by MADIT and other studies.

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IMPLANTABLE CARDIOVERTER DEFIBRILLATOR: CLINICAL ISSUES AND NEW INDICATIONS

Which Patients with ICD May Really Benefit from DDD Pacing, and Which Won't?

A.S. Montenero, T. Sanna, G. Pelargonio, F. Bellocci and P. Zecchi

Introduction

The efficacy of implantable cardioverter-defibrillators (ICD) in preventing sudden death has been shown by several trials. Nonetheless two functions need to be improved: (1) the identification of arrhythmias other than VF (supraventricular or ventricular fibrillation) in order to reduce inappropiate shocks, (2) the quality of cardiac pacing. Dual-chamber pacing should be the stimulation method of choice in patients with depressed sinus node function, or in those who are pacemaker dependent, when effective atrial pacing and sensing can be achieved. In contrast, patients with an implatable cardioverter defibrillator (ICD) who also need antibradycardia pacing, can currently receive only fixed rate ventricular pacing, even though most of them have depressed sinus node function. Furthermore, positive hemodynamic effects of atrioventricular sequential pacing in patients with left ventricular dysfunction have been described so far [1, 2]. In fact the preservation of atrioventricular synchronization can result in a positive effect on the morbility and perhaps on the mortality of pacemaker dependent patients [1].

Reasons for Pacing in ICD Patients

A need for antibradycardia pacing other than that required after defibrillation can be related to: (1) the presence of some conventional pacemaker indications at the time of ICD implant, (2) a permanent pacemaker already implanted before the ICD implant, (3) persistent bradycardia, whether or not related to AARx (Anti-Arrhythmic Therapy) at the time of ICD implant.

Pacing and ICD Patients

In patients with a previously implanted DDD pacemaker and those with some degree of AV block, DDD pacing (or VDD, depending on the sinus node func-

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tion), would be more adequate than VVI pacing. Moreover in patients with persistent bradycardia or some degree of sinus node dysfunction (sick sinus syndrome), subsequent VVI pacing results in mild to moderate pacemaker syndrome which requires the programming of a ventricular rate lower than the spontaneous sinus cycle length.

Currently pectoral transvenous nonthoracotomy cardioverter defibrillators only offer VVI pacing and when a dual-chamber stimulation is indicated, a permanent transvenous DDD pacemaker insertion is required, either before or after ICD implantation. In case of need for both devices, adverse interactions between the two systems can occur: they include pacemaker non-capture, undersensing, transient inhibition after ICD discharge as well as ICD oversensing or failure to detect VF [2, 3]. In particular Geiger recently reported interaction in 38% of patients who where implanted with both devices, despite careful lead implantation, bipolar pacing and extensive testing [4]. Furthermore this author described a potentially significant interaction, not previously reported, that consisted of a rise in DFT (Defibrillation threshold) following pacemaker implantation which might result in a suboptimal therapy for VF. Since the upcoming generation of ICD can also offer dual-chamber pacing, but with no more expensive cost and larger size, it would be important to make an appropriate selection of which kind of patients can require a DDDICD.

Selection of Candidates for DDDICD

To identify patients who require dual-chamber stimulation at the time of ICD implantation would be by now of permanent importance for improving their quality of life. Most of these patients can be easily identified on the basis either of a previous electrophysiological study or of a Holter recording, even if a simple surface ECG can sometimes show the presence of conduction disturbance of persistent bradycardia. Moreover some ICD patients require additional pharmacological therapy, for frequent episodes of VT, that can determine persistent bradycardia, despite normal sinus function in basal condition. Thus it would be reasonable to select patients also on the basis of both the number of the expected episodes of VT and the need for potentially bradycardia - inducing pharmacological treatment.

Prevention of atrial fibrillation still remains an issue in patients implanted wth ICD to avoid inappropriate shock and to improve hemodynamics. Initially performed primarily for bradycardia dependent atrial fibrillation with good results, more recent data show benefits of atrial pacing in the absence of primary bradyarrhythmia disorder.

Dual-chamber ICD permits atrial pacing without the need for another generator or other leads, making prevention of atrial fibrillation more feasible in ICD patients. Thus, it would be reasonable to provide prospective data on this issue.

LV Function and DDD Pacing

Atrioventricular synchronous pacing represents a clinical benefit for patients with an already depressed left ventricular function.

The increasing interest in the beneficial effects of cardiac pacing in patients with depressed left ventricular function deserves further comments. In fact, although limited, the experience with DDD pacing in dilated cardiomyopathy is promising, at least in selected patients.

Dual-chamber pacing with an optimal or short AV delay has been shown to improve symptoms and to decrease need for further hospitalization due to worsening of heart failure, but there is no current evidence of a higher survival rate with this treatment [5].

Nonetheless, atrioventricular pacing may improve hemodynamics in patients with compromised left ventricular function and may also decrease episodes of atrial fibrillation due to atrial overload. An improvement, during DDD pacing, of echocardiographically derived cardiac index by 36% and 50%, respectively, and a significant increase in exercise capacity has been recently demonstrated in two patients implanted with DDDICD [5]. In view of well known coexistence of moderate and severe left ventricular dysfunction in ICD patients, the availability of atrial pacing could benefit hemodynamics and survival.

Arrhythmia Detection and DDDICD

Antitachycardia pacing (ATP) is a reliable technique to treat ventricular tachycardia (VT) and this function is frequently activated in the last generation ICD to reduce the need for shocks. Although efficacious, the use of ATP is often limited; in fact slower VT often cannot be distinguished from some types of supraventricular arrhythmias or from sinus bradycardia solely on the basis of the sensed ventricular electrogram.

Thus inappropriate shocks for supraventricular arrhythmias are known to occur in up to 20% of all patients and in 25% of those with history of atrial fibrillation [6]. Various methods have been proposed to overcome this problem while still remaining in a single-chamber ventricular architecture.

In the third generation of ICD, ventricular intervals or signal morphology have been used to classify tachycardias: rate, RR stability, sudden onset, R wave with wide morphology. These criteria increased sensitivity for monomorphic ventricular tachycardia (VT), nonetheless many supraventricular tachycardias, mainly atrial fibrillation, still are identified as VT. The recent introduction of dual-chamber ICD has extended the capabilities of ICD technology in arrhythmia detection. These devices now independently sense in the atrium and ventricle and use sensing algorithms relating both signals to diagnose supraventricular and ventricular tachyarrhythmias. They permit several patterns of shock to reset supraventricular or ventricular arrhythmias or both arrhythmias simultaneously. Only one clinical experience has been reported for DDD ICD at this time [7]. The

DEFENDER 9001 ICD has been the first implanted device which includes atrial based criteria to reject SVT from therapy (PARAD^{TM}).

Seventy patients received a DEFENDER 9001 and were eligible for the follow-up of 8.5 ± 7 months. Although PARAD^{TM} resulted in a high specificity in detecting atrial tachycardias, inappropriate shocks were still observed on AF at the nominal VT persistence program [7]. Thus a new PARAD+^{TM} has been designed and it is reasonable to hope that sensitivity and specificity on supraventricular arrhythmias detection will improve. Preliminary data from PARAD+ simulation are encouraging, althought limited by (a) the small number of patients, (b) short episode duration, (c) lack of onset of the induced arrhythmias, and (d) lack of therapy delivery.

However a dual-chamber arrhythmia diagnosis algorithm that incorporates both temporal and morphological criteria outperforms a ventricular rate-only algorithm.

Future generation of ICD should incorporate information from both cardiac chambers into arrhythmia detection algorithms so that safety and efficacy of the electrical therapy can be improved.

Conclusion

More than 15 years of research and development have produced devices which combine complex diagnostic with therapeutic parameters and capabilities. The recent introduction of DDD ICD has improved ICD technology in both arrhythmia detection and treatment. Prevention of inappropriate shocks is mandatory and this is larger a matter of the overall population of patients implanted with an ICD.

Moreover, patients with poor left ventricular function, or persistent bradycardia can represent a group in which DDDICD further improves the clinical outcome.

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Can Alternative Pacing Therapy Solve the Problem of Heart Failure Death in ICD Patients?

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The automatic implantable cardioverter-defibrillator (ICD) was originally conceived by Mirowski [1] as a device for detecting and terminating potentially lethal ventricular tachyarrhythmias. There is general agreement that the device has demonstrated its ability to significantly reduce the incidence of sudden cardiac death [2, 3], which has been definitively demonstrated by important prospective studies like MADIT and AVID [4]. This has resolved the question of whether the ICD is able to reduce overall mortality [5]. Nevertheless cardiac mortality remains 15% to 20% at 2 years in ICD patients [6,7].

It is obvious that the mortality benefit of ICD, despite significant reduction of sudden tachyarrhythmic death, is limited by the extent of left ventricular dysfunction. In addition to the problem of ventricular dysfuntion treatment, prevention of ischemia is also extremely important [4]. Heart failure and ventricular tachyarrhythmias are "fellow travelers" as demonstrated by the fact that the vast majority of patients who receive ICDs have at least a moderate degree of left ventricular dysfunction.

By virtue of marked reduction in sudden death attributable to ICD treatment most patients will live long enough to experience "late conversion" of their mode of death. This "unnatural history" is a reflection of advances in prevention of sudden death and better treatment of heart failure thus altering the mode of death. The concept of "late conversion" of the modality of death is substantially different from that referred to by other investigators as an explanation of failure of the ICD to reduce total mortality. The limitation of the concept of "conversion" as originally expressed by Kim [8, 9] is that one considers the patient at the time when ventricular arrhythmias predict imminent death due to end-stage heart failure. Measured at this point in time, the "survival benefit" of the ICD would appear small. However as demonstrated by Sweeney [10], a more dynamic long-term process is present. A marked reduction in sudden death rate in the ICD group in heart transplant candidates appears to be erased by higher nonsudden death rates throughout follow-up. The net effect of reduced sudden death on total mortality is thereby continously marginalized.

The results of Metha [11] and Sweeney [10], who subdivided ICDrecipients into two subgroups based upon ejection fraction (LVEF ≥30% or <30%) and

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those who experienced at least one appropriate shock compared to those who remained free of any arrhythmic event after ICD implantation, suggest that successful termination of recurrent ventricular tachyarrhythmias by the ICD yields the same outcome as with patients having a similar degree of left ventricular dysfunction but no recurrent tachyarrhythmias. These data are consistent with the results of Levine [12] and Grimm [3] demonstrating that total cardiac mortality remained significantly higher in the subgroup of patients with severely depressed ventricular ejection fraction (≤ 30%), regardless of whether there were appropriate ICD discharges or not.

In patients with severely impaired left ventricular function (LVEF < 25% to 30%) and advanced symptomatic congestive heart failure (NYHA III-IV) there is no significant benefit of ICD despite in significant levels of sudden tachyarrhythmic death. High incidence of non-sudden death is likely to be prohibitive, and conversion of the mode of death by ICD from sudden to nonsudden death will occur early, as recently reported by Sweeney [10].

The fact that overall mortality remains 30% to 40% at 5-year follow-up in various ICD subgroups with reduced LVEF (less than 30%-35%) and advanced functional class (NYHA ≥ II-III), despite tailored conventional drug therapy of heart failure, indicates that there is a need for optimization of congestive heart failure (CHF) treatment by alternative non-pharmacological approaches (Table 1).

Several non-pharmacological therapies have been proposed for the optimatization of drug therapy in patients with congestive heart failure. Pacing therapy has been recently described as a possible supportive option to best medical treatment in patients with poor ventricular function and symptoms of severe congestive heart failure [13, 14].

Hochleitner [14] first reported long-term beneficial effects of dual chamber pacemaker therapy using short atrioventricular (AV) delay of 100ms in 16 patients with severe CHF (NYHA class IV), idiopathic dilated cardiomyopathy and in whom conventional drug therapy had failed. A striking improvement in heart failure symptoms could be achieved. This first non-randomized study, however, has several sources of bias in data interpretation and shortcomings. Yet, it indicated that pacing therapy may be an option for improvement of heart failure. Similarly, we have previously demonstrated significant clinical improvement in patients with ischemic dilated cardiomyopathy in whom atrial sensed ventricular stimulation (VDD) with shortened AV delay was performed [15]. Although other pacing studies did not demonstrate significant changes either in hemodynamic parameters or with functional status [15, 16], it is interesting to note that at least some patients showed impressive improvement with dual-chamber pacemaker implantation using shortened AV delay [17, 18]. More recently, Foster et al. [19] and Bakker et al. [20], using an innovative approach of simultaneous right and left ventricle stimulation (or biventricular pacing), have shown dramatic hemodynamic as well as clinical improvement with acute testing and short-term follow-up, respectively. The non-uniform benefit data of a conventional dual-chamber pacemaker therapy or of biventricular stimulation in patients with congestive heart failure can be explained in many ways: the use of different pacing modali-

Table 1. Comparison of different studies including patients with moderate to severe heart failure

	MADIT [4]		GESICA [22]		CHF-STAT [23]		Sweeney et al. [10]		
	ICD	Conv.	Amio.	Plac.	Amio.	Plac.	ICD	AAD	No Therapy
No. Patients	95	101	256	260	338	336	59	53	179
NYHA II	63[a]	67[a]	20.4	21.5	56.3	54.7	-	-	-
NYHA III			48.0	48.5	42.4[d]	44.0[d]	3.2[c]	3.5[c]	3.5[c]
NYHA IV			31.6	30			-	-	-
SR (%)	N.A.	N.A.	70	72.3	84.8	84.6	79.7	56	56
LVEF (%)	27	25	20	19	<30[b]	<30[b]	18.2[c]	17.9[c]	19[c]
CHF Rx (%)	52	51	100	100	100	100	100	100	100
LBBB (%)	7	8	26.6	26.9	N.A.	N.A.	N.A.	N.A.	N.A.
Study Duration (Yrs)	5		2		3.5		5		
Total Mortality (%)	16	39	41.4	33.5	30.6	29.2	43.1	60.6	52.7
SCD rate (%)	3	13	15.2	12.3	19	22	15.4	49.3	36.9
NSCD rate (%)	7	13	20.3	16.9	10	12	32.7	22.2	25.1

NYHA, functional class according to New York Heart Association criteria; SR, sinus rhythm; LVEF, left ventricular ejection fraction; CHF Rx, percentage of patients treated by medical therapy for congestive heart failure; LBBB, left bundle branch block; SCD, sudden cardiac death; NSCD, non-sudden cardiac death.

[a]patients in NYHA class II and III have been counted together

[b]no details on the exact LVEF but the majority of patient population (67.3% and 56.7%, respectively) had a LVEF less than 30%

[c]all values are considered as mean of the NYHA class (standard deviation has been omitted)

[d]patients in NYHA class III and IV have been counted together

ties, the fact that no single mechanism or abnormality is postulated in patients with advanced CHF, and also that there exists a complex relationship between electrical and mechanical effects produced by pacing.

The chronic end-diastolic volume and pressure overloading causes alteration of atrioventricular valve competence and atrial dysfunction. This reduces the filling time which in turn reduces stroke volume. Elongation of cardiac myocytes and disarrangements of the extracellular matrix may be the predominant contribution to heart failure in certain clinical entities; loss in myocytes which results in fibrosis may also contribute to alteration in the rearrangement of both specialized as well as working myocardial cells resulting in conduction disturbances. Conduction disturbances are then worsening the global and regional pump function. Electrocardiographic signs of these conduction defects are prolongation of P-Q interval, P wave widening and bundle branch block abnormalities.

Appropriate pacing, therefore, can find its rationale for heart failure treatment by interrupting the vicious cycle of failing. An indication for pacing in heart-failure patients may be found when there is a prolongation of the atrioventricular delay, a reduction of the filling time and, finally, when the ventricular activation sequence is changed.The potential impact of each of these mechanisms on the improvement of cardiac function in patients with reduced ejection fraction and symptoms of severe CHF has been recently discussed by us [21].

Intraventricular conduction defects frequently occur in patients with markedly reduced ventricular function, and symptoms of moderate to severe heart failure with or without documented VT or VF. These conduction disturbances are often left bundle branch blocks occurring in about 30% (Table 1). Left bundle branch block seems to negatively affect the long-term prognosis of patients with CHF. Cardiac death rate has been reported to parallel the width of the QRS complex in patients with poor left ventricular function. The progression of global as well as regional impairment of ventricular function determined by the left bundle branch block could possibly be prevented by appropriately pacing either the left ventricle or both ventricles simultaneously, thus reducing or eliminating large intraventricular or interventricular conduction delays. In addition, the mechanical asynchrony between the anterior portion and the posterolateral site of the left ventricle, by means delaying the appropriate closure of both mitral valve leaflets, causes an important backward gradient between the ventricle and the atrium. The prevention of deleterious prolongation of mitral regurgitation time by appropriate pacing technique could substantially reduce the mitral regurgitation, thus determining a reduction of the ventricular chronic volume overload.

Conclusions

Various theoretical as well as clinical data indicate that improvements of CHF, may be obtained in selected patients by modifying the atrioventricular delay and/or eliminating ventricular asynchrony through the use of dual-chamber sequential pacemaker therapy or chronic biventricular pacing.

Since an important proportion of ICD candidates or patients who already have ICDs present with conduction disturbances amenable toelectrical correction, it seems logical that the long-term prognosis of thissubset of ICD patients will benefit by this approach. On the otherhand, many large multicenter studies in patients with severe CHF whohave intraatrial/intraventricular conduction delays also showed that theincidence of SCD despite optimized tailored therapy for CHF stillremains significant.

Therefore, there is reason to believe that future electrical treatment of CHF could be performed by complex devices capable of appropriate pacing as well as backup cardioversion-defibrillation.

Randomized multicenter studies need to be undertaken in order to validate the concept of "pacing for heart failure" combined with ICD therapy showing benefit in terms of clinical symptoms, quality of life and measurable hemodynamic improvement. There is no doubt, that this will also have a positive impact on overall survival in these patients who have a poor outcome otherwise.

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Have MADIT and Recent Post Myocardial Infarction Amiodarone Studies Changed the Classical Indications for ICD Implantation?

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Introduction

Sudden cardiac death still accounts for approximately 200 000 to 400 000 premature deaths in the USA [1] and thus continues to be a major challenge in today's cardiology. Within the last 12 months, several well controlled prospective studies have been published concerning the value of prophylactic implantation of the cardioverter-defibrillator (ICD) [2] and the administration of amiodarone to improve survival of patients after myocardial infarction [3, 4]. For the practicing cardiologist and even more so for the electrophysiologist, these trials pose the question whether one of these studies, taken alone or combined, impact on current indications for the implantation of the ICD. Therefore, it is the purpose of this short review to summarize the main findings of these major trials and put them into perspective with respect to our current therapy aiming at preventing sudden cardiac death.

Accepted Indications for ICD Implantation

At present, guidelines for implantation of the ICD have been published by various organizations and institutions on both sides of the Atlantic ocean [5, 6]. In general terms, ICD implantation is considered as an accepted indication in patients with one or more episodes of documented ventricular tachycardia or fibrillation in whom no alternative therapy (i.e. electrophysiologically guided antiarrhythmic drug therapy or surgery) has been found to be effective. Similarly, spontaneous, recurrent ventricular tachycardia/fibrillation, despite the best alternative therapy, is also considered as an accepted ICD indication. Prior to the publication of MADIT [2], no data for the *prophylactic* use of an ICD were available in patients without a preceding episode of sustained ventricular tachycardia or fibrillation.

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MADIT: a Step Ahead

As reported in more detail elsewhere in this volume, MADIT is the first prospectively designed trial concerning the use of ICD implantation in patients without a history of sustained ventricular tachyarrhythmias. In essence, to be included in this trial, patients with documented prior myocardial infarction, a left ventricular ejection fraction of ≤ 35% and asymptomatic nonsustained ventricular tachycardia on Holter monitoring were screened for inducibility of sustained ventricular tachyarrhythmias. If a sustained ventricular tachycardia or ventricular fibrillation was reproducibly inducible but subsequently not suppressible by intravenous procainamide, patients were randomized to receive an ICD (n = 95 patients) or the best conventional therapy (n = 101 patients). The latter consisted of administration of amiodarone in 74/93 cases (80%). After a mean follow-up of 27 months, significantly less patients randomized to the ICD arm had died than in the conventional arm (15 vs 39 patients; hazard ratio 0.46 (0.26-0.82); $p = 0.009$) [2]. This led to the premature termination of the trial by the data safety and monitoring board in March of 1996. In Table 1, the results of this study in terms of the primary endpoint, total mortality, are detailed. Despite this impressive result, several issues have to be kept in mind when one tries to extrapolate the results of MADIT to other patient populations. The patients enrolled in MADIT represent a highly selected subgroup of post infarction survivors whose most important risk factor is undoubtedly reflected by their inducibility at electrophysiological testing in the setting of depressed LV function. On the other hand, MADIT appears to be not the classical postinfarction study since three quarters of the patients were enrolled in the trial more than 6 months after their index infarction [2], a time window generally considered to represent the interval with the highest risk for postinfarction survivors. The fact that no prospective registry of screened but not included patients was kept makes it difficult to determine the denominator population from which the MADIT patients have been selected. Moreover, there was a difference concerning the proportion of patients treated with β-blockers: only 6% of the patients in the conventional group was receiving β-blockers compared to

Table 1. Mortality in the MADIT study (from [2])

Cause of death	Conventional therapy (n = 101 patients)	ICD therapy (n = 95 patients)
Cardiac cause	27	11
Primary arrhythmia	13	3
Nonarrhythmia	13	7
Uncertain	1	1
Noncardiac cause	6	4
Unknown cause	6	0
Total number of deaths	39	15

31% in the ICD group. Although not independently related to primary outcome endpoint, this appears to be an important point given the fact that amiodarone seems to work particularly well when given simultaneously with β-blockers (see below). Finally, the relatively small patient sample and the unexplained high number of nonarrhythmic deaths as well as deaths from unknown cause in the conventional arm (Table 1) are factors which have to be considered carefully. Therefore, the results of this important study apply only to the specific patient subset enrolled which has been estimated to represent at best 1% of all survivors of myocardial infarction [7]. Nevertheless, MADIT has told us that prophylactic ICD implantation *can* result in improved survival in carefully selected patients after myocardial infarction. For this selected patient cohort, but *only for this population*, MADIT has therefore indeed changed our classical ICD indications.

Impact of Recent Amiodarone Trials on ICD Indications

Most recently, two large-scale prospective trials have been published which evaluated the efficacy of amiodarone in post infarction survivors: the EMIAT [3] and the CAMIAT [4] studies. In Table 2, the most pertinent features of both these tri-

Table 2. Study characteristics and main findings of the EMIAT and CAMIAT post infarction amiodarone studies (from [3] and [4])

	EMIAT	CAMIAT
Inclusion window post MI	5-21 days	6-45 days
Inclusion criteria	LVEF ≤ 40%	≥ 10 VPBs/h or ns VT
Primary endpoint	All-cause mortality	Arrhythmic death plus resuscitated VF
Patients	1486: 743 placebo 743 amiodarone	1202: 596 placebo 606 amiodarone
Follow-up period	21 months (mean)	1.79 years (mean)
Main findings		
Primary endpoint	No difference in all-cause mortality[a]	Arrhythmic death + resus. VF: 48.5% risk reduction by amiodarone ($p = 0.029$)
Secondary endpoint	35% risk reduction in arrhythmic death ($p = 0.05$)	No difference in all-cause mortality[a]

MI, myocardial infarction; LVEF, left ventricular ejection fraction; ns VT, nonsustained ventricular tachycardia; VF, ventricular fibrillation
[a]Note that in neither study was there a significant amiodarone-associated improvement in all-cause mortality

als are compared along with the main study findings. Perhaps the most important difference concerns the various primary endpoints of these studies, namely total mortality as applied in EMIAT and arrhythmic death/resuscitated ventricular fibrillation in CAMIAT. Most remarkable, all-cause mortality was not reduced by amiodarone in both these trials when compared to the placebo group. There was, however, a significant reduction in the primary endpoint of CAMIAT, the composite of arrhythmic death and resuscitated VF [4]. Similarly, EMIAT demonstrated a significant reduction in arrhythmic death associated with the use of amiodarone [3]. In both trials it was demonstrated that amiodarone was significantly more effective in patients in whom β-blocker therapy was simultaneously administered [8, 9]. These retrospective analyses indicate that β-blockade may be necessary for amiodarone to exert its antiarrhythmic and particularly its mortality lowering effects, a finding which should also be taken into account when considering the results of MADIT (see above).

It appears noteworthy that neither EMIAT nor CAMIAT were statistically powered to detect differences in all-cause mortality smaller than 33%. This was the major reason that led these investigators to pool their results together with 11 previous studies comparing amiodarone to placebo. These so-called ATMA meta-analysis (Amiodarone Trials Meta-Analysis) results were reported most recently [10]. This meta-analysis comprised a total of 6553 patients, 5101 of whom were enrolled in post infarction studies and 1452 in congestive heart failure trials. As the main result of this retrospective statistical analysis, an odds ratio of 0.87 (95% confidence intervals: 0.78-0.99; $p = 0.03$) in all-cause mortality associated with the use of amiodarone could be demonstrated [10]. This 13% risk reduction in total mortality was associated with a 29% risk reduction in arrhythmic death ($p = 0.0003$). Furthermore, the meta-analysis provided evidence for a similar efficacy of amiodarone in patients with an LVEF of ≤ 35% compared to those with an LVEF > 35%. When the findings of the individual studies and of the meta-analysis are taken into consideration, it appears that these observations do not directly impact on current ICD indications. On the other hand, these data do by no means support the use of amiodarone in *all* survivors of myocardial infarction as primary prevention of sudden or cardiac death. For the practicing clinician, amiodarone appears to be a valuable drug for instance for patients who, after their infarct, are suffering from symptomatic arrhythmias such as VPBs, couplets or runs, since none of the major trials provide evidence that amiodarone administration is harmful. This is clearly in variance with other studies such as the CAST or the SWORD trials [11-13]. To risk stratify such patients further, the observations made by the MADIT investigators indicate the use of electrophysiological testing. It is, however, important to realize that this method of risk stratification has never been compared to other noninvasive risk stratifiers such as heart rate variability [14], baroreflex sensitivity [15], or T-wave alternans [15]. Thus, there is a need of further studies evaluating these different methods by direct comparison.

Clinical Summary

MADIT is the first study to support the prophylactic use of the ICD in a well defined subpopulation of coronary patients at high risk of sudden cardiac death. Accordingly, the current ICD indications should be adjusted for this particular patient population which appears to comprise only a minority of infarct survivors. Future studies should aim at evaluating the efficacy of the ICD in patients subjected to noninvasive risk stratification soon after myocardial infarction. Whereas the amiodarone studies have demonstrated the relative safety of its use after myocardial infarction, individual studies failed to show benefit in terms of reduction of all-cause mortality. These placebo-controlled studies obviously do not directly impact on the use of the ICD. However, the prematurely terminated AVID trial [14] which compared amiodarone therapy to the ICD in VT/VF survivors clearly demonstrated a survival benefit for those patients treated with the ICD even when all-cause mortality was considered [15]. Accordingly, what can be derived from the above described results is that it appears that the ICD should be the preferred therapeutic approach in patients surviving an episode of ventricular tachycardia or fibrillation. AVID, therefore, supports the currently accepted ICD indications with solid scientific data for the first time thereby clearly impacting on device use in the future.

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What Have We Learned from the US Experience on the Prophylactic Use of ICDs Following MADIT?

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Referred to as the "single most important arrhythmia study of the 90's", the Multicenter Automatic Defibrillator Implantation Trial (MADIT) has had a profound effect on the worldwide practice of cardiac electrophysiology [1]. While the conclusions of the study recommend a dramatic change in therapy application for selected high-risk asymptomatic patients, the actual implementation of these recommendations has not been previously reported. We will review the MADIT experience in the United States (U.S.), placing it in historical perspective, in the first year since conclusion of the study.

Background

Initiated in 1990, the MADIT study was a randomized, multicenter trial comparing conventional therapy, the majority of which comprised amiodarone use, with a U.S. approved implantable cardioverter defibrillator (ICD). Details of the prospective study design were published in 1991 [2]. Patients enrolled were free of arrhythmia symptoms presenting with silent demonstration of nonsustained ventricular tachycardia in the setting of a previous remote myocardial infarction and LV dysfunction (EF 0.35). At screening electrophysiology study, patients were inducible into sustained ventricular tachycardia or fibrillation not suppressible with intravenous procainamide. Additional inclusion and exclusion criteria are reviewed in the primary manuscript [1]. The Data and Safety Monitoring Committee terminated the study on March 24, 1996 and the results were first presented on May 16, 1996 accompanied by international publicity. These results revealed a 54% lower death rate in patients randomized to the ICD. The study recommended that all patients who met the enrollment criteria receive a prophylactic defibrillator, as was done for the conventional therapy group upon study completion.

Several criticisms of the study surfaced [3]. These included cost implications, proarrhythmia issues, and an admonition that the true MADIT patient is not often seen in clinical practice. Each of these has been addressed in formal pre-

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sentations. The cost issues were recently summarized by Mushlin et al. where the cost-benefit of ICD application to this patient subgroup was found to be less expensive ($23 000-$27 000 per life-year saved) than many accepted conventional treatments such as TB skin testing and dialysis [4, 5]. The cost-effectiveness of ICD therapy has been further improved by advances in device therapy resulting in less invasive insertion techniques [6]. Proarrhythmia issues, originally included in the submitted draft of the primary paper, were later presented in a separate publication [7]. This data revealed that none of the conventional therapy cardiac deaths occurred in patients on Class IC antiarrhythmic agents and that only 6 of 39 deaths were on any Type I drug. This issue was further supported by the concurrent publication of two amiodarone trials (EMIAT and CAMIAT) showing a lack of proarrhythmia in similar patients [8, 9]. Concerns about extrapolation of the study results to other populations and an encouragement to await further trials has also been addressed [7, 10]. The recent conclusion of the Antiarrhythmics vs Implantable Defibrillator (AVID) trial, showing statistically significant benefit of the ICD over antiarrhythmic drug therapy in cardiac arrest survivors, has directly addressed this concern [11].

The MADIT indications define a specific population. This has been estimated to range from 16 000 – 50 000 new U.S. patients annually. This number could exceed the total current U.S. ICD implant volume (approximately 26 200 in 1996). In addition, there is a substantial backlog of patients who meet the MADIT criteria whose index MI was not in the past year. Thus, the question arises, "Have the MADIT results impacted ICD implantation practice patterns?".

Data Available

There is a paucity of data available regarding ICD implantation practice patterns in the U.S. Traditional data registries do not capture MADIT indications separate from other indications. However, we do know that U.S. ICD implant rates have increased. Due to multiple factors, implant rates have increased about 18% annually prior to MADIT. As shown in Figure 1, growth in the U.S. market jumped in the first quarter of 1997, the first three months after the December 26,1996 publication of the study. This increase was 29%, compared to an anticipated 18% annual growth rate. This represents a 63% increase in anticipated market growth. Thus, with indirect evidence, it does appear that the U.S. market is growing as a result of the publication of the MADIT results.

Not all of this excess growth can be attributed to MADIT patients alone. It has been estimated that at least half of the recent growth can be attributed to patients who previously would not have been referred for ICD therapy [12]. For example, our (SLH) ICD implantation rate has increased 20% annually for the past two years with only about 25% of this growth estimated to be due to MADIT referrals. However, as a MADIT investigation center, the recent increase in referrals for MADIT indications may have been influenced by our prior participation in the study.

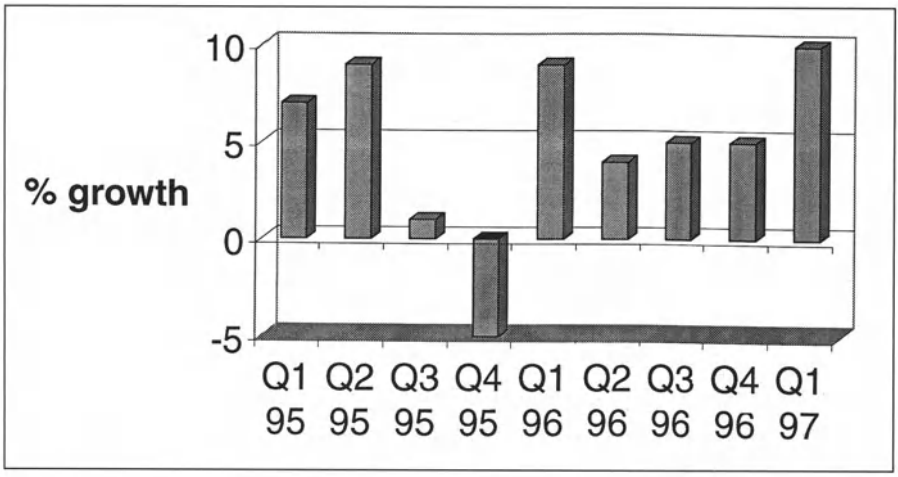

Fig. 1. Growth of the U.S. ICD market by quarters from 1995 through March, 1997. Values are displayed as the percentage growth over the preceding quarter

Interestingly, it does appear that some of the excess increase in ICD referrals are for traditional (non-MADIT) indications which may be partly attributable to the publication of the MADIT results. We refer to this as "MADIT creep". The theory is that referring physicians may now consider other arrhythmia patients for ICDs, since a randomized trial has shown benefit of the ICD for the MADIT indication. These patients, who have had a cardiac arrest or other previously appropriate indication for an ICD, are now referred as the study has helped to further legitimize ICD therapy. In addition, the concurrent publicity over the apparent relative inefficacy of amiodarone and other antiarrhythmic agents has eliminated the previous excuse for avoiding referral for ICD therapy [8-11]. Thus, the increase shown in Figure 1 in ICD market growth may be partly attributed to MADIT creep.

The incremental percentage growth in the U.S. ICD market is shown in Figure 2. As it is evident there is substantial quarter to quarter variability in market growth. Thus, while the 10% growth observed in the first quarter of 1997 is the largest observed in recent years, its relative significance is unknown. Future results will help to better define the significance of the trend.

Physician Survey

Physician responses to market surveys may also represent an estimate of the impact of the MADIT study. One such survey of 59 practicing cardiologists and internists revealed interesting responses to two questions (Fig. 3). Although most respondents personally expressed an agreement with the MADIT findings, they also expressed skepticism that others would embrace the study's recommendations.

The second question in Figure 3 points out one issue which may represent a

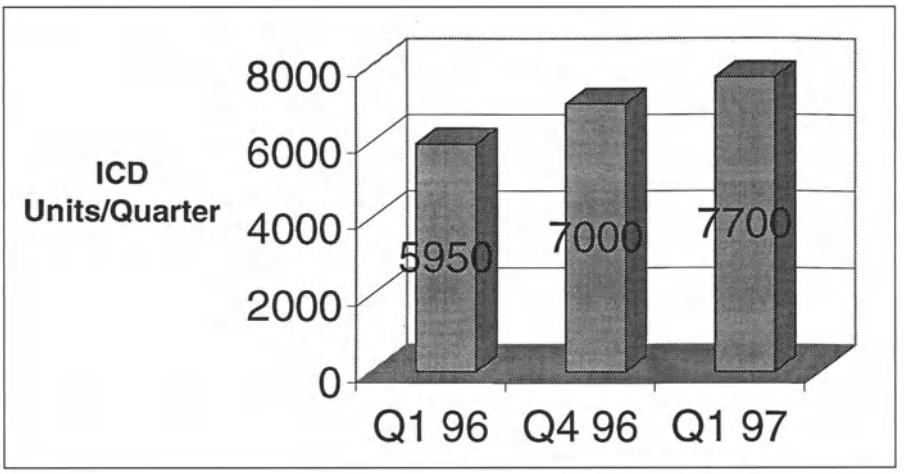

Fig. 2. ICD implant volume in the U.S., expressed as devices inserted by quarter. The same quarter comparison between first quarter 1996 and 1997 shows a 29% increase

On a strictly medical basis (excluding cost and other factors), would you follow the MADIT protocol for patients fulfilling the MADIT criteria?

72% yes
9% no
19% maybe

How long do you believe it will take (after the New England Journal of Medicine publication, local seminars and other publications) for 50% of cardiologists who are not Holter monitoring asymptomatic, low EF patients, to start doing so?

8% 3 months
7% 6 months
32% 12 months
46% > 12 months
6% never

Fig. 3. Selected responses of a physician practice survey of 59 U.S. cardiologists (through April 10, 1997) [12]

stumbling block to MADIT study acceptance. The MADIT inclusion criteria require expensive non-invasive tests to be performed in order for patients to be considered for further expensive invasive screening and device implantation. Despite the results of the cost-effectiveness study, managed care medicine encourages physicians to avoid expensive screening tests unless warranted by symptoms [4]. Specifically, Holter monitor usage flattened after publication of the Cardiac Arrhythmia Suppression Trial (CAST) results [13]. The physicians

surveyed in the study, shown in Figure 3, believe that a reversal of this tendency will be slow in coming.

Historical Experience

Traditionally, physician practice patterns have been slow to change despite publicity of new approaches. For example, as long ago as 1983, a task force from the North American Society of Cardiac Pacing and Electrophysiology (NASPE) suggested that dual-chamber pulse generators are indicated in 60% - 80% of all implants [14]. However, it took 12 years (until 1995) before the implant volume reached 60%.

Similarly, proven therapies for other cardiac conditions from β-blockers for MI prophylaxis to angiotensin-converting enzyme inhibitors for congestive failure, to anticoagulants for atrial fibrillation, were all accepted at rates slower than authorities recommended [15-17]. Acceptance appears to develop gradually for several years after initial publication. Even recommendations that result in avoidance of prescription of medication are slow to be accepted, as evidenced by the response to the CAST results [13, 18].

Conclusion

The MADIT study closed in March, 1996, was first presented in May, 1996 and was published in December, 1996. Since then, marketing efforts have been directed at U.S. physicians to alter practice patterns to refer appropriate patients for screening and, when appropriate, ICD implantation. Based on non-peer review publicity, initial acceptance was slow. However, since publication of the primary article, ICD implant volumes have jumped from 1975 to over 2500/month, up 29% comparing first quarter 1997 to 1996. Much of this growth can be attributed to the referral of MADIT eligible patients as well as to MADIT creep, increased referral of non-MADIT patients directly resulting from the study's findings.

History has shown us that major clinical practice patterns develop slowly in the United States; therefore, despite the recent increase in the number of patients referred for ICD therapy, it is likely that ICD implantation rates will continue to grow gradually for several years to come.

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Risk Stratification of Post-MI Patients. What Are the Limitations of MADIT? What Does the Future Hold in Store?

M. Brignole[1] and C. Menozzi[2]

ICD Reduces Total Mortality in Post-Myocardial Infarction (Post-MI) Patients at High Risk of Arrhythmic Sudden Death

The Axiom of Overall ICD Survival

That the implantable cardioverter-defibrillator (ICD) prevents sudden death, and does so more effectively than any other therapy, is clear and inarguable. Aside from countless eyewitness accounts of cardiac arrest being aborted by ICDs, published reports have, from the very beginning, clearly documented the remarkable effectiveness of this device in terminating lethal ventricular arrhythmias [1-4]. In patients who received the ICD the incidence of sudden death was reduced to < 2% at 1 year and ≤ 6% at 5 years. Thus, by the late 1980s, accumulated data from around the world provided ample proof that the ICD was highly effective at doing exactly what it was designed to do and that no other therapy provided the same level of protection against sudden death. The fact that the ICD prevents sudden death leads immediately to a truth that is so self-evident and indisputable as to constitute an axiom [4]. The axiom states that the ability of the ICD to measurably prolong survival depends on the population of patients to which it is applied. Indeed, in a given population followed for a given period of time, the ICD will measurably prolong overall survival whenever the risk of sudden death from ventricular tachyarrhythmias is sufficiently greater than the risk of dying from all other causes combined.

Data from Randomized Secondary Prevention Trial

The study by Wever et al. [5, 6] was a randomized study of comparison between ICD and conventional therapy – including electrophysiology-guided therapy and myocardial revascularization when appropriate – in sudden death survivors. In spite of the small number of enrolled patients, this study clearly demonstrated a prolonged overall survival and a favorable cost-effectiveness ratio in patients treated with ICD as first choice.

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Data from Randomized Primary Prevention Trial

The Multicenter Automatic Defibrillator Implantation Trial (MADIT) [7] has shown that the ICD significantly reduces total mortality in patients with post-MI, depressed left ventricular ejection fraction, nonsustained ventricular tachycardia and inducible non-suppressible (with procainamide) ventricular tachyarrhythmia on electrophysiological study.

Patients eligible to enroll had the following characteristics:
- a myocardial infarction more than 3 weeks old
- left ventricular ejection fraction ≤ 35%
- documented electrocardiographic runs (3 to 30 consecutive beats) of nonsustained ventricular tachycardia.

Exclusion criteria were:
- NYHA class IV
- recent indication (during the past 3 months) for coronary artery revascularization
- previous cardiac arrest or syncopal ventricular tachycardia

The Limitations of MADIT

How Many Patients Do Have the Characteristics of the MADIT Subjects?

In the original paper we can read that recruitment started on December 27th, 1990; the trial was terminated on March 24th, 1996. It was very hard to recruit the less than 200 suitable patients who accepted to participate in a randomized trial. Is the number of potential candidates lower than was expected or was the motivation of the investigators insufficient to identify all possible candidates?

Lack of the Study Flow Diagram

In order to put this management strategy into perspective, it is necessary to be aware of several factors concerning the modalities of patient recruitment. It is a pity that consistent logs were not kept on all the eligible patients that did not qualify in the end on the basis of the results of the stimulation study: what proportion of patients had non-inducible arrhythmias during base-line electrophysiological studies, in what proportion did the arrhythmias become non-inducible after procainamide therapy, and what was the outcome in these groups, including procedure-related complications. All this information is lacking. Moreover, the investigators do not provide information on the outcome of the 57 (23%) of the 253 patients fulfilling all the inclusion criteria but refusing to participate in the trial.

Were Patients with Sustained Non-syncopal Ventricular Tachycardia Included?

The original report does not mention if any patient had had sustained, uniform, well tolerated ventricular tachycardia prior to recruitment. This type of ventricu-

lar tachycardia is not mentioned in the exclusion criteria; only ventricular fibrillation or syncopal ventricular tachycardia are cited as arrhythmia desorders excluding eligibility. If some investigators, for instance, include only patients who, apart from electrocardiographically documented nonsustained ventricular tachycardia also had one or more episodes of sustained, well tolerated ventricular tachycardia, the results of the investigation would be biased.

Time Interval between Infarction and Enrolment

The initial report only says that 76% of the conventional treatment patients and 75% of the ICD patients were recruited 6 months or more after the last myocardial infarction. This fact has many potential implications. It would be of great interest to know how long after the last MI patients were actually recruited. Months or years after? Wellens [8] has shown that the time interval between the first myocardial infarction and sudden death was 6.5 ± 5.3 years (median 5 years). What was the reason for recruitment? Were these patients reevaluated because of the worsening of their clinical status, for example an episode of heart failure or angina, or were they recruited during an occasional ambulatory visit? Why did they undergo the Holter monitoring which had revealed nonsustained ventricular tachycardia? It is obvious that the magnitude of the pre-test risk does influence the subsequent outcome.

Conventional Therapy

One of the chief difficulties in the interpretation of the trial is that treatment with implantable ICD was compared with another active therapy, namely, an amalgam of antiarrhythmic drugs, many of which we now know to be harmful. Antiarrhythmic drug therapy was referred to in the trial as "conventional therapy". Conventional therapy is therapy that is known to be beneficial and that, in the absence of a contraindication, should be given to everyone. In patients with a previous MI such therapies would include β-blockers, angiotensin-converting enzyme inhibitors, aspirin, and lipid-lowering drugs but not antiarrhythmic drugs. The lower non-arrhythmic cardiac mortality observed in the ICD arm (7 vs 13 patients) could reflect the fact that antiarrhythmic therapy was unbalanced in the 2 study arms.

Amiodarone

At one month 80% of the patients in the conventional treatment arm versus 2% of the patients in the ICD arm were on amiodarone therapy. The overall mortality was slightly higher among amiodarone patients compared to conventionally treated patients not receiving amiodarone: 36% to 26% respectively. Thus, amiodarone raises as a potential cause of death.

β-Blockers

β-blockers were used more frequently in the ICD patients as compared to the conventional treatment group (28% vs 9%; $p = 0.001$). Although we are confident that the results of the MADIT depend on the use of the ICD and not of β-blocking agents, there are many reports in the literature showing that β-blockers may reduce total and sudden mortality in post-MI patients. Early studies on timolol [9], propranolol [10] and metoprolol [11] showed a total mortality reduction of 39%, 26% and 36% respectively. Not only was overall mortality reduced, but sudden cardiac death was reduced as well. Among 1884 patients in the timolol post-MI trial [9], followed an average of 17 months, death occurring within one hour was reduced by 70%. The particular benefit of β-blockers in high risk patients with a history of congestive heart failure was shown for propranolol in the BHAT trial [12]: both relative and absolute reduction of sudden death were substantially greater (by 4- to 10-fold) in those with a history of heart failure vs those with no heart failure. In a meta-analysis of 25 trials of chronic β-blockade after acute MI, representing 23 000 patients, long-term (> 1 year) mortality reduction averaging 23% (95% Confidence Interval (C.I.): from 16% to 30%) were found [13]. In a recent study [14], carvedilol, an agent with both β- and α-blocking effects plus antioxidant actions, has been shown to decrease mortality in patients with chronic heart failure by 65% (95% C.I. from 39% to 80%). Other recent large scale trials [15, 16] have not fully clarified the effects of β-blockers on morbidity and mortality in patients with heart failure. Admittedly, the population of these large trials did not include, or only marginally included, the MADIT population profile. Therefore, their results should not be extrapolated to the MADIT patients. Nevertheless, the question arises whether β-blockers could be an efficacious alternative treatment of MADIT patients. What could MADIT results have been if β-blockers had been extensively used in the conventional arm instead of antiarrhythmic drugs?

How Should the Results of MADIT Be Incorporated into Daily Practice?

The results of this trial (as well as the results of every trial) should not be extrapolated to other populations of patients and criteria for screening of patients must be strictly followed. The afore-mentioned limitations of the trial makes the risk stratification of the patients difficult to perform. **Thus, it is unclear who to treat with prophylactic ICD even if we are confident that ICD reduces total mortality in post-MI patients at high risk of arrhythmic sudden death.**

What Does the Future Hold in Store?

To date, the only therapy that has been proven to reduce total mortality in post-MI patients with nonsustained ventricular tachycardia and depressed left ventricular ejection fraction is the ICD. Other therapeutic alternatives (including β-blockers) should be compared with the ICD in the future. ICD should be viewed at

present as the standard treatment modality for patients with the MADIT profile.

Ongoing Clinical Trials

The following are some ongoing primary prevention trials:
- Multicenter Unsustained Tachycardia Trial (MUSTT) [17]. This study compares electrophysiologically guided therapy versus no therapy in patients with coronary heart disease, ejection fraction ≤ 40% and nonsustained ventricular tachycardia. ICD is used in the subgroup of non-responder patients.
- Dilated Cardiomyopathy Trial (CAT) [18]. A comparison of ICD vs no ICD in patients with dilated cardiomyopathy, NYHA class II or III and left ventricular ejection fraction ≤ 30%.
- Defibrillat [19]. A comparison of ICD vs no antiarrhythmic therapy in patients on transplant waiting list, NYHA class III, left ventricular ejection fraction ≤ 30% and nonsustained ventricular tachycardia.
- MADIT II [20]. A comparison of ICD vs no ICD in post-MI patients with left ventricular ejection fraction ≤ 30%.

In their editorial comment, Friedman and Stevenson [21] state that it would be prudent to wait for the results of other important clinical trials already in progress before finally deciding what MADIT has taught us on the basis of a single clinical trial involving fewer than 200 patients.

Simpler Stratification Procedures

It is likely that non-invasive methods will be developed to characterize patients at high risk of electric sudden death. Late potentials and heart rate variability have been suggested as a non-invasive alternative to programmed stimulation. It should be kept in mind that the MADIT profile included not only inducibility but also the inability to suppress arrhythmia with procainamide.

Economic and Technological Concerns

There are economic and technological concerns regarding this new indication. During the second half of the MADIT study, using transvenous implantation which is the rule today, the cost-effectiveness ratio was $22 000 per life-year-saved [22]. Saksena et al. [23] reported a cost-effectiveness ratio of $10 000-15 000 with pectoral implants. Such ratios are equal to or better than many currently accepted medical therapies: mild arterial hypertension, coronary artery by-pass grafting, angioplasty, heart transplantation, trombolysis, hemodialysis, cholesterol-lowering drugs [6, 24, 25]. Is the industry going to develop a cheaper and simpler ICD for primary prevention patients? What is cheaper for the industry: to develop several models or one single basic model of device? Friedman and Stevenson [21] have calculated that approximately 1.3 million patients annually survive a myocardial infarction in the United States, of whom 16 000 would probably fit the clinical profile of the patients who underwent randomization in MADIT. They

have estimated that the cost of identifying, evaluating, and implanting ICD in these 16 000 patients would be over $1 billion annually, not including the cost of follow-up evaluation. In Italy, the national cardiological associations ANMCO-SIC have estimated that approximately 150 000 patients annually survive a myocardial infarction. Given that 1% of these patients fit the MADIT profile, DRG-based cost of ICD implant would be 52.5 billion Lire. For physicians, cost considerations for effective therapies are economic, political and ethical issues, which have to be addressed by the appropriate authorities.

Organization of a Program for Primary Prevention Therapy

A program for prevention of sudden death in post-MI patients is efficacious if all citizens who are potential candidates for ICD implant can be screened and their risk stratified. The development of such an ambitious program goes beyond the power of electrophysiologists and involves the global organization of the national health care system. Several issues, concerning personnel, educational programs for the physicians and the patients, appropriation of resources, etc., must be properly addressed.

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VENTRICULAR TACHYARRHYTHMIAS: UNCOMMON FORMS

Idiopathic Left Ventricular Tachycardia: What Is New in Pathophysiology? When and How to Perform RF Ablation?

R. Cappato

In 1979, Zipes et al. [1] reported about a peculiar category of ventricular tachycardia characterized by a QRS 0.12 to 0.14 s long, a right bundle branch block configuration and a left deviation of the electrical axis. Further reports have confirmed that this arrhythmia occurs in individuals who are otherwise healthy (idiopathic, I) and originates from the postero-inferior left ventricular septum (left ventricular tachycardia, LVT), as postulated by Zipes et al. [1]; in addition, the modality of onset during programmed electrical stimulation as well as the response to pharmacologic agents have suggested that the mechanism that is most probably responsible for ILVT is reentry [2].

Treatment is indicated if the patient is symptomatic because of the arrhythmia and especially when the arrhythmia has resulted in a tachycardiomyopathy. In asymptomatic patients, treatment with antiarrhythmic therapy is questionable. In fact, although the prognosis in these patients is essentially regarded as a benign one, sudden death has been occasionally reported [3]; in addition, one may not exclude that in a minority of patients who die from a primary ventricular arrhythmia, the initial event consists of an idiopathic ventricular tachycardia degenerating into ventricular fibrillation.

In 1987, Fontaine et al. [4] reported cure of idiopathic VT by means of high-energy direct-current (DC) application. Recently, the advent of radiofrequency current (RFC) catheter ablation has proven to be highly efficacious and safe for the curative treatment of these arrhythmias [5] and is presently being used as the first-line invasive strategy in most centers.

In the present paper, we report our experience in radiofrequency current catheter ablation in patients with ILVT.

Methods

Patients

Five patients (4 males, 1 female; age 32.8 ± 13 years) with recurrent episodes of sustained monomorphic tachycardia exhibiting on the 12-lead ECG a right bund-

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le branch block morphology and left superior axis deviation were referred to our institution for curative treatment. Symptoms were palpitations in four and presyncope in one. In all patients an average of 2 antiarrhythmic drugs (range, 1 to 3) had proven to be ineffective to control symptoms. The idiopathic nature of the underlying arrhythmia was established in all patients as defined by normal cardiac examination, baseline surface ECG, chest X-ray, echocardiogram, left and right ventriculogram and coronary angiogram.

After written informed consent had been obtained, a bicycle-exercise test and an electrophysiologic study were performed to assess the inducibility of clinical tachycardia. If it was inducible at least 3 times, left ventricular endocardial mapping and subsequent RFC ablation were performed. Recording of the earliest activation in the ventricle provided evidence for the ventricular origin of the tachycardia. The success of the ablation procedure was verified by an electrophysiologic study and/or by an additional bicycle-exercise test performed 5 days after the therapeutic procedure. Follow-up was performed on an outpatient basis every three months. An ECG at rest and during exercise and a 24-hour Holter-ECG were performed in each patient.

Stress test

In all patients, a bicycle-exercise testing was performed in a supine position: after a warm-up phase set at the work threshold of 50 watts for 3 minutes, stress was increased in a stepwise fashion by 25 watts every 3 minutes until maximal calculated heart rate was achieved. Criteria for discontinuation included ST-segment depression > 0.15 mV in any of the surface ECG leads, fatigue, abnormal blood pressure response, angina pectoris, dyspnea, and sustained ventricular arrhythmias.

Electrophysiologic study

Two 6-F quadripolar catheters (5 mm interelectrode distance) were advanced from the right femoral vein into the right ventricle and positioned at the apex and at the septal aspect of the outflow tract. After positioning of the catheters, a bolus of 100 U/kg heparin was given intravenously, followed by an additional bolus of 5000 U heparin intravenously every four hours. Five surface ECG leads (II, III, aVL, V1, V6) and 2 intracardiac electrograms were recorded at a paper speed of 100 mm/s on a Siemens Mingograf recorder (Siemens-Elema, Solna, Sweden). Programmed electrical stimulation was performed with stimuli of 0.5 ms pulse width and an amplitude of twice the diastolic threshold (UHS 20, Biotronic GmbH). All endocardial recordings were filtered at 15 to 500 Hz. Stimulation protocols included two different basic cycle lengths (510, 440 ms) with up to three extrastimuli at two right ventricular sites (apex, outflow tract) and a burst stimulation of the right ventricular apex at cycle lengths of 350-270 ms. If the clinical ventricular tachycardia could not be induced, stimulation was repeated during isoproterenol infusion. The endpoint of the protocol was either a

reproducible induction of the clinical ventricular tachycardia for three times at the same coupling interval from the same site or finishing the whole protocol.

Ablation

After the clinical ventricular tachycardia was initiated, an additional steerable 7F quadripolar catheter with a large (4 mm) electrode tip was inserted into the right femoral artery and advanced into the left ventricle. This catheter was used for left ventricular endocardial mapping and ablation. Three surface ECG leads (II, III, aVL) and three bipolar intracardiac electrograms (LV-MAP, RVAP, RVOT) were simultaneously recorded at a paper speed of 100 mm/s during endocardial mapping. Left ventricular endocardial mapping was performed during sinus rhythm and during persistent ventricular tachycardia. Endocardial activation times of local ventricular potentials and, if present, of Purkinje fibers activation potentials recorded from the tip of the mapping catheter were measured relatively to the QRS complex onset. During sinus rhythm, pace mapping was performed with a pacing rate identical to the rate of clinical ventricular tachycardia. Pace mapping during persistent ventricular tachycardia was performed with a pacing rate 10-to-15 ms lower than the rate of the clinical ventricular tachycardia. A 12-lead surface ECG (I-III, aVR, aVL, aVF, V1-V6) was recorded at a paper speed of 25 mm/s and the QRS morphology during pacing was compared with the QRS morphology during clinical ventricular tachycardia.

Pace mapping was defined as excellent (class 1) if ≥ 11, as good (class 2) if 10, or as bad (class 3) if ≤ 9 surface ECG leads during pacing were identical to the QRS morphology during ventricular tachycardia. RFC pulses were delivered during sinus rhythm if (a) an excellent pace mapping was obtained and (b) a Purkinje activation potential was detected which preceded the onset of the ventricular local activation. RFC pulses during ventricular tachycardia were delivered at the site of earliest ventricular activation preceded by a distinct Purkinje-fiber activation potential, regardless of the quality of the pace mapping during ventricular tachycardia. A 500 kHz RF current generator (HAT 200 S, Dr Osypka GmbH) was used as an energy source. The RFC pulse delivery was released in a unipolar mode (large tip electrode of the mapping catheter versus a large skin electrode positioned on the back of the patient).

Results

Characteristics of ventricular tachycardia

A VT was reproducibly induced by programmed electrical stimulation and was also interrupted with premature ventricular stimulation or rapid ventricular pacing in all patients. In two patients, the VT was also inducible during bicycle-exercise test. The electrocardiographic characteristics of induced ventricular tachycardias were identical to those of clinically documented ventricular tachycardia.

Localization of ventricular tachycardia

The site of origin of ventricular tachycardia was identified in the inferoseptal region of the left ventricle in all patients. Catheter mapping of the left ventricle during sustained ventricular tachycardia showed the earliest ventricular activity at the inferior part of the mid-left ventricular septum (area 5) in 4 patients, preceding the QRS onset by 20 ms in two of them and by 5 ms in the other two. In another patient, the earliest local ventricular activity (– 10 ms) was recorded one cm cranially to the inferior midseptum (area 5-2). In the remaining patient, the earliest ventricular activity (– 20 ms) was recorded between the inferior midseptal and the inferior apicoseptal region of the left ventricle.

Endocardial mapping

Endocardial mapping aimed at encircling the site of earliest local ventricular activation was performed during sustained VT and during sinus rhythm. An average number of 19 (range 13-23) recordings at 7 (average, range 4-8) different sites was taken.

In one patient, catheter manipulation led to termination of the tachycardia with subsequent inability to re-induce it either during baseline and after isoproterenol infusion. Pace mapping was used as an additional criterion to guide the delivery of 3 RFC pulses at the site of block.

Fragmentation of local ventricular potential or delayed potentials was not detected in any patient either during sinus rhythm or tachycardia. During tachycardia, the earliest local ventricular activation was preceded (5-15 ms) by a distinct Purkinje-fiber potential in all patients. During sinus rhythm, endocardial recording was systematically attempted from the area in which the earliest site of ventricular activation during persistent ventricular tachycardia was observed. In all patients, the earliest endocardial activation was identified by an activation characterized by a Purkinje potential followed by a local ventricular potential preceding the onset of QRS by –10 to –30 ms and –15 to +10 ms, respectively. Purkinje potentials could also be recorded in areas outside the site of earliest local ventricular activation during ventricular tachycardia as well as during sinus rhythm. At these sites, Purkinje-to-ventricular activation intervals were occasionally shorter than at unsuccessful sites during tachycardia; in addition, the Purkinje-to-ventricular activation interval was usually longer during sinus rhythm than during tachycardia.

Pace mapping

Pace mapping was performed during VT in 3 patients and during sinus rhythm in 5 patients. All pacing sites were located close to the area of earliest local activation during tachycardia. During VT, an average number of 19 (range 18-27) recordings at 10 (average, range 6-18) different sites was sampled. Pace mapping during sinus rhythm was performed with an average number of 19 (range 18-27)

attempts at 14 (average, range 3-19) different sites. Excellent pace mapping could be achieved at least once within the area of earliest local ventricular activation during ventricular tachycardia as well as during sinus rhythm in all patients, but it could also be achieved at sites different from the area of earliest local ventricular activation. Slight catheter movements during repeated pace-mapping within nearly the same area (identical catheter position with biplane fluoroscopy associated with minimal changes in the morphology of endocardial potentials) resulted in a different pace-mapping classification.

Ablation

RFC ablation abolished the clinical tachycardias in five patients. Successful pulses were delivered during tachycardia in 3 patients and during sinus rhythm in the remaining 2. In one more patient, catheter-induced mechanical VT block did not allow validation of the efficacy of RFC pulses delivered at the site of block.

Patient 1. Three RFC pulses were delivered. During the first pulse, the rate of the VT slowed down and a change in the QRS morphology during current application was observed. After 14 s, radiofrequency current application was discontinued due to impedance rise. After interruption of current delivery, the ventricular tachycardia persisted and the QRS morphology returned to the clinically documented situation. During the second application the VT was not affected and current delivery had to be terminated after 13 s due to impedance rise. The third pulse led to VT termination after 4 s; this was preceded by an increase in VT rate. Pace mapping was excellent before the first and the successful third ablation attempt and good before the second application. Endocardial activation of Purkinje-fiber potential and local ventricular potential occurred earlier at successful site (-35 ms, -20 ms) compared to the unsuccessful sites (-20 ms, -15 ms and -20 ms, -5 ms, respectively).

Patient 2. Two ablation attempts were performed. The first pulse led to an increased rate of VT which resulted in its termination 3 s after current onset, but thereafter the clinical tachycardia could be reinduced. During the second application, the rate of the VT slowed down and resulted in its termination after 4 s. After this ablation attempt, the clinical tachycardia could not be re-induced. Pace mapping before both radiofrequency current applications was class III. Local activation times of Purkinje-fiber potential and ventricular potential were earlier at the succesful site (-20 ms, -10 ms respectively -10 ms, ±0 ms), similarly to what observed in patient 1.

Patient 3. Four RFC applications were delivered in this patient, three of which during VT and one during sinus rhythm. Current delivery during the first pulse resulted in a ventricular tachycardia with a different QRS morphology at leads V2 and V3. The following two applications did not influence the VT. The last ablation attempt was performed during sinus rhythm in the presence of a local Purkinje and ventricular potential preceding the QRS onset by -25 ms and -15 ms, respectively. The endocardial activation time during sinus rhythm was quite similar compared to those at the first ablation attempt (-25 ms, -10 ms) recorded also

during sinus rhythm. Pace mapping was excellent in both cases. After the last RFC application, no VT could be re-induced.

Patient 4. After interruption of the clinical VT during catheter manipulation, the ablation procedure was continued during sinus rhythm, as guided by endocardial activation times and pace mapping. A total number of 8 pulses were delivered. During all but one application, ventricular premature beats or automatic ventricular activity with a QRS morphology identical to the clinical VT were observed. The Purkinje-fiber activation potential preceded the onset of QRS ranging from −10 ms to 0 ms. Pace mapping before current application ranged from class I (4 times), to class II (1 time) and class III (3 times). After the last RFC pulse, initiation of clinical tachycardia was attempted, but could not be achieved either during baseline and after isoproterenol infusion.

Patient 5. One single pulse delivered in the inferobasal septal region resulted in definitive termination of the clinical VT and inability to re-induce it thereafter. The earliest Purkinje and ventricular potentials were recorded at sites proximal to the successful one, but in which class III pace-mapping was obtained during VT. At the successful site, the P-V interval became longer after definitive conversion to sinus rhythm.

Follow-up. All patients underwent a control electrophysiologic study 5 days after the ablation procedure; no VT was inducible in any patient. In the 2 patients in whom the clinical VT was inducible during the ergometric test before ablation, no VT was inducible during a repeated test 4 days after ablation.

During a follow-up of 12 months (average, range 12-16 months) 5 patients remained asymptomatic without any antiarrhythmic drug. The remaining patient became symptomatic due to frequent monomorphic ventricular premature beats or nonsustained ventricular runs (up to 8 consecutive beats) and was successfully treated with sotalol (160 mg/day) in combination with flecainide (100 mg/day).

Discussion

The data from this study confirm that RFC ablation is a safe and efficacious technique to provide definitive treatment of idiopathic VT. This arrhythmia most commonly originates from the inferior septal region of the left ventricle [6-8]; however, an origin of the focus from the left ventricular free wall has been occasionally described.

The characteristic ECG pattern with a right bundle branch block and a left axis deviation argues in favor of a site origin close to the posterior fascicle. The high success rate of RFC ablation in these arrhythmias also supports an endocardial location of the arrhythmogenic focus. The use of pace mapping with similar QRS appears to be not specific due to the possible capture of the Purkinje fiber network at site remote from the origin of the tachycardia.

With regard to the mechanism, reentry appears to be the most likely one due to the following observations: 1) induction and termination of the clinical tachycardia with appropriately timed beats; 2) an inverse relationship between the pre-

mature coupling interval and the echo interval; 3) progressive fusion, as defined according to the classic criteria [9].

The exact dimension of the reentrant circuit is not known, but may vary from one patient to another. Although during tachycardia a Purkinje activation potential generally precedes the onset of the local ventricular activation at successful sites, the Purkinje network appears unlikely to be a crucial component of the reentry circuit, as suggested by the occasional finding: 1) earliest Purkinje activation potentials at unsuccessful rather than at successful sites; and 2) longer Purkinje-to-ventricular activation intervals during sinus rhythm than during tachycardia (10).

In conclusion, these data confirm that the advent of RFC ablation has dramatically changed the therapeutic approach to several forms of clinical arrhythmias; in addition, data from electrophysiologic findings obtained before and after RFC pulse delivery suggest that reentry in ILVT might not necessarily require Purkinje tissue as a critical limb.

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Idiopathic Right Ventricular Outflow Tract Tachycardia: Which Substrate, Mechanism and Therapy?

A. Proclemer and C. Fresco

Ventricular tachycardias (VT) may occur in patients who have no clear evidence of organic heart disease. So-called idiopathic VT accounts for 12%-17% of all cases of VT [1, 2]. In approximately 70%-80% of cases idiopathic VT originates from the right ventricular outflow tract (RVOT) and the ECG aspect is characterized by left bundle branch block (LBBB) and inferior axis (IA) morphology [2, 3]. Idiopathic RVOT-VT presents two main clinical forms: (1) *repetitive monomorphic VT, and (2) paroxysmal stress-mediated sustained VT.* The first arrhythmic pattern includes repetitive ectopies and paroxysms of nonsustained VT with the same morphology, the second is typically characterized by episodes of VT induced by stress, exercise or catecholamine infusion. Some patients can have either form of RVOT-VT, and during exercise stress testing they show initial suppression of nonsustained VT, final induction of sustained VT or relapse of the arrhythmia immediately after the peak exercise. Finally, a third form of the RVOT arrhythmic syndrome includes frequent and/or repetitive *monomorphic* (LBBB-IA) *ventricular premature beats* without sustained VT episodes.

Substrate

RVOT arrhythmias have been extensively studied by noninvasive and invasive methods. Conventional diagnostic studies may reveal mild or nonspecific abnormalities, pathophysiological significance of which is unclear and may be related to the presence of VT or to the inclusion in some studies of non-heterogeneous patient groups. The ECG of patients with idiopathic RVOT arrhythmias is normal in over 90% of cases and time-domain signal-averaged ECG does not demonstrate late potentials in the majority of cases. Echocardiography is very useful to discriminate between patients with clear evidence of arrhythmogenic right ventricular cardiomyopathy and patients with idiopathic VT. In the latter group minor enlargement of the right ventricle (RV) and little areas of abnormal wall motion of the RVOT can be demonstrated in approximately 10% of cases [4-9]. Moreover, few patients present mild left ventricular dysfunction and mitral valve

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prolapse. In some patients transesophageal echocardiography can detect previously unrecognized RV abnormalities, such as increased trabeculations of the apex and of the infundibulum. Hemodynamic studies did not reveal specific abnormalities of the RV in most of the reports [7, 8, 10]. An increase of the RV volume and of the diastolic pressure and a reduction of the RV ejection fraction have been decribed in few cases. The clinical value of these abnormalities is probably benign, because patients with idiopathic RVOT-VT show a favorable long-term prognosis and do not reveal progressive heart disease during the follow-up [2, 3, 7]. RV endomyocardial biopsy demonstrated in earlier series a not negligible incidence of abnormal findings, ranging from 40% to 100% [1, 2]. These histologic abnormalities were either nonspecific, such as fibrosis, myocellular hypertrophy, small vessel disease, or were compatible with acute myocarditis or arrhythmogenic cardiomyopathy of the RV. However, considering only the studies with strict inclusion criteria for idiopathic RVOT-VT, even target biopsy at various sites of the RVOT did not show particular abnormalities [10].

On the contrary, magnetic resonance imaging (MRI) of the RV appears as a very useful diagnostic technique in patients with apparently idiopathic LBBB-IA arrhythmias. In the series of Carlson et al. [6] cine MRI revealed structural and functional abnormalities of the right ventricle in 22 of 24 patients with RVOT-VT (95%), in 17 of 44 cases with other cardiovascular diseases (39%), and only in 2 of 16 normal subjects (12.5 %). In patients with RVOT-VT most of these abnormalities were characterized by focal areas of decreased systolic wall thickening confined to the RVOT. In the two control groups such abnormalities were not localized in the RVOT and appeared qualitatively different. Globits et al. [11] examined 12 patients undergoing radio-frequency catheter ablation for symptomatic RVOT-VT (by MRI). Echocardiogram was normal in all patients. Right ventricular volumes and ejection fraction of patients with RVOT-VT showed no difference in comparison to normals, but in 9 of 12 arrhythmic patients cardiac MRI showed various structural abnormalities including focal wall thinning, RVOT dilatation, and/or RVOT fatty infiltration. In the Gill et al. study [12], including 16 patients with sustained VT, the MRI scan was abnormal in three of seven patients with normal echo- and angiogram. The most frequent abnormality was a thin area of the RVOT wall with dyskinesis and failure to thicken during systole. In a study by our group [13] we compared MRI scans in 19 patients with frequent (> 100 per hour), monomorphic RVOT extrasystoles and in 10 volonteers without structural heart disease. MRI studies included spin-echo and gradient-echo sequences in the standard planes. Patients with extrasystoles showed wider dimensions of RVOT compared to the control group. Mean anteroposterior and transverse diameters were 39.6 ± 4.6 mm vs 29.9 ± 4.8 mm ($p < 0.01$) and 27.5 ± 3.8 mm vs 20.5 ± 2.5 mm. ($p < 0.01$), respectively. Wall motion and morphological abnormalities were present in 16/19 (84%) patients, and were confined to the anterolateral wall in 15/16 cases. All normal subjects had normal MRI findings ($p = 0.008$). No clear correlation was found between the site of wall abnormalities and the QRS aspect of ectopies on the frontal plane and on precordial leads. Only patients with anterior location of decreased systolic wall thickening typically presented a

QRS configuration suggestive of an anterior origin of VPB (right inferior axis and late transition). Patients with anterolateral and lateral wall abnormalities of the RVOT showed both right or left inferior axis configuration and either early or late transition. The similarities between the results obtained in our series and in previous studies [6, 11, 12] suggest that VT and extrasystoles arising in the RVOT may share the same substrate and represent two expressions of a single arrhythmic syndrome. Other reported similarities include the site of origin, identified by both earliest endocardial activity and pace-map, electrophysiological results and response to radio-frequency ablation therapy [3, 14-16]. However, the origin of the RVOT abnormalities detected by cardiac MRI is unclear. We cannot exclude that these anatomic and functional abnormalities of the RVOT could be due to the electro-mechanical influence of frequent ectopy and/or runs of nonsustained VT, but this hypothesis could be tested properly only by repetition of cardiac MRI after long-term suppression of RVOT ectopies. Alternative pathophysiologic explanation may be related to the embryological origin of the tract as recently suggested [15], or to the presence of a localized form of cardiomyopathy [5, 6, 13].

Mechanism

Enhanced automaticity of a RVOT focus, local reentry, and triggered activity have been proposed as the three possible electrophysiological mechanisms of the RVOT arrhythmias. The studies by Lerman et al. [3, 10] convincingly demostrated that most forms of RVOT tachycardias are due to *catecholamine-mediated delayed after depolarizations.* This model of triggered activity depends on the stimulation of cAMP, which causes an increase in intracellular calcium. RVOT-VT are in fact defined "adenosine sensitive", because this drug attenuates cAMP activation through the activation of inhibitory G-protein. Adenosine effects are highly specific for the identification of this mechanism. Both repetitive monomorphic RVOT-VT and exercise induced RVOT-VT are sensitive to adenosine, confirming a similar electrophysiological matrix. The mechanism of triggered activity is supported by the difficult induction of RVOT-VT with programmed ventricular stimulation, by the facilitating effect of isoproterenol infusion on VT induction by ventricular pacing and by the cycle length dependence of VT appearance.

Treatment

Patients with isolated or repetitive extrasystoles arising in the RVOT show a wide clinical spectrum. The majority of patients are asymptomatic or suffer only mild palpitations and, therefore, do not need antiarrhythmic treatment. Patients with invalidating symptoms can be effectively treated by β-blockers. Our first-choice drug is nadolol in daily doses of 20-80 mg, but other β-blockers such as atenolol are effective. Class IC drugs, like propafenone and flecainide, and class III drugs,

particularly sotalol, have been effectively administered as second-choice treatment. Even in patients with RVOT-VT antiarrhythmic drug therapy is not mandatory for arrhythmia prevention, because long-term prognosis is benign and symptoms can be mild and infrequent. RVOT-VT appears more responsive to antiarrhythmics (AA) than VT secondary to organic heart disease and favorable arrhythmia control can be obtained with all classes of AA drugs. The choice of drug usually depends on the results of non-invasive diagnostic tests (Holter monitoring, exercise provocative testing) and of ventricular stimulation. Beta-blockers and sotalol showed a good efficacy (above 50%) particularly in patients with VT provoked by stress, exercise, or isoproterenol infusion [7, 9]. Class IA and IC agents were also effective in 30%-50% of cases, primarly reducing the ectopic activity and thus the triggering impulse for VT induction [4, 7]. Calcium channel blockers, mainly verapamil, presented favorable results in only 20%-30% of patients [3].

Ablation

The effects of radio-frequency (RF) catheter ablation in the treatment of RVOT-VT have been reported in many studies [14-22]. These series usually included either patients with long-lasting symptoms refractory to conventional antiarrhythmic drugs or patients with brief history of syncopal VT. Techniques for identifying the target sites of ablation included activation mapping and pacemapping. *Activation sequence mapping* of the RV is performed once the clinical VT is present or induced by ventricular stimulation in baseline state or by isoproterenol infusion. Presystolic endocardial activation may be recorded over a relatively large area of the RVOT. Successful ablation sites show an activation time of 10-50 ms relative to the onset of the QRS complex, but there is not a cutoff value of prematurity predictive of effective VT interruption. In one single case, however, the activation time at the successful ablation site was earlier than at the unsuccessful sites. Bipolar electrograms do not show fractionation or low amplitude potentials, but sometimes a little sharp potential precedes the local activity. During activation mapping, QS morphology and prematurity of downstroke onset at unfiltered unipolar recordings are an useful criterion to localize the target sites for RF ablation. In patients with noninducible VT, LBBB-IA extrasystoles with the same ECG morphology of clinical VT are useful target arrhythmias. Elimination of these RVOT ectopies is in fact a good predictor of long-term clinical success.

Pacemapping is the other reliable and practical tool to identify the effective ablation sites. Pacemap is performed during sinus rhythm at a cycle length similar to the spontaneous VT, or during VT at a rate faster than the tachycardia rate. The optimal pacemap in all series demonstrated a very short interval between the artificial stimulus and the QRS due to the absence of a slow conduction area. Moreover, a good match in the QRS morphology should be present in at least 11-12 leads. The site of the best pacemap generally coincides with the site of earliest activation time. In the study of Wilber et al. [17] the frontal-plane QRS axis was a

good predictor of the site of the optimal pacemap. A negative QRS in lead I was associated with a site close to the septal attachment of the free wall, an isoelectric QRS with a site on the mid free wall of the RVOT, a positive QRS with a site on the posterolateral RVOT free wall. In summary, early endocardial activation time is a useful guide to the region of VT origin, but pacemapping has to be used to localize that site more precisely.

Clinical Studies

In the study by Klein et al. [18], RF ablation eliminated VT in 12/12 patients whose arrhythmia arose from the RVOT (anteroseptal origin in 10). The mean number of RF pulses was 5.8 and an average of 3 pulses was required. No complications were reported. During a mean follow-up period of 10.8 months the patients had not had spontaneous VT, nor inducible VT at electophysiologic study six weeks after the procedure. In the large series of Coggins et al. [19] RVOT-VT was ablated in 17/20 patients (85%) after a mean of 8.4 RF pulses. The successful sites of ablation were concentrated in the anteroseptal region of the RVOT in 13 cases, in the posteroseptal area in 3, and in the anterolateral area in 1. After ten-month follow-up three patients presented VT recurrences, that were treated by drugs (two) or by a second ablation (one). Mowsowiz et al. [20] evaluated the effects of RF ablation in 18 consecutive patients with RVOT-VT. The number of RF applications to achieve success ranged from 2 to 21 (mean 8 per patient). The anatomic locations for successful ablations were in the mid- to anterior superior RVOT septum in 16/18 patients. After one-year follow-up symptomatic VT recurred in 5 of the 16 patients. They underwent a second successful procedure by RF energy delivery to the same region of the RVOT septum. The two patients in whom ablation was not successful had VT origin outside the high RVOT septum (close to His electrogram in one case and on the left side of the septum in the other). De Roy et al. analysed the short and long term results of RF ablation in 19 patients with sustained and nonsustained RVOT-VT [21]. Acute total success was obtained in 14 cases, partial reduction of the arrhythmia in 2. In two patients the early results could not be tested for the absence of any arrhythmia during the procedure. The VT origin was localized just beneath the pulmonary valve in 12 cases, in the mid-inferior RVOT septum in the others. A deep negativity in lead aVL and not in lead I appeared to be a sensitive marker of a septal origin of VT. In the 20.5-month follow-up 3/18 patients had nonsustained VT recurrences and six still had frequent RVOT ectopies. Thus, 50% of cases had only mild arrhythmic recurrences. On the basis of modified SF-36 H.S. physical activity, invalidating palpitations during work and daily activity, the importance of palpitation but not the emotional status, improved significantly after RF ablation. In a recent study, Chinushi et al. [22] focused their attention on morphological variations of QRS in 16 patients with nonreentrant idiopathic RVOT-VT. In ten patients with a single VT aspect activation mapping localized the VT origin in a narrow site ($< 0.5 \times 0.5$ cm), because the earliest presystolic electrogram significantly precedes the surrounding local electrograms. In the remaining 6 patients VT

showed minor difference of the QRS aspect and during the same VT similar activation times were observed in an area of the RVOT extending 1.0 x 2.0 cm. For each VT aspect the electrograms at the target area revealed morphological and activation sequence variations. The acute success rate of RF application was 94% (15/16 patients). The total number of RF pulses was 8.6 per patient, but a larger number of effective RF applications was required to interrupt VT arising from a wide area compared to those required for a VT from a narrow site (8.3 vs 3.1). Lerman et al. [10] tested the efficacy of RF ablation in 9 patients with repetitive monomorphic RVOT-VT. The effective site of RF ablation was the anteroseptal region of the RVOT in 3 patients, the anterolateral in 5, and the superior left interventricular septum in 1. Three patients had VT with two morphologies (RBBB and LBBB with the same inferior axis), suggesting a common origin with exit sites to the left and right of the septum. In patients with RBBB aspect the arrhythmogenic focus has been ablated by delivering RF energy between the right and the left sites of the septum. The patient who was not cured had a favorable pacemap close to the pulmonic valve and thus ablation was not attempted. Finally, in ten patients with severe symptomatic RVOT extrasystoles, Zhu et al. [16] reported total suppression of ectopic beats after 2.6 RF pulses. No patient had recurrence of symptomatic RVOT premature beats after the ten-month follow-up. The elimination of RVOT extrasystoles by a lower number of applications than in patients with RVOT-VT was hypothetically related to smaller or more superficial ectopic foci.

In conclusion, the acute success rate of RF ablation is about 90% and the complications are rare. The target sites of ablation are usually confined to the septum area of the RVOT. In some cases, the absence of RVOT arrhythmias during the procedure and the low reproducibility may cause very long ablation session and fluoroscopy time. During the follow-up period the arrhythmia recurrences are unusual and the clinical benefit is confirmed by the improvement in the quality of life. However, to definitely assess the role of catheter ablation in these patients long-term clinical and instrumental results are needed.

Conclusions

RVOT arrhythmic syndrome includes ventricular premature beats and sustained or nonsustained VT episodes with LBBB-IA morphology. The common substrate is characterized by subtle morphological and functional abnormalities localized to the RVOT, that are very well detected by cardiac MRI. The pathophysiological role of these abnormalities, however, is still unknown. The main arrhythmogenic mechanism of the RVOT-VT is due to catecholamine-mediated delayed afterdepolarizations and triggered activity. Finally, although the long-term clinical course is generally favorable, RF ablation is an effective and safe technique in treating patients with symptomatic or drug refractory RVOT arrhythmias.

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Long QT Syndrome: from Molecular Biology to Clinical Management

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The last few years have witnessed a dramatic progress in the molecular biology of the congenital long QT syndrome (LQTS). The impact of these discoveries on the understanding of LQTS, and also of other diseases in which control of the cardiac action potential is important, has been recently reviewed by a multidisciplinary task force [1]. This progress has largely resulted from the partnership between molecular biologists and the clinical investigators who had made available the extraordinarily large number of LQTS families with a very well characterized phenotype enrolled in the International Registry co-ordinated by Moss and Schwartz.

Genetic heterogeneity exists in LQTS [2] and five to six genes are probably involved. Three of them have been identified: the genes for LQT1 (LQTS linked to chromosome 11), for LQT2 (LQTS linked to chromosome 7), and for LQT3 (LQTS linked to chromosome 3).

The gene for LQT1 is KvLQT1 which, when co-expressed with minK, produces the I_{Ks} current [3, 4]. KvLQT1 is also responsible for the Jervell and Lange-Nielsen syndrome, the variant form of LQTS with congenital deafness, as a homozygous deletion-insertion was detected in two affected families [5]. The gene for LQT2 is HERG, a potassium channel that carries the I_{Kr} current. The gene for LQT3 is SCN5A, the cardiac sodium channel gene, and the 3 mutations described so far [6, 7] affect a region important for sodium inactivation.

Expression of the mutant SCN5A genes [8, 9] has shown that they produce a gain of function. These mutations result in a small, sustained inward current sufficient to disrupt the normal balance between inward and outward currents during the plateau phase, and hence prolong cardiac action potential. This persistent inward current is blocked by mexiletine, a Na^+ channel blocker [9], and by lidocaine [10].

Expression of the mutant HERG genes has led to the identification of two main consequences [11]. Some of the mutant proteins do not form functional channels and interact with normal HERG channel when expressed in *Xenopus oocytes*. This implies that patients with these mutations will probably express half the normal number of channels carrying I_{Kr}. Other mutant channels do not

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express detectable currents, but cause a dominant negative suppression of the normal HERG function; thus, patients with these mutations will have a major reduction in I_{Kr} with a large effect on ventricular repolarization.

Clinical Correlates

The three different mutations appear to produce a different electrocardiographic phenotype [12]. A different shape of the T wave has been reported to be present in LQT1, LQT2, and LQT3 patients, with the latter group being more obviously recognizable because of a distinctive, late-appearing T wave that often has a biphasic morphology. A certain degree of overlap exists, particularly between LQT1 and LQT2.

A first attempt to correlate the various mutations and clinical responses to different interventions has already provided novel information [13]. However, the very limited size of the population under study calls for caution in the extrapolation of the results.

The Na^+ channel blocker mexiletine appears to produce a considerable shortening of the QT interval in most LQT3 patients, only a modest one in LQT1 patients, and mixed responses in LQT2 patients. Exceptions do exist.

Heart rate increase produces a rather marked shortening of the QT interval among LQT3 patients; surprisingly, but in agreement with experimental observations in a cellular model of LQT2 and of LQT3 [14], this effect was much less evident among LQT2 and LQT1 patients. A potential inference is that LQT3 patients may be at lesser risk of syncope during physical exercise, when the progressive heart rate increase may allow appropriate QT shortening. These patients may also be those less likely to be protected by β-blockers that would produce an excessively low heart rate and would prevent an adequate heart rate increase during exercise.

Finally, there are now data obtained in over 200 genotyped and symptomatic patients on potentially different associations between triggering events and the various genotypes [15]. The most striking difference is the one present between LQT1 and LQT3 patients. Whereas only exceptionally did LQT1 patients have their cardiac events at rest or during sleep, this occurred in the majority of LQT3 patients. Conversely, whereas two out of three LQT1 patients had cardiac events during exercise, this occurred only in less than 15% of LQT3 patients. LQT2 patients show an intermediate picture, more similar to LQT3 than to LQT1 patients.

These data support the observation made on the response to heart rate increases by LQT3 patients and indicate that it is not exercise the most important risk factor for them. The previously puzzling clinical observation, that some LQTS patients were more at risk when they were resting than during exercise, may now be explained on the basis of the specific and differential effect of the various genetic mutations. The same data also indicate that LQT1 patients are at risk almost exclusively during exercise and during emotions occurring in the

awake state, thus when heart rate is definitely elevated. This suggests that these patients may be those in whom β-blockers are particularly effective.

Therapeutic Implications

A shortening in the QT interval can be produced by Na^+ channel blockade in LQT3 patients [13] and by an increase in the extracellular concentration of potassium in LQT2 patients [16]. An evaluation of the specificity of the latter effect must await data on LQT1 and LQT3 patients.

Even though QT shortening is by no means a guarantee of protection from life-threatening arrhythmias, these data suggest that it may be appropriate to test the potential value of mexiletine, which is available for oral use, specifically in patients with SCN5A mutations. In patients with HERG mutations it is logical to test various ways of increasing the extracellular K^+ concentration. Potassium infusions represent only an experimental tool. Oral K^+ supplements in combination with K^+ sparing agents are worth testing as well as K^+ channel openers. In patients with KvLQT1 mutations the most rational approach would be to use an I_{Ks} activator, whenever such a compound may become available for clinical use.

The impressive correlation between specific mutations and critical alterations in the ionic control of ventricular repolarization makes this syndrome a unique model which allows a correlation between genotype and phenotype, thus providing a direct bridge between molecular biology and clinical cardiology [17].

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Arrhythmogenic Right Ventricular Cardiomyopathy: Which Role for Apoptosis?

M. Valente, F. Calabrese, A. Angelini, C. Basso and G. Thiene

Apoptosis: Definition, Mechanisms and Genes

Necrosis and apoptosis, the two main patterns of cell death, are different processes. Necrosis usually is the result of severely disturbed extracellular environmental conditions and affects cell groups or a whole tissue or organ compartment. Apoptosis instead is a part of a "programmed" process and involves scattered cells. It is intrinsic to normal cells in embryogenic development, normal tissue turnover and clone selection in lymphoid cells.

Majno and Joris recently reviewed the historical development of the apoptosis concept [1]. The first description was made by Flemming in regressing ovarian follicles and correctly interpreted as a physiological phenomenon [2]. Later Gräper understood its role not only in epithelial tissue turnover but also in the developing embryo [3]. Finally Kerr clearly outlined the morphological features of the process and called it "apoptosis" compairing death of scattered cells to dead leaves falling from a tree in autumn [4].

In the apoptotic process (Fig. 1) the cell looses surface structures like contact regions and becomes isolated from its viable neighbors. There is volume reduction and distortion of cell shape with formation of buds containing cytoplasmic organelles and also nuclear fragments. Cytoplasmic organelle integrity is maintained, except for some dilatation of smooth endoplasmic reticulum, but striking nuclear changes occur. The nucleus becomes pycnotic, chromatin condenses under the nuclear membrane usually in half moon or toroid shaped masses. Nuclear pores concentrate in the few regions in which condensed chromatin does not lie adjacent to the membrane. The nucleus is frequently broken up into fragments, which together with a few cytoplasmic organelles constitute a membrane-bounded apoptotic body. The apoptotic bodies are promptly phagocytosed by neighboring cells and inflammatory response does not occur.

On the contrary, cell necrosis is characterized by cell and organelle swelling, due to increased membrane permeability (Fig. 1); the "point of no return" coincides with two ultrastructural mitochondrial changes: high amplitude swelling and the appearence of matrix densities. Afterwards both plasma and internal

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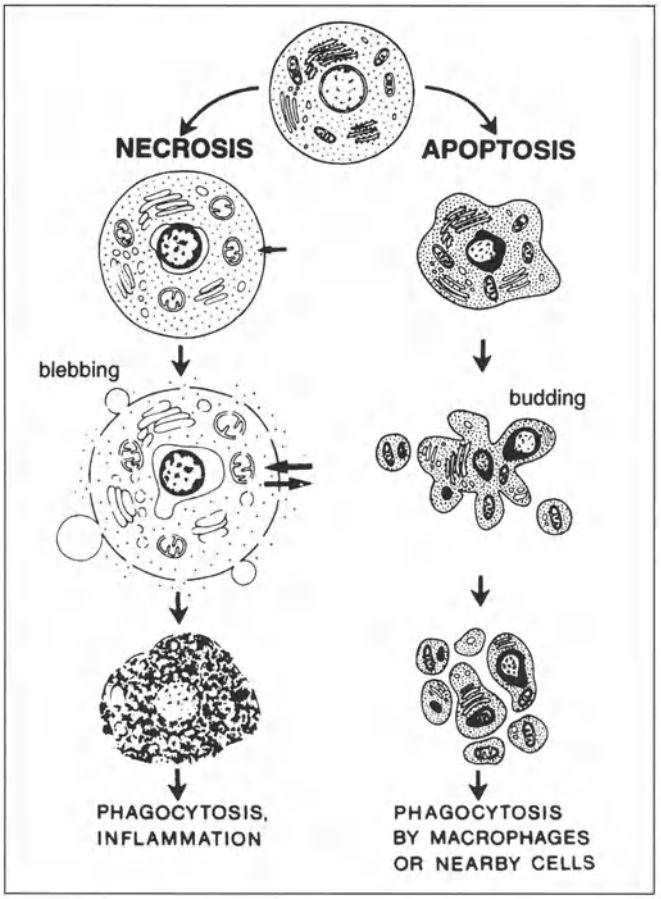

Fig. 1. Schematic representation of phenomena featuring necrosis vs apoptosis (from [1] modified)

membranes begin to rupture, while nuclear structures appear relatively intact. Necrosis causes the release of substances which induce an inflammatory response. In necrosis there is ATP depletion, usually due to hypoxia, which leads to formation of a series of so-called reactive oxygen intermediates such as free radicals and to impairment of membrane ion pumps.

Apoptosis instead is an active, energy requiring process and several pathways must exist for activation of the cell death program. From the biochemical point of view, a central role in determining the apoptotic process is played by an endogenous Mg++ and Ca++ dependent endonuclease which cleaves the internucleosomal DNA stretch. Deoxyribonucleic acid is broken into fragments which are multiples of nucleosomes and are responsible for the typical ladder pattern in agarose-gel electrophoresis [5]. Fragmented DNA may be also labeled by an "in situ" nick translation technique at the level of a single cell in formalin fixed tissues [6].

Much of our current knowledge concerning the genetic programmes involved in regulation of apoptosis has been derived from studies in the nematode *Ceanorrhabditis elegans* in which programmed cell death has been divided into four distinct stages, each controlled by a specific set of genes identified as "ced" (cell death defective) [7]. These stages concern decisions as to whether or not the cell will die, the cell death itself, engulfment of the dead cell by phagocytes and degradation of the engulfed dead cell. Among this set of genes, there is one, the ced-9 gene, which determines whether or not the cell will die. The ced-9 gene is highly homologous to the human bcl-2 gene. Among the genes which regulate apoptosis, bcl-2 is a major apoptosis suppressing gene, and p53 and c-myc are primary apoptosis-promoting genes. Bcl-2 belongs to a family of genes including bax and bcl-x. The bcl-2 protoncogene encodes a protein associated with intracellular membranes (mitochondria, endoplasmic reticulum and perinuclear membrane). The bcl-2 and bax proteins form homodimers and heterodimers, and it has been proposed that this interaction is involved in the regulation of bcl-2 function [8]. Bcl-2 protein inhibits apoptosis whereas bax protein accelerates programmed cell death. So downregulation of Bcl-2 may cause apoptosis, because this leads to an increase of Ca++ through the ER membranes, releasing the DNAse [9]. Increased cytosolic Ca++ may also activate latent enzymes, including transglutaminase [10]. Transglutaminase might be involved in the alteration of the cytoadhesive properties of apoptotic cells [11].

Other genes involved in apoptosis regulation are c-myc and p53 gene. Normally c-myc is required for entrance into the cell cycle in response to a growth factor signal [12]. When c-myc is expressed under growth arrest conditions, apoptosis results. The p53 protein is involved in the cellular response to DNA damage [13]. When DNA damage occurs, expression of the p53 protein induces arrest of the cells in the G1 phase of the cell cycle and triggers apoptosis if DNA repair mechanisms fail.

Another enzyme involved in apoptosis in nematodes is a protein similar to interleukin-1β-converting enzyme (ICE), a cysteine protease that might have nuclear proteins such as RNA polimerase and nuclear lamins as substrate [14]. Interleukin-1β-converting enzyme is functionally homologous to granzyme B, a protease responsible for apoptosis caused by cytotoxic T cells by perforin/granzyme system [15]. Cytotoxic T cells induce apoptosis also with another mechanism, the FAS/FASL system. FAS, also called APO-1 or CD95 is a member of the TNF/nerve growth factor receptor family and is expressed in a variety of cells, including those of the thymus, liver, heart and kidney; the FAS ligand (FASL) is a protein that belongs to the tumor necrosis factor family and is expressed in activated T cells and causes apoptosis when binding to FAS [16].

Apoptosis and the Heart

In recent years, the concept of apoptosis has swept through the fields of biology and medicine and it has not escaped the attention of cardiovascular researchers.

It is well known that much of the normal morphogenesis of the human heart begins after birth. The conduction system structures, sinus node, AV node and His bundle, undergo morphological changes after birth and James provided evidence many years ago that myocyte death is involved in this process [17]. The same author later demonstrated apoptotic bodies in the sinus nodes surgically excised from patients with the long QT syndrome and suggested that apoptosis plays an important role in postnatal morphogenesis and in pathology of the human heart [18-20].

Apoptosis has also been demonstrated in end-stage heart failure [21], in experimentally-induced cardiomyopathy [22], atherosclerosis [23], restenosis [24], acute myocardial infarction [25] and acute and chronic heart transplant rejection [26, 27]. Apoptosis related with changes in bcl-2 and bax expression has been detected in failing human hearts [28].

Postnatal involution of the right ventricular myocardium is a normal process due to lung inflation, diminution of the right ventricular pressure and ductus arteriosus closure. It is highly probable that this myocardial involution is a programmed process and may be due to myocyte apoptosis [19]. In rats, programmed cell death is absent in fetal heart but affects the myocardium postnatally; the right ventricle is much more involved than the left one and apoptosis is inversely related to bcl-2 expression [29].

Apoptosis in Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a primary heart muscle disorder of unknown cause that is characterized pathologically by the progressive loss of myocardium with fibro-fatty replacement [30-32]. It is often familial (nearly 30%) with an autosomal dominant inheritance [33]. Gene defects have been recently mapped both to chromosome 14 and 1 [34-36].

It is unclear how this genetic background predisposes to myocardial loss, and genetic predisposition to apoptosis is a very suggestive theory. The persistence in childhood and adulthood of apoptotic signals and/or the loss of some anti-apoptotic mechanisms may cause progressive loss of myocytes in the right ventricle. The recently identified DAD1 (defender against apoptotic cell death) gene has been found to map to chromosome 14, which is involved in ARVC [37, 38]. In the presence of a trigger of apoptosis, a defect in the DAD1 gene (e.g. point mutation) could therefore be responsible for programmed myocardial cell death. Apoptosis can be triggered not only by the "internal clock", but also by various external agents such as hyperthermia [39, 40], hypoxia [41], hepatic toxins [42], anti-cancer drugs [40, 43], and viruses [44-47]. Any of these triggers could activate progressive myocardial apoptosis in patients with a genetic predisposition to the disease. Occurrence of apoptosis in ARVC has been recently demonstrated by Mallat et al. [48] in specimens obtained at autopsy.

To establish whether myocyte loss in ARVC occurs as a result of programmed cell death (apoptosis), we studied endomyocardial biopsies from 20 affected

patients by histology, in situ DNA labelling technique (TUNEL) and electron microscopy [49]. Apoptotic myocytes were observed in 7 cases (35%) (Fig. 2, 3). A positive correlation was noted between apoptosis and "acute" signs and symptoms (angina, pyrexia, ST segment elevation, slightly raised CPK and ESR levels). The index of myocyte apoptosis (AI) was observed to be high in the 4 patients who were studied at clinical onset of disease, lower in the 3 who had a 2-12 month history and negative in the 13 patients with a longstanding history of ARVC. In the seven positive cases the average AI was 24.4. The high number of apoptotic cells observed may be explained by the fact that biopsies are always taken in the right ventricular free wall at the junction with the interventricular septum near the apex, which is one of the main sites of fibro-fatty replacement. In the same seven cases a few endothelial cells also showed TUNEL positivity for apoptosis (Fig. 3c).

Apoptosis is not strictly a marker of cell suicide, but it may be induced by factors like cytotoxic T lymphocytes and antibody-dependent cytotoxic cells which in few minutes produce an endonuclease-like fragmentation of target cells DNA. The "acute" signs and symptoms present in some cases of ARVC might be due to the presence of a trigger such as a virus, and cellular apoptosis might be caused by cytotoxic T lymphocytes. It is also possible that an autoimmune process is involved in ARVC and acute signs would be the clinical markers of myocytes apoptosis induced by antibody-dependent cytotoxic cells. Moreover the evidence of apoptosis not only in myocytes but also in a few endothelial cells suggests that

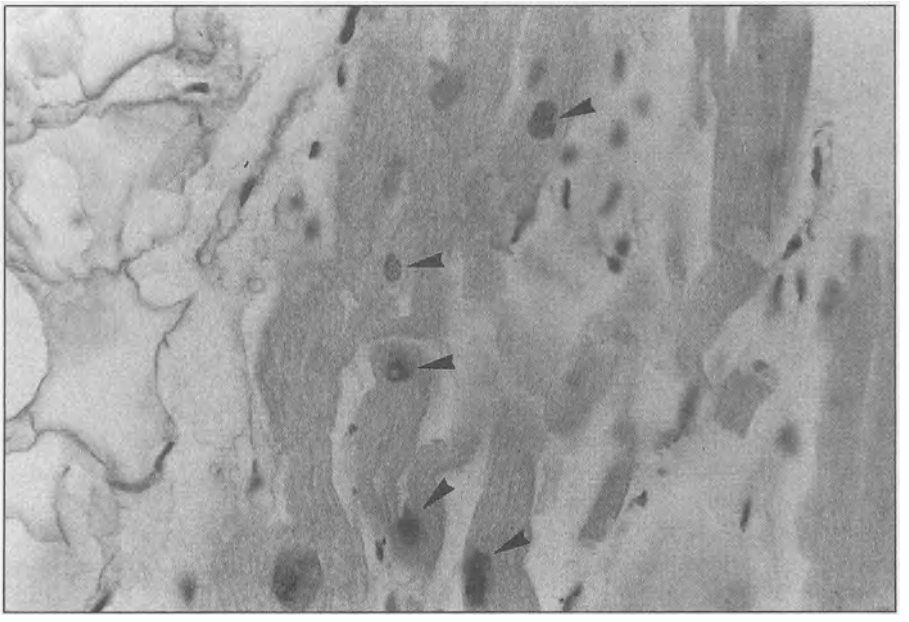

Fig. 2. Myocardial histologic sections after TUNEL assay. Apoptotic myocytes (*arrows*) adjacent to fibro-fatty tissue. Original magnification x480

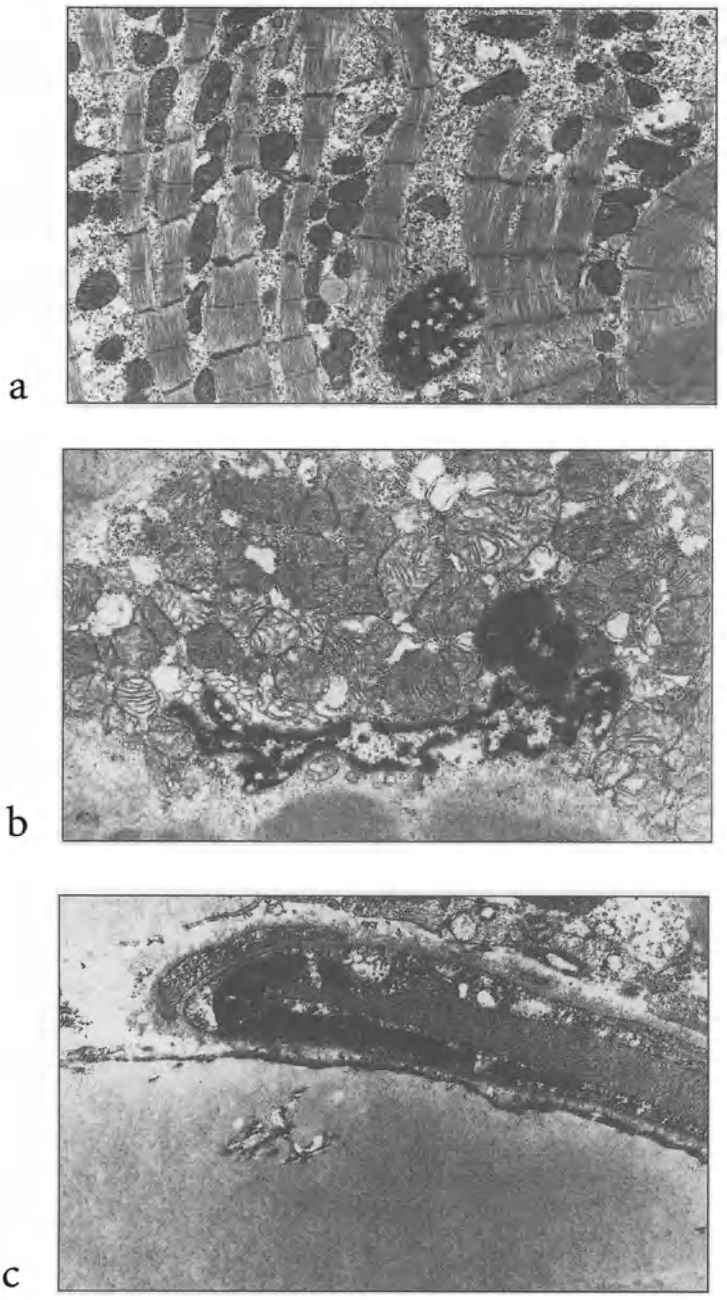

Fig. 3 a, b, c. Ultrastructure of apoptosis in arrhythmogenic right ventricular cardiomyopathy: (a) the apoptotic myocyte shows irregular, dense maze-like condensation of nuclear chromatin (original magnification, x12.000) (b) apoptotic myocyte with heavily lobulated nucleous, chromatin condensation and margination in the setting of normal cytoplasmic organelles (original magnification, x18.000), and (c) endothelial cell in advanced stage of apoptosis with pronounced margination and condensation of chromatin (original magnification, x20.000)

these cells are probably affected by the triggers of apoptosis at the same time as myocytes and their loss may cause ischemia and contribute to myocardial loss.

Whatever the etiopathogenetic mechanism of ARVC is, it is clear that recurring bouts or continuous apoptosis lead to replacement of destroyed myocardium by fatty or fibro-fatty tissue. The evidence of apoptosis as a mechanism of myocardial death opens new avenues not only to get an insight in the pathogenesis of ARVC, but also to conceive new therapeutic strategies. As agents inducing apoptosis are used in tumor therapy [50, 51], agents inhibiting apoptosis may be considered in preventing or retarding progressive myocardial loss in ARVC.

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How to Diagnose and Manage Right Ventricular Cardiomyopathy Today

T. Wichter, M. Borggrefe and G. Breithardt

Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a frequent cause of ventricular tachyarrhythmias and cardiac arrest in young patients with apparently normal hearts. The cardiomyopathy is characterized by a localized or generalized myocardial atrophy predominantly affecting the right ventricle with subsequent infiltration by fatty and fibrous tissue [1]. The arrhythmogenic substrate is formed by islands of surviving strands of hypertrophied myocytes, predisposing for localized slow conduction and reentrant arrhythmias. The predominant sites of involvement in ARVC are the outflow tract, apex and subtricuspid area of the right ventricle, which were described as the "triangle of dysplasia" [2]. Left ventricular involvement has been described in patients with extensive ARVC and a long history of arrhythmias [3].

Clinical Presentation

ARVC usually presents with ventricular tachyarrhythmias. Associated symptoms may range from palpitations, paroxysmal tachycardias, dizziness or syncope, and (rarely) cardiac arrest. Ventricular ectopy or tachycardia usually shows left bundle branch block configuration and frequently occurs during or immediately after exercise. The majority of patients presents with sporadic episodes of sustained monomorphic ventricular tachycardia (VT), which are frequently well tolerated despite high rates because of normal left ventricular function. Others present with frequent or repetitive nonsustained VT. Polymorphic VT or ventricular fibrillation are rare [2, 4]. However, sudden death may occur as the first manifestation of ARVC, which is now recognized as a significant cause of sudden unexpected death, particularly in young patients [1, 5]. Cardiac enlargement on routine chest X-ray or clinical signs of heart failure are uncommon as early manifestations of ARVC and occur almost exclusively in patients with advanced stages of the disease and a long history of arrhythmias.

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Epidemiology and Pathogenesis of ARVC

The cause of ARVC is still unknown. An occurrence of ARVC within families has been reported by many authors [6], including the affection of twins. This indicates that ARVC may be a familial cardiomyopathy with a specific genetic background. Recently, genetic loci were mapped to chromosomes 1 and 14 [7, 8]. However, these loci have not yet been confirmed by others and further genetic heterogeneity is expected.

The true prevalence of ARVC is unknown because the correct diagnosis is frequently not made due to absent or mild symptoms, incomplete diagnostic work-up or nondiagnostic borderline findings. Therefore, a complete diagnostic approach including noninvasive imaging techniques, cardiac catheterization, right and left ventricular angiography, endomyocardial biopsy and electrophysiological study has been recommended in order to make the correct diagnosis in patients with ventricular tachyarrhythmias and apparently normal hearts [9, 10].

Diagnosis of ARVC

Clinical diagnostic hallmarks of ARVC are spontaneous ventricular arrhythmias with left bundle branch block configuration, electrocardiographic abnormalities of repolarization during sinus rhythm and abnormal right ventricular structure and wall motion. Therefore, ECG during sinus rhythm and VT as well as echocardiography and right ventriculography are essential baseline diagnostic methods. If available, magnetic resonance imaging gives further valuable information. Invasive electrophysiologic study of antiarrhythmic medication, exercise tests and isoproterenol provocation are essential for the characterization of the arrhythmia and clinical decision making concerning antiarrhythmic treatment.

Recently, diagnostic criteria have been proposed by an international study group on ARVC [11] (Table 1). Major and minor criteria include structural, histological, electrocardiographic, arrhythmic, and genetic factors. Two major criteria or one major plus two minor criteria or four minor criteria from different groups confirm the diagnosis of ARVC. These diagnostic criteria and the score system still require prospective evaluation.

12-lead ECG

Typical ECG-features of ARVC include a QRS prolongation and abnormalities of repolarization in the right precordial ECG leads during sinus rhythm. In the majority of patients, right precordial T-wave inversions are present. A QRS prolongation >110 ms in leads V_1 to V_3 has been suggested as a diagnostic marker with 100% specificity and 55% sensitivity [12]. In patients with extensive ARVC, low amplitude potentials may be detected at the end of the QRS complex of lead V_1 and V_2. These deflections have been termed "epsilon waves" and reflect delayed ventricular activation in parts of the right ventricle [2].

Table 1. Criteria for the diagnosis of ARVC (from [11])

I. Global and/or regional RV dysfunction and structural alterations (*)	*IV. Depolarization/Conduction abnormalities*
Major - Severe dilatation and reduction of RV-EF with no (or mild) LV impairment - Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulges) - Severe segmental dilatation of the RV	Major - Epsilon waves or localized prolongation of the QRS complex in right precordial leads (>110 ms in V1-V3) Minor - Late potentials (signal-averaged ECG)
Minor - Mild global RV dilatation and/or EF-reduction with normal LV - Mild segmental dilatation of the RV - Regional RV hypokinesia	*V. Arrhythmias* Minor - LBBB type VT testing (sustained or nonsustained) on ECG, Holter, exercise testing - Frequent ventricular extrasystoles (>1000/24 hours on Holter)
II. Tissue characterization of walls	*VI. Family History*
Major - Fibrofatty replacement of myocardium on endomyocardial biopsy	Major - Familial disease confirmed at necropsy or surgery Minor - Familial history of premature sudden (<35 years) due to suspected ARVC - Familial history of ARVC, clinical diagnosis based on present criteria
III. Repolarization abnormalities	
Minor - Inverted T-waves in right precordial leads (V2 and V3) (age >12 years, absence of RBBB)	

Two major criteria or one major plus two minor criteria or four minor criteria from different groups confirm the diagnosis of ARVC
ECG, electrocardiogram; LBBB, left bundle branch block; RBBB, right bundle branch block; VT, ventricular tachycardia; RV, right ventricle; LV, left ventricle
*detected by echocardiography, angiography, magnetic resonance imaging or radionuclide scintigraphy

Signal-averaged ECG

More frequently, these low amplitude signals in the terminal portion of the QRS complex are detected using the high-resolution signal averaged ECG ("late potentials") [13, 14]. The presence of late potentials indicates structural heart disease but is very unusual in idiopathic ventricular arrhythmias. Therefore, the signal-averaged ECG may be helpful to distinguish minor forms of ARVC from idiopathic VT. Furthermore, it may be useful for the identification of high-risk subgroups and the prediction of drug-nonresponders among patients with ARVC [14].

Holter Monitoring

In patients with ARVC and frequent ventricular arrhythmias, Holter monitoring may be useful for the documentation of arrhythmias and for the assessment of drug efficacy, particularly when the clinical arrhythmia is not inducible during

programmed electrical stimulation. On antiarrhythmic drug treatment, Holter monitoring may be used to demonstrate or exclude proarrhythmic drug effects.

Exercise Testing and Response to Isoproterenol Infusion

Since ventricular arrhythmias in ARVC are frequently exercise-induced or catecholamine-sensitive, exercise testing and intravenous application of isoproterenol are very useful for the provocation of the clinical arrhythmia [15]. Isoproterenol provocation may also be helpful for the facilitation of VT induction during programmed electrical stimulation [16]. In patients with reproducible provocation of VT during or immediately after exercise testing or isoproterenol infusion, these tests are valuable tools in the diagnostic assessment of ARVC and evaluation of antiarrhythmic treatment.

Invasive Electrophysiologic Study

Programmed electrical stimulation represents an essential diagnostic tool for the characterization of ventricular tachyarrhythmias in ARVC as well as for the risk stratification and decision making concerning antiarrhythmic treatment modalities. In the majority of patients with sporadic episodes of sustained monomorphic VT, the clinical arrhythmia is reproducibly inducible during programmed ventricular stimulation. However, additional isoproterenol infusion may be required in some patients to facilitate VT induction [16]. Multiple VT morphologies ("pleomorphism") are frequent in patients with generalized right ventricular involvement and dysfunction but less common in localized disease. In patients with only nonsustained VT or frequent ventricular ectopies, sustained VT is less frequently inducible by programmed stimulation. The most important applications of programmed electrical stimulation are electrophysiologically guided serial drug testing and endocardial mapping preceding radiofrequency catheter ablation [16].

Chest X-ray

The chest X-ray is normal in the majority of patients with ARVC. Only in cases with a significant enlargement of the right ventricle, there are signs of cardiomegaly and dilated right ventricular outflow tract (lateral view).

Echocardiography

Characteristic echocardiographic features of ARVC are localized or generalized right ventricular dysfunction with focal aneurysms, bulgings or sacculations, dilatation of the right ventricular outflow tract or global right ventricular enlargement. A frequent but nonspecific finding is a highly reflective prominent moderator band [17, 18].

The diagnostic value of echocardiography in ARVC is controversial because of

its limited sensitivity. Due to the retrosternal location of the right ventricular free wall as the predominant site of right ventricular abnormalities in ARVC, localized structural and functional abnormalities may not be detectable.

Magnetic Resonance Imaging (MRI)

The major advantage of magnetic resonance imaging is its unique capability to detect and localize the presence and extent of abnormal adipose tissue within the myocardium by an increase of signal intensity in areas of fatty infiltration. Abnormal myocardial fat infiltration must be differentiated from epicardial adipose tissue which is frequently present in various clinical conditions. Other structural abnormalities of ARVC like focal wall thinning and localized aneurysms can also be detected by MRI [19-21]. Dynamic cine images allow accurate measurement of right ventricular volume and demonstration of localized right ventricular wall motion abnormalities [19].

Radionuclide Imaging

Radionuclide ventriculography has frequently been used for the noninvasive study of right and left ventricular function. An abnormal right ventricular contraction pattern was reported to be associated with a high specificity and positive predictive value but only moderate sensitivity. Phase analysis was used to demonstrate regional right ventricular contraction abnormalities during sinus rhythm and to localize the site of origin of the arrhythmia during well tolerated sustained VT [22].

Recent studies demonstrated localized sympathetic myocardial dysinnervation of the septal and posteroseptal left ventricle in the majority of patients with ARVC using ^{123}I-meta-iodobenzylguanidine (MIBG) SPECT scintigraphy [23]. The tracer is a norepinephrine analogue and indicates postganglionary presynaptic noradrenergic uptake. Sympathetic dysinnervation may be related to the occurrence of ventricular tachyarrhythmias because an imbalance of sympathetic innervation results in a so-called "catecholamine hypersensitivity" facilitating dispersion of refractoriness with reentrant arrhythmias and delayed afterdepolarization with triggered activity.

Right ventricular angiography

Right ventricular angiography is still considered as the gold standard of imaging techniques in the diagnosis of ARVC. However, the morphology and geometric shape of the normal right ventricle is complex and variable. Therefore, the interpretation of angiographic morphology and function of the right ventricle is sometimes difficult. Also, the accuracy of calculated right ventricular volumes and ejection fraction is limited since their calculation is based on geometric assumptions. Characteristic angiographic findings of ARVC are localized aneurysms, bulgings or sacculations with akinesia or dyskinesia. Horizontal and

hypertrophied trabeculae with deep fissures are frequently present. Regional dilatation of the outflow tract of localized hypokinesia is a frequent but nonspecific finding which may be difficult to distinguish from normality [24, 25].

Endomyocardial Biopsy

Typical histological findings from endomyocardial biopsies are fibrofatty infiltration of the right ventricular myocardium. However, the criteria of abnormal adipose content varies considerably in different studies and ranges from 3% to 50% fat in the biopsy specimen [26, 27]. Large scale morphometric studies addressing this problem are still lacking. Due to the localization of the disease, endomyocardial biopsy is associated with a significant sampling error, resulting in a reduced sensitivity. Therefore, only positive findings are diagnostic and a negative biopsy result does not exclude the diagnosis. In order to improve the sensitivity, multiple biopsy specimens from favored areas ("triangle of dysplasia" [2]) including the free wall and areas of documented wall motion abnormalities have been recommended. However, this may be related with an increased risk of complications including right ventricular perforation and tamponade.

Management of ARVC

Medical Treatment

Prospective randomized trials on antiarrhythmic drug efficacy in patients with ARVC are not available. The largest retrospective study of acute and long-term results of antiarrhythmic drug treatment in ARVC was published by Wichter et al. [16], including 147 patient in the latest series [28, 29]. In 92 of 147 patients (63%), serial drug testing identified an effective drug which completely suppressed the arrhythmia. Independent predictors of drug failure were extensive right ventricular contraction abnormalities and inducible VT during programmed stimulation [28]. In another 15% of patients, the drug showed partial efficacy, rendering VT induction more difficult. Sotalol was effective in 69% of patients compared with only 18% for class I antiarrhythmic drugs. Amiodarone was no alternative since the lack of response to sotalol predicted failure of amiodarone during electrophysiologically guided serial drug testing. However, a combination of amiodarone with β-blockers has been reported with clinical efficacy rates similar to sotalol by other groups. Whenever possible, antiarrhythmic drug efficacy should be evaluated by serial programmed electrical stimulation [15]. In patients with nonreentrant VT, verapamil and β-blockers have been reported to be effective in up to 50% of cases [16].

Catheter Ablation

In patients with drug-refractory VT, radiofrequency catheter ablation is a therapeutic alternative. Acute success can be achieved in approximately 75% of

patients in whom VT is rendered noninducible [28-31]. About half of these patients still require antiarrhythmic drug treatment. However, despite these satisfactory acute results, there is a high incidence of recurrences during long-term follow-up [28-30], partly resulting from the development of new arrhythmogenic foci during a progressive long-term course of ARVC. Therefore, it has been recommended that catheter ablation should only be considered in patients with a single morphology of well tolerated VT and a localized form of right ventricular involvement of ARVC.

Surgical treatment

Various surgical approaches from localized ventriculotomy at the site of earliest activation to a total disconnection of the right ventricular free wall have been performed in patients with ARVC and drug-refractory VT [2, 32, 33]. Localized surgical procedures carry a risk of arrhythmia recurrence due to new forms of VT during disease progression. The total disconnection procedure has been performed in selected patients with diffuse right ventricular involvement and multiple sites of VT [32, 33] but is associated with a high incidence of acute postoperative right heart failure. For these reasons, surgical procedures are currently limited to the very rare patients with no other treatment option. In selected rare cases with progressive and severe heart failure resistant to conventional therapy, cardiac transplantation may be considered.

Implantable Cardioverter-Defibrillator (ICD)

In patients with ARVC and drug-refractory VT unsuitable for catheter ablation (extensive disease or multiple arrhythmogenic foci) or serial drug testing (no inducible VT after an episode of survived cardiac arrest or severe side-effects on drugs), the implantation of an ICD system is a therapeutic option with increasing importance [34, 35]. The introduction of transvenous ICD systems, antitachycardia pacing capabilities, biphasic shock waveforms with reduction of defibrillation thresholds and improved battery longevity has increased the indications and significantly reduced the morbidity and mortality of ICD treatment. In our experience, the risk of serious procedure-related complications is low. However, an adequate placement of the transvenous defibrillation lead for appropriate pacing and sensing results may be difficult due to the structural alterations of the right ventricular myocardium [34, 35]. The available data indicate that appropriate ICD therapies occur in the majority of ARVC patients during the first years of follow-up. In many patients, these therapies were presumably life-saving because of a high rate of VT recurrences. It can therefore be assumed that in selected high-risk patients with ARVC with otherwise normal life-expectancy, ICD implantation may improve the long-term prognosis and survival with a favorable cost/benefit ratio.

Prognosis and Risk Stratification

Patients with ARVC and effective medical treatment, as determined by serial electrophysiologic testing, appear to have a good long-term prognosis provided regular long-term drug intake and the absence of severe progression of right ventricular disease. However, long-term management of these patients with regular follow-up visits appears to be crucial in order to improve long-term patient compliance. Patients without effective medical treatment have a high incidence of VT recurrences. Mortality rates of up to 20% after 10 years or 2.5% per year have been reported on uncontrolled empiric medical therapy [28, 36-38]. Extensive right ventricular involvement and enlargement, inducibility of VT, a history of cardiac arrest and the presence of late potentials were identified as additional independent predictors of arrhythmic events during follow-up [28, 37]. However, further improvements in risk-stratification are needed to better identify patients at high risk, who require aggressive pharmacological or nonpharmacological treatment.

The overall mortality in ten years on treatment ranges between 5% and 20% when different therapeutic strategies are compared. Best results regarding long-term survival appear to be achievable by treatment strategies including serial drug testing guided by programmed stimulation and ICD-implantation in selected high-risk patients who proved to be drug-refractory or in whom serial drug testing is not applicable due to noninducibility of VT after an episode of survived cardiac arrest.

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"Brugada Syndrome": A Structural Cardiomyopathy or a Functional Electrical Disease?

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Summary

Five years ago we described a new syndrome characterised by an electrocardiographic pattern consisting of right bundle branch block with elevation of the ST segment in leads V1-V3 and sudden death caused by rapid polymorphic ventricular arrhythmias. None of the initially described patients had any demonstrable form of heart disease. Nowadays, thanks to international cooperation, we have obtained long-term information on a large cohort of patients with this syndrome. Data on 63 patients (57 males, mean age 38 ± 17 years) were analysed. Twenty-seven patients (43%) had a family history of sudden death. Extensive noninvasive and invasive examinations, including echocardiography, left and right ventricular angiography, heart biopsies, ergonovine tests, and nuclear magnetic resonance failed to show any form of structural heart abnormality. Findings during these tests were characteristically different from those in right ventricular dysplasia. The electrocardiographic response to ajmaline or procainamide and the transient normalisation of the electrocardiogram during follow-up were characteristic of this syndrome and not found in right ventricular dysplasia. Genetic testing in a large family with approximately 50% affected members excluded by linkage analysis the gene abnormalities so far described in right ventricular dysplasia. During follow-up up to 10 years, no patient developed or was suspected to develop any form of structural heart disease. In terms of prognosis, this syndrome is associated to a high recurrence of ventricular fibrillation in patients who have already suffered from one or multiple episodes of aborted sudden death. Most worrying is, however, that asymptomatic persons with this electrocardiographic pattern are also at high risk of sudden death. Amiodarone and β-blockers do not protect against sudden death. The only valuable therapy at present is an implantable cardioverter-defibrillator.

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Introduction

In 1992 we described 8 patients who survived one or multiple episodes of aborted sudden death and who had a peculiar electrocardiographic pattern (Fig. 1). The electrocardiogram showed a right bundle branch block-like QRS complex with ST segment elevation in leads V1-V3 in the absence of any demonstrable structural heart disease [1]. Since then, there have been several reports on this syndrome in the literature, suggesting that this disease is much more common than previously suspected [2-6]. After our initial publication we identified intermittent and concealed forms of the syndrome [7]. In patients with the Brugada syndrome the electrocardiogram may transiently normalize during follow-up and become abnormal again later on (intermittent forms). The intravenous administration of

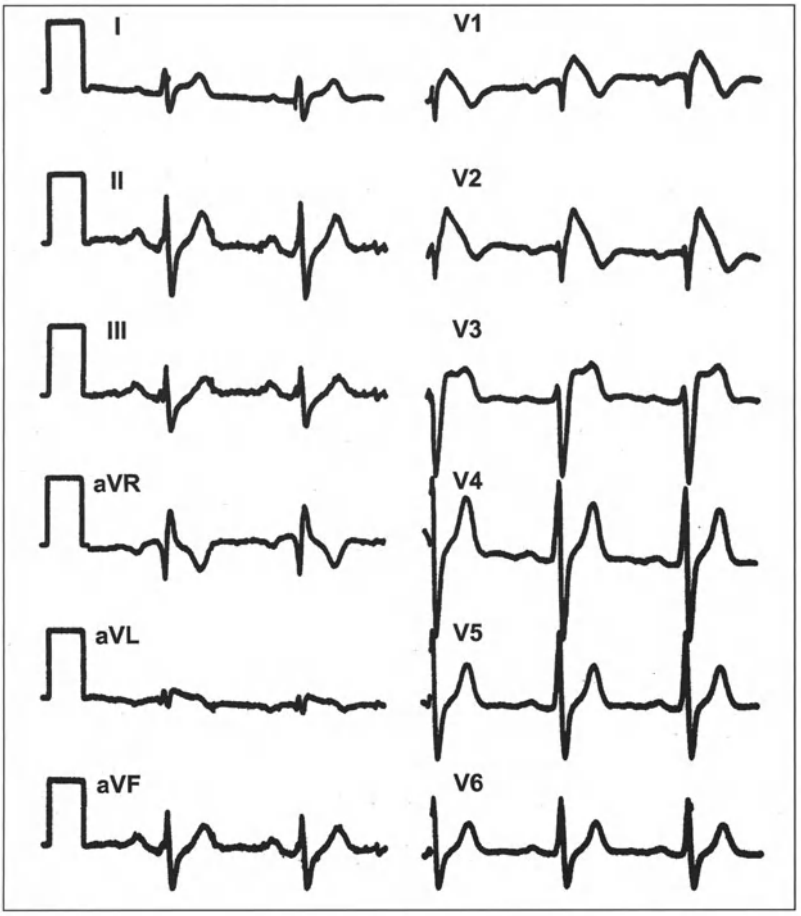

Fig. 1. A typical 12-lead electrocardiogram at 25 mm/s paper speed in a patient with the Brugada syndrome. Note the right bundle branch block-like pattern and the peculiar ST segment elevation in leads V1-V3

ajmaline or procainamide to patients classified as "idiopathic" ventricular fibrillation may uncover the electrocardiographic abnormalities typical of the syndrome (concealed forms). We have obtained information on a large cohort of patients with this syndrome during long-term follow-up. Centers and physicians who kindly and freely provided data to us are listed in appendix I. Although we have additional information from the literature on more than 70 additional patients, only patients specifically presented to us were included here.

Patients and Methods

The patient population consisted of 56 males and 7 females with a mean age at the time of diagnosis of 38 ± 17 years. There were 27 patients with a family history of unexpected sudden death, and 9 individuals were family members of symptomatic patients. In all 63 patients extensive noninvasive and invasive examinations excluded all known forms of structural heart disease. These tests included clinical history, physical examination, 12-lead electrocardiogram, transthoracic echocardiography, and extensive laboratory evaluation in all patients. An exercise test was done in 55 patients and an ergonovine test in 53. Right and left ventricular angiography and coronary angiography were performed in 43, 48, and 49 patients respectively. Endomyocardial biopsies were obtained in 17 patients. A nuclear magnetic resonance of the heart was done in 22 patients. Treatment strategies were decided by the attending physician. Frequently, however, we provided advice from the available data at the time of contact. In general, treatment consisted of an implantable cardioverter-defibrillator for patients who survived one or more episodes of aborted sudden death, in combination or not with amiodarone or a β-blocker, a β-blocker, a prophylactic implantable defibrillator or no treatment for the asymptomatic individuals who had the typical electrocardiographic pattern of the syndrome.

Information on patient status at the last follow-up was obtained from the treating physician. Patients were considered to have suffered a new arrhythmic event if they suffered an episode of documented syncopal ventricular arrhythmia, sudden death, or received an appropriate shock from an implantable defibrillator.

The Kaplan-Meier method was used to estimate the probability of survival and event-free follow-up. The statistical significance of the differences was assessed using the log rank test. Cross-tabs comparisons were done using Chi-square analysis. Data are presented as mean ± 1 standard deviation.

Results

The abnormal electrocardiographic pattern was first identified after one or multiple episodes of aborted sudden death in 32 patients, or after a syncope of unclear etiology in 9 patients. These 41 patients were considered *symptomatic* patients for the purposes of follow-up and comparison. The remaining 22 patients were *asymptomatic* at the time the electrocardiographic abnormalities

were identified. This was the case during a routine electrocardiographic control in 13 patients, and because of screening after sudden death of a family member in the remaining 9 patients. During follow-up, 6 of the 22 asymptomatic patients developed (aborted) sudden death. Thus, 43 of the 63 patients (73%) with this electrocardiogram have developed symptoms at least once during their lifetime. The age at the time of the first arrhythmic event varied from 2 to 77 years, with a mean of 41 ± 18 years.

Programmed electrical stimulation induced ventricular fibrillation or long-lasting polymorphic ventricular tachycardia in 37 of 46 patients (80%). Inducibility was similar in symptomatic and asymptomatic patients, respectively 78% and 86%, (p value not significant).

Thirty-five patients received an implantable cardioverter-defibrillator, and 15 patients received antiarrhythmic drug treatment (β-blocker or amiodarone). The remaining 13 patients received no treatment at all. During follow-up, 31% of patients with an implantable defibrillator received an appropriate shock. Five patients treated with only antiarrhythmic drugs, and 4 patients in the no therapy group developed (aborted) sudden death ($p < 0.0005$ as compared to the implantable defibrillator). Data on recurrent arrhythmic events and sudden death depending upon the treatment group are shown in Figures 2 and 3. No variables

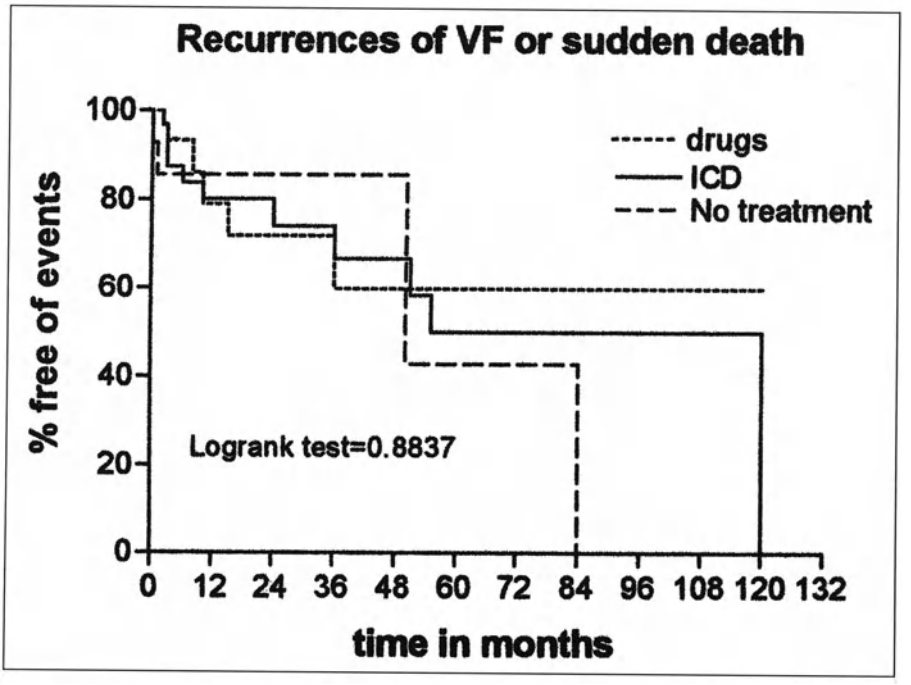

Fig. 2. Recurrences of ventricular fibrillation and occurrence of sudden death depending upon treatment strategy (drugs, implantable defibrillator – ICD – or no treatment). The incidence of events during follow-up was similar in the three groups. Drugs (amiodarone and β-blockers) do not protect against sudden death (Fig. 3)

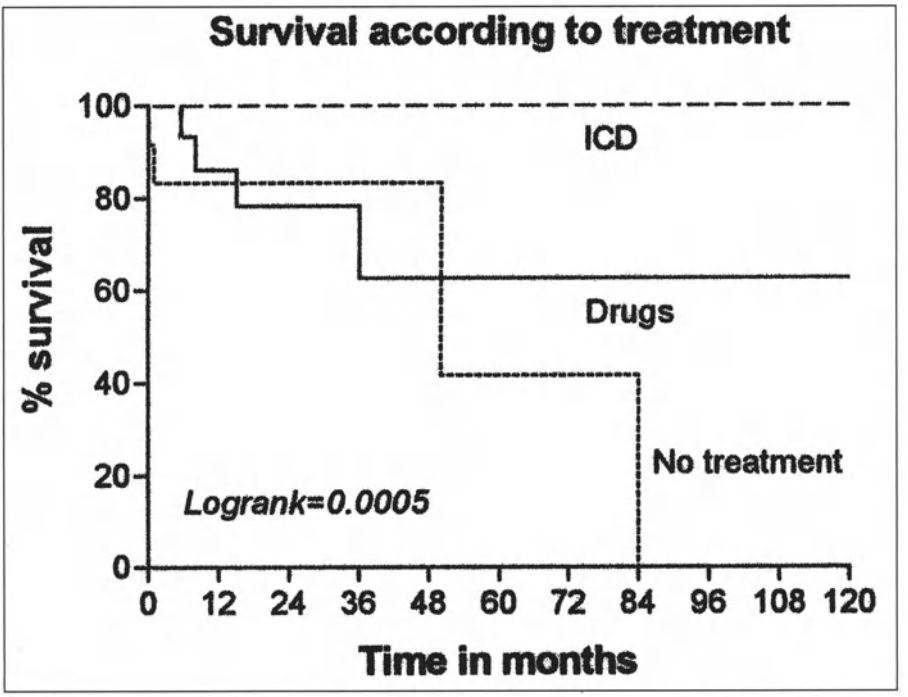

Fig. 3. Survival according to treatment. Treatment with drugs or no treatment is associated to a high incidence of sudden death. The implantable defibrillator (ICD) protects against sudden death in spite of a similar incidence of recurrent arrhythmias (Fig. 2)

Table 1. Characteristics of patients with and without an arrhythmic event during follow-up

	Arrhythmic event		
	Yes	No	*p* value
Total	20 (32%)	43 (68%)	
Men/women	18/2	38/5	ns
Age (years)	41 ± 18	42 ± 16	ns
β-blockers	5	7	ns
Amiodarone	3	2	ns
No treatment	4	9	ns
Implantable defibrillator	11	24	ns
Inducible at EPS	13	24	ns
Non-inducible at EPS	2	7	ns
No EPS	5	12	ns
Symptomatic at diagnosis	14	27	ns
Asymptomatic at diagnosis	6	16	ns
Family history of sudden death	8	19	ns

EPS = electrophysiologic study

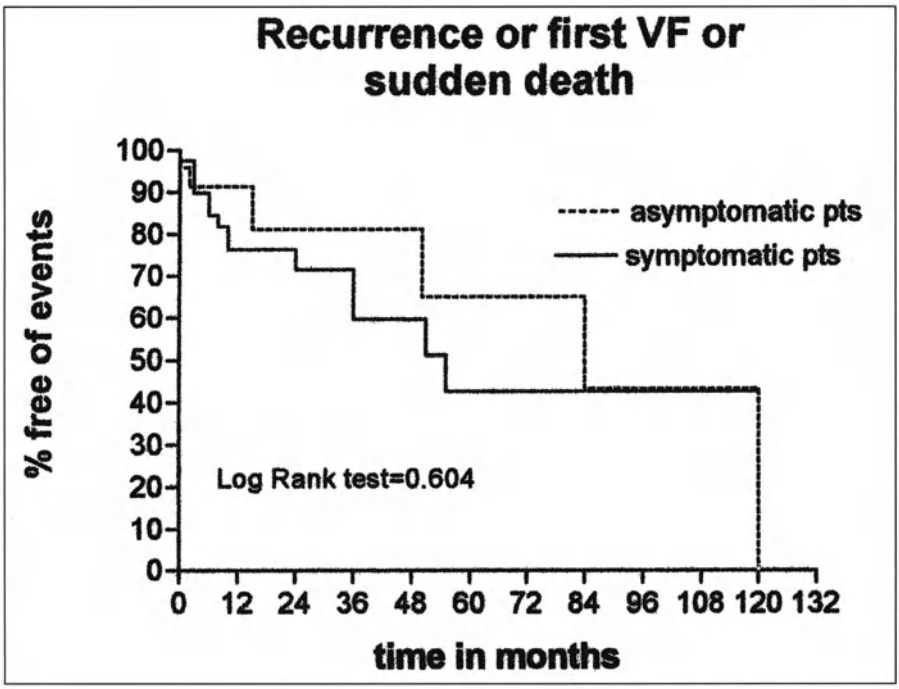

Fig. 4. Recurrent arrhythmic events in symptomatic patients and first occurrence of an arrhythmic event in asymptomatic patients. The curves clearly illustrate that asymptomatic patients have the same prognosis as symptomatic patients

were found to be predictable of outcome, with the exception of the implantation of a cardioverter-defibrillator (Table 1) (Fig. 3).

Figure 4 illustrates the arrhythmic event free survival of symptomatic and asymptomatic patients. Asymptomatic patients developed as many first arrhythmic events during follow-up as symptomatic patients developed recurrences of their first arrhythmia episode. Fourteen of the 41 (34%) symptomatic patients had a recurrent arrhythmic event, and 6 of the 22 (27%) asymptomatic patients suffered from a first arrhythmic event during follow-up (p = NS).

Comparison of the Brugada Syndrome to Right Ventricular Dysplasia and Other Causes of Sudden Death in Apparently Healthy Individuals

There exist many causes of sudden death in apparently healthy individuals and it may be beyond the scope of this study to compare patients with the Brugada syndrome to patients with other well known and identifiable forms of sudden death. However, it is certainly necessary and justified to compare our patients to patients with so-called "idiopathic" ventricular fibrillation and patients with the syndrome of right ventricular dysplasia. As shown in Figure 5, any patient with

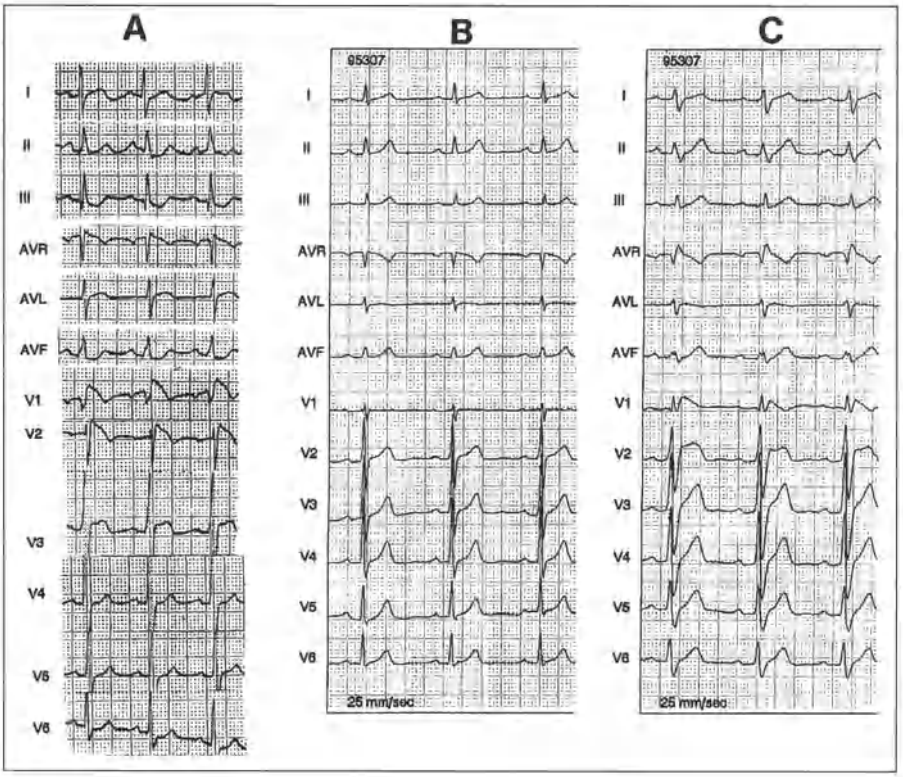

Fig. 5. A patient with the Brugada syndrome who suffered from aborted sudden death. Panel A shows the typical electrocardiogram. In panel B the electrocardiogram has normalized a few months later. Administration of intravenous ajmaline (panel C) uncovers the abnormalities again. Patients with "idiopathic" ventricular fibrillation must be challenged with ajmaline or procainamide to uncover this syndrome

"idiopathic" ventricular fibrillation should be tested with intravenous ajmaline (1 mg/kg body weight given over 3-5 min) or procainamide (10 mg/kg body weight given over 10 min) before accepting the diagnosis of "idiopathic" ventricular fibrillation. Many of these patients are concealed forms of the Brugada syndrome which can be unmasked by ajmaline or procainamide. Although the treatment of "idiopathic" ventricular fibrillation is at the moment similar to treatment of the Brugada syndrome, that may change in the future when the genetic abnormalities in the Brugada syndrome become better understood and a specific therapy will be possible. It is therefore of crucial importance to correctly identify patients with Brugada syndrome who present with a normal electrocardiogram and look like "idiopathic" ventricular fibrillation.

Some publications [8-9] have suggested that patients with the Brugada syndrome are actually variants of right ventricular dysplasia. We are going to cut this discussion short by referring to Table 2, where the differences between the two diseases are summarized. The two publications never explained which was the

Table 2. A comparison of noninvasive and invasive findings in patients with Brugada syndrome and in patients with right ventricular dysplasia

	Brugada syndrome	RVD
ECG	RBBB+ST elevation V1-V2 with intermittent changes	Negative T's V1-V3 without intermittent changes
Exercise	Decreases ST elevation	No effects
Isoproterenol	Decreases ST elevation	No effects
Proc/Aj	Increases ST elevation	No effects
Arrhythmias	Polymorphic VT/VF	Monomorphic VT
Echocardiogram	Normal	RV dilatation, aneurysms
NMR	Normal	Fatty infiltration
PET	Normal	Unknown
Biopsies	Normal	Fatty infiltration, fibrosys
Angiography	Normal	RV dilatation, aneurysms, loss of trabeculation
HV interval	Prolonged (30%)	Normal
Family history	Yes (43%)	Yes (incidence unknown)
Genetic abnormalities in chromosomes 1,14	No	Yes

ECG, electrocardiogram; Proc/Aj, administration of intravenous procainamide or ajmaline; NMR, nuclear magnetic resonance; PET, positron emission tomography; RBBB, right bundle branch block; RV, right ventricle; RVD, right ventricular dysplasia; VF, ventricular fibrillation; VT, ventricular tachycardia

"gold standard" for the diagnosis of right ventricular dysplasia, a disease which, in our opinion is overdiagnosed by some groups without any scientific basis. Irrespective of the pathophysiologic mechanisms involved in the Brugada syndrome, it is clear that the electrocardiogram which we described is a marker of sudden arrhythmic death both in symptomatic and asymptomatic individuals.

Discussion

The available data show that patients with an electrocardiographic pattern of right bundle branch block and ST segment elevation in leads V1 to V3 are at risk of sudden death. These patients have no structural heart disease and do not develop any form of known heart disease during follow-up, particularly right

ventricular dysplasia. It is also clear that authors diagnosing right ventricular dysplasia should make an effort to obtain true scientific information on how to diagnose right ventricular dysplasia. There exists no controlled study on the sensitivity and specificity of biopsies or post-mortem findings, and there exist no blind studies on the sensitivity and specificity of pathologic findings in right ventricular dysplasia. Thus, and although patients with the Brugada syndrome are clearly different from patients diagnosed as right ventricular dysplasia (Table 2) we must first conclude that a diagnosis of right ventricular dysplasia remains in most cases an approximation and is frequently a totally obscure diagnosis. That may explain why some groups of rhythmologists apparently see dozens of dysplasias a year, while most rhythmology groups with extremely large patient populations do not see a dozen in a life time. Until scientific and more accurate data become available on right ventricular dysplasia, a discussion about the differences and similarities between the Brugada syndrome and right ventricular dysplasia makes little sense. In terms of the two publications suggesting right ventricular dysplasia as the cause of the Brugada syndrome, one should not forget that even if the diagnosis or right ventricular dysplasia was correct, there exists the possibility that these two patients suffered from two diseases at the same time: right ventricular dysplasia *and* the Brugada syndrome.

Patients with the Brugada syndrome have a high incidence of recurrent arrhythmic events during follow-up. The data presented here clearly show that the only effective therapy is the implantable defibrillator. It is very worrying to observe that also asymptomatic patients have a poor prognosis. It may be difficult to justify the prophylactic implantation of a defibrillator to all patients with the described electrocardiographic pattern. The available data suggest, however, that this may be the safest approach. We realize very clearly the implications of such a decision. The alternative (sudden death) is, however, much worse. We have tried to find predictors of sudden death in the asymptomatic individuals and of recurrences in the symptomatic population. Unfortunately, so far no data seem to be predictive, including the induction or not of a ventricular arrhythmia during programmed electrical stimulation of the heart.

In conclusion, patients with the described abnormal electrocardiogram are at high risk of sudden death (first or recurrent episode). Pharmacologic treatment with amiodarone or a β-blocker does not provide sufficient protection against sudden death, but the implantable defibrillator does. The Brugada syndrome is a distinct, genetically determined, clinical entity whose mechanisms will be the matter of intensive and interesting research in future years. This condition is underdiagnosed because there exist intermittent and concealed forms of the syndrome. Hopefully, rapid progress in the understanding of the genetic abnormalities and their manipulation will allow appropriate treatment and prevention of sudden death.

Whatever the electrophysiologic mechanisms, we agree with the statement of Dr Scheinmann [9]: "Patients with a pattern of right bundle branch block, ST segment elevation, and no structural heart disease are at risk for malignant ventricular arrhythmias".

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VENTRICULAR TACHYARRHYTHMIAS: MANAGEMENT

Management of Ventricular Tachyarrhythmias: Is Correction of Ischemia Sufficient?

F. Di Pede, G. Zuin, G. Turiano and A. Raviele

It is well known that patients with ischemic heart disease are prone to ventricular tachyarrhythmias and to sudden death.

Sudden death remains a major medical and social problem accounting for 300 000-400 000 deaths per year in the USA [1]. Half of all cardiac deaths are sudden and about 50% of all sudden deaths occur in patients with known ischemic heart disease [1]. The final event leading to sudden death is ventricular fibrillation in the majority of cases [2]. Many mechanisms are involved in the pathogenesis of ventricular fibrillation including ischemia, electrophysiological abnormalities and heart failure. However the precise mechanism producing ventricular fibrillation in the clinical setting is often elusive and therapeutic measures cannot be easily focused on the causes. Consequently clinicians spend their efforts treating or preventing the ultimate cause of sudden death, ventricular fibrillation, essentially by antiarrhythmic drugs and by implantable cardioverter-defibrillator (ICD). An indirect demonstration of our unability to recognize the cause of ventricular fibrillation and sudden death in the individual patient is the growing use of ICD, a device capable of interrupting any sustained ventricular tachycardia irrespective of the mechanisms involved in the genesis of the arrhythmia.

The possibility of preventing ventricular tachyarrhythmias and sudden death in selected patients by treating ischemia is an intriguing topic. The treatment of the individual patient by stand-alone antiischemic measures requires proving the followings:

1. That the cause of the ventricular tachyarrhythmia is ischemia
2. That no other factor is responsible for the ventricular tachyarrhythmia
3. That ischemia can be successfully treated.

Acute Ischemia as Cause of Ventricular Tachyarrhythmias

Acute ischemia produces immediate electrical mechanical and electrophysiological dysfunction of the myocardium. Electrophysiological abnormalities constitute a setting suitable for reentry and triggered activity. The most frequent arrhythmias occurring during experimental ischemia are ventricular premature

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beats, runs of self-terminating ventricular tachycardia, ventricular fibrillation and rapid ventricular tachycardia degenerating into ventricular fibrillation [1]. Hypertrophied tissue or tissue healed after previous injury is more susceptible to the destabilizing effects of ischemia [1].

Ischemia related arrhythmias occurring in a clinical setting (acute myocardial infarction and transient ischemia) have essentially the same characteristics as arrhythmias observed in animal experiments: monomorphic ventricular tachycardia is generally transient; sustained forms are much rarer and are polymorphic; ventricular fibrillation is usually sustained and induces severe hemodynamic deterioration [3, 4].

Another mechanism capable of producing life-threatening arrhythmias is reperfusion. Animal studies and clinical observations have demonstrated that, shortly after the restoration of coronary blood flow, ventricular arrhythmias including ventricular fibrillation may develop [1].

However ischemia related ventricular arrhythmias occur only in a minority of ischemic episodes and are relatively more frequent during prolonged painful episodes with ST elevation in patients with preexisting healed ischemic injury [5, 6]. These data suggest that the pathogenesis of ischemic ventricular fibrillation requires other facilitating factors. Actually experimental data underline the importance of autonomic reflexes as factors that favour the precipitation of ventricular fibrillation during acute ischemia [7].

The importance of acute ischemia as a mechanism for sudden death is also supported by data collected from sudden death victims: acute myocardial infarction is present in 20% of cases [8]; chest pain precedes the loss of consciousness in about 60% of cases [9]; significant coronary stenosis can be found in 70% of cases [10]; "acute coronary lesions" are detectable in up to 95% of cases [11]. Moreover data concerning sudden death survivors indicate that ischemia may be present in the majority of cases as demonstrated by the presence of potentially ischemic segments (severe coronary stenosis in an artery supplying viable myocardium) in a significant proportion (56%-61%) of patients [12, 13].

Other Causes of Ventricular Tachyarrhythmias

Arrhythmic Substrate

Ventricular tachyarrhythmias may be primarily generated by electrophysiological abnormalities. Histopathological and electrophysiological studies have demonstrated that areas of preexisting infarcted myocardium showing myocytes encased in fibrous tissue may constitute a locus of electrophysiological abnormalities that help set the stage for occurrence of reentrant circuits [14]. Electrophysiological abnormalities favouring reentry are heterogeneous refractoriness and slow conduction that permit reentrant excitation and reproducible induction of sustained monomorphic ventricular tachycardia and more rarely ventricular fibrillation by programmed electrical stimulation [15].

The occurrence of sustained monomorphic ventricular tachycardia does not require an ischemic trigger. Ventricular premature beats and mechanisms involving concealed slow conduction may initiate the arrhythmia. Ischemia may act as a promoting factor or may contribute to the degeneration into ventricular fibrillation. Hemodynamic compromise during rapid ventricular tachycardia may precipitate ischemia, inducing a vicious cycle that culminates in cardiac arrest [15].

The importance of anatomical and electrophysiological substrates derives also from data gathered in sudden death victims and cardiac arrest survivors. Abnormalities of left ventricle produced by healed infarction are present in about 60% of sudden death victims and one third of patients have left ventricular aneurysms [15]. Electrophysiological derangements related to anatomic abnormalities may be noninvasively detected by signal-averaged electrocardiogram (late potentials) in 9%-53% of survivors of out-of-hospital cardiac arrest [16]. Ventricular tachyarrhythmias can be induced, by means of programmed electrical stimulation, in nearly 3 out of 4 patients with ischemic heart disease surviving cardiac arrest unrelated to acute myocardial infarction. Monomorphic sustained ventricular tachycardia accounts for 63%, polymorphic sustained ventricular tachycardia or ventricular fibrillation accounts for 18% [15]. The induction of monomorphic sustained ventricular tachycardia is indicative of an arrhythmic substrate with clinical implications, while the clinical significance of the induction of polymorphic sustained ventricular tachycardia or ventricular fibrillation remains uncertain. The importance of the arrhythmic substrate is attested by the close relationship between ventricular arrhythmias inducibility and the subsequent sudden death rate: patients with sustained ventricular tachycardia inducible by programmed electrical stimulation have an unfavorable outcome with a high recurrence rate of ventricular tachyarrhythmias and sudden death irrespective of left ventricular function or ischemia [17, 18].

The proportion of detection of late potentials [16] and of inducibility of sustained ventricular tachyarrhythmias [12] is lower in patients with ventricular fibrillation than in patients with sustained monomorphic ventricular tachycardia, suggesting that the arrhythmic substrate is absent in some patients with ventricular fibrillation and that other mechanisms are involved in the genesis of the ventricular tachyarrhythmias in these patients.

In summary data collected in the "ischemic field" and in the "electrophysiologic field" clearly show that ventricular fibrillation is the tipical arrhythmia generated by ischemia, while monomorphic sustained ventricular tachycardia generally requires the presence of an arrhythmic substrate.

Heart Failure

Patients with heart failure irrespective of the etiology are prone to sudden death. In heart failure, sudden death may be due both to ventricular tachyarrhythmias and to bradyarrhythmias or to electromechanical dissociation [19]. In the majority of patients with heart failure, ventricular tachyarrhythmias may be generated by the same mechanisms mentioned above (ischemia, electrical abnormalities).

In some cardiac arrest survivors ischemia and electrical abnormalities cannot be identified and other poorly understood mechanism are involved, as neurohumoral and metabolic factors. However left ventricular function is the most important variable with prognostic implications in survivors of a cardiac arrest [18].

Recent studies have demonstrated that left ventricular dysfunction may be due not only to irreversible damage of myocardium, like a scar, but may be the result of potentially reversible conditions like hibernating or stunned myocardium [20]. It has been shown that patients with non-contractile but viable myocardium are prone to sudden death and that myocardial revascularization can prevent sudden death [21]. Therefore evidence of non-contractile but viable myocardium may identify a pathophysiologically unstable condition susceptible of new ischemic events and of ventricular tachyarrhythmias. These data underline the role of ischemia in conditions usually not considered as "ischemic".

Identification of Patients in Whom Ventricular Tachyarrhythmias Are Caused by Ischemia

Clinical studies have demonstrated that patients surviving a cardiac arrest or suffering from monomorphic ventricular tachycardia with a demonstrable arrhythmic substrate (inducible sustained ventricular tachycardia) or with severe left ventricular dysfunction have an unfavorable long-term prognosis with recurrent cardiac arrest or sustained ventricular tachycardia despite therapy [17, 18].

On the contrary, patients surviving a cardiac arrest without an arrhythmic substrate and with preserved left ventricular function have a better outcome [17, 18]. In these patients the presenting arrhythmia is usually ventricular fibrillation, and angiographic and ergometric studies demonstrate high prevalence of severe multivessel disease and of ischemia suggesting that ischemia may play a role in the genesis of ventricular fibrillation [12, 15]. The better outcome is probably due to the prevention of ventricular fibrillation by treating ischemia.

Actually it has been demonstrated that in patients with ischemic heart disease the therapy of ischemia by means of drugs or surgical revascularization improves survival and reduces the mortality rate of sudden death in some subsets of patients. The β-blockers clearly demonstrated a protective effect against sudden death after myocardial infarction (32% to 50% reduction of sudden death) [22].

Coronary bypass surgery demonstrated a beneficial effect on sudden death in patients with chronic coronary artery disease in the ECCS randomized trial but not in the CASS randomized trial [23, 24]. However observational data coming from CASS database show that surgical therapy has an independent beneficial effect on sudden death [25].

It is noteworthy that patients enrolled in the ECCS had better left ventricular function and worse Canadian functional class than patients enrolled in CASS. These data suggest that the prevention of sudden death by surgical therapy can be obtained more likely in patients with heavy ischemic burden without large chronic structural abnormalities of myocardium potentially constituting an arrhythmogenic substrate.

The effects of revascularization in patients with ventricular tachyarrhythmias have not been fully elucidated and data are lacking. Some authors have shown that revascularization may modify the arrhythmogenic substrate in selected groups of patients, thus preventing the induction of ventricular tachyarrhythmias by programmed electrical stimulation in a significant proportion [26-30] (Table 1). Kelly et al. [29] have reported that in survivors of cardiac arrest with inducible ventricular fibrillation by programmed electrical stimulation and good left ventricular function, revascularization abolishes inducible arrhythmias and allows a near event-free follow-up. On the contrary, in patients with inducible monomorphic ventricular tachycardia and depressed left ventricular function, revascularization does not prevent arrhythmia induction nor arrhythmia recurrence or sudden death during the follow-up.

Table 1. Effects of myocardial revascularization on inducibility of ventricular tachyarrhythmias

Author/year	N. pts	PRE OP PES		POST OP PES	
		VT	VF	VT	VF
Garan et al (1983) [26]	17	11	4	6	0
Fonger et al (1988) [27]	23	19	0	12	0
Kron et al (1989) [28]	8	0	5	0	1
Kelly et al (1990) [29]	50	22	11	18	1
Manolis et al (1993) [30]	56	41	6	28	2
Total	154	93	26	64	4

pts, patients; PRE OP PES, preoperative programmed electrical stimulation; POST OP, postoperative; VT, ventricular tachycardia; VF, ventricular fibrillation

The beneficial effects of β-blockers and revascularization have also been observed in patients who had survived an out-of-hospital cardiac arrest or had recurrent ventricular tachyarrhythmias treated with ICD. In these patients β-blocker administration and coronary bypass surgery were associated with later ICD discharge and bypass surgery was associated with a better survival [31].

Some authors have specifically studied the efficacy of stand-alone antiischemic therapy in reducing the incidence of sudden death in subsets of patients with ventricular tachyarrhythmias [29, 30, 32-35] (Table 2). Every et al. [33] evaluated retrospectively the effects of bypass surgery on recurrent cardiac arrest in 265 patients resuscitated from hospital cardiac arrest. From this cohort 85 patients underwent coronary bypass surgery and 180 were treated medically. Patients treated with surgery had a higher ejection fraction, were less likely to have had a remote history of heart failure and the incidence of angina before the cardiac arrest was higher. During the follow-up (mean period 4.9 years) 11% of surgically treated patients and 42% of medically treated patients had a second cardiac arrest. After adjustment for other possible confounding factors, the use of bypass surgery was associated with a 52% lower risk of subsequent cardiac

Table 2. Follow-up of patients with ventricular tachyarrhythmias treated with myocardial revascularization

Authors year	N. pts	N. pts S/M	EF (%)	FOLLOW-UP month (mean)	SD/VF	NSCD
Tresch et al 1985 [32]	49	S: 49	n.r.	55	6	5
		M: 0	-	-	-	-
Kelly et al 1990 [29]	50	S: 50	46	39	2	3
		M: 0	-	-	-	-
Every et al 1992 [33]	265	S: 85	51	59	11	11
		M: 180	41	59	76	36
Manolis et al 1993 [30]	36	S: 56	36	28	2	5
		M: 0	-	-	-	-
Wiesfeld et al 1995 [35]	69	S: 14	46	21	0	1
		M: 55	27	21	13	4
Total		S: 254	47.6	55.7	21(8.3%)	25(37.8%)
		M: 235	37.7	55.7	89(37.6%)	40(17%)

S, surgical therapy; M, medical therapy; EF, ejection fraction; SD, sudden death; VF, ventricular fibrillation; NSCD, non sudden cardiac death

arrest. More recently Wiesfeld et al. [35] tested a strategy to modify the pathophysiological mechanism (primarily ischemic or primarily arrhythmic) responsible for the arrhythmia in 82 patients with ventricular tachyarrhythmias and previous myocardial infarction. Ischemia was considered the primary cause of the event in patients with more than 90% stenosis in a coronary supplying viable myocardium. Fourteen patients had these characteristics and were treated by antiischemic therapy including drugs, PTCA and bypass surgery. Ischemia was not considered the primary cause of the event in patients without significant coronary stenosis in vessels other than the infarct-related artery and in those without demonstrable ischemia. The non-ischemic group was formed by 55 patients who were treated by antiarrhythmic drugs selected by programmed electrical stimulation, catheter ablation, arrhythmia surgery, or ICD. The remaining 13 patients had intermediate characteristics and were treated both with antiischemic and antiarrhythmic measures. Patients with ischemia-related arrhythmias had better left ventricular function, less prevalence of left ventricular aneurysm and greater prevalence of ventricular fibrillation as presenting arrhythmia. During a mean period of 21 months none of the patients with ischemia-related

arrhythmias died suddenly. On the contrary, 9 patients with the arrhythmic pattern and 2 patients with the mixed pattern died suddenly. Ventricular tachyarrhythmia recurrence had a similar behavior: none in the ischemic group, 11 patients in the arrhythmic group and 2 patients in the mixed group. These results suggest that accurate evaluation of clinical and angiographic data allow the correct identification of those patients in whom ischemia is the major determinant of ventricular tachyarrhythmias and that the treatment of ischemia is sufficient to prevent arrhythmia recurrence and sudden death.

From these data it is possible to delineate the clinical profile of patients with purely ischemic ventricular tachyarrhythmias and cardiac arrest:

1. Ventricular fibrillation as presenting arrhythmia
2. Inducibility of ischemia by stress test
3. Severe coronary stenosis in an artery supplying viable miocardium
4. Non-inducibility of monomorphic ventricular tachyarrhythmias by programmed electrical stimulation
5. Good left ventricular function.

The first 3 characteristics indicate that ischemia may be the cause of the ventricular tachyarrhythmia and the last 2 characteristics indicate that no other clinically indentifiable factor (arrhythmic substrate or heart failure) is involved in the occurrence of the arrhythmia.

The prevention of "ischemic ventricular tachyarrhythmias" by means of antiischemic therapy (myocardial revascularization) raises some problems:

1. Revascularization may be uncomplete in some patients
2. Ischemia can be produced not only by the well known mechanisms involved in chronic stable angina but also by acute thrombosis or spasm generating acute coronary syndromes (unstable angina, acute myocardial infarction).

Up to now we do not have any clinical, angiographic or laboratory parameters capable of recognizing patients who will develop acute coronary syndromes in the future. These aspects can explain the inability of myocardial revascularization to completely prevent sudden death and suggest caution in the management of patients surviving a cardiac arrest by stand-alone antiischemic therapy. An additional problem derives from the scarcity of data concerning this specific subject in comparison with the large experience gathered with other therapies of ventricular tachyarrhythmias such as ICD or drugs. However the analysis of the outcome of patients with purely ischemic ventricular fibrillation (Table 2) treated with antiischemic measures offers encouraging results and the sudden death rate is similar to that obtained in patients treated with ICD (less than 2% per year) [36].

Conclusions

In conclusion, the strategy of stand-alone antiischemic therapy for the prevention of ventricular tachyarrhythmias may be applicable only in a minority of patients and requires accurate evaluation of all possible mechanisms leading to ventricu-

lar tachyarrhythmias in the individual patient: ischemia, electrophysiological substrate and left ventricular function.

In patients with monomorphic ventricular tachycardia acute ischemia is not likely to be the cause of the arrhythmia, and consequently antiarrhythmic therapy (ICD, ablation, drugs) is the best approach.

In patients with ventricular fibrillation as presenting arrhythmia, ischemia is probably the cause of the arrhythmia in those subjects with the features of the "purely ischemic arrhythmia" (coronary severe stenosis, inducible ischemia, good left ventricular function, sustained ventricular tachycardia not inducible by programmed electrical stimulation), and an antiischemic treatment may be the best choice.

Patients with inducible ventricular fibrillation at baseline programmed electrical stimulation and with inducible ischemia need a reevaluation by programmed electrical stimulation after antiischemic therapy. If they become noninducible, antiischemic therapy may be appropriate.

In patients with some but not all of the "purely ischemic arrhythmia" features, and with evidence of ischemia, the therapeutic option has to be based on the individual patient and probably a therapeutic strategy based both on antiischemic measures and on ICD may be appropriate in the majority of cases.

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Appropriate Indications for the Implantable Defibrillator

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Introduction

After more than 15 years of clinical use, the appropriate indications for the implantable cardioverter-defibrillator (ICD) remain in controversy. The reasons for this controversy have nothing whatever to do with the efficacy of the device itself, since the ICD has proven remarkably effective in doing what it was designed to do, namely, preventing sudden death from ventricular arrhythmias [1-5]. Instead, the controversy stems from three factors: a) the relative expense and inconvenience of the ICD as opposed to other available therapies; b) confusion as to whether the device prolongs overall survival as well as preventing sudden death; and c) failure to note that in some patients the ICD can be useful (and therefore effective) without appreciably improving the risk of sudden death or improving overall survival.

The Expense and Inconvenience of ICDs

ICDs are very expensive. For an ICD system, the cost for the hardware itself (the generator and leads) ranges from $15 000 to $25 000 (US). When physician fees and hospitalization are added, the total expense to implant an ICD often reaches $30 000 to $35 000. Obviously, using ICDs in large numbers of patients will place a significant strain on any health care system.

Despite improvements in the ICD implantation procedure itself over the past five years, neither the implantation nor the long-term management of these devices are simple endeavors. While on a superficial level the ICD itself has become much more "pacemaker-like," the device and its management remain much more complex than for even the most sophisticated pacemaker. Device selection, lead placement, intra-operative testing, programming for optimal arrhythmia management, follow-up and troubleshooting remain highly complex, and yet critically important tasks. Physicians who have not dedicated a substantial proportion of their careers to the management of arrhythmias and the use of antitachycardia devices are not likely to have favorable clinical results using ICDs.

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Both the expense of the ICD (at a time when the rising cost of health care is a major societal problem) and the complexity of the device create a strong inclination, among policy makers and many physicians, to seek alternative therapies even where adequate alternatives might not exist.

Confusion Regarding Prolongation of Overall Survival

There is no argument over the fact that prolongation of overall survival is the appropriate outcome to measure, at least for those patients in whom the ICD is being used to prevent sudden death. After all, if survival is not prolonged, what good does it do to prevent sudden death? Unfortunately, this appropriate notion has led to an inappropriate definition of "efficacy" for the ICD, namely that the ICD is effective only if it prolongs overall survival. This misguided definition creates much of the confusion surrounding the appropriate use of the ICD.

In fact, the ICD was designed to prevent sudden death. If it prevents sudden death, it is effective by definition. The fact that we also want the device to prolong overall survival (in addition to preventing sudden death), simply means that we have to be careful how we use it.

Indeed, since the ICD prevents sudden death from ventricular arrhythmias, its effect on overall survival can be stated as an axiom [6]. That axiom is as follows: the ability of the ICD to prolong survival depends, completely and solely, on the population of patients to which it is applied.

To successfully prolong overall survival with the ICD, it must be used in a population of patients that meets two criteria. First, the risk of sudden death from arrhythmias must be high in that population; and second, the risk of death from other causes (over the time period of follow-up) must be relatively low. If either the risk of sudden death is low, or the risk of death from other causes is high, then one will not be able to demonstrate an improvement in overall survival with the ICD.

A corollary of this axiom of overall ICD survival is that, if a clinical trial fails to show a benefit in overall survival with the ICD, that trial offers no implications relative to the efficacy of the ICD itself. The results of such a trial would simply indicate the failure to enroll sufficient patients in whom the prevention of sudden death by the ICD would result in a measurable improvement in overall survival. Such results would imply something about patient selection, but not about the ICD itself.

Therefore, much confusion is created by trials such as AVID [7] which promise to measure, at last, the "true" efficacy of the ICD (by randomizing enrolled patients to ICD versus drug therapy). In fact, what such trials are actually measuring is only the relative effect of the indiscriminate use of the ICD in a broad, heterogeneous population of patients. Whether or not these trials show the ICD to be "effective," their results will imply nothing regarding the ability of the ICD to prolong survival in appropriately selected patients.

Unfortunately, proponents of the AVID-like studies will attempt to convince insurance carriers and government agencies that they have actually measured the true efficacy of the ICD. If they are successful, the "approved indications" for the

ICD are likely to be inappropriately stifled or inappropriately expanded by the results of such studies. In contrast, more useful clinical trials with the ICD would recognize that the device is merely a potentially useful tool (a tool that prevents sudden death), and accordingly, would attempt to identify well-defined subsets of patients in whom prevention of sudden death also prolongs overall survival.

Such confusion on how to interpret the prolongation in overall survival by the ICD therefore creates confusion regarding the appropriate indications for the device.

The ICD Can Be Useful without Prolonging Survival

The advent of tiered-therapy ICDs (devices that can terminate some ventricular tachycardias painlessly, using antitachycardia pacing schemes) created a new indication for these devices. Now they can be implanted for the purpose of painlessly terminating arrhythmias in patients who have recurrent, monomorphic ventricular tachycardias. In general, patients presenting with such arrhythmias (as opposed to those presenting with ventricular fibrillation or polymorphic ventricular tachycardia) have a relatively low risk of dying suddenly. Therefore, the ICD, while it may be indicated, has relatively little chance of prolonging survival in such patients. The fact that the ICD can be effective while not having the potential to improve survival (in at least one subset of patients) creates even more confusion regarding the appropriate indications for this device.

Accepted Indications for the ICD

With this background, let us consider the current accepted indications for the ICD, as derived from the recommendations of the North American Society of Pacing and Electrophysiology [8] and the American College of Cardiology/American Heart Association [9].

Class I indications. Class I indications are those for which a broad consensus exists.

These include:

1) Patients with episodes of spontaneous sustained ventricular tachycardia or fibrillation in which neither EP testing nor spontaneous arrhythmias can be used to guide therapy.
2) Patients with recurrent, spontaneous sustained ventricular arrhythmias despite drug therapy guided by electrophysiological testing or by noninvasive methods.
3) Patients with spontaneous sustained ventricular tachyarrhythmias in whom antiarrhythmic drug therapy is limited by intolerance or noncompliance.
4) Patients with persistently inducible, sustained ventricular tachyarrhythmias despite best drug or ablation therapy.

Class II indications. Class II indications are those for which a consensus does not always exist.

These include:

1) Patients with syncope of unknown origin in whom sustained ventricular tachyarrhythmias are inducible during electrophysiological testing, and in whom drug therapy cannot be used for reasons similar to those listed in items "I3" and "I4" above.
2) Patients who have the screening profile used in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) [10]. This profile includes: a) prior myocardial infarction; b) left ventricular ejection fraction of less than or equal to 35%; c) episodes of spontaneous nonsustained ventricular tachycardia; d) inducible ventricular tachycardia that cannot be suppressed by intravenous procainamide or other Class I antiarrhythmic drug during electrophysiological testing. MADIT is the first randomized trial to have established a truly prophylactic indication for the ICD, in that MADIT patients had not yet had sustained ventricular tachyarrhythmias. While aspects of MADIT have been criticized by some, most electrophysiologists are impressed by its results, and consider patients fulfilling the MADIT profile to be candidates for the ICD. The United States Food and Drug Administration was sufficiently convinced by the results of MADIT to rapidly expand the approved indications for the ICD to include such patients.

Patients Who Meet Accepted Indications but Are Unlikely to Be Helped

The most striking drawback to these generally accepted indications for the ICD is that they address only the characteristics of patients' arrhythmias, and not the characteristics of the patients themselves. In terms of the axiom of overall ICD survival, they address only one of the two criteria necessary for prolongation of survival to be realized, namely, that recipients of the ICD should have a high risk of sudden death from ventricular arrhythmias.

The accepted indications entirely fail to address the second criterion: that recipients of an ICD should be likely to survive for a substantial period of time if sudden death can be prevented. One could implant the ICD in a population of patients who all meet the acceptable indications for the device, and still fail to achieve a favorable overall result.

It is the obligation of the clinician to always ask that second question when faced with a decision as to whether to implant an ICD: "Yes, the patient has a life-threatening arrhythmia that meets acceptable implantation criteria for the ICD. But is he or she likely to have significant overall benefit if prevention of sudden death can be achieved?" Unless the answer to this second question is also yes, the ICD most often should not be used.

Patients Who Do Not Meet Accepted Indications but May be Helped (possible future indications)

Presently, only a few tens of thousands of patients worldwide receive the ICD each year, in contrast to the more than 300 000 individuals who die suddenly each year

in the United States alone, and in contrast to the vastly larger number of patients who (by virtue of their underlying cardiac disease) are at high risk for sudden death.

Except for the small subset of high-risk patients meeting the MADIT profile, in order for an ICD to be indicated, candidates must have already experienced (and survived) sustained ventricular tachyarrhythmias. The huge majority of individuals who die suddenly have never experienced prior sustained arrhythmias, and therefore never would have been candidates for an ICD.

Most victims of sudden death come from the pool of patients who have significant underlying cardiac disease, such as prior myocardial infarction, a history of congestive heart failure, or reduced left ventricular ejection fraction. It is very likely that some subsets of these patients (i.e., patients with risk factors but no manifest sustained arrhythmias) would benefit from ICD insertion. MADIT was the first trial to successfully identify such a subset. The Multicenter Unsustained Tachycardia Trial (MUSTT) and the CABG-PATCH trial [7] also seek to expand the indications for the prophylactic use of the ICD.

Even if these trials are successful, however, the vast majority of potential victims of sudden death will still not be candidates for the ICD. Given the continued cost and complexity of ICD systems, making a large impact in the worldwide incidence of sudden death will probably never be possible with the ICD. Such an impact will almost certainly require a breakthrough outside of the realm of implantable antitachycardia devices.

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The ICD Cannot Impact *Non-Arrhythmic* Mortality. Or *Can* It?

S. NISAM

Introduction

The implantable cardioverter defibrillator (ICD) has been established as the *gold standard* in terms of reducing *sudden death* resulting from lethal ventricular tachyarrhythmias [1, 2]. Many large series have shown that the rate of sudden death in patients with a history of such arrhythmias has been reduced to approximately 1% per year, well below the 20%-25% incidence of sudden death observed in major studies of patients treated with antiarrhythmic drugs [3-6]. Nevertheless, there continues to be considerable debate on whether this protection against sudden death translates to meaningful prolongation of life. Or, is sudden arrhythmic death from ventricular tachycardia or fibrillation simply a manifestation of advanced cardiomyopathy from which the patient succumbs shortly after, even if temporarily saved by the ICD?

Much of this debate stems from the intriguing observation, noted by several researchers [7-9], that the ICD not only reduces sudden arrhythmic deaths, but also deaths not directly attributable to arrhythmic causes. It is an instrument that automatically detects and converts dangerous ventricular tachyarrhythmias, thereby virtually eliminating *sudden death* as the mode of exitus for endangered patients. As such, the ICD has of course no means of reversing congestive heart failure or death from other serious cardiomyopathies. But the *fact* is that, in *multiple* large ICD series, not only is the incidence of arrhythmic death reduced, but also that of non-sudden death. The debaters' conclusions, logically enough, have similar refrains: "...in some way the ICD patients were inherently less sick." [7] Or, "The only explanation for the 'improvement' in non-sudden death in the ICD patients is that they were intrinsically healthier." [8] It is this apparent *anomaly* – the ICD's impact on *non-sudden deaths* – which we wish to examine in this paper.

Sudden and Non-Sudden Deaths

The classic comparison so often cited is the report by Herre et al. for long term outcome of patients treated with amiodarone [3], compared to *apparently* simi-

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lar patients in Winkle et al.'s ICD series [10] (Table 1). As seen clearly in this table, the rate of sudden death at five years for the ICD patients was 4%, well below the 21% for the amiodarone treated cohort; but, the rate of non-sudden death was also nearly double in the amiodarone treated patients, 41% at five years compared to only 22% for the ICD.

Table 1. Mortality: total, arrhythmic, and non-arrhythmic

Major series of patients with VT/VF		Follow-up[a] (Yrs)	Total (%)	Arrhythmic (%)	Non-Arrhythmic (%)
Herre [3]	Amiodarone (N = 462)	5	62	21	41.0
Winkle [10]	ICD (N = 270)	5	26	4.4	21.6
Newman [11]	Amiodarone (N = 120)	3	49	10	39.2
	ICD (N = 60)	3	22	5	16.7
Wever [12]	Conv'l AARx (N = 31)	2.25	35.5	12.9	22.6
	ICD (N = 29)	2.25	13.7	3.4	10.3
MADIT [13]	Conv'l AARx (N = 101)	2.25	38.6	12.9	25.7
	ICD (N = 95)	2.25	15.8	3.2	12.6

VT/VF = ventricular tachycardia/fibrillation; ICD = implantable cardioverter defibrillator; Conv'l AArx = conventional antiarrhythmic drug therapy; MADIT = Multicenter Automatic Defibrillator Implantation Trial.
[a]Follow-up times indicated above are *actuarial* in Herre, Winkle and Newman series; and *mean* in Wever and MADIT series.

The critical risk factors and demographics of the patients in the two series appear very similar, e.g. the mean left ventricular ejection fraction was 34% for the ICD patients, slightly worse than the 36% for the amiodarone treated patients; and the ICD patients had failed a mean of 3.1 drug trials, compared to 2.6 for those treated by amiodarone. Importantly, both studies took place concurrently during the late 1980s (and coincidentally, within a few kilometers of one another!). The second example shown on Table 1 comes from Newman et al.'s well-known *matched controls* study, which took place some three years later [11]. This study compared outcomes for sixty patients treated with ICDs who were matched to 120 patients with equivalent baseline variables (left ventricular ejection fraction, presenting arrhythmia, age, underlying heart disease, and drug therapy status) who were treated with amiodarone. Once again, the sudden death rates were lower for the ICD treated patients, 5% vs. 10% at 3 years, $p < 0.01$; but, once again– and presumably not expected – the incidence of non-arrhythmic deaths was about half in the ICD cohort compared to the amiodarone control group: 16.7% vs 39.2%, $p < 0.01$.

As shown in Table 1, several other examples seem to tell the same story. The importance of the studies by Wever et al. and of the Multicenter Automatic Defibrillation Implantation Trial (MADIT) is that these were *randomized, prospective* studies [12, 13]. In the Netherlands study, sixty survivors of sudden

death were randomized to ICDs vs conventional therapy [12]. The results at an average follow-up of 27 months, showed that conventionally treated patients had nearly four times the incidence of sudden death, 12.9% vs 3.4%, and over double the number of non-arrhythmic deaths, 22.6% vs 10.3%, compared to those randomized to ICD therapy. In MADIT, once again, the incidence of deaths classified as non-arrhythmic or uncertain was much lower in the ICD treated patients, compared to those randomized to conventional therapy, 12.6% vs 25.7%, respectively [13]. To summarize Table 1, whether one uses concurrent historical controls, matched case control studies, or randomized, prospective trials, the results consistently demonstrate dramatically lower rates of *both* non-arrhythmic deaths as well as arrhythmic deaths in all these studies.

Why? How Can the ICD Reduce Non-Arrhythmic Deaths?

The first and appropriate answer is that it *cannot.* But, what is important in analyzing this situation is that we are comparing two treatment strategies. A far more probable explanation is that – rather than the *observed* results being a benefit due to the ICD – they may simply reflect antiarrhythmic drugs' *contributing* to non-arrhythmic deaths. We noted this curious disparity previously, and tried to speculate on the possible reasons [14] (Table 2): a) negative inotropic effects of antiarrhythmic drugs could be contributing to late, non-arrhythmic mortality; b) recurrence of sustained ventricular tachycardias despite antiarrhythmic drug therapy, which – in contrast to patients treated with ICDs – can last for hours or possibly days, eventually leading to irreversible heart failure; c) less regular follow-up, and

Table 2. Possible explanations for lower non-sudden death in ICD patients

Possible cause	Possible mechanism
a) Negative inotropic effects of AARx	Could be contributing to late, non-arrhythmic mortality
b) Long-lasting VT episodes	In contrast to ICDs terminating them within seconds, can last for hours or days, leading to irreversible CHF
c) Less regular follow-up	Hence, less aggressive attention to CHF or other problems
d) Drug proarrhythmia	May in itself not be fatal, but could lead to progressive degeneration of cardiac function
e) Non-compliance	Drug withdrawals, for side effects or other reasons, may leave the patient unprotected. This is not possible with ICDs
f) Lengthy drug trials or "run-in" periods	May render such patients "intrinsically sicker" by the time they are actually discharged on the chosen AARx

AARx = antiarrhythmic drug therapy; ICD = implantable cardioverter defibrillator; VT = ventricular tachycardia; CHF = congestive heart failure.

consequently, less aggressive attention to heart failure or other problems for the drug-treated patients. Not included in our previous list, but also plausible explanations are: d) drug proarrhythmia, which may in itself not be fatal, but could lead to progressive degeneration of cardiac function; e) drug discontinuation, due to side effects or other reasons, may leave the patient unprotected from both arrhythmic and other problems; f) problems related to lengthy drug trials or "run-in" periods, which – in contrast to a patient discharged within days of receiving a pacemaker like ICD – may indeed render such patients "intrinsically sicker" by the time they actually receive the chosen antiarrhythmic regimen.

Discussion

In the early years of implantable defibrillator therapy, the peri-operative mortality and morbidity associated with thoracotomy implantation had obvious and sometimes significant impact on the survival curves. Added to this fact, we had previously noted from the large CPI clinical data base, that the increase in mortality with these traumatic implantation procedures seemed to extend *beyond* the 30-day period following the implantation, adding approximately 4% *additional* mortality by 12 months [15]. In sharp contrast, implants of recent years have peri-operative mortalities in the 0% - 0.5% range, and late sequelae – related to the procedure itself – are virtually nil. (We are not forgetting about early and late complications associated with ICD therapy, but these rarely have *mortality* implications, which is our main focus). As a consequence, all-cause mortality in *recent* ICD series has ranged between 4.5%-8% at two years [16-22].

The other main change from the early period of ICD therapy concerns the great advances in the treatment of heart failure and ischemia management. With regard to this point, Moss et al. emphasized the important contribution of optimal heart failure therapy, which – when combined with the sudden death protection provided by the ICD – enabled the extremely high risk MADIT patients to achieve such low mortality [13]. Nearly two thirds of the MADIT patients were in NYHA Class II or III heart failure and 55% received ACE-inhibitors during the course of the study. For the reasons explained above, we believe that for the MADIT patients randomized to the ICD, this therapy not only virtually eliminated their sudden deaths, but also spared them long, debilitating episodes of sustained VT. Thus they were afforded greater *opportunity* to profit from ACE inhibitors, diuretics, etc. The numbers in MADIT support this reasoning: not only were the sudden deaths lower in the ICD limb (3 vs 13 in the conventional treatment limb), but also the non-sudden deaths (12 vs 26, respectively). From this data plus the analysis of the incidence of appropriate shocks (60% of the MADIT ICD-treated patients received shocks within the first two years, Fig. 1), it is evident that there were *many* VT episodes quickly terminated in the ICD limb, which unfortunately were not terminated in the conventional limb. Despite *equivalent* heart failure treatment, patients in the conventional limb suffered a far higher number of pump failure deaths, consequent to such arrhythmias.

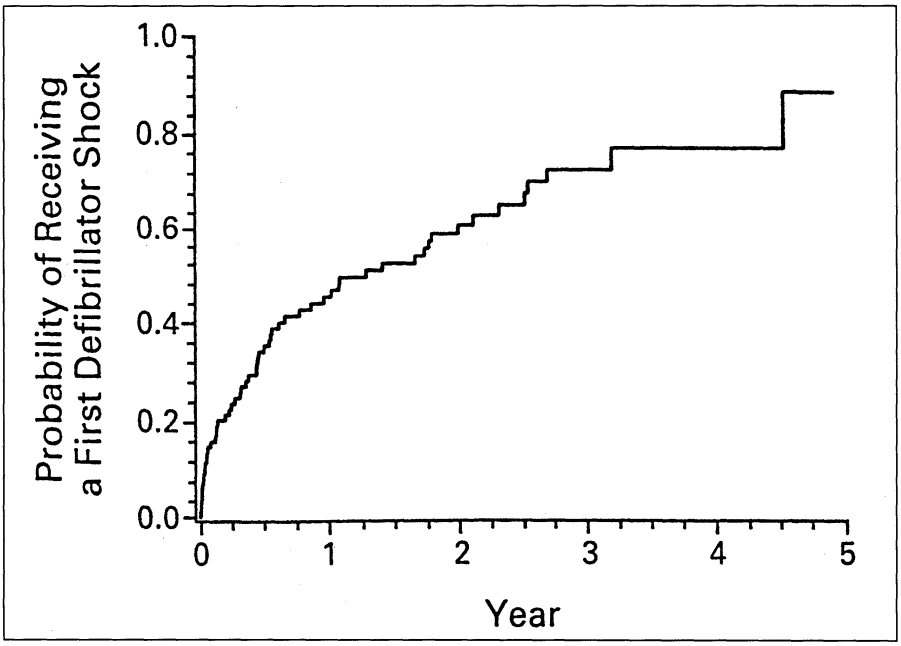

Fig. 1. Incidence (Kaplan-Meier) to first ICD shock in patients randomized to implantable cardioverter defibrillator in MADIT trial (from [13])

It is interesting to examine how different the scenario is in EMIAT: despite the reduction of arrhythmic deaths by 34% with amiodarone compared to placebo, there was an equivalent *excess* of non-sudden deaths, completely nullifying the overall survival benefit of amiodarone [23]. In a recent article [24], we drew attention to this quite *different impact on mortality* of the ICD in MADIT, compared to amiodarone in EMIAT. We have included Table 3 and Figure 2, taken from this earlier work, as they show this important difference quite vividly. It is important when looking at this difference to remember that both these studies were *randomized, prospective* trials, and that three quarters of the control limb patients in MADIT were on amiodarone.

There are two other points concerning the preceding analysis which warrant further discussion. Saksena et al. have brought attention to a difference in *safety*

Table 3. Cause of death in EMIAT and MADIT

	All causes	Arrhythmic	Non-Arrhythmic[a]
EMIAT placebo (N = 743)	102	50	52
EMIAT amiodar. (N = 743)	103	33	70
MADIT conv'l Tx (N = 101)	39	13	26
MADIT ICD (N = 95)	15	3	12

[a]Includes deaths from *unknown* causes (from [24]).

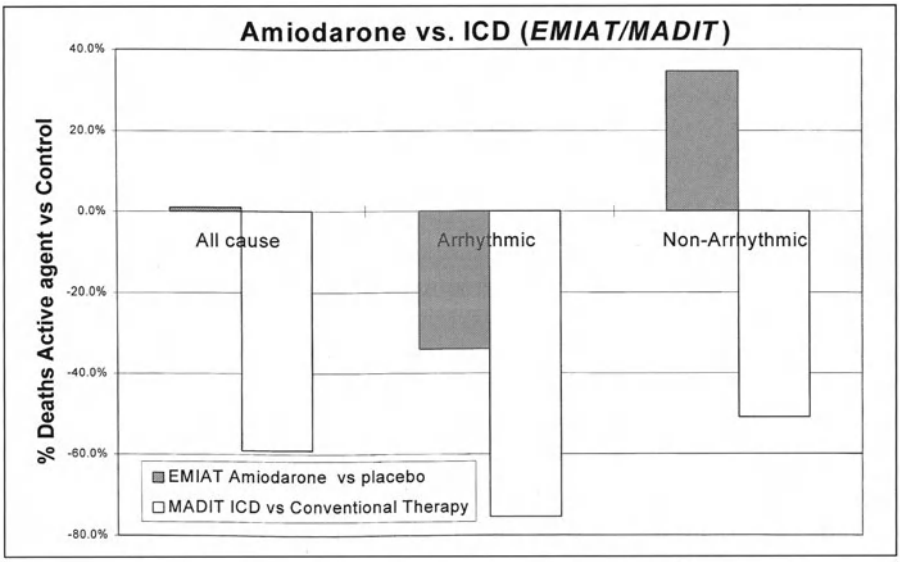

Fig. 2. Comparative mortality impact of the ICD in MADIT versus that of amiodarone in EMIAT. The mortality impact of amiodarone in EMIAT was calculated by comparing the percentage of deaths for patients on amiodarone vs placebo in EMIAT. The mortality impact of the ICD in MADIT was calculated by comparing the percentage of deaths for patients randomized to ICDs vs conventional therapy. These ratios were calculated for each cause of death: all-cause, arrhythmic, and non-arrhythmic (from [24])

between treating patients with modern, pectorally implanted ICDs and antiarrhythmic drugs [25]. They and we [24] have pointed out that major drug series like ESVEM, CASCADE, and others have reported significant 30-day mortality rates, ranging from 3%-5% [3, 6, 26, 27]. Saksena's paper also drew attention to high drug withdrawal rates, and concluded, "*In the comparative equation, device therapy compares favorably with drug therapy, particularly for very serious/fatal complications.*". The second point comes from a well-thought out analysis by Böcker et al. in their recent article appearing in the "Evidence-based Cardiology" section of the European Heart Journal [28]. They note that much of the debate concerning the life-prolonging benefit of the ICD emanates from "...data from the Montefiore group [29,30] (concerning) ... non-sudden deaths ...causally related to arrhythmias." They point out this result "...seems to be a rare finding as it has not been reported in most studies. In our series of 462 patients treated with a third-generation ICD in combination with endocardial leads, we have observed only two cases of arrhythmia-related non-sudden deaths...".

In closing, we need to acknowledge that the reasons we have suggested to explain the lower non-sudden death rates in ICD patients are speculative. But the findings are not speculative, there is now considerable *evidence* supporting them, some of which we have provided herein. Ultimately, it is the facts that count, *whatever the mechanism*! So, to answer the question we started out with, *Can the ICD impact non-arrhythmic mortality?* NO. *Can it do it better than anti-arrhythmic drugs?* YES.

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How to Select Patients for ICD Implantation

G. VERGARA

Premise

Continuous improvements have characterized the Implantable Cardioverter-Defibrillator (ICD) in the last decade. Both «technological» and «clinical» features have been involved leading to an easier implanting procedure and to a better «clinical performance».

In contrast, the pharmacological treatment is lacking new antiarrhythmic drugs thus the only reliable weapon we can use today is amiodarone, like 20 year ago.

As a result of these different trends, i.e. impressive progress in the ICD therapy vs no progress in the pharmacological treatment, the hierarchy of the therapeutic options in the management of patients with malignant ventricular tachyarrhythmias (MVTA) has changed in the past few years.

Patient Selection for ICD Implantation

Patient selection for ICD implantation is a step-by-step medical process (Fig. 1). The first step concerns the search for the possible occasional triggers of the MVTA (ischemia, electrolytic imbalance, etc.). The underlying heart disease must be carefully evaluated and its treatment optimized. The decision on the need for an antiarrhythmic therapy is the end point of this step.

The second step concerns the choice of the therapeutical option. According to the arguments reported in the premise and to the results of the recent trials MADIT and AVID, the ICD therapy can now be considered as the first choice treatment in the MVTA management. The RF catheter ablation is the first choice in case of ventricular tachycardia presenting with subcontinuous recurrences and can be considered for patients with well tolerated monomorphic ventricular tachycardia. The pharmacological treatment is lower in the hierarchy of therapeutic options; nevertheless it cannot be considered obsolete.

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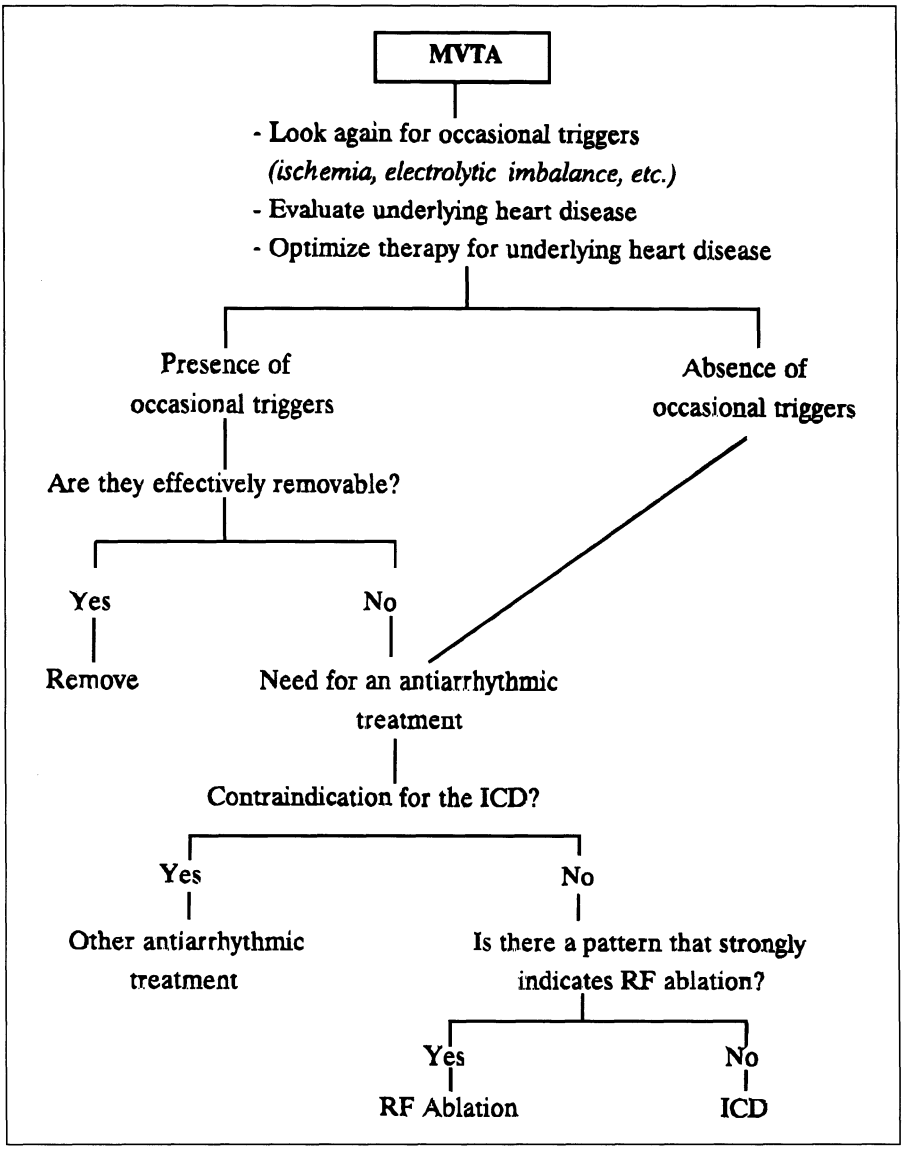

Fig. 1. Screening of patients with MVTA

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SYNCOPE: ADVANCES IN PATHOPHYSIOLOGY AND DIAGNOSIS

Adenosine-Induced Paroxysmal Atrioventricular Block: a New Possible Cause of Unexplained Syncope?

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Adenosine 5' triphosphate (ATP) and its related nucleoside, adenosine, are ubiquitous biological compounds which exert a potent depressant activity on the atrioventricular (AV) node; this can result in transient atrioventricular block (AVB). ATP and adenosine are released from myocardial cells under physiological and pathological conditions (for example in the case of myocardial oxygen supply-demand imbalance) and have similar effects. The negative dromotropic action of ATP is due to its rapid catabolism to adenosine and the subsequent action of adenosine at purinoceptor sites [1-4]. Inadvertent AVB has sometimes been observed after exogenous ATP or adenosine infusion in patients undergoing electrophysiological studies [4], in patients with paroxysmal supraventricular tachycardia [5], and in patients undergoing adenosine stress testing for the diagnosis of coronary artery disease [6, 7]. At higher doses, an intravenous bolus of ATP or adenosine has been seen to cause transient AVB in many patients with neurally-mediated syncope or sick sinus syndrome, and in controls; the AVB has sometimes been associated with a prolonged asystolic ventricular pause [8-10].

Therefore, because of its powerful negative effect on AV conduction, we hypothesized that an increased susceptibility of the AV node to adenosine may play a role in the genesis of some cases of unexplained syncope. The aims of the present study were to evaluate: the normal range of responses to an intravenous bolus of ATP (ATP test) in control subjects without syncope; and the diagnostic value of ATP testing in patients with syncope of unexplained origin (SUO).

Protocol of The ATP Test

ATP (20 mg) was dissolved in 10 cc of saline solution and injected very rapidly (< 3 seconds) into a suitable antecubital vein with the patient in the supine position. Continuous recording of electrocardiographic tracing and non-invasive beat-to-beat arterial blood pressure by means of the Finapres method [11, 12] were performed during, and for 2 minutes after, drug administration. For the

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purpose of this study, we evaluated the longest RR interval and the maximum drop in systolic blood.

Methods and Results

The study was made up of two parts. In part 1, we evaluated the ATP test in a group of patients with SUO and in controls. In part 2, we validated the ATP test in a group of patients who had the fortuitous electrocardiographic recording of a spontaneous syncope caused by a transient asystolic pause.

Part 1

We evaluated the effects of ATP test in a group of 60 patients (57 ± 19 years, 31 males) with SUO and in 90 control subjects without syncope (55 ± 17 years, 46 males). SUO patients were selected among 494 patients referred to our Units for investigation of syncope between January 1995 and December 1996 (Fig. 1). In controls, the upper 95th percentile of the maximum RR interval distribution during ATP-induced AVB was 6000 ms. In the syncope group, 28% of patients had a maximum RR interval above this limit ($p = 0.000$). The distribution of the maximum RR interval below the 95th percentile was similar in the two groups (Table 1).

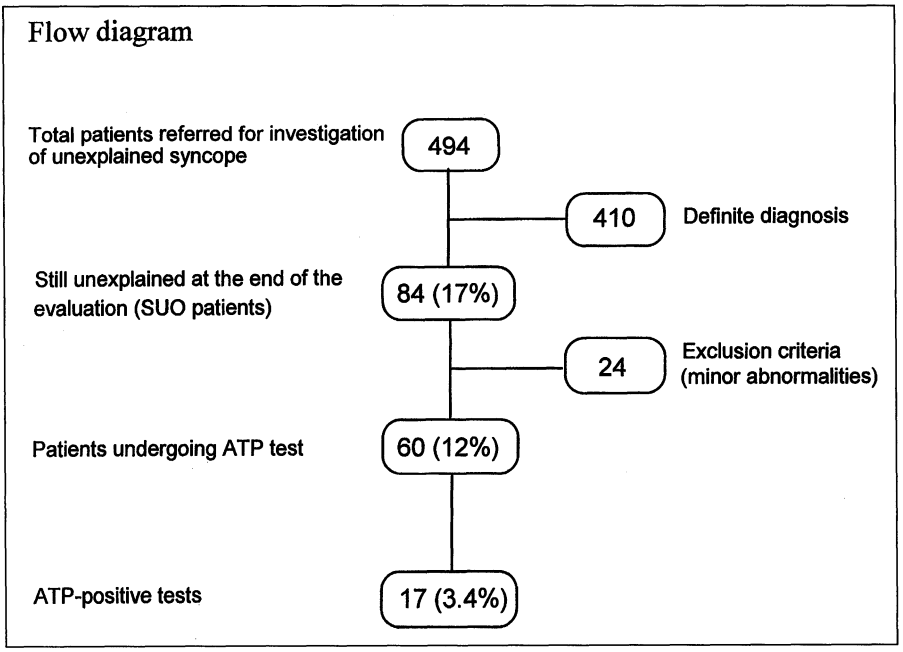

Fig. 1. Patient selection protocol

Table 1. Comparison between subjects without syncope and SUO patients

		Control group (n=90)		SUO group (n=60)		*p*
RRmax, ms:						
≥ 8000	(≥ 99th percentile)	1	(1%)	9	(15%)	0.001
≥ 6000	(≥ 95th percentile)	4	(5%)	17	(28%)	0.000
3600-5999	(75th-95th percentiles)	20	(22%)	10	(17%)	0.268
1600-3599	(50th-75th percentiles)	24	(27%)	15	(25%)	0.487
1000-1599	(25th-50th percentiles)	22	(24%)	9	(15%)	0.255
< 1000	(< 25th percentile)	20	(22%)	9	(15%)	0.359
Systolic blood pressure drop, mmHg:						
≥ 80	(≥ 99th percentile)	1	(1%)	3	(5%)	0.176
≥ 55	(≥ 95th percentile)	9	(10%)	12	(20%)	0.069
30-54	(50th-95th percentiles)	36	(40%)	28	(47%)	0.261
< 30	(< 50th percentile)	45	(50%)	20	(33%)	0.03

Part 2

We validated the ATP test in 24 patients who had the fortuitous electrocardiographic recording of a spontaneous syncope caused by a transient asystolic pause (AVB in 15 and sinus arrest in 9). The ATP test caused AVB with an asystolic pause ≥ 6000 ms in 53% of the patients with documented AVB, but in none (0%) of the control group patients with documented sinus arrest ($p = 0.01$). Among the patients with spontaneous AVB, the ATP test was abnormal in 6 (86%) of the 7 patients in whom all conventional investigations for syncope had been negative and in 2 (25%) of the 8 patients who had shown positivity ($p = 0.03$) (Table 2). The case of a patient affected by adenosine-sensitive AVB is shown in Figure 2.

Table 2. Validation of ATP test in patients with spontaneous asystolic syncope

Spontaneous syncope	Conventional investigation[a]	ATP test (RRmax ≥ 6000 ms)	
AV block (n = 7)	Negative	6 (86%)	*
AV block (n = 8)	Positive	2 (25%)	*
Sinus arrest (n = 9)	Positive	0 (0%)	**

*$p = 0.03$
**not significant
[a]Carotid sinus massage, tilt testing, AV conduction abnormalities (EKG, EPS), sick sinus syndrome

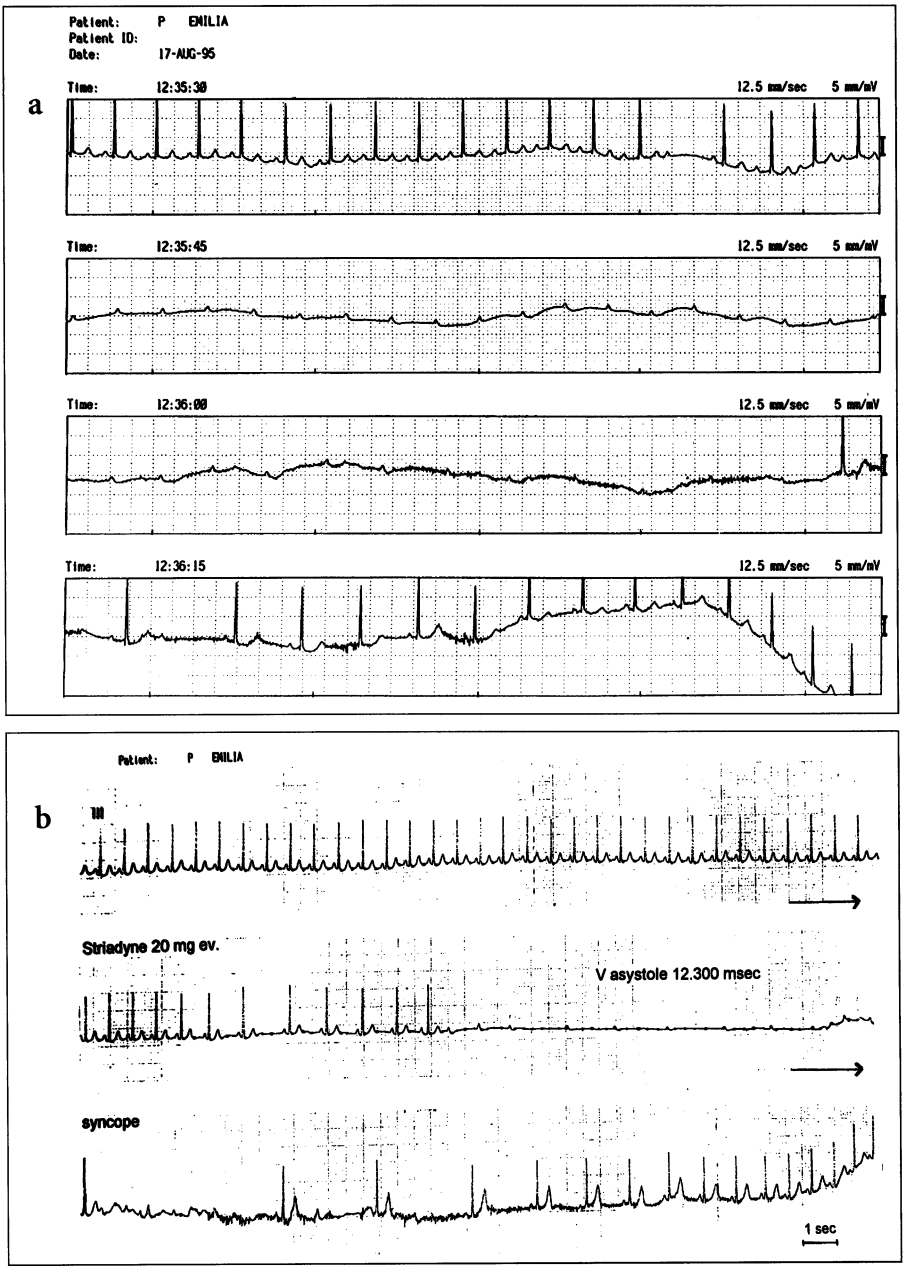

Fig. 2a, b. Case report (see Table 2). **a.** Ambulatory electrocardiographic monitoring. The strips show continuous rhythm recording. After an initial single blocked P wave, paroxysmal AVB with an asystolic pause of 30 s occurs. A normal heart rhythm promptly resumes at the end of the episode. **b.** ATP test (continuous strips). An I.V. bolus of 20 mg of ATP causes AVB and syncope. Note that a slight sinus bradycardia occurs during the late phase of asystole both during spontaneous and ATP-induced episodes

Conclusion

The main result of this study is that the patients with SUO show an increased depressant effect of exogenous ATP on AV conduction properties in comparison with those without syncope. Since an increased susceptibility to ATP was also found in patients who had a negative work-up and the fortuitous documentation of syncope caused by transient AVB, we can suppose that, in patients with SUO, an abnormal asystolic response to the ATP test suggests the diagnosis of syncope due to a paroxysmal AVB. In our institutions, ATP testing led to such a diagnosis in 28% of SUO patients and in 3.4% of all patients referred for study of syncope.

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Carotid Sinus Syndrome: What Is the Clinical Relevance of the Vasodepressor Component and How to Manage It?

C. Menozzi[1] and M. Brignole[2]

Carotid sinus syndrome is diagnosed in patients with syncope who are found to have an hyperactive carotid sinus reflex to the carotid sinus massage test and a negative work-up. Hyperactive carotid sinus reflex is present if the carotid sinus massage produces asystole exceeding 3 s (a cardioinhibitory response) or a reduction in systolic blood pressure exceeding 50 mmHg (a vasodepressor response). These limits were chosen by Franke [1] among a large population of healthy subjects and patients with various diseases. They have been accepted widely even if they represent a workable compromise since an asystolic pause of 3 seconds and a decrease of blood pressure of 50 mmHg can also be observed in subjects without syncope. The reproduction of spontaneous symptoms during the carotid sinus massage seems to add specificity to the definition of the syndrome.

Among the overall population of patients with carotid sinus syndrome, the prevalence of the pure vasodepressor type varies from 5%-15%, when the massage is performed only supine [2-4], up to 37%, when the massage is performed both in supine and in standing positions [5].

A vasodepressor reflex of 50 mmHg or more is present in most patients with the cardioinhibitory form, but the slowing of heart rate may mask the hypotensive blood pressure response unless carefully observed. From systematic observations of patients undergoing carotid sinus massage during continuous intra-arterial pressure monitoring [6, 7] or during beat-to-beat noninvasive techniques [8, 9], we would conclude that nearly all patients have varying and mixed responses to massage.

Pathophysiology of the Vasodepressor Reflex

Afferent nerves serving the carotid sinus reflex originate from baroreceptors located in the wall of the carotid sinus at the bifurcation of the common carotid artery. These join the glossopharyngeal nerve, which projects to the brain stem. Efferent impulses pass via the vagus nerve and sympathetic chain to sinoatrial and atrioventricular nodes and to peripheral vasculature. The exact site of the

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lesion in the reflex arc in carotid sinus syndrome remains unknown. Both afferent and efferent pathways would, however, appear to be intact, and a central abnormality of baroreflex gain has been postulated [3, 10, 11]. The cardioinhibitory response can be abolished with atropine, suggesting that it is vagally-mediated [2, 5]. Less is known of the pathophysiology of the vasodepressor response even if it is likely to be due to a passive reflex withdrawal of sympathetic outflow [6, 8, 9]. In a recent study [12], sympathetic inhibition caused by carotid sinus massage was demonstrated by means of direct microneurographic recording of sympathetic nerve activity. The patients with carotid sinus syndrome showed propensity toward an enhanced decline of systolic blood pressure in the upright position when compared with matched patients without carotid sinus syndrome [13]. Orthostatic hypotension was found in 27%-34% of patients [9, 13]. A symptomatic VVI-pacemaker effect, namely the sudden fall of blood pressure and related symptoms caused by the onset of stimulation in the standing position, is present in 21%-30% of the carotid sinus syndrome patients [14, 15]. The association of orthostatic hypotension and VVI-pacemaker effect with carotid sinus syndrome suggests that an abnormality of the neurovascular compensatory mechanisms is also involved. It probably potentiates the carotid sinus reflex and plays a role in the genesis of the syncope.

The vasodepressor reflex of the carotid sinus syndrome has not been studied as well as the cardioinhibitory reflex because of the limitations of noninvasive sphygmomanometric methods of measuring arterial blood pressure. Data from a few studies using invasive [6, 7] or noninvasive [8, 9] techniques of beat-to-beat blood pressure measurement showed that the duration of the cardioinhibitory reflex roughly coincides with the duration of the carotid sinus massage. The maximal asystolic pause is always observed within a few beats of the application of manual pressure on the carotid sinus, whereas the vasodepressor reflex peaks at the end of the carotid sinus massage or a few seconds later, persists for > 30 seconds after the end of the massage and, sometimes lasts 1 or 2 minutes. The timing of these responses is consistent with direct vagal stimulation and associated acetylcholine release and the rapid inactivation by acetylcholine esterase; the delayed blood pressure responses are attributed to indirect withdrawal of peripheral sympathetic vascular tone, mediated by slow-conducting amyelinic fibers [6] and to the delayed activation of a sympathetic compensatory mechanism of hypotension [8].

Diagnosis

A standardized method of execution of the carotid sinus massage does not exist yet. Owing to the delayed onset of the vasodepressor reflex, a long-duration (10 seconds or more) massage seems to be preferable in order to elicit a full vasodepressor response. Vasodepressor responses are elicited supine only in a minority of cases and more than half would be missed if carotid sinus massage was not repeated in the upright position [9, 16, 17]. Therefore, carotid sinus massage must

be performed both in supine and in standing position. In the cardioinhibitory forms, the carotid sinus massage should be repeated after intravenous administration of 0.02 mg/kg atropine to assess the contribution of the vasodepressor component (which may otherwise be hidden) [2, 5, 18]. Atropine administration is preferred to temporary dual-chamber pacing as it is simpler, less invasive and easily reproducible [18]. Even if sphygmomanometric method is usually sufficient for the diagnosis, a beat-to-beat noninvasive measurement of arterial blood pressure is required for a more accurate evaluation of the vasodepressor reflex.

Clinical Characteristics: Comparison with Other Forms

The clinical features of the pure vasodepressor form do not seem to differ substantially from those of mixed and cardioinhibitory forms even if, in the vasodepressor form, the baseline systolic blood pressure seems to be lower and male predominance is absent [8]. In the study by McIntosh et al. [9], the number of syncopes and their severity (defined as related injuries and unwitnessed episodes) were similar in all groups of patients. Due to the advanced age of patients, various underlying cardiac abnormalities are associated in most cases in every group [9, 19]. Survival of the vasodepressor carotid sinus syndrome is not significantly different from that of the mixed and cardioinhibitory forms, overall mortality being 34% at years [19]. Little is known about the syncopal recurrence rate in patients with pure vasodepressor form.

Treatment of the Vasodepressor Reflex (mixed type or pure vasodepressor type)

Asymptomatic carotid sinus syndrome requires no treatment. The first point to answer is whether there is a need for treating patients with carotid sinus syndrome. Again, there is no consensus among physicians. In general, the frequency and severity of symptoms will determine the medical approach. Most patients probably could receive a proper explanation of the problem and careful follow-up without treatment. However, the severity of the attack (injury vs non-injury), the circumstances before the attack (for instance, a clear trigger mechanism that can be avoided) and the patient's occupation and needs will help determine the need for and type of treatment [3].

The treatment of significant vasodepressor responses is still not satisfactory. Almquist et al. [7] assessed the effectiveness of AV sequential pacing and pharmacological interventions in the prevention of vasodepressor responses in eight patients with carotid sinus syndrome. Sequential pacing did not significantly alter the mean induced fall in systolic pressure (–60 ± 12 mmHg [control] vs –48 ± 19 mmHg [sequential pacing]). Similarly, neither pharmacological muscarinic blockade (atropine) nor combined muscarinic and β-blockade significantly attenuated

the induced fall in systolic pressure (–43 ± 16 mmHg with atropine; –47 ± 18 mmHg with atropine plus propanolol, both nonsignificant vs sequential pacing alone). On the other hand, intravenous norepinephrine and oral ephedrine significantly blunted the induced drop in systolic pressure (–19 ± 12 mmHg with norepinephrine; –21 ± 11 mmHg with ephedrine; both $p < 0.01$ vs sequential pacing alone).

Medical trials with drugs for the vasodepressor response are scarce. Mineralocorticoids which increase blood volume have been used in some patients [17]. Ephedrine and dihydroergotamine have provided the best results in some patients [2, 3, 7]. Unfortunately, their poor bioavailability or side effects limit the use of these drugs when given orally. In our experience, side effects are attenuated using α-adrenergic antagonists, ethylephrine or midodrine; when uneffective, we prescribe leg compression stockings.

With the advent of pacemaker therapy, the surgical denervation of the carotid sinuses is no longer justified in cardioinhibitory and mixed forms of carotid sinus syndrome. However, in selected patients with the pure vasodepressor response, who do not respond to medical therapy, carotid sinus denervation may still be a relatively good option [3].

Cardiac pacing (either VVI or dual-chamber) does not affect the vasodepressor reflex. Therefore, it is not indicated in the pure vasodepressor form. Owing to its powerful effect on cardioinhibitory reflex, cardiac pacing (either VVI or dual-chamber) proved to be more efficacious than no treatment for the prevention of syncopal recurrences during the long-term follow-up in mixed carotid sinus syndrome [20]. Nevertheless, the coexistence of an important vasodepressor reflex clearly explained why syncopal recurrences occur in a minority of patients. For example, in a large series of patients, we have recently estimated a recurrence rate of 7% and 20% at 1 year and 5 years respectively [21].

Causes of Syncopal Recurrence in Patients with Carotid Sinus Syndrome Treated with Pacemakers

Hypotension is the main mechanism of recurrence of syncope in paced patients.

Vasodepressor Carotid Sinus Reflex

By means of a beat-to-beat noninvasive measurement method using photoplethysmography (the Finapress technique), we have recently demonstrated that an important long-lasting vasodepressor effect (defined as systolic blood pressure drop > 50 mmHg) is elicited by carotid sinus massage in 84% of patients affected by carotid sinus syndrome, including those who are usually categorized as affected by the cardioinhibitory form [8]. In the patients with vasodepressor form systolic blood pressure values remained below the initial values for a longer time and were significantly lower than those observed in the patients with cardioinhibitory form. The patients with mixed form showed an intermediate pat-

tern. The initial fall of systolic blood pressure was of similar extent in all the forms of the carotid sinus syndrome, but the patients with the vasodepressor form were characterized by a longer duration and greater entity of the decrease. These results point out the importance of the vasodepressor reflex in patients with the carotid sinus syndrome.

Impaired Blood Pressure Control

The patients with carotid sinus syndrome showed a propensity toward an enhanced decline in systolic blood pressure in the upright position when compared with matched patients without carotid sinus syndrome [13]. Orthostatic hypotension was found in 27%-34% of patients [9, 13]. A symptomatic VVI-pacemaker effect, namely the sudden fall in blood pressure and related symptoms caused by the onset of stimulation in the standing position, is present in 21%-30% of carotid sinus syndrome patients [14, 15]. The association of orthostatic hypotension and VVI-pacemaker effect with carotid sinus syndrome suggests that an abnormality of the neurovascular compensatory mechanisms is also involved. This probably potentiates the carotid sinus reflex and plays a role in the genesis of the syncope.

Positive Response to Head-Up Tilt Testing in Carotid Sinus Syndrome Patients

We have observed a 2.7-fold increase in the risk of syncopal recurrence after pacemaker implantation in patients with cardioinhibitory or mixed forms of carotid sinus syndrome [21]. Indeed, among a group of 169 patients followed up for a mean of 33 ± 22 months, syncope recurred in 21% of 70 patients who had had a positive response to tilt testing at the time of pacemaker implantation, and in 9% of 99 patients who had had a negative response. The predictive value of the test was independent of any of the following factors, which were unable to predict syncopal recurrence during follow-up: age, gender, underlying heart disease, mode of pacing (DDD or VVI), type of carotid sinus syndrome, history of syncope. Data from a small study [22], regarding patients implanted with a specially designed implantable pacemaker able to detect all asystolic episodes lasting > 3 s, showed that those patients with a positive response to both carotid sinus massage and head-up tilt testing had recurrence of both asystolic and non-asystolic episodes, whereas those with only a positive response to carotid sinus massage (and negative tilt testing) had recurrence of only asystolic episodes. Thus, the association of a positive response to carotid sinus massage and tilt testing suggests that a more complex autonomic disease involving multiple receptors and pathways is present. When both carotid sinus massage and tilt testing are positive in the same patient, both asystolic and non-asystolic symptoms may be expected to occur.

Effects of Chronic Vasodilator Therapy

We have recently investigated 32 hypersensitive carotid sinus patients (mean age 73 ± 9 years; 20 males) who were affected by one or more episodes of syncope occurring during chronic (> 6 months) treatment with angiotensin-converting enzyme inhibitors, or long-acting nitrates, or calcium-antagonists or an association of these [23]. The patients were randomly assigned to continue or to discontinue vasodilators; carotid sinus massage was repeated 2 weeks after randomization. By the end of the study period, syncope had been induced by carotid sinus massage in 81% of patients in the "on-vasodilator" group and in 62% of patients in the "off-vasodilator" group (p not significant). The cardioinhibitory reflex was of similar magnitude in the 2 groups, being found in 50% of patients in each group, with a maximum ventricular pause of 7.1 ± 2.7 s and 6.7 ± 1.8 s, respectively. Hypotension was more severe and persisted for a longer time in the "on-vasodilator" group, taking more than 2 minutes to return to baseline values (Fig. 1). Thus, in patients affected by carotid sinus hypersensitivity, chronic vasodilator therapy does not have a direct effect on carotid sinus reflexivity. Nevertheless, the persistence of hypotension for a longer time after the end of the massage suggests that vasodilators cause an impairment of baroreflex compensatory mechanisms, which become unable to restore a sufficient systemic and cerebral blood flow. Thus, in patients affected by carotid sinus hypersensitivity, vasodilator therapy could indirectly potentiate the severity of the clinical manifestations of the syndrome.

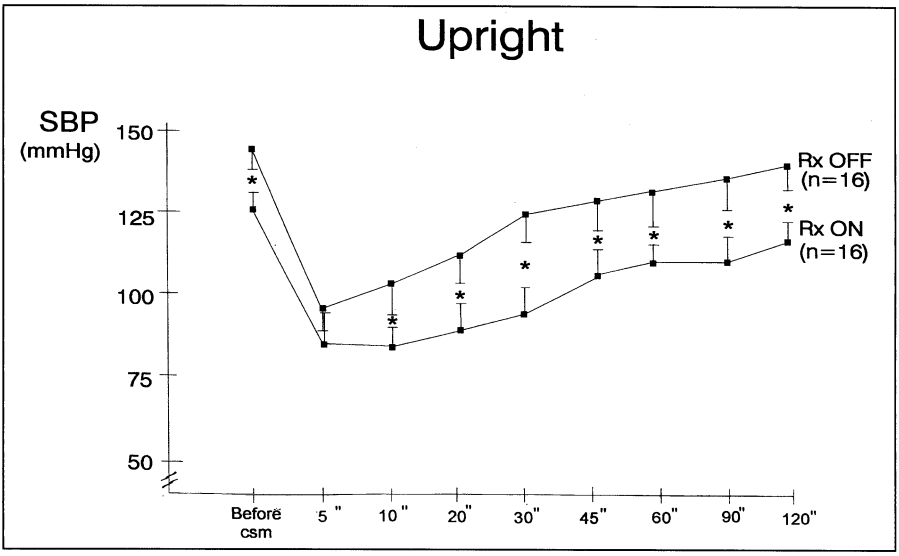

Fig. 1. The effect of vasodilator discontinuation on the behavior of systolic blood pressure (mean value ± SE) during carotid sinus massage performed in the upright position.
SBP, systolic blood pressure; HR, heart rate; Rx OFF, drug discontinuation group; Rx ON, drug continuation group)
* $p < 0.05$

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Current Insight on the Pathophysiology of Vasovagal Syncope: What Have We Learned?

C.A. MORILLO[1,2] AND J.C. VILLAR[1]

The mechanisms leading to the development of the vasovagal response have fascinated physiologists and physicians for centuries. The first description of a vasodepressor response may have been inadvertently provided by John Hunter (1728-1729) when he wrote: "I bled a lady but she fainted and while she continued in the fit the colour of the blood that came from the vein was a fine scarlet. The circulation was very languid [1]." Hunter may have described the effects of vasodilatation during a vasovagal syncopal episode provoked by controlled hypovolemia [2, 3]. Not until this century, did Sir Thomas Lewis [4] provide a cardinal observation in the mid 1920s when he demonstrated that prevention of bradycardia with atropine did not reverse the blood pressure fall without affecting the onset of syncope. This finding led Lewis to hypothesize that a peripheral mechanism that rested in the blood vessels was essential for the development of the vasodepressor response. This chapter will focus primarily on recent evidence obtained from studies that have assessed heart rate variability, arterial and cardiopulmonary baroreflex sensitivity, and muscle sympathetic nerve traffic in subjects with vasovagal syncope (VVS).

Left ventricular vagal-C mechanoreceptor activation mediated by an increased background sympathetic activity that leads to a reflex increase of vagal efferent traffic and withdrawal of sympathetic activity have been usually purported as the mechanism of VVS [5, 6]. However, the consistent observation of vasovagal responses elicited in heart transplant recipients [7-9] suggests that alternative mechanisms should be involved in the development of VVS [10]. Assessment of the physiological mechanisms that regulate blood pressure and heart rate is essential to understand the mechanism of VVS.

Heart Rate Variability

Several studies have recently addressed the role of autonomic control of heart rate in subjects with VVS [11-15]. Assessment of time and frequency domain

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oscillations of heart rate variability in the supine position has consistently shown that autonomic balance of heart rate is unaffected in the resting position in both syncopal and non-syncopal subjects. These findings suggest that orthostatic stress may be necessary to trigger the autonomic abnormalities that mediate the vasodepressor response.

Morillo et al. [11] reported an impaired response of heart rate variability during the initial 5 minutes of orthostatic stress (Fig. 1). We documented a reduced LF/HF ratio associated with persistence of HF oscillations during tilt. Additionally, the percent change in low-frequency oscillations was significantly lower in the syncopal group when compared with the non-syncopal group. These findings were interpreted as an impaired efferent vagal tone withdrawal possibly related to impaired arterial baroreceptor response to orthostatic stress. Other investigators [12-14] have confirmed our initial observations, and have provided further insight into the role of autonomic balance and the vasovagal response.

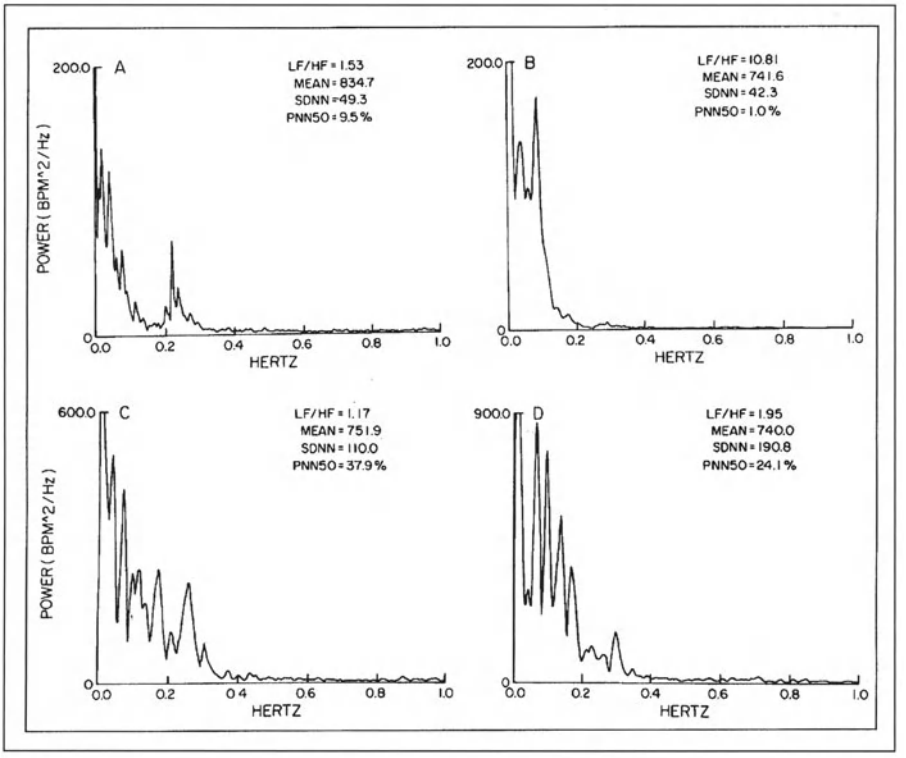

Fig. 1A-D. Power spectra of heart rate variability in the supine position **(A)** and after 5 minutes of 60° upright tilt **(B)** in a healthy volunteer, and in an age and sex-matched **(C, D)** patient with vasovagal syncope. Panel **A** shows the normal distribution of low-frequency (LF) and high-frequency (HF) power with a LF/HF of 1.53, associated with an increase in LF power and HF withdrawal, resulting in a 10-fold increase in LF/HF ratio after tilt (panel **B**). An abnormal response to tilt is shown in panel D with a persistence of HF power and moderate increase in LF power (reproduced with permission from [11])

Lepiscovka et al. [13] assessed blood pressure and heart rate variability using time-frequency mapping. These investigators documented elevated vagal activity during orthostatic stress for both blood pressure and heart rate variability that identified patients prone to VVS. The same investigators [14] also assessed the role of slow cardiovascular oscillations of heart rate and blood pressure in subjects with VVS triggered by upright tilt testing. Augmented low-frequency oscillations (0.01-0.05 Hz) in blood pressure were observed at the onset of tilt, followed shortly by a significant reduction in amplitude and irregular oscillations with disappearance of these rhythms shortly before the onset of syncope. The physiological basis of these blood pressure oscillations remains unclear. It has been postulated that these rhythms may reflect the central regulation of the autonomic nervous system integration at brain stem level [14]. Therefore, it may be speculated that reduction of blood pressure slow rhythms before the onset of syncope is an early sign of central sympatho-inhibition that results in baroreflex gain resetting with subsequent baroreflex inhibition at the time of syncope [15].

In summary, we currently know that baseline autonomic balance is intact in the supine position in subjects with recurrent VVS. Orthostatic stress triggers a series of autonomic changes that mediate the vasovagal response, primarily increased or impaired vagal withdrawal during the early stages of tilt and sympatho-inhibition prior to the onset of VVS.

Arterial and Cardiopulmonary Baroreceptors

The role of arterial and cardiopulmonary baroreceptors in subjects with VVS has been assessed by several investigators. Impaired arterial baroreflex gain may be critical for the maintenance of orthostatic tolerance. Convertino et al. [16] and Eckberg and Fritsch [17] markedly reduced cardiovagal baroreceptor sensitivity in healthy subjects after 30 days of head-down tilt. Orthostatic tolerance was markedly impaired, and four subjects became syncopal within 5 minutes of standing. A greater reduction in arterial baroreflex sensitivity was documented in the fainting subjects suggesting a primary role of arterial baroreceptor compliance in orthostatic tolerance. France [18] documented decreased descending spontaneous arterial baroreceptor sensitivity at rest in a group of subjects that presented a vasodepressor response during blood donation. These findings have been further documented in larger groups of subjects by Mosqueda-Garcia et al. [19], and Morillo et al. [20]. Both investigators reported a blunted arterial baroreceptor response to pharmacological challenges with nitroprusside and phenylephrine, in patients with tilt-induced VVS (Fig. 2). Furthermore, lower baroreflex sensitivity was able to predict the outcome of upright tilt [20]. Similarly, differences in baroreflex sensitivity have been recently reported in subjects with vasodepressor and cardioinhibitory responses [21]. The spontaneous response of the arterial baroreflexes during upright tilt has recently been reported by Jardine et al. [22]. These authors reported an increased sensitivity at rest with important fluctuations of the baroreflex sensitivity prior to the onset of symptoms. It is clear therefore that challenging the arterial baroreceptor closed-

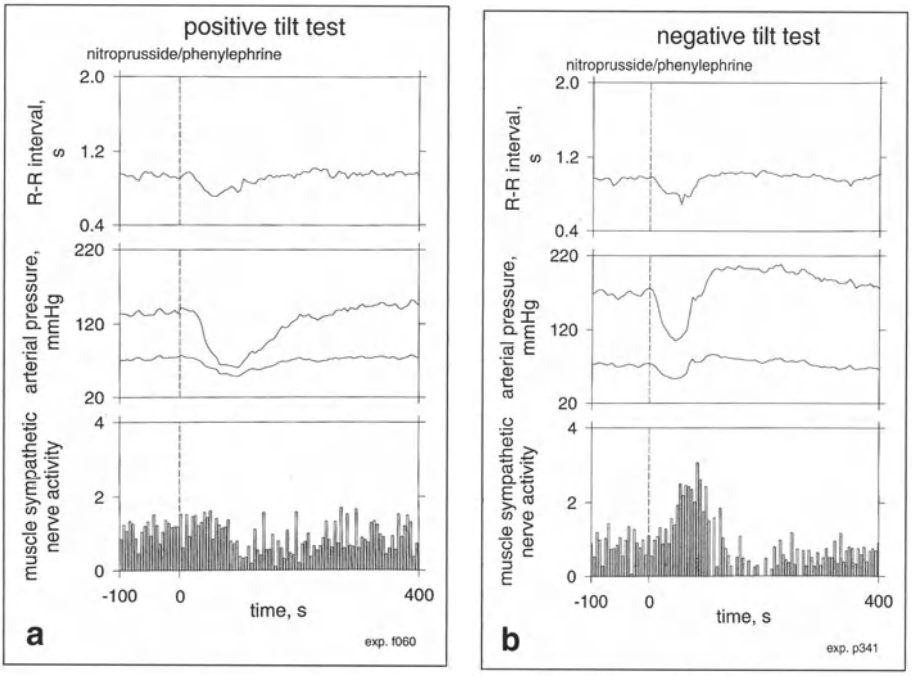

Fig. 2 a,b. Acute response to vasoactive agents in the supine position in a patient with vasovagal syncope induced during tilt (**a**), and in a control subject (**b**). RR interval, systolic and diastolic blood pressure and 5 second averages of muscle sympathetic activity are shown. The broken line indicates the time of administration of nitroprusside followed after 60 seconds by a bolus injection of phenylephrine. Marked impairment in the sympathetic baroreflex outflow is demonstrated by a lack of increase in sympathetic traffic

loop system during orthostatic stress contributes significantly to the pathophysiology of VVS.

The role of cardiopulmonary baroreceptors has also been assessed in patients with VVS. Sneddon and co-workers [23] reported an augmented cardiopulmonary baroreceptor response to lower body negative pressure. The same investigators documented impaired vasoconstrictor responses immediately after assuming the upright position, long before the onset of VVS [24]. Thomson and colleagues [25] documented a significant reduction in forearm vascular resistance during erect exercise in subjects with recurrent VVS compared with a control group. The same group reported a smaller decrease in splachnic venous volume in VVS patients [26]. Paradoxical splachnic venodilatation or failure to vasoconstrict in both resistance and capacitance vessels result in VVS.

A reduced blood volume has been documented in patients with VVS, however, orthosthatic changes in plasma volume and capillary filtration are comparable between VVS subjects and controls. El-Sayed and Hainsworth [27] correlated plasma volume, carotid baroreceptor sensitivity (with a neck chamber) and orthostatic tolerance (time in which subjects became presyncopal or syncopal in

response to HUT plus lower body suction). Plasma volume had a positive linear correlation with orthostatic tolerance and a negative correlation with baroreflex sensitivity. The incidence of vasodepressor responses is reduced after randomly assigning patients to a high salt intake compared to placebo, supporting the role of plasma volume [28].

The role of venous pooling during VVS has been studied by Hargraves and Muir [29] who noted a greater increase in calf venous volumes with reduced venous variability after orthostatic stress. Blood volume regulation and venous pooling during orthostatic stress can be altered in VVS patients by impairing the baroreflex loop activity, reducing plasma volume, and marked venous pooling by decreased muscular venous activity or extrinsic skeletal muscle contraction.

Muscle Sympathetic Nerve Activity (MSA)

Several investigators have reported lower sympathetic nerve traffic during VVS triggered by upright tilting or lower body negative pressure [15, 30-33]. Smith et al. [30] reported an abrupt decrease in MSA that preceded the onset of bradycardia by 20 seconds. Similarly, we observed higher levels of MSA during upright tilt in VVS patients compared to controls [15], followed shortly by an abrupt cessation of sympathetic activity at the onset of syncope (Fig. 3). In contrast, Mosqueda-Garcia et al. [31] reported a progressive decrease of MSA during tilt in subjects with VVS. In addition, we have documented a marked reduction in sympathetic baroreflex outflow activity when subjects were challenged with a venous bolus of nitroprusside [32]. These findings suggest that impaired arterial baroreflex-mediated outflow sympathetic activity plays a significant role in VVS. However, the existence of central sympatho-inhibition associated with central baroreceptor resetting cannot be ruled out with the current evidence.

Conclusions

Several lessons may be derived from the current knowledge of VVS pathophysiology. First, it is unlikely that the sole mechanism for VVS is related to paradoxic activation of ventricular mechanoreceptors. Second, vagal efferent response is not appropriately suppressed by orthostatic stress in subjects prone to VVS. Third, arterial and cardiopulmonary baroreceptor gain is impaired at rest and early on after orthostatic stress. Fourth, baroreflex sympathetic outflow response to abrupt reductions in blood pressure is markedly impaired in VVS patients. Fifth, sudden cessation of muscle sympathetic venoconstrictor activity is the final precipitant of VVS. Future research should address the role of central sympatho-inhibition and baroreflex gain resetting in the precipitation of the vasovagal response.

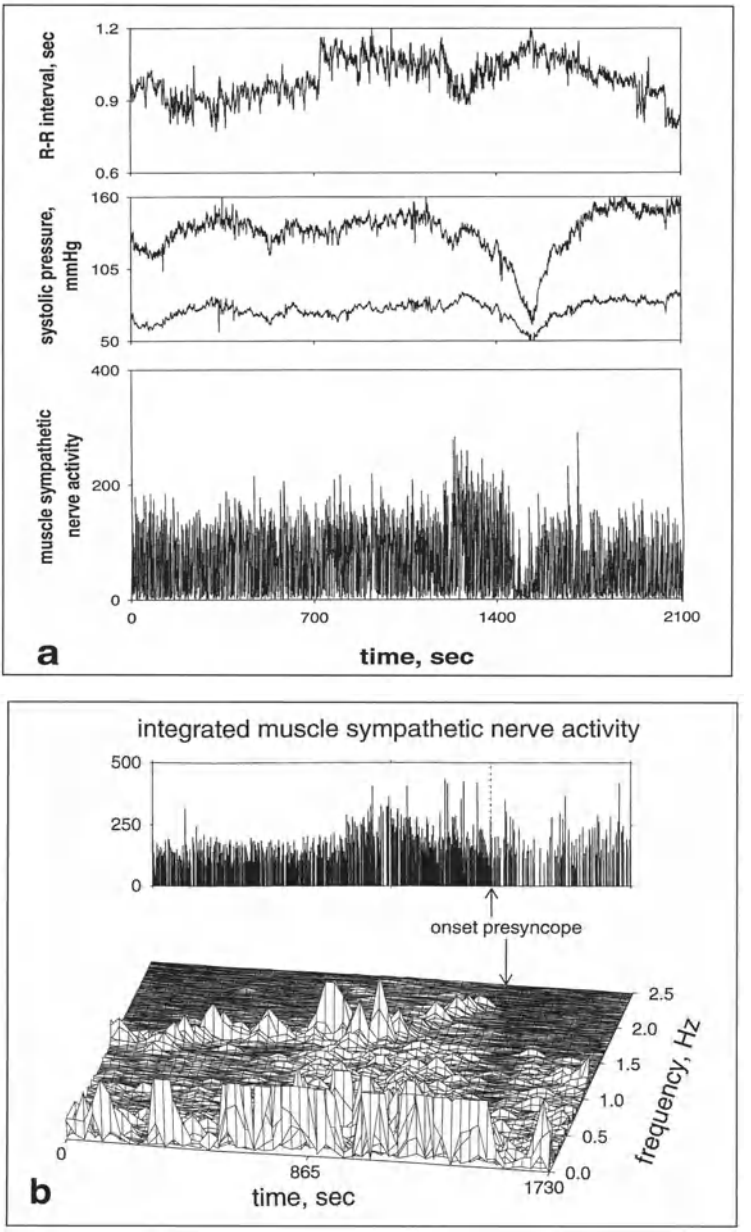

Fig. 3 a,b. Muscle sympathetic nerve activity during vasovagal syncope provoked during60° tilt. Panel **a** shows from top to bottom R-R interval, systolic/diastolic blood pressure and integrated muscle sympathetic nerve activity. A progressive drop in blood pressure is associated with mild increase in sympathetic activity followed by abrupt cessation of sympathetic activity at the time of syncope (1400 s). Panel **b** depicts the power spectral analysis of muscle sympathetic nerve activity during tilt. Low frequency oscillations are present and abruptly disappear at the time of syncope. Similarly, the heart rate driven oscillations of sympathetic activity are markedly reduced prior to syncope (2.0 Hz).

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What Is the Role of Neurohumoral Agents in the Genesis of Vasovagal Syncope?

P. Alboni[1], M. Dinelli[1] and E. Degli Uberti[2]

Arterial and cardiopulmonary baroceptor reflexes are the major neural control mechanisms that regulate arterial pressure and vascular tone in humans.

Arterial baroceptors located in the aortic arch and the carotid sinus discharge in response to stretch induced by arterial pressure waves. These receptors send afferent signals to the brain stem that inhibit efferent sympathetic activity to the heart and peripheral circulation and stimulate efferent parasympathetic activity to the heart. The mean firing rate of these receptors is related strictly to the level of arterial pressure. Hence, when arterial pressure increases, the firing rate of these receptors rises, resulting in sympathetic withdrawal and parasympathetically-mediated bradycardia. Conversely, when blood pressure falls, the firing rate of these receptors decreases, resulting in sympathetic excitation and withdrawal of parasympathetic activity leading to tachycardia.

Cardiopulmonary receptors are located in the pulmonary vasculature and in the heart, predominantly in the inferoposterior wall of the left ventricle. These receptors discharge during systole and their firing rate is related directly to the force of myocardial contractility as well as stretch as determined by the level of cardiac filling pressures. Like arterial baroceptors, cardiopulmonary receptors send afferent signals (via the non-myelinated vagal C-fibers) to the brain stem that inhibit sympathetic efferent activity. When cardiac filling is reduced, the discharge of these receptors falls and their inhibitory influence on sympathetic efferent activity declines, resulting in increased sympathetic drive. Conversely, with increases in cardiac filling, these receptors increase their firing rate, resulting in sympathetic withdrawal.

A variety of diseases can interfer with normal control of arterial pressure and cause symptoms. The hallmark of these conditions is vasovagal syncope, which is characterized by a sudden fall of arterial pressure, sometimes followed by bradycardia.

The various types of neurally-mediated syncope are believed to have common pathophysiological elements as well as differences in triggering factors, afferent and efferent neural arcs and central nervous system processing that ulti-

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mately result in hypotension and loss of consciousness. For all the types of vasovagal syncope there are facilitating factors such as emotional state, volume depletion and upright position. Receptors that respond to pain, mechanical stimuli and temperature appear to serve as the origins of the afferent signals triggering the various neurally-mediated syncopes. For example, in carotid sinus hypersensitivity, the carotid artery baroceptors and in vasovagal syncope, the left ventricular mechanoreceptors serve as triggers. Similar receptors in the aortic arch, carotid arteries, atrial and ventricular myocardium, respiratory tree, bladder and gastrointestinal tract may trigger various other neurally-mediated syncopes. The afferent pathway consists of neural fibers (e.g. vagal C-fibers in vasovagal syncope) that transmit signals to the central nervous system sites (the medulla, particularly the nucleus solitarius). The efferent outflow results in vasodilation and bradycardia. Several data suggest that a high sympathetic tone facilitates the vasovagal syncope by sensitizing the left ventricular mechanoreceptors. The "paradox" of high catecholamine levels which inhibit the cardiovascular centers in the brain stem and consequently the efferent sympathetic outflow is commonly accepted. In fact catecholamines increase myocardial contractility resulting in an increase in ventricular fractional shortening and a decrease in end-diastolic volume. These changes are believed to paradoxically activate ventricular C-fiber mechanoreceptors. The resultant surge in neural traffic to the brain stem mimics the conditions seen during hypertension and induces a sympathetic withdrawal and consequently a "paradoxic" increase in peripheral vasodilation and bradycardia.

Catecholamines and Vasovagal Syncope

Investigations carried out by utilizing different methods during tilt-induced syncope evidenced a high sympathetic tone before the loss of consciousness, likely facilitated by displacement of intravascular volume towards the lower part of the body:

- Yamamoto et al. [1] investigated heart rate variability and power spectral analysis during tilt test in syncopal patients and in control subjects. It was shown that in syncopal patients there was a markedly increased sympathetic activity preceding syncope;
- with the use of echocardiography during tilt test, it was demonstrated that patients with vasovagal syncope had an exaggerated myocardial contractility when compared to control subjects [2, 3];
- premonitory increases in circulating catecholamines appear to characterize the spontaneous vasovagal syncope [4, 5].

Chosy et al. [6] observed approximately 30% greater urinary epinephrine and norepinephrine concentrations in fainters prior to spontaneous vasovagal syncopal episodes compared to control subjects. Similar findings have been reported in tilt-induced syncope, with the increased catecholamine being primarily epinephrine [7-10]. Balaji et al. [8] and Sra et al. [9] observed an increase in both plasma epinephrine and norepinephrine during tilt; at the onset of vasovagal syncope,

epinephrine increased further on, whereas norepinephrine remained practically unchanged. The authors interpreted the latter as an expression of inhibition of adrenergic activity through an activation of ventricular mechanoreceptors induced by the enhanced myocardial contractility. On the basis of these observations, it is commonly accepted that the increase in circulating catecholamines, above all epinephrine, before the onset of syncope is not only reactive, but may in fact be part of the triggering mechanism, possibly increasing receptor sensitivity. However, the reason why in susceptible subjects syncope occurs only a few times in their life, while an increase in sympathetic tone occurs a myriad of times, remains a mystery. It is clinically evident that higher central nervous system centers are frequently involved in initiating spontaneous syncopal episodes. They probably also play an important role in facilitating the appearance of loss of consciousness in susceptible patients, thereby partially accounting for the variability in occurrence of syncopal events. Clearly, fear, pain and unpleasant experiences can instigate hypotension-bradycardia episodes. Several lines of evidence suggest that certain neurotransmitters may play a role in eliciting vasovagal syncope.

Neurotransmitters and Vasovagal Syncope

Neurotransmitters that may play a role in eliciting or facilitating vasovagal syncope by inhibiting the neuroadrenergic system include opioid peptides, serotonin, endogenous nitric-oxide, arginine vasopressin, adenosine and galanin. The most extensively investigated are opioid peptides and serotonin.

Opioid peptides

Opioids may inhibit the sympathetic system either centrally or peripherally [11]. Moreover, opioids may have negative inotropic and chronotropic actions and reduce reflex discharge of cardiac or peripheral receptors [11]. The high concentration of opioid-containing nerve cells and receptors found in the brain stem cardiovascular centers has generated interest in the possible physiological regulation of baroceptor mechanisms by endogenous opioids. In animal studies, using a rabbit model of hemorrhagic hypotension, administration of an opioid agonist (metenkephalin) produced hypotension and bradycardia [12]. Naloxone, an opioid receptor blocker, administered either intravenously or intracisternally, prevented the vasodepressor response induced by progressive hemorrhage [13]. The observation that naloxone can enhance baroreflex sensitivity in normal subjects suggests that endogenous opioids have an inhibitory effect on baroreflex mechanisms [14]. Wallbridge et al. [15] evidenced an increase in plasma β-endorphin which preceded the onset of tilt-induced vasovagal syncope; it was concluded that opioid mechanisms seem to be implicated in the pathophysiology of vasodepressor syncope. In a subsequent paper [16] the same authors evidenced that intravenous naloxone administered during tilt test failed to modify either the time of syncope or the vasodepressor response. Therefore, the authors question whether

the increase in plasma β-endorphin has a pathophysiological role or represents a nonspecific neuroendocrine response.

Serotonin

There has been increasing interest in the role played by serotonin in modulating central nervous system sympathetic neural outflow and thereby participating in the vasovagal reflex [17, 18]. Intracerebral serotonin has been reported to inhibit sympathetic neural outflow in general while increasing adrenal sympathetic stimulation [17]. This finding is compatible with the occurrence in neurally mediated syncope of hypotension due to vasodilation in conjunction with accentuation of adrenal epinephrine release. In an analogous setting, experimental studies revealed that serotonin plays an important role in mediating the hypotension-bradycardia response during severe hemorrhage. In fact, using a cat model, Elam et al. [19] showed that depletion of serotonin stores blunts the sudden decrease in arterial pressure and heart rate during hemorrhage. In addition, administration of the serotonin receptor blocker methylsergide during acute hemorrhage had a marked pressor effect [20]. On the basis of these observations, serotonergic mechanisms appear to play an important role in the regulation of blood pressure and heart rate and fluctuations in central serotonin levels may play a role in the pathogenesis of vasovagal syncope. With this knowledge, clinical trials utilizing selective serotonin reuptake inhibitors to prevent neurally mediated syncope have been undertaken [21, 22]. These trials have demonstrated that serotonin reuptake inhibitors can be successfully utilized to treat recurrent vasovagal syncope in some patients. Both fluoxetine hydrochloride and sertraline hydrochloride have been effective in reducing both clinical and tilt-induced syncope in 55% of patients with recurrent vasovagal syncope unresponsive to other forms of therapy. However, these results have not been obtained in controlled studies.

Conclusion

We have some knowledge on the role of autonomic nervous system and neurotransmitters in the pathophysiology of vasovagal syncope but it does not allow us to draw conclusions. In susceptible patients syncope occurs a few times during their life and we do not know which factor is responsible for the occasional loss of integration in cerebral function leading to sudden fall of blood pressure.

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Vasovagal Syncope: To Tilt or Not to Tilt?

R. SUTTON

Introduction

Tilt testing for the investigation of the clinical problem of syncope was introduced in the mid 1980s [1,2]. It represented an advance in the approach to this clinical arena, which had always offered serious challenges to physicians, because it became possible to reproduce the patient's symptoms in front of the clinician. Furthermore, this gave an opportunity for monitoring of many physiological variables allowing greater understanding of the mechanism of vasovagal syncope, if not its trigger. Syncope is an infrequent event for most sufferers, once per month can be considered often, implying that it is extremely difficult to observe an attack by any type of monitor. Herein lies the value of tilt testing but more than 10 years of clinical experience have placed its benefits in perspective and, as other clinical tests, it is not perfect.

History of Tilt Testing

Tilt testing has been used by physiologists for generations in order to obtain a controlled upright posture for experiments and, in aerospace medicine, tilt tests are used in the understanding of some of the effects of space flight on the body [3]. In the mid 1980s at least four groups were approaching tilt testing from different standpoints. At Westminster Hospital we were searching for a brain lesion in carotid sinus syndrome by attempting to assess whether the hypothalamic connections were intact. We had reasoned that the effect of erect posture might be abnormal if the links between the vasomotor centre, hypothalamus and pituitary were disturbed [4]. Serendipitously, we experienced a high rate of syncope during tilt in these carotid sinus syndrome patients which surprised us. So we elected to investigate, in the same way, a group of patients who had presented syncope but in whom we had not found a cause despite extensive evaluation. These patients also had a high rate of syncope during tilt. This prompted study of age matched non-syncopal control subjects who did not faint under these condi-

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tions resulting in the first clinical paper on the value of tilt testing for the diagnosis of syncope [1]. At the same time the Mayo Clinic group was using upright posture in their electrophysiological studies [5], workers at the Cleveland Clinic came to tilt testing from investigation of hypertension [2] and, at Toronto General Hospital, Waxman's approach was probably most similar to ours in trying to assess the participation of the medulla in cardiovascular control [6].

The early publications were dramatic [1,2] and inspired adoption of tilt testing in many centres, to the extent now that the investigation could almost be described as ubiquitous. During development of clinical tilt testing there has been a trend toward finding fewer tilt positive patients, reducing, perhaps, from > 60% [1] to approximately 20%-25% in recent reports [Brignole - personal communication and our own data unpublished]. Presumably this is explicable by a wider application of the test. Concurrently, there has been a persistent tilt positive rate amongst normal controls [7]. This is not at all surprising as it is almost certain that any subject may experience vasovagal syncope given sufficiently adverse circumstances. No other test for clinical diagnosis of this condition has emerged in the last decade, thus, there is still no gold standard with which to compare tilt testing and estimates of sensitivity and specificity must be considered exactly that and no more. Reproducibility of tilt positive results has also been challenged: initially, it was shown to be high [8] but this has also shown a decline. It appears that tilt positive patients who are severely symptomatic have a better reproducibilty than those more mildly affected [9].

It was hoped that tilt testing would play an important role in the evaluation of treatments for vasovagal syncope but there are accumulating numbers of reports which indicate that tilt testing should not be relied upon in this context [10,11]. An exception may be those severely affected but they are few and could only make sufficient numbers for a trial when a large number of centres participates.

To Tilt or Not to Tilt?

This is a clinical question to which the answer is almost always – tilt! Tilt testing is an inexpensive investigation which even at 20%-25% positive outcome offers a high yield. It is a test which should be placed early in the investigation profile. Furthermore, it is a safe test with very little reported morbidity and to the author's knowledge only 3 deaths amongst, perhaps, many hundreds of thousands of tilts now performed worldwide. The diagnosis of a cause of syncope remains a dominantly clinical skill where the greatest emphasis is placed on the history, especially that provided by an observer of an attack. Information derived from this history will direct the investigational approach. Where there is some warning of the impending attack, preceding pallor, subsequent nausea or vomiting and no skin flushing in the recovery period, the first test after clinical examination and resting 12 lead electrocardiography should be a tilt test. For these patients the yield of positive results will be much higher than 25% but it will, using the Westminster protocol passive tilt at 60° without drug challenge, still fall well short of 100%:

help in this context comes from a drug challenge which has from the outset been isoproterenol [isoprenaline] in some cases [6] but more recently European centres have used glyceryl trinitrate with considerable success [12, 13]. Most centres employ the drug challenge at the end of a period of passive tilt usually lasting 30 minutes or more. A large measure of agreement has been reached in the methodology as shown by the American College of Cardiology consensus document on tilt testing [14]. With the addition of a drug it is thought that a vast majority of vasovagal patients will be diagnosed. Thus, considerable expenditure on ambulatory monitoring or invasive electrophysiological studies can be avoided. On the other hand patients who give no history of warning of an impending attack, become orientated very rapidly after an attack, are observed to show flushing of the skin during recovery, or who present an arrhythmia at the time of examination or on 12 lead electrocardiography, are not those for whom a tilt test should be ordered early in the investigation. For these patients ambulatory recordings may be best if the rhythm has not been fully assessed at the first examination. Rarely is invasive electrophysiology needed for this group. However for those with structural heart disease this technique is often very valuable [15]. Another diagnostic tool is now becoming available [16]: implantable Holter monitors or loop recorders. Time will reveal the true value of these invasive devices which offer no therapy.

Tilt testing is now carried out in huge numbers, many thousands per year, all over the world and the reports of morbidity and mortality are very limited. Three deaths are known to have occurred making the test considerably safer than exercise stress testing. So far as morbidity is concerned in our experience there are rare episodes of atrial tachyarrhythmias, mainly atrial fibrillation, which resolve spontaneously after the test. Thus, it can be regarded as a safe test.

Other uses of tilt testing beyond the strict investigation of syncope are now developing and include assessing hypotensive therapy, diagnosis in atypical epilepsy, sudden unexpected infant death syndrome, and many more areas [17, 18].

The Future of Tilt Testing

This simple and cheap, highly diagnostic and safe investigation will continue to play a role in the investigation of syncope until another, better way of presenting the patient's symptoms to the physician is developed.

Conclusion

Whenever in doubt about syncope - tilt!

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Syncope: How Should It Be Evaluated Today?

W.N. KAPOOR

Epidemiology

Syncope is defined as a sudden transient loss of consciousness and postural tone that spontaneously resolves without electrical or chemical cardioversion. Clinical assessment is usually sufficient to separate syncope from other states of altered consciousness such as dizziness, vertigo, seizure, coma and narcolepsy. Syncope is a common problem in all age groups. In the U.S. it accounts for approximately 1% of hospital admissions and 3% of emergency room visits. Syncope is common in young adults (12%-48% of healthy young adults report loss of consciousness) although most do not seek medical attention. In one study of elderly, people over age 75 years had an annual incidence of 6%; 23% had previous lifetime syncopal episodes.

Etiology

The etiologies of syncope can be classified into four broad categories (Table 1). The largest group consists of neurally-mediated or neurocardiogenic syncope which is loss of consciousness resulting from sudden reflex vasodilation and/or bradycardia. The entities under this group include syndromes such as vasovagal, vasodepressor, situational (micturition, cough, defecation, and swallow), and carotid sinus syncope. Neurally-mediated etiology is also likely in syncope in association with exercise, especially immediately post-exercise in individuals without structural heart disease. Drugs such as nitroglycerine may also cause vasovagal syncope. Some psychiatric illnesses such as generalized anxiety and panic disorders, and depression may lead to neurally-mediated syncope.

A second major category is orthostatic hypotension which has many causes. Orthostatic hypotension may be due to age-related physiologic changes, medications, volume depletion, and diseases affecting the autonomic nervous system. The elderly may rarely experience post-prandial syncope as a result of hypotension after meals.

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Table 1. Etiologies of syncope (adapted from [11])

Neurally-mediated syndromes

- Vasovagal
- Situational
  - micturition
  - cough
  - swallow
  - defecation
- Carotid sinus syncope
- Neuralgias
- High altitude
- Psychiatric disorders
- Others (exercise, selected drugs)

Orthostatic hypotension

Neurologic diseases

- Migraines
- TIA's
- Seizures

Decrease cardiac output

Obstruction to flow

- Obstruction to LV outflow
  - aortic stenosis, IHSS
  - mitral stenosis, myxoma
- Obstruction to RV outflow
  - pulmonic stenosis
  - PE, pulmonary hypertension
  - myxoma

Other heart disease

- Pump failure
  - MI, CAD, coronary spasm
- Tamponade, aortic dissection

Arrhythmias

- Bradyarrhythmias
  - Sinus node disease
  - Second and third degree atrioventricular block
  - Pacemaker malfunction
  - Drug-induced brady-arrhythmias
- Tachyarrhythmias
  - Ventricular tachycardia
  - Torsades de Pointes (e.g. associated with congenital long QT syndromes or acquired QT prolongation)
  - Supraventricular tachycardia

TIA, transient ischemic attack; LV, left ventricular; RV, right ventricular; MI, myocardial infarction; CAD, coronary artery disease

The third category, neurologic disorders, are infrequent causes of syncope. Disorders to consider include transient ischemic attacks (TIA), migraines, and seizures.

The fourth category includes a large group of cardiac etiologies: diseases associated with severe obstruction to cardiac output (due to lesions of the left or right side of the heart), ischemia and arrhythmias.

Studies of unselected syncope patients published in the 1980s showed that clinical vasovagal syncope was diagnosed in 25%, organic heart diseases in 4%, arrhythmias in 14%, orthostatic hypotension in 8%, and seizures in less than 10%. Each of the other etiologies was found in less than 5% of patients and unexplained syncope in 34%. Currently, the proportion of patients with unexplained syncope is probably substantially lower with wider use of event monitoring, tilt testing, electrophysiologic studies, attention to psychiatric illnesses, and recognition that syncope in the elderly may be multifactorial.

Approach to Evaluation

The clinical assessment and ECG form the initial step in the evaluation of patients with syncope. This assessment may lead to a diagnosis or provide suggestive evidence for specific entities (e.g., signs of aortic stenosis or IHSS). These clues can be pursued with further testing to confirm or exclude these entities as the causes of syncope. In a large group of patients, however, the initial clinical evaluation does not lead to a specific diagnosis or point to a potential cause of syncope. These patients can be divided into two groups: those with structural heart disease or abnormal ECG and those without underlying heart disease. Patients with structural heart disease or abnormal ECG should undergo Holter monitoring (or monitoring in a telemetry unit) and if diagnostic arrhythmias are found, treatment can be initiated. Patients with nondiagnostic or negative Holter monitoring but with multiple syncopal episodes, can be further evaluated using loop monitoring. Patients with nondiagnostic loop monitoring or those with one or rare episodes of syncope should undergo electrophysiologic studies for the evaluation of possible arrhythmic syncope.

In patients without structural heart disease or abnormal ECG but with multiple episodes of syncope, tilt testing and psychiatric evaluation should be considered as the initial areas of investigation. Loop monitoring may also be considered for detection of arrhythmias (especially bradyarrhythmias or sustained ventricular tachycardia, SVT) in patients with clinical suspicion of arrhythmic syncope but without known structural heart disease. Patients with one episode of syncope can be followed closely without further workup if clinical evaluation is negative and psychiatric illnesses are not clinically suggested as a cause of syncope.

Diagnostic Tests

History and Physical Examination

The history and physical examination lead to a potential cause of syncope in approximately 45% of patients. Additionally, most of the organic cardiac diseases causing syncope (e.g., pulmonary hypertension, aortic stenosis, pulmonary embolism) are usually suspected clinically and can be confirmed by specific testing.

Laboratory Tests

Routine blood tests and glucose tolerance test rarely yield diagnostically helpful information in assigning a cause of syncope.

Diagnosis of Arrhythmias

Arrhythmias are diagnosed by ECG, Holter monitoring, loop event recorders, and electrophysiologic studies. Surface ECG and rhythm strip leads to causes of syncope in less than 5% of patients but this test is recommended in most patients with syncope since abnormalities found (such as bundle branch block) may guide further evaluation or if a specific diagnosis is made, treatment can be instituted immediately.

Ambulatory (or Holter) monitoring has been difficult to interpret in patients with syncope. In only 4% symptoms are reported concurrently with arrhythmias thus leading to a specific diagnosis. In another 17%, symptoms occur (dizziness or syncope) but are not associated with arrhythmias, potentially excluding arrhythmias as a cause. In approximately 79% of patients there are no symptoms during monitoring. In this group, finding brief or no arrhythmias does not exclude arrhythmic syncope since arrhythmias are episodic and may not be captured during monitoring. When there is high likelihood of arrhythmic syncope, such as brief loss of consciousness without prodrome, abnormal ECG, or presence of structural heart disease, further evaluation is needed for the diagnosis of arrhythmias as a cause of syncope. Ambulatory monitoring (for 24 hours) is recommended for patients with high likelihood of arrhythmias as defined above.

Loop event monitors are recorders that attempt to capture a rhythm during syncope after the patient has regained consciousness, since at least 4-5 minutes of retrograde recording is possible and monitors can be worn for several weeks. Symptoms with concurrent arrhythmias are found in 8%-20% of patients with recurrent spells and in an additional group there are symptoms without concurrent arrhythmias. This test is recommended in patients with recurrent syncope when there is a high probability of arrhythmias as a cause.

Electrophysiologic testing (EPS) should only be considered after thorough clinical and noninvasive evaluation using history, physical examination, ECG, ambulatory monitoring and other noninvasive and directed tests. Abnormal EPS is primarily found in patients with recurrent unexplained syncope who have organic heart disease (left ventricular dysfunction, coronary or valvular disease, or hypertrophic cardiomyopathy) or abnormal ECG (e.g., bundle branch block). Abnormal EPS is found in approximately 50% of patients studied and findings mainly consist of ventricular tachycardia and conduction system disease. The sensitivity and specificity of EPS for detection of bradyarrhythmias is reported to be low. It is recommended that patients with syncope and structural heart disease or abnormal ECG should undergo EPS if clinical assessment is suggestive of arrhythmic syncope and noninvasive testing with Holter or loop monitoring have been non-diagnostic.

Upright Tilt Testing

Maintaining the patient in an upright position for a brief duration on a tilt table has become a common method of testing for predisposition to vasovagal syncope. Approximately 50% of patients with unexplained syncope have a positive response to passive tilt testing (without using chemical stimulation). Positive response is defined as provocation of syncope in association with hypotension and/or bradycardia. With addition of isoproterenol during tilt testing, overall positive responses increase to approximately 64%. Specificity of passive testing is approximately 90% (range 0%-100%) and with isoproterenol it is approximately 75% (range 35%-100%). When repeat testing is performed on the same day or days later, a reproducibility of 65%-85% is reported in most studies. An initial negative study is rarely positive on repeat testing.

Upright tilt testing is recommended in patients with recurrent unexplained syncope in whom cardiac causes have been excluded or are not likely. Initial testing is recommended using a passive protocol for 30-45 minutes. In patients with a negative passive test and a high likelihood of neurally-mediated syncope clinically (e.g., young patient with concurrent autonomic symptoms), additional testing with isoproterenol is recommended. It is not possible to recommend any protocol for this test. Women of childbearing age should undergo a pregnancy test prior to tilt testing since tilt testing should be avoided in pregnant women. Older patients (age greater than 50) or patients with a history of ischemic heart disease should also undergo stress testing prior to tilt testing since isoproterenol and precipitating hypotension is best avoided in patients with significant ischemic heart disease. Tilt testing is generally contraindicated in patients with cerebrovascular disease.

In patients with positive results (showing symptoms identical to spontaneous symptoms in association with hypotension and/or bradycardia), therapy can be planned with β-blockers, disopramide, anticholinergic agents, fludrocortisone plus salt, fluoxitine, theophylline and other agents. Pacemakers are rarely used. Small controlled trials of drug therapy have not reported decreased recurrence rates. Further studies of the effectiveness of the drugs or pacemakers are needed prior to recommending specific therapies.

Other Tests

Cardiovascular testing such as echocardiogram, stress testing, ventricular function studies and cardiac catheterization are recommended for clarification of specific finding noted on history and physical examination. Myocardial band isoenzyme of creatinine kinase (CK-MB) should be obtained when myocardial infarction is suspected clinically or by ECG. Signal-averaged ECG for detection of low amplitude signals (late potentials) has a sensitivity of 73%-89% and specificity of 80%-90% for prediction of induced sustained ventricular tachycardia in patients with syncope. This test does not establish a diagnosis but may occasionally help select a group of patients more likely to have ventricular tachycardia.

Autonomic function studies are generally not needed in patients with orthostatic hypotension since clinical evaluation often provides clues to its etiology. EEG and head computed tomography (CT) scans are rarely useful in determining a cause of syncope. They may be valuable when seizure is suspected clinically or there are focal neurologic symptoms in association with syncope.

Management

Most syncope patients can be evaluated and treated as outpatients. Patients are admitted to the hospital if a rapid diagnostic evaluation is needed mainly because of concerns about serious arrhythmias, sudden death, newly diagnosed serious cardiac disease (e.g., aortic stenosis, myocardial infarction), and new onset of seizure or stroke. Patient with evidence of possible acute ischemia or infarction on ECG, chest pain, CHF, and those taking medications capable of provoking malignant arrhythmias should be admitted. Occasionally, admission may also be needed for treatment when etiology is clear (e.g., management of dehydration or subarachnoid bleed). In the large group of patients with unexplained syncope after initial history, physical examination, and ECG, presence of structural heart disease and abnormal ECG are important in decision making regarding admission to the hospital. Elderly patients are often hospitalized for a rapid workup because of the concern about asymptomatic presence of underlying heart disease (especially coronary disease).

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VASOVAGAL SYNCOPE: THERAPY

Is Tilt Testing Really Useful for Selecting Vasovagal Therapy?

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Introduction

Head-up tilt test (HUT) was first described as a diagnostic tool for vasovagal syncope (VVS) in 1986 by Kenny et al. [1]. Since then, interest surrounding the test has increased dramatically, and it has been extended not only for diagnostic purposes but also in the management of patients with VVS. Most patients with VVS do not need to be treated, but in selected patients, with recurrent and severe episodes, treatment can be warranted.

HUT makes it possible to recognize the susceptibility of an individual patient to develop a vasovagal reaction in response to a specific trigger, such as passive tilting, with or without pharmacologic challenge. Several studies have tried to analyze the diagnostic accuracy of the test, that is its sensitivity and specificity. The great variability in the tilt test protocols used by different authors makes it difficult to reach a uniform conclusion. Specificity seems to be quite high [1-6], but its real value depends on the angle of tilting as well as on the use of different drugs and their dosage [7-10]. However, sensitivity has not been well studied, mainly because it is difficult to define, on a clinical basis, criteria that allow diagnosis of vasovagal syncope with certainty and which could be used as the gold standard [11]. In this context, although HUT seems to be a very useful tool for the etiologic diagnosis of patients with syncope of unknown origin [12], its diagnostic accuracy has not yet been well established.

The use of HUT in the management of these patients has many limitations, but it can be considered in some situations. In this chapter we will discuss the possible usefulness and limitations of using HUT in the management of patients with VVS.

Contribution of HUT in the Etiologic Diagnosis of VVS

Prognosis and treatment of patients with syncope depend on its etiology. Patients with VVS are known to have a good prognosis in terms of survival,

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whereas the outcome of patients with cardiogenic syncope is much more difficult to predict [13]. On the other hand, whereas there is no general agreement on how to treat VVS, the management of most cardiologic causes of syncope seems to be better established. In most classical clinical series in which patients with syncope were studied, up to 50% of the population remained without an etiologic diagnosis [13]. The cause of syncope in these series was determined mainly by anamnesis, physical examination and baseline ECG [13]. Some authors have considered that, in order to accept that a syncope has a vasovagal etiology, a trigger must be identified, usually a painful or a stressfull stimulus or medical instrumentation such as venopuncture [14]. Otherwise, structural heart disease or intraventricular conduction defects have been considered to be predictors of cardiogenic syncope, especially bradyarrhythmias or malignant ventricular tachyarrhythmias [15, 16]. Thus, young patients with normal ECG and without organic heart disease have a high probability of having VVS, whereas older persons with abnormal ECG and organic heart disease, or in whom syncope develops suddenly without apparent triggers, have a higher probability of having a cardiogenic syncope. However, these patients can also develop VVS, and the presence of a positive HUT, when other cardiogenic etiologies have been excluded, means that a vasovagal etiology of their syncopal episodes can be considered [6, 17].

In our experience, up to 38% of patients with sudden syncope had a positive response to HUT [18], and 25% of patients with syncope of unknown origin and intraventricular conduction defects in baseline ECG and in whom the electrophysiologic study was normal, had a positive response to HUT [19], suggesting a vasovagal etiology. Other authors have observed that in patients with supraventricular arrhythmias [20, 21] or sick sinus syndrome [22], syncope can be related more to a vasodepressor reaction than to the hemodynamic consequences of their arrythmias. In these cases the performance of HUT, either alone or in combination with electrophysiologic studies, may help shed light on the different components of syncopal episodes.

In conclusion, in patients with syncope of unknown origin in whom the diagnosis cannot be determined based on clinical evaluation, HUT may allow one to establish the etiology, which is helpful in formulating the therapeutic approach.

Characterization of Vasodepresor and Cardioinhibitory Components of Syncopal Episodes

As syncope usually occurs in unpredictable situations, it is almost impossible to document the underlying mechanisms of the episodes. HUT can be considered, in some way, as an experimental model for triggering vasovagal reactions in humans, and it allows observation of the behavior of arterial blood pressure and heart rate, not only during the episode but also immediately before and during the recovery phase. According to the magnitude and sequence of the vasodepressor and cardioinhibitor components, the vasovagal responses have been classified as vasodepressor, cardioinhibitory or mixed [23].

Although variations in the reproducibility on the type of responses have been recognized, either between two repeated tests [24, 25] or between the acute response to HUT compared with the spontaneous clinical episodes [26], it has been suggested that the behaviour of blood pressure and heart rate during HUT can be used for selecting the initial therapy in those patients in whom treatment is considered. Patients in whom the positive response to HUT is preceded by sinus tachycardia, or in whom the response develops during isoproterenol infusion, are considered to be the best candidates for β-blocker therapy [27], whereas those patients in whom heart rate does not increase before the episode, are considered to respond less to β-blockers [28], and consequently the initial selection in these patients should be etilephrine or fludrocortisone. Finally, patients presenting a severe cardioinhibitory response to HUT are those who could potentially benefit from a pacemaker implantation [29]. Although the effectiveness of pacemaker implantation has not been critically demonstrated [30], some authors have proposed implantation of bicameral pacemakers in a very selected subgroup of patients with a marked cardioinhitory response, who have severe and recurrent syncopal episodes and who are refractory to other medical treatments, with the purpose either of preventing recurrences or at least decreasing the severity of their clinical episodes [29]. As the real effectiveness of this therapy has not yet been fully established, the decision about pacemaker implantation should be individualized.

Possible "Therapeutic" Effect of HUT

The natural history of VVS is not well known. In fact, most of the information about its evolution has been obtained in the so-called "HUT era". The vast majority of series analyzing this aspect has shown a recurrence rate of 30% after a positive response to HUT during a two-year follow-up [31]. Sheldon et al. observed a significant decrease in the incidence of syncopal episodes from a median rate of 3 episodes per month before HUT, to 0.3 episodes per month after a positive response to HUT [32]. In our experience, the syncopal incidence dropped significantly from 0.08 episodes/patient/month before HUT, to 0.04 episodes/patient/month after HUT ($p < 0{,}01$) [33]. These data, added to the observation that with repeated tests there is an increase in the rate of negative responses [34, 35], have lead to the suggestion that the performance of HUT by itself may, in some patients, have a "therapeutic" effect in preventing recurrences. Nonetheless, this beneficial effect has not been critically demonstrated. Although its possible mechanisms are not well understood, some explanations have been advocated. HUT is usually performed on patients with recurrent episodes who, despite several tests, do not know the etiology of their episodes. Thus, the additional uncertainty about their prognosis may lead to a degree of anxiety that can facilitate recurrences. Therefore, the recognition of the etiology and the reassurance that they have a good prognosis in the follow-up, can help reduce patients' anxiety, and can consequently have a favorable impact on recurrence. Besides, the identification of their clinical prodromal symptoms during the test can help the

patients recognize these symptoms before the episodes, and can either help prevent them, or take measures to decrease their severity. It is also possible that the development of a vasovagal episode during HUT has some kind of "preconditioning" effect by itself, and thus prevents new syncopes.

Therapeutic Trials

Different therapeutic strategies have been suggested, according to the pathophysiologic hypotheses of VVS. However, up to now, there has not been clear evidence of their effectiveness. In order to use HUT to assess the efficacy of a given treatment, the test should fulfil two conditions: 1) have a high reproducibility and 2) have a result that could be considered as a surrogate in predicting clinical recurrences.

The reproducibility of HUT has been evaluated by differents authors. Nevertheless the results are not uniform. On one hand, the reproducibility of an initial negative test is higher than the reproducibility of an intitial positive one. On the other hand, the literature has shown a great variability in the reproducibility of an initial positive test (between 36% and 90%) [36-38]. The lack of uniformity in these results can not only be due to the different protocols used but also to the great variability in the time interval between the initial and the repeated tests. Despite these limitations, most of the studies that have addressed the efficacy of the different therapeutic interventions in VVS, were non-controlled trials [39-42], and have considered obtaining a negative test under a certain treatment as synonymous of its effectiveness. Of the few controlled trials published up to now, those that involved sequential tests under placebo and drugs, showed that up to 50% of patients who were under placebo had a negative HUT [34, 35], and that with the performance of repeated tests, there was a progressive drop in the rate of positive responses, irrespective of whether patients were on active treatment or placebo. To assess the possible influence of the number of tests and/or the different time intervals between tests on the reproducibility of HUT, we designed a study with sequential tests at different time intervals. In this study, we observed that the reproducibility of an initial positive test was 64%, irrespective of whether the second test was performed one or two weeks after the baseline test [24]. Also we observed that with repeated tests, there was a progressive loss in the rate of positive responses [24].

On the other hand, the studies on the follow-up after HUT have failed to show any correlation between the type or severity of the response to HUT and the recurrences at follow-up [26, 44, 45]. Thus, although at this time, we do not have enough data for considering a positive response to HUT as a marker for predicting recurrences at follow-up, clinical controlled trials are necessary for establishing the real effectiveness of the different therapeutic options on the response to HUT [46, 47].

Assessment of Therapeutic Efficacy in Clinical Management of Patients with VVS

According to the data presented here, it seems clear that, in an individual patient, the conversion of a baseline positive HUT to a negative test under a specific treatment cannot be considered as a marker of effectiveness, as it has been shown that the negativization can be due to many other causes. On the contrary, a persistent positive response to HUT under treatment may be a marker of "underprotection" of the drug towards vasovagal reactions.

Conclusion

In this paper we have discussed the possible role of HUT in the management of patients with VVS.

Taking into account that the diagnosis of any pathological process is essential for its treatment, it can be considered that HUT, which allows diagnosis of VVS in many patients, can contribute to the selection of treatment in some of these patients. On the other hand, HUT can allow identification of both the vasodepressor and cardioinhibitory components during the vasovagal response, and consequently can guide the selection of the initial therapeutic approach in patients in whom treatment is warranted.

Although not fully proved, it has been suggested that HUT may contribute to reducing the rate of relapses among selected patients with recurrent and refractory VVS.

As the natural history of VVS is unknown, it is difficult to assess the real effectiveness of the different therapeutic options throughout the follow-up, and thus, HUT can be used to perform controlled trials to identify which drugs may help in the treatment of the different patients.

However, it is important to point out that, in clinical practice, the negativization of HUT under treatment cannot be taken as being synonymous with effectiveness.

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Neurocardiogenic Syncope: What Role for Serotonin?

B.P. GRUBB

Recurrent episodes of neurocardiogenic (or vasovagal) hypotension and bradycardia that are sufficiently profound to result in syncope, offer not only a diagnostic and therapeutic challenge to the clinician, but also a fascinating challenge to the physiologist who seeks to understand why these episodes occur. Beginning with Sir Thomas Lewis' original description of the disorder, a number of individuals have speculated on the potential physiological mechanisms involved [1]. However, these speculations remained highly theoretical, as there existed no way to either confirm or deny them. This picture changed dramatically in 1986 when Kenny et al. in their landmark paper reported that head upright tilt-table testing could reliably induce episodes of neurocardiogenic syncope in predisposed individuals [2]. This newfound ability to reproducibly provoke these episodes in a controlled laboratory setting permitted detailed observations and recordings of multiple parameters to be made before, during and immediately following a syncopal event [3-5]. Thus, there has been a virtual explosion of data over the last several years concerning the pathophysiology of neurocardiogenic syncope [6]. These observations have accumulated a body of data suggesting that sudden fluctuations in the central nervous system neurotransmitter serotonin (5-hydroxytryptamine or 5-HT) may play a pivotal role in the production of the hypotension and bradycardia that characterizes neurocardiogenic syncope. This paper will review serotonin's role in central nervous system function and cardiovascular regulation, present observations on its potential role in neurocardiogenic syncope, and lastly will review data on the clinical use of the serotonin reuptake inhibitors in the therapy of recurrent syncope.

Serotonin: Discovery and Physiology

A number of various neurotransmitters have been found to participate in the regulation and maintenance of neural function. Among these are what are known as the monoamine compounds which include not only serotonin but also adrenaline, noradrenaline, acetylcholine, glutamate, dopamine, substance P, and

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other neuropeptide substances. The Italian investigator V. Erspamer and associates in 1937 had purified a compound from the enterochromaffin cells of the mucosa of the gastrointestinal tract that was capable of inducing strong uterine contractions. Their initial name for this substance was "enteramine" [7]. Shortly thereafter, Rapport and Page in 1948 isolated a similar vasoconstrictive substance from cow's blood and name it serotonin (combining the words "serum" and "tone" [8]). Serotonin was then identified chemically as 5-hydroxytryptamine (5-HT). Dr. Erspamer's group in Italy then identified that the chemical make-up of "enteramine" was also 5-hydroxytryptamine [9]. Serotonin was first found in brain tissue in 1953, and over the ensuing decade groundbreaking investigations by Bard et al. and by Dahlstrom and Fuxe had established the general pattern and distribution of serotonin-containing neurons throughout the entire central nervous system [10, 11]. The serotonergic neurons of the central nervous system are most densely found in the area of the midline raphe nuclei of the midbrain and medulla (or brain stem). These nerves give off extensive projections to nearly the whole of the brain and spinal cord [12]. These serotonin-containing neurons are most closely concentrated along the dorsal raphe nucleus from where (in conjunction with the medial raphe nuclei) projections travel to the medial forebrain bundle. From this point nerve fibers emanate to sections of the hypothalamus, limbic system, cerebral cortex and striatum. The spinal cord also receives descending projections from the raphe obscurus and raphe magnus nuclei, as well as a few projections from the ventrolateral medulla [13]. There exist two morphologically different types of axon terminals in serotonin-containing nerves [14]. The first of these are termed "D fibers" and appear quite fine and have multiple small varicosities. They originate in the dorsal raphe nucleus and give off extensive projections. Second are the "M fibers" which appear beaded and have large spherical varicosities. They begin at the median raphe nuclei and give off short, thin fibers with numerous and intricate branches. D fibers predominate in the striation, while M fibers are concentrated in the dentate gyrus. Both M and D fibers are seen in the cerebral cortex.

Serotonin: Production and Regulation

Serotonin is synthesized from both neurons and enterochromaffin cells starting with the basic amino acid L-tryptophan, which is 5-hydroxylized to 5-hydroxytryptophan (5-HTp). The rate limiting step in serotonin synthesis appears to be tryptophan, and it is possible that raising dietary levels of tryptophan could affect serotonin levels [15]. The 5-HTp then is decarboxylated to serotonin (5-HT) via the enzymatic action of aromatic L-amino acid decarboxylase. Following synthesis, serotonin is stored in secretory granules in several pools. Serotonin's stimulation of postsynaptic receptors is terminated by its re-uptake into the presynaptic area by a substance known as the 5-HT transporter. The major metabolite of serotonin is 5-hydroxyindol acetic acid (5-HIAA [16, 17]).

Serotonin: Receptors

As early as the mid-1950s it had become apparent that there are at least three major groups of serotonin receptors. At first these were determined on the basis of their pharmacological properties, however for the last 15 years the use of radioligand binding has uncovered the existence of multiple serotonin receptors [7, 14]. Recently it has been possible to clone these receptors once they have been identified, allowing for detailed characterizations to be made. Currently it is believed that there are at least three major subtypes of serotonin receptors [18]. These have been labeled as (a) guanine nucleotide binding G protein coupled receptors, (b) Ligand-gated ion channels, and (c) transporters. One interesting observation has been that these receptors seem to vary considerably in their sensitivity to serotonin. At the same time it has become evident that some serotonin receptors are linked to other different second messenger systems, and that more than one second messenger may be coupled to the same receptor. More recently it has been shown that other neurotransmitters may exist with serotonin on the same nerve terminal, (most often the neuropeptides such as enkephalin, galanin, somatostatin and substance P) and can modify the effects of a given receptor subtype [19].

A number of studies have shown that serotonin is important in the regulation of a number of different bodily functions. These include mood, heart rate, blood pressure, appetite, body temperature, aggressiveness, pain, sleep and endocrine function [14]. Current investigations are looking at whether a single receptor or combination of receptor subtypes control a specific function. New imaging modalities such as Positron Emission Tomography are allowing much more detailed observations to be made.

Serotonin: Role in Cardiovascular Regulation

Psychiatrists have pioneered the discovery that serotonin plays a major role in the pathogenesis of depression and in obsessive-compulsive disorders. At the same time neurologists have found that serotonin is an important component in the pathogenesis of migraines. At the same time other investigators have explored serotonin's role in cardiovascular regulation. Early into these investigations it was realized that tryptophan had little or no direct effect on blood pressure, while 5-hydroxytryptophan does [20]. Studies have demonstrated that either the intravenous or the intracerebral ventricular infusion of 5-HTp in animals results in a sudden decline in blood pressure, heart rate and sympathetic activity [21, 22]. Later, investigators found that (in a cat model) following pretreatment with a decarboxylase inhibitor, the depressor actions of 5-HTp are abolished [23]. Interestingly a study by Antonacco found that 5-HT alone had little effect on blood pressure in a dog model, but if given after the administration of a MAO inhibitor, it demonstrated significant depressor effects [24]. Kuhn et al. have reported that the central conversion of 5-HTp to 5-HT (or serotonin) appears to

be the principal action underlying the aforementioned vasodilation caused by 5-HTp [20].

With respect to neurocardiogenic syncope, it has been reported that the key event leading to hypotension and bradycardia is sudden sympathetic withdrawal [25-27]. Nearly identical observations have been made with regards to the sudden hypotension and bradycardia that can occur during acute hemorrhage, (which represents a situation more easily reproduced in animal models [28, 29]). In experiments using this model it was found that following a controlled bleed there would be a sudden decrease in renal sympathetic nerve activity [30, 31]. However, if the animals were pretreated with either the serotonin blocking agent methysergide or P-chloropnenylaline (PCPA: an inhibitor of serotonin synthesis) the results were decidedly different [32]. PCPA could eliminate the reflex hypotensive action of acute hemorrhage, while methysergide caused an increase (instead of the expected decrease) in sympathetic nerve activity, suggesting a critical role for serotonin in the inhibition of vagal afferent nerve activity during acute hemorrhage [33]. Abboud has reported that the injection of serotonin into the cerebral vasculature produced excitation of adrenal sympathetic nerve activity, inhibition of renal sympathetic nerve output, and hypotension [34]. All of these actions could be blocked by the administration of PCPA, suggesting that serotonin may act at a central level to inhibit sympathetic output, (and that the serotonin antagonists might prove clinically useful in preventing syncope).

Serotonin's effects in humans have been studied by Matzen et al., who employed specific serotonin receptors given during head upright tilt [35]. The administration of methysergide (a 5-HT_1 and 5-HT_2 receptor antagonist) significantly decreased tilt-induced alterations in serum norepinephrine, prolactin, β-endorphin and plasma renin activity, while at the same time having little effect on the heart rate or blood pressure responses. 5-HT_2 receptor blockage with katanserin decreased the tilt time the subject tolerated, but with little or no hormonal effect. Ondansetron (a 5-HT_3 receptor blocker) had no effect on cardiovascular tilt tolerance or the pituitary-adrenal response, but abolished the adrenomedullary response. Virtually identical observations have been made by Theodorakis et al., with both investigators concluding that control serotonergic mechanisms were at work in the integration of the cardiovascular and endocrine responses that occurred during central volume depletion in man [36].

Serotonin: The Selective Serotonin Re-Uptake Inhibitors

The selective serotonin re-uptake inhibitors (or SSRIs) constitute a distinct class of pharmacologic agents distinguished by their ability to produce a reversible blockade of the uptake carrier of serotonin at the synaptic cleft [37]. Through their inhibition of serotonin re-uptake, these agents augment the extracellular levels of serotonin, resulting in an increased activation of the serotonin receptors that exist at a particular synapse [38]. The SSRIs have little effect on norepinephrine, α- or β-receptors, histamine or muscarinic receptors. As a result of the aug-

mentation in intrasynaptic serotonin concentration, the release of 5-HT is somewhat diminished while the spread of nerve impulse formation is increased. Interestingly, even though these effects may be seen within a matter of days after beginning these drugs, the actual therapeutic actions are usually not seen for at least four to six weeks [39]. It is presently felt that during this interval there is a progressive increase in extracellular 5-HT concentration which results in a continuous decrease in postsynaptic receptor density (a process called "down regulation"). Any nerve receptor may become desensitized due to a constant high level of agonists. This desensitization process is actually felt to protect against overstimulation at the synaptic cleft when greater than normal amounts of neurotransmitters are released. It is presently thought that the major therapeutic effects of the SSRIs occur due to the postsynaptic receptor reduction that they produce.

The first serotonin re-uptake inhibitor was an agent called zimelidine, which was quickly withdrawn due to an unacceptable number of side effects. The next agent introduced was fluoxetine hydrochloride, which enjoyed widespread popularity as an antidepressant. Shortly thereafter the related agents sertraline hydrochloride and paroxetine hydrochloride were introduced onto the market. Since then three slightly different agents have become available [37]. Venlafaxine possesses not only serotonin re-uptake inhibition, but has some norepinephrine re-uptake blocking activity as well. Nefazadone exhibits a high degree of selective action for the 5-HT_2A receptor site [40]. Lastly, the agent redux has been released, which seems to possess a high amount of appetite suppression and thus is used principally as a weight reduction agent.

In addition to the SSRIs two very specific serotonin receptor site blocking agents have been developed. Sumatriptan is a very effective drug that is able to stop migraine headaches by means of direct blockage of the 5-HT_1CD receptor areas. The drugs ondansetron and granisetron have direct blocking effects at the 5-HT_3 receptor sites, and are amazingly effective at stopping the nausea and vomiting that occur due to chemotherapy or anesthesia.

A recent quite fascinating observation has been that β-blocking agents may possess significant central serotonin receptor blocking activity in both animals and humans, principally acting at the 5-HT A and B receptor subtypes [41, 42]. It is certainly possible that these effects may contribute to the therapeutic actions that β-blockers exhibit in the treatment of neurocardiogenic syncope, migraines, and in the prevention of sudden cardiac death [43].

Serotonin and Syncope

The term "neurocardiogenic syncope" refers to a transient period of hypotension and bradycardia which occurs due to a failure of the autonomic nervous system to adequately compensate for a given stress [44]. Although the exact mechanisms involved are still the subject of considerable debate, the phenomenon seems related to a sudden decrease in ventricular preload following a sudden increase in peripheral vascular pooling of blood. Usually when this occurs following the

assumption of upright posture, there is a relatively gradual fall in venous return to the right heart resulting in a decrease in mechanoreceptor firing. This reduced activity is sensed by the brain stem which responds with an increase in sympathetic output that produces an increase in the force of ventricular contractions, in heart rate, and in peripheral vascular resistance. Neurocardiogenic syncope is felt to occur when the fall in venous return to the heart is abrupt (due to greater than normal degree of peripheral vascular pooling of blood) resulting in extremely vigorous ventricular contractions that activate mechanoreceptors that would usually only respond to stretch. This rapid increase in nerve traffic to the brain stem produces a pattern that usually reflects extreme hypertension and thereby elicits an apparent "paradoxic" sympathetic withdrawal with resultant vasodilation and bradycardia. The details of this mechanism are reviewed elsewhere [45].

As discussed in relation to hemorrhagic shock, an important component of the process resulting in neurocardiogenic syncope involves sudden sympathetic withdrawal. This withdrawal appears quite similar to that produced by the injection of serotonin into the intercerebral ventricular areas, raising the possibility that the vasodilatation and bradycardia seen in syncope may have a central serotonergic component.

After it was incidentally noted that patients who suffered from both depression and neurocardiogenic syncope had a significant improvement in either problems after receiving serotonin re-uptake inhibitors, we began to explore the possibility of using these agents in nondepressed patients with recurrent syncope. Our first study evaluated the use of fluoxetine hydrochloride in the management of 16 patients (9 women, 7 men with a mean age of 42 ± 21 years). Each patient had either been intolerant of, or continued to have syncope despite treatment with β-blockers, scopolamine, fludrocortisone, or disopyramide [46]. Each of the subjects in the study group took fluoxetine hydrochloride 20 mg a day for one month. Each patient was then retilted at that time and was also followed clinically. Three patients had to stop therapy due to the development of side effects. Of the 13 patients who remained on fluoxetine, 7 (44% of the total or 53% of those who stayed on the agent) became both tilt negative and continued to be asymptomatic over a 19 ± 9 months follow-up period. Shortly after this we evaluated a similar serotonin re-uptake inhibitor, sertraline hydrochloride, in children and adolescents with recurrent syncope who were refractory to or intolerant of other therapies [47]. Here a total of 17 patients were given sertraline hydrochloride at 50 mg daily for one month. As before, head upright tilt-table testing was performed after this period and the patients were then followed for clinical recurrences. Interestingly, 3 patients had to discontinue therapy due to side effects. Of the 19 patients remaining, a total of 9 were rendered asymptomatic clinically and tilt-table negative, while 5 remained tilt positive. Notably over a mean follow-up period of 12 ± 5 months the tilt negative patients remained asymptomatic while on sertraline. More recently Dan et al. evaluated the use of the more selective agent nefazadone in patients with refractory syncope and noted a 70% response rate to therapy [48]. It is not entirely clear how the serotonin re-uptake inhibitors have their effects in neurocardiogenic syncope. It has

been postulated that because of their facilitation of nerve transmission, these drugs cause a down regulation of postsynaptic receptors in the brain stem. A postsynaptic down regulation in receptor density would have much the same effect as blocking them, and result in a blunted response to sudden shifts in cerebral serotonin levels. A study conducted by Williamson et al. was a randomized trial of sertraline, atenolol and disopyramide in recurrent neurocardiogenic syncope. They reported that the efficacy of sertraline in controlling recurrent syncope was similar to atenolol and disopyramide. Patient tolerance appeared to be best with sertraline [49].

Therefore, the aforementioned discussion supports the concept that serotonergic mechanisms play a vital role in the processes leading to neurocardiogenic syncope. This process may be the final common pathway for syncope, for as Sutton et al. have pointed out, activation of left ventricular mechanoreceptors by orthostatic stress or hemorrhage are not the only stimuli that can provoke neurocardiogenic syncope. Indeed a variety of stimuli such as extreme emotion, fright, or the sight of a needle or of blood may provoke syncope. Temporal lobe seizure activity may also result in sudden sympathetic withdrawal and resultant hypotension leading to syncope [50]. A brilliant series of recent experiments has shown that direct electrical stimulation of the anterior cingulate gyrus of the limbic system in a cat brain can trigger an episode of neurocardiogenic hypotension and bradycardia [51].

The metabolic functions of the brain must be working normally to be able to provide for a normal amount of synthesis, transport and discharge of neurotransmitters. Several factors, such as severe emotional activity, anxiety or epileptic episodes may disturb normal neurohumoral metabolism such that the usual integration of cerebral function, leading to a condition that some have termed "brain failure [52]." These changes can be astonishingly rapid in appearance, especially in those patients with an enhanced susceptibility due to pre-existing deficiencies in neurotransmitter production [53]. At present our hypothesis is that some people demonstrate a predisposition to neurocardiogenic syncope due to relatively low levels of central serotonin production. This in turn leads to a compensatory increase in postsynaptic receptor density producing a type of hypersensitivity to sudden fluctuations in serotonin release. This mechanism is surprisingly similar to the proposed process by which migraine headaches occur. Clearly, more extensive research will be necessary to better define serotonin's role in these processes.

Serotonin: SSRIs in Other Hypotensive Disorders

Carotid sinus syndrome (CSS) is an important cause of syncope in older patients. Although the trigger for episodes involves stimulation of the carotid body area, the responses elicited are quite similar to those seen in neurocardiogenic syncope. Many investigators feel that there is a strong central mechanism, and studies have shown that part of the process involves sudden sympathetic withdrawal resulting in hypotension and bradycardia [53]. Although dual-chamber cardiac

pacing can adequately address the bradycardia associated with episodes, it does little for the hypotension associated with peripheral vasodilation [54]. Therefore in patients with CCS who have a large vasodilatory component, dual-chamber cardiac pacing may not fully abort episodes [55]. To determine if SSRIs would be helpful in this group, Grubb et al. studied two patients with recurrent syncope due to CSS who continued to have episodes despite dual-chamber pacing. Both received an SSRI (either fluoxetine or sertraline) and after 4-6 weeks of therapy were both clinically symptom free, and repeated carotid sinus stimulation failed to provoke episodes [56]. This concept has been explored further by Dan et al. who employed SSRIs in patients with CSS as primary therapy. In a small group of patients he found that the SSRIs had a similar success rate to that of permanent pacemaker implantation [57].

Two recent studies have uncovered an association between depression (where central serotonin levels are known to be low) and hypotension [58, 59]. After successful treatment of depression with SSRIs, blood pressures also tend to return to normal. At the same time it has been found that the powerful SSRI venlafaxine may cause hypertension in patients being treated for depression. These observations lead us to investigate the effect of SSRIs in patients with severe orthostatic hypotension. Disorders of autonomic function leading to orthostatic hypotension are both common and quite debilitating. Usually idiopathic in origin, orthostatic hypotension may frequently occur in conjunction with diabetes. These patients are often difficult to treat and respond poorly to current therapies. Grubb et al. have reported on the effects of fluoxetine hydrochloride in 5 patients suffering from otherwise refractory orthostatic hypotension [60]. Two patients had a marked improvement, 2 reported moderate improvement, while 1 reported having no improvement. Almost identical findings were seen in a second study using venlafaxine hydrochloride [61].

Conclusions

The neurotransmitter serotonin appears to play a pivotal role in the brain's ability to regulate both heart rate and blood pressure. Sudden alterations in central serotonin levels may contribute to the development of disorders such as neurocardiogenic syncope and carotid sinus hypersensitivity. Several studies have suggested that the serotonin re-uptake inhibitors may be effective in the treatment of these disorders. Although the exact mechanism by which they act is still unclear, it is speculated that the prolonged re-uptake inhibition that these agents cause produce an increase in intrasynaptic serotonin concentrations with a resultant decrease in postsynaptic serotonin concentrations. Another possible action is that these agents may result in a feedback inhibition that retards further release presynaptically. Clearly, more detailed and better controlled studies will be required to better determine serotonin's exact role in neurovascular control, and to better understand how its manipulation may provide for new and exciting treatment modalities.

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Development of an Implantable Drug Delivery System for the Treatment of Vasovagal Syncope: a Dream or a Real Prospect?

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Syncope is a common clinical problem. It accounts for approximately 3% of all emergency room visits and for 1% of all hospital admissions [1]. Syncope has a vasovagal origin in the majority of non-hospitalized patients (about 70%) [1]. Vasovagal reaction may occur both in pediatric and adult patients and is characterized by sudden vasodilatation, bradycardia or both, with resultant hypotension and loss of consciousness.

Pathophysiology of Vasovagal Syncope

The exact pathophysiologic mechanism of vasovagal syncope is incompletely understood. In normal individuals, assumption of passive upright posture produces a reduction in venous return and cardiac output with an immediate decrease in arterial pressure that is compensated for by a reflex arterial vasoconstriction and concomitant tachycardia essentially mediated by arterial baroreceptors [2]. In patients prone to vasovagal reaction, instead of these compensatory adjustments, an abnormal reflex may develop which leads to paradoxical reduction in sympathetic vasoconstrictor outflow together with an increase in parasympathetic activity resulting in vasodilatation and bradycardia [3]. It has been postulated that the pathologic reflex responsible for vasovagal syncope is caused by an inappropriate activation of the ventricular mechanoreceptors (C fibers) located in the base of both the left and right ventricles, as a consequence of a vigorous contraction of the adrenergically stimulated heart around a relatively empty ventricular cavity [4-6]. However, the pathophysiology of vasovagal syncope is probably not so schematic and uniform in all patients and other mechanisms are likely to play a role in eliciting the reflex [7]. For example, in some cases it is likely that the afferent signals arise from sites different from ventricular mechanoreceptors, such as atrial and pulmonary baroreceptors, or even directly from higher CNS centers. In other cases it is probable that a decreased

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sensitivity or an inadequate or delayed response of carotid and aortic baroreceptors that have a feedback function, may contribute to syncope. An abnormality in the central processing of afferent signals is another possible cause that may also explain the excessive concentration (often observed during vasovagal syncope) of certain centrally released neurotransmitters and vasoactive agents, such as endorphins, serotonin, nitric oxide, and vasopressin. Finally, we cannot exclude that in particular subjects the defect is in the efferent limb of the reflex arch and consists, for example, in an increased responsiveness of peripheral cardiac and/or vascular receptors to neurohumoral mediators.

Therapy of Vasovagal Syncope

In the majority of subjects, vasovagal syncope is a benign problem due to the very rare occurrence of syncopal spells and the presence of characteristic triggering factors and prodromal symptoms that allow the patient to assume a supine position or other evasive action and avoid physical injury. In these cases, specific treatment is usually not indicated and syncope may be prevented by simple measures such as avoidance of prolonged sitting or standing, resting in supine position after meals, avoidance of crowded or hot places, avoidance of strenuous exercise in a warm environment, and elimination of potentially hypotensive drugs [8]. In other subjects, however, especially elderly people, syncopal episodes are much more frequent and often occur in the absence of predictable circumstances and warning symptoms. These episodes may be accompained by important trauma and constitute the so-called atypical or malignant vasovagal syndrome. In these cases, specific treatment is generally recommended [8].

The therapy of vasovagal syncope comprises pharmacologic as well as non-pharmacologic options. Several drugs with different effects have been proposed for the prevention of vasovagal syncope, such as β-blockers, disopyramide, anticholinergic agents, scopolamine, alpha-agonists, theophylline, serotonine reuptake inhibitors such as fluoxetine hydrochloride, fludrocortisone, dihydroergotamine, and verapamil [8]. Drug treatment of vasovagal syncope may be empirical or guided by head-up tilt testing. The real efficacy of the different drugs proposed for the prevention of neurally mediated syncope is difficult to establish because of limited information being available regarding the natural history of vasovagal syncope and the dearth of randomized, controlled studies. However, the wide spectrum of pharmacologic agents proposed for treatment of vasovagal syncope probably reflects not only the great variety of pathophysiologic mechanisms underlying the vasovagal reaction in different patients but also the insufficient or partial efficacy of currently available drugs. Among the non-pharmacologic options, support stockings, high-salt diet, and increased water intake are all helpful measures for patients with important venous pooling or with dehydration and hypovolemia [8]. Implantation of a dual-chamber pacemaker has been often utilized for patients with marked cardioinhibition associated with vasodepression but the results up to now are still controversial [9, 10].

Rationale for the Development of an Implantable Drug Delivery System

Vasovagal events, like many other autonomic nervous system disturbances, have a cyclic and unpredictable course with usually brief periods of symptom recrudescence (so-called "clusters") alternated to sometimes very long periods of quiescience and asymptomatic status [11]. Thus, a chronic therapy with drugs does not seem a rationale in the majority of cases and is often associated with important or intolerable side effects as well as poor patient compliance, especially in young people. Moreover, prevention of vasovagal reaction usually requires high drug plasma levels at the time of event occurrence [12] that are difficult to reach with a chronic oral administration. It is also noteworthy that electrical treatment with a pacemaker, even if effective, only rarely leads to a complete elimination of symptoms [9] because of the hypotensive effects of the vasodepressor reflex that is practically present in all patients, generally precedes cardioinhibition and bradycardia [13] and is not amenable to correction or reversion by cardiac pacing.

For all these reasons, it seems logical and desirable to develop an implantable drug delivery system for treatment of vasovagal syncope, that should be coupled with a dual-chamber pacemaker. Such a device would allow the automatic, "on demand" delivery of a bolus of a cardioactive or vasoactive drug, previously recognized to be effective and safe in preventing tilt-induced syncope, together with the activation of a sequential cardiac pacing. In this way, it would be possible to avoid the unnecessary administration of drugs in the intervals between symptoms, thus practically eliminating the possibility of side effects and considerably improving patient compliance. At the same time, this system would assure more complete control of symptoms by simultaneously counteracting both hypotension and bradycardia.

Key Issues for Development of an Implantable Drug Delivery System for Treatment of Vasovagal Syncope

There are a number of key issues to be addressed prior to implementation of such a system. They include:

- The choice of a reliable marker for an imminent vasovagal faint
- The search for the most appropriate drug to be used to this purpose
- Conception and building of the device

In the following sections each of these issues will be briefly discussed.

Choice of the Marker for an Imminent Vasovagal Faint

The detection of a sensor capable of predicting the imminent occurrence of a vasovagal event is essential for initiating an early enough therapeutic intervention to abort syncope. Different markers have been proposed to this regard [14]. Among these, we have to mention an abrupt heart rate drop response [10],

changes in heart rate and blood pressure variability, the relationship between heart rate and concomitant QT interval changes, a decrease in right ventricular pressure and dP/dt max [15], an increase in peak endocardial acceleration [16], an increase in respiratory rate and volume minute, and a reduction in cerebral blood flow. However, it is important to note that only a few of these potentially useful parameters have been systematically tested parameters up to now. Indeed, at the present time, the "on line" measurement of many of these parameters is not yet practicable.

A detailed review of all these different parameters proposed has been published [14]. Among the markers really investigated to date, only the detection of an abrupt heart rate drop response has proven to be quite valuable, with limitation to those patients showing reproducible cardioinhibitory response during their syncopal spells [10]. All the other parameters have given disappointing or contrasting results [15, 16]. However, slowing of heart rate is, conceivably, not the best indicator for early recognition of vasovagal faint. Indeed, bradycardia is almost always a secondary or late phenomenon compared to vasodepression [13]. Thus, it is clear that much further investigation is necessary in the future to discover, test and implement into an implantable device, a sensor or a combination of sensors capable of detecting a vasovagal event sufficiently soon to start a useful device intervention (drug infusion and pacing).

Search for the Most Appropriate Drug

As previously discussed, many drugs have been proposed for the chronic oral treatment of vasovagal syncope [8]. However, only a few of them have the characteristics that are indispensable for the intermittent use required in an implantable pump. The ideal drug for this purpose should be fast-acting, to minimize intervention delay as much as possible and should act only for as long as is strictly necessary [17]. The immediate onset of action is crucial to reach the goal of aborting syncope while the short duration of action is a desirable condition to eliminate or reduce side effects and to permit repeated drug infusions, if necessary. The drug selected for use with an implantable drug delivery system should be stable over time at body temperature for at least several months and should require infrequent refilling of the drug reservoir [17].

Among the theoretically potential candidates, esmolol and phenylephrine are probably the most appropriate agents for this application. Esmolol is a short-acting β-blocker that has been already employed during head-up tilt testing as a means to predict the efficacy of other β-blockers with longer duration, such as metoprolol, that are more suitable for chronic oral treatment of vasovagal syncope [18]. Phenylephrine is an α-agonist drug that is currently used to treat hypotensive crises and to assess baroreflex sensitivity after myocardial infarction. Both drugs, however, are only theoretically useful for the application with an implantable pump and their real efficacy must be still assessed during acute laboratory testing.

Phenylephrine is very attractive. Its action is almost immediate [19], the half-life is 5 minutes [20], and the drug is safe and well tolerated at a recommended

dosage of 0.2-1.0 mg (as bolus) [19, 21, 22]; moreover, in sterile water for injection phenylephrine is stable for up to 84 days at 60° [23]; finally, 10 ml of the drug preparation contain 25 mg of the active principle. We are starting an evaluation of this drug during head-up tilt testing to assess its ability in aborting tilt-induced vasovagal syncope.

Conception and Building of the Device

As mentioned above, an implantable pump for the treatment of vasovagal syncope should be combined with a dual-chamber pacemaker. Indeed, vasovagal reaction generally has two components, a vasodepressor and a cardioinhibitory one, and both need to be corrected to avoid syncope. In an ideal device for the treatment of vasovagal syncope, the two functions of drug therapy and electrical therapy should be integrated into a single system with the main control of the device calling for either infusion or pacing or both. Conceivably, the most practical approach for drug delivery in this system would be to infuse the drug in the right cardiac chambers, by using the same catheters introduced for pacing. In this way, the drug would enter circulation readily from the right ventricular location, which would be important for rapid mixing and dispersion [17]. Obviously, the drug pump that should be incorporated into an implantable device for the treatment of vasovagal syncope should have all the necessary elements, such as drug reservoir, telemetry, electronic controls, and power source.

The realization of such a device, at the present time, is not easy and has to await the discovery of a reliable sensor for early recognition of a vasovagal event as well as laboratory and clinical evaluation of the most appropriate drugs for this application. Nevertheless, the concept of an implantable device for treatment of vasovagal syncope is intellectually intriguing and with the formidable technology of today has a good chance of being implemented.

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Sensor for Early Recognition of Imminent Vasovagal Syncope

D.G. Benditt and K.G. Lurie

Introduction

As a rule, vasovagal syncopal episodes tend to occur as solitary or very infrequent events in most patients. Consequently, in terms of preventive therapy, few patients require more than reassurance, and most of the remainder are adequately managed using any of several prophylactic pharmacological treatment strategies (e.g., salt/water retention, beta-adrenergic blockade, disopyramide, midodrine, etc.). Occasionally, however, syncopal events persist. In such cases, implantable therapeutic devices designed to both recognize an imminent vasovagal faint, and initiate treatment automatically (e.g., pacemakers with specialized pacing algorithms, or combined pacemaker-drug infusion systems), may prove beneficial.

The ultimate utility of implantable devices for prevention of vasovagal faints is critically dependent on two developments: 1) techniques capable of identifying an imminent faint at an early enough stage to permit useful intervention, and 2) rapid onset treatment strategies effective enough to abort the process. This discussion focuses on the first of these issues.

Pathophysiogy of the Neural Reflex in Vasovagal Syncope

Detailed review of the pathophysiology of vasovagal syncope is beyond the scope of this report (see for example [1-4]). Nevertheless, a brief overview may permit better understanding of the opportunities and difficulties associated with identifying indicators of an imminent vasovagal event.

In general, most neurally-mediated faints (e.g., vasovagal syncope, carotid sinus syndrome, post-micturition syncope, etc.) are the result of transient cerebral hypoperfusion due to a combined circulatory disturbance in which both peripheral vasodilatation (vasodepressor component) and marked or relative bradycardia (cardioinhibitory component) result in inadequate cerebrovascular perfusion pressure. In the case of the vasovagal faint, the routes of afferent neural

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traffic which trigger these efferent reflex responses are not well established. In certain instances, such as syncope associated with fear or emotional upset, the cerebral cortex clearly plays an important role in initiating and/or 'interpreting' the afferent signals. However, in most cases, the origin of the afferent signals is less certain, and any of a variety of peripheral 'receptors' which respond to mechanical or chemical stimuli, or pain have been implicated.

Ultimately, afferent neural impulses whether from cortical or peripheral sites are believed to converge in the medulla at the nucleus tractus solitarius, which lies near the nuclei of the vagus nerve, the vasomotor centers, and the hypothalamus. However, details regarding the manner in which the central nervous system processes afferent signals, thereby initiating an inappropriate rather than a physiologically desirable hemodynamic response, is virtually impossible to address with available methodologies. It is likely that interaction occurs not only among neural inputs, but also with centrally released neurotransmitters/neurohumors. In regard to the latter, endorphins, serotonin, nitric oxide, and vasopressin have been the subject of particular interest.

The efferent limb associated with the vasovagal faint incorporates both neural and humoral aspects. In regard to the neural contribution, vasodilatation is thought to be primarily the result of diminished sympathetic vasoconstrictor activity, whereas the cardioinhibitory response in humans is principally due to enhanced efferent vagal tone. Epinephrine, norepinephrine, and vasopressin appear to be the most important of the circulating humoral contributions to the efferent limb. However, vasoactive peptides (e.g., vasoactive intestinal peptide, calcitonin gene related peptide), nitric oxide, and purinergic agonists (e.g., adenosine) may also play a role, perhaps by attenuating synaptic norepinephrine release and thereby contributing to vasodilatation.

A final element in the 'vasovagal reflex' is the feedback limb provided by the arterial baroreceptor system. In theory, this system would be expected to act to prevent syncope by stemming the tide of evolving vasodilatation and bradycardia. In fact, it seems likely that the often large fluctuations in heart rate, blood pressure, and other circulatory markers such as subcutaneous blood flow, observed during tilt-table induction of vasovagal faints, are indicative of attempted baroreceptor compensation [5, 6]. In some cases circulatory stability is achieved and the faint is aborted. Often, however, such efforts are insufficient and a faint results.

Potentially Useful Markers of an Imminent Neurally-Mediated Faint

In order to develop implantable systems for diagnosis and treatment of neurally-mediated syncopal disorders, indicators of an imminent vasovagal event that are suitable for use in compact implanted devices (i.e., limited energy and size) are needed. To derive such markers, each limb of the reflex can, in theory, be targeted. However, from a practical perspective only certain aspects of the efferent and feedback loops are approachable by currently available implantable technology.

Figure 1 depicts the basic elements of the neural reflex pathways in vasovagal syncope, and indicates a number of markers that might be useful. However, to date relatively few of these potential diagnostic markers have been systematically studied, and in many cases 'on-line' measurement is not yet practicable. Furthermore, even preliminary evaluation of a diagnostic marker depends on the ability to reproduce the vasovagal faint under controlled conditions. In this regard studies in tilt-table testing or lower body negative pressure laboratories are essential. Nevertheless, there remains uncertainty as to whether the 'induced faint' is identical to the spontaneous event in the same 'free-living' patient.

Direct or Surrogate Recordings of Vagal Efferent Neural Signals

The possibility exists that recognition of altered parasympathetic nervous system activity could be employed as a means of suggesting an imminent faint in susceptible individuals. In theory, direct vagus nerve recording is possible. However, implementation of such a system has yet to be accomplished, and even if it were,

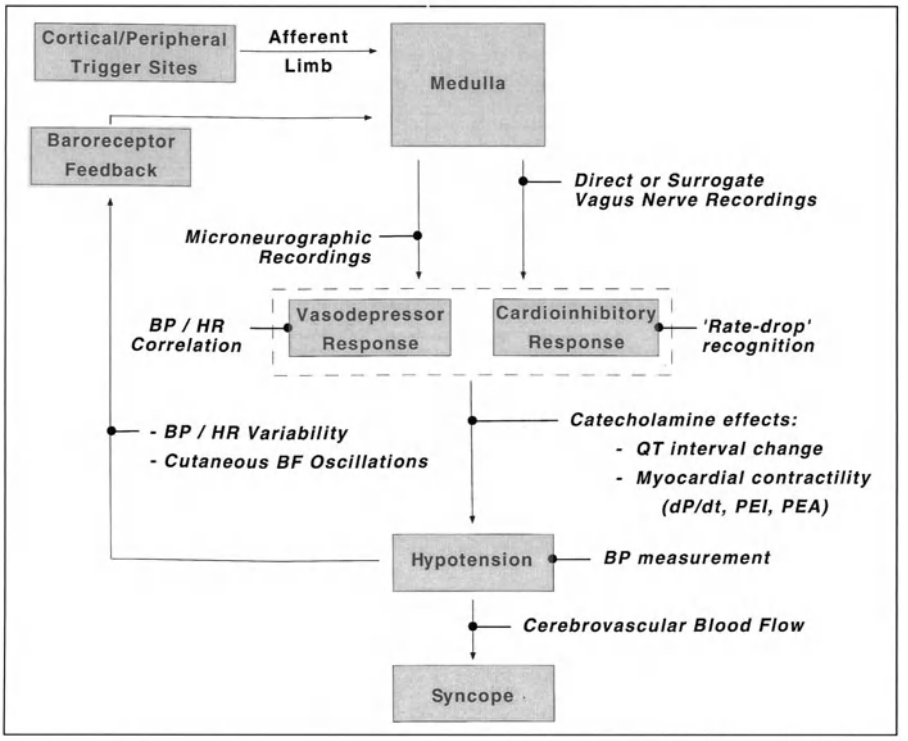

Fig. 1. Block diagram illustrating the major elements (indicated in boxes) believed to participate in the neurally-mediated reflex associated with vasovagal syncope. Measurements of theoretical value in detecting an imminent vasovagal faint are indicated in italics, along with the portion of the reflex network they most closely reflect. See text for further discussion

there is uncertainty that direct recordings could be effected in a sufficiently simple manner to permit widespread clinical acceptance.

If recognition of changes of vagal nerve traffic have any utility in the identification of imminent vasovagal events, it is more likely that such changes will be detected through surrogate measures of vagal activity rather than direct recordings. Thus, changes in respiratory pattern or sinus arrhythmia (see heart rate variability later) might be investigated. In regard to the former, changes in respiration (rate, tidal volume) may occur either voluntarily or perhaps involuntarily (since respiratory control centers are close to the medullary traffic pattern thought to be occurring in neurally-mediated syncope) in an attempt to stabilize the hemodynamic state. Conceivably, respiratory variations may act to improve venous return in tenuous circumstances, thereby affecting baroreceptor activity. Alternatively, changes in respiratory pattern may affect processing of baroreceptor afferent signals centrally. In any event, currently there is insufficient information to speculate on the potential utility of any surrogate measures of parasympathetic activity in this setting.

Sympathetic Neural Efferent Activity (vasodepressor response)

Microneurographic recordings from efferent sympathetic nerves have provided important physiological research information. Such recordings have also been accomplished successfully in the clinical laboratory, and in theory could be useful in identifying an imminent vasodepressor response. However, it is unknown whether all sympathetic nerve activity is affected simultaneously during a vasovagal faint, and at an appropriately early time. Indeed, in an example of a microneurographic recording obtained during a spontaneous vasovagal event [7], sympathetic activity appears to diminish only after a considerable preceding period of hypotension. Further, somewhat surprisingly the diminution of sympathetic neural activity coincides more closely with onset of bradycardia.

Despite the intuitive appeal of sympathetic nerve recordings as a potential marker for vasovagal syncope, the methodology for obtaining these recordings is far too cumbersome for use in implantable systems. Indeed, even maintaining a single recording in a well stabilized limb during tilt-table testing has proved to be a challenge [8]. Maintaining long-term recording from one or more nerves has yet to be accomplished. Potentially, it may be possible to transplant a sympathetic nerve to the pulse generator pocket thereby facilitating long-term recording in the future. For the time being, however, it seems that a more feasible approach would be to try and obtain surrogate measures of sympathetic nerve activity from nearby skeletal muscle.

'Rate-Drop' Recognition

To date, the abrupt drop in heart rate associated with certain cases of cardioinhibitory syncope is the only marker to have been studied as a trigger to initiate a treatment intervention (i.e., cardiac pacing). In this regard, Benditt et al [9] report-

ed findings in 37 patients with carotid sinus syndrome, or vasovagal syncope, or both. Prior to pacing, these patients had been very symptomatic, experiencing on average 47±173 syncopal episodes each over the preceding 42± 62 months. During post-pacing follow-up of 191±145 days, 85 percent of patients indicated absence or diminished frequency of symptoms, or less severe symptoms. Overall, the findings suggested that provision of high rate pacing after detection of abrupt onset heart rate slowing was beneficial in this select group of very symptomatic patients. Thus, detection of abrupt rate-drop response may be useful as part of a diagnostic algorithm for those instances where clinical vasovagal syncope is reproducibly characterized by a detectable cardioinhibitory element.

Sensors Reflecting Effects of Changes of Sympathetic Neurohumoral State on the Heart

It has long been recognized that increased levels of circulating catecholamine, particularly epinephrine, are characteristic of the pre-syncope phase in patients with susceptibility to vasovagal faints [1-4, 10]. Therefore, in the absence of practicable techniques for direct in vivo measurement of circulating catecholamines, indirect methods suggesting their increase may be useful as part of a diagnostic algorithm. To this end, both changes in myocardial contractile performance as well as catecholamine-induced changes in cardiac conduction intervals may be useful measures.

A vigorous myocardial contraction, presumably resulting from increased circulating catecholamines and diminished central volume (e.g., upright posture, dehydration, fright, etc.), has been closely associated with vasovagal faints. Consequently, recognition of an abrupt increment in contractile activity (especially in the absence of increased physical activity) may be indicative of an imminent faint. To date, changes in right ventricular pressure, pre-ejection index (PEI) and dP/dt [11], and measurements of peak endocardial acceleration (PEA) have been studied [12]. Right ventricular pressure alone appears to be unsuitable due to the small magnitude of the changes in a chamber as compliant as the right ventricle. PEI, although reported to be useful to trigger rapid pacing in one patient with severe orthostatic hypotension [13], also appeared to exhibit only small and highly variable changes. On the other hand, right ventricular dP/dt max fell about 30 percent (median) from peak value beginning about 2 minutes before syncope, thereby offering an index of potential value for further research. In regard to PEA, recordings have been obtained from an endocardial microaccelerometer located in a pacing electrode during induced vasovagal faints [12]. In this configuration, although the lead is in the right ventricular cavity, prior studies suggest that the recording closely tracks left ventricular dP/dt. Nevertheless, syncope occurred with both low and high PEA values. Consequently, this theoretically desirable approach was disappointing.

An altered sympathetic neurohumoral environment may also be detectable through changes on certain cardiac electrophysiological measures. In this regard, recognition of altered relationships between certain conduction intervals (AV interval, QT interval) and concomitant heart rate (R-R interval) are readily

accomplished by current implantable systems. However, whether these methods can provide adequate warning of imminent faints is as yet unknown. Our own laboratory has focused on assessing the relationship between changes in heart rate and the concomitant QT interval as cardioinhibitory syncope evolves. In theory, the elevated circulating catecholamines accompanying vasovagal syncope may be expected to result in a shorter QT interval than anticipated, given the slowing heart rate typical of the onset of many vasovagal events. Preliminary findings tend to support the concept, but the relationships are not yet sufficiently delineated to permit an assessment of utility.

Hemodynamic and Cerebral Blood Flow

The early recognition of diminishing cerebral blood flow could be among the most specific indicators of an imminent faint. Perivascular flow probes, using ultrasonic or perhaps laser Doppler techniques, might be capable of providing such information. However, miniaturizing such systems to limit power consumption and facilitate implantation is as yet an unmet challenge.

Heart Rate, Blood Pressure, and Blood Flow Variability

Heart rate, blood pressure, and blood flow variability are recognized accompaniments of evolving vasovagal faints. It is likely that the observed oscillations at least in part reflect attempts by the arterial baroreceptor system to fend off the evolving faint. Whether the early recognition of such oscillations can be used to predict an imminent faint is as yet uncertain.

Heart rate oscillations (i.e., heart rate variability, HRV) during induced vasovagal faints have been studied primarily to provide insight into neurophysiologic changes associated with tilt-induced syncope [5,14]. Specifically, HRV findings support the concept that susceptible individuals manifest a relative failure of parasympathetic withdrawal immediately following assumption of the upright posture. Conceivably, this observation could form part of a detection algorithm, but the time required to make HRV measurements remains an important limitation. Some form of 'rolling' method could be useful, but it is uncertain whether such an approach could respond promptly enough to recognize a rapidly evolving syncopal event. Subcutaneous blood flow oscillations may be used in a similar manner, but the measurement technique (i.e., Laser Doppler) may not be readily adaptable to an implanted device.

Conclusions

Early reliable detection of an impending vasovagal faint provides the opportunity for automatic delivery of preventive therapies ranging from cardiac pacing and parenteral drug delivery, to neural stimulation. Findings to date, although very preliminary, suggest that no single sensor system will be sufficient. However, the

combination of several synergistic sensor systems may prove effective, thereby opening the way to what appears to be a very promising new application for implantable devices.

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Is Echocardiographic Investigation Useful for Establishing the Chronological Sequence of Events in Tilt Induced Syncope?

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Introduction

Neuromediated syncope is a clinical event experienced by nearly 20% of the adult population [1]. Using the head-up tilting test (HUT) we can reproduce the syncope in more than 50% of these subjects [2]; furthermore we can investigate the pathophysiology of the event utilizing echocardiographic [3] or hemodynamic [4] monitoring during the test.

Many hypotheses have been proposed in order to elucidate the sequence of events that generate cerebral hypoperfusion and thus syncope. The reduced venous return and the decrease in ventricular loading in the upright position constitute the common elements of the proposed cascade of events that lead to syncope [5]. Some authors maintain that the following step is due to a reactive ventricular hypercontractility; this provokes stretching of myocardial mechanoreceptors and, by spinal integrated reflexes, inhibition of vascular tone and/or decrease in heart rate [3, 6]. Other authors maintain that the two ventricles have different consequences of the lower venous return: while the right ventricle decreases its end-diastolic volume just after the beginning of HUT, the left ventricle can compensate its loading by a greater displacement of blood from lungs so that ventricular hypercontractility does not necessarily occur [7]. In fact, in some reports the left ventricle ejection fraction does not increase or even decreases during HUT [8].

Blood flow dynamics have rarely been investigated by Doppler-echocardiography during HUT. Papers on this topic report a change of atrioventricular flow characterized by a reduction of the global forward flow with a main decrease of the early diastolic ventricular loading and a relative increase of late diastolic loading [9-11]. These studies have also stressed the different adaptation of the two sides of the heart because pulmonary flow compensates the left ventricular loading for the immediate decrease of right ventricular stroke volume.

In order to verify which hypothesis could better explain the pathophysiology of neuromediated syncope, we have performed an echo-Doppler investigation during HUT on a group of patients who previously experienced syncopes and a

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control group of asymptomatic subjects. The results of the present study have been compared with the reports of the main papers on this topic.

Methods

Population

Fourteen consecutive patients (6 males, 8 females; mean age 40 ± 21 years) with syncope of unknown origin after extensive clinical and instrumental evaluation and positive HUT, and 10 asymptomatic control subjects (4 males, 6 females; mean age 38 ± 18 years) with no history of syncope or pre-syncope, were studied. All the patients and control subjects were free from heart disease and none used vasoactive drugs. All patients had at least 1 syncopal episode (range 1-20, mean 3±5) during a period of time ranging from a few days to many years. The mean interval between the last syncope and HUT was 20 days (range 1-40 days).

Head-up Tilt Test

Informed consent was obtained in all cases. The test was always performed in the morning between 9 and 12 a.m., after an overnight fasting, in a quiet room with dimmed lights. A motorized tilt table with foot-plate support for weight-bearing was used. Blood pressure (by means of an Ohmeda Finapress 2300 photoplethysmographic device) and heart rate (by means of ECG limb leads I, II and III) were continuously monitored and recorded.

After an initial evaluation with the patient in supine position for 10 minutes, the test was initially performed at a 60 degree angle for 20 minutes without medication. If syncope did not develop the subject received a fixed dose of 300 mcg of sublingual nitroglycerin and continued to be tilted at the same angle for an additional 20 minutes [12]. A positive response was defined as reproduction of the spontaneous syncope in association with hypotension and/or bradycardia.

Echocardiographic Evaluation

Two-dimensional and Doppler echocardiography was performed in the supine position, every 5 minutes until the end of HUT and – in patients with positive response – at the onset of symptoms and at induction of syncope. The apical four and five-chamber views were used and images were stored on videotape.

- Two-dimensional echocardiography. The following variables were obtained: end-diastolic (EDRVA) and end-systolic (ESRVA) right ventricular area; end-diastolic (EDLVA) and end-systolic (ESLVA) left ventricular area; right ventricular (RVFAC) and left ventricular (LVFAC) fractional area change.
- Doppler-echocardiography. By positioning the sample volume of pulsed Doppler just distal to the open atrioventricular valves the following parameters were calculated: the velocity time integral of early diastolic (VTI-E), late dias-

tolic (VTI-A) and total diastolic flow (T-VTI). By positioning the sample volume 0.5 cm inside the outlet in left atrium of right superior pulmonary vein the total pulmonary flow (T-VTI pulm) was obtained. Finally, utilizing continuous wave Doppler of left ventricle outflow, we calculated the velocity time integral of aortic forward flow (VTI-aortic). All Doppler parameters were normalized for heart rate by dividing them by the square root of R-R interval of ECG.

Statistics

All data were expressed as mean ± SD and analyzed by using the two-tailed Student's "t" test of paired and unpaired data and chi-square test with Yates' correction, as appropriate.

Results

None of the control subjects experienced syncope during HUT. Six patients had positive HUT during the drug-free phase and 8 after the administration of nitroglycerin. Heart rate and diastolic blood pressure increased and systolic pressure slightly decreased during the drug-free phase in all subjects. After the administration of nitroglycerin there was a decline in systolic and diastolic pressure and increment in heart rate in all subjects. At the moment of syncope 11 patients had a significant reduction of blood pressure and heart rate, while 3 patients exhibited only a reduction in blood pressure (Table 1).

Two-dimensional Echocardiography

At the beginning of orthostatism both ventricles reduced their end-diastolic areas. EDRVA progressively reduced its dimension throughout HUT; its decrease was slightly stronger and faster in HUT positive patients (Table 2). EDLVA, soon after the initial drop, exhibited small and not significant changes during the entire intermediate phase in all subjects; later, in HUT positive patients, it quickly decreased as long as the onset of syncope. In all subjects FAC (Fractional area change in %) showed a slow decline throughout the test in both ventricles, although the reduction was more marked and uniform on the right side of the heart. In HUT positive patients at the onset of syncope we observed a scattering of LVFAC values: in 4 patients it increased, in 7 it did not show significant variations and in 3 it decreased.

Doppler-echocardiography

At the beginning of HUT we observed a reduction of the ratio between early and late diastolic velocity-time integrals (VTI-E / VTI-A) caused by a reduction of VTI-E and a relative increase of VTI-A. This behavior was documented on the right as well as on the left side of the heart in all subjects. In HUT positive patients the increase of VTI-A normalized for R-R interval, thus independent

Table 1. Heart rate and blood pressure during hut (mean ± SD)

	SUPINE		*5 MIN*		*10 MIN*		*15 MIN*		*25 MIN*		*35 MIN*		*SYMPT*		*SYNC/END*	
	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)
HEART RATE	68	70	81*	82*	82*	83*	84*	82*	106*	100*	110*	103*	54*	–	44*	105*
(bpm)	±12	±14	±18	±16	±18	±19	±18	±17	±20	±18	±22	±19	±18	–	±22	±25
SYSTOLIC	140	138	131	132	131	130	130	132	110*	125	103*	112*	80*	–	30*	120*
(mmHg)	±16	±13	±18	±14	±13	±15	±18	±16	±23	±20	±20	±18	±15	–	±10	±20
DIASTOLIC	70	72	77*	78*	78*	78*	78*	79*	70	73	68	71	60*	–	30*	76
(mmHg)	±18	±19	±19	±20	±18	±20	±20	±19	±19	±20	±15	±19	±12	–	±9	±18

(+), positive HUT; (−), negative HUT; Sympt, onset of symptoms; Sync/end, syncope or end of HUT; * $p < 0.05$ versus supine

Table 2. 2-D echocardiographic parameters during HUT (mean ± SD)

	SUPINE		*5 MIN*		*10 MIN*		*15 MIN*		*25 MIN*		*35 MIN*		*SYMPT*		*SYNC/END*	
	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)
EDRVA (cm^2)	19.8 ±5.2	18.1 ±3.8	16.8* ±3.9	15.8* ±4.1	15.6* ±3.2	15.6* ±3.7	14.4* ±2.8	15.1* ±4.2	12.5* ±3.2	13.1* ±3.2	12.8* ±3.8	13.4* ±4.2	10.8* ±2.8	–	11.4* ±4.7	12.2* ±3.8
RVFAC (%)	38 ±4.5	41 ±5.8	36 ±6.2	38 ±6.7	36 ±4.1	38 ±3.8	35* ±3.8	38 ±4.2	31* ±4.4	35* ±4.8	32* ±3.2	34* ±5.1	29* ±6.5	–	25* ±8.9	33* ±5.1
EDLVA (cm^2)	34.7 ±4.3	35.8 ±5.1	32.5 ±3.6	33.7 ±3.8	33.8 ±4.8	33.4 ±4.6	32.7 ±4.2	34.1 ±5.2	30.0* ±2.8	31.9* ±2.8	30.0* ±4.7	31.5* ±3.7	28.5* ±3.2	–	24.7* ±5.4	30.6* ±4.5
LVFAC (%)	42 ±3.5	43 ±4.1	41 ±4.2	42 ±4.5	43 ±3.8	41 ±4.1	41 ±5.2	42 ±3.4	41 ±6.4	40 ±5.2	39 ±4.3	38* ±3.9	36 ±13.8	–	30* ±6.5	37 ±6.8

EDRVA, end-diastolic right ventricular area; EDLVA, end-diastolic left ventricular area; (+), positive HUT; (−), negative HUT; Sympt, onset of symptoms; Sync/end, syncope or end of HUT; RVFAC, right ventricular fractional area change; LVFAC, left ventricular fractional area change; * $p < 0.05$ versus supine

from heart rate, was found to be more pronounced than in subjects with negative HUT at the onset of symptoms, and it suddenly dropped soon after (Tables 3 and 4).

Total forward tricuspid flow (T-VTI) exhibited progressive decrease throughout the test and the velocity of its reduction was greater in HUT positive patients as already documented for EDRVA. Mitral flow changes paralleled the changes of EDLVA. In fact, mitral T-VTI exhibited small variations in early and intermediate phases; later, in HUT positive patients, it rapidly fell down near the onset of syncope. A similar trend was exhibited by the aortic flow. Total pulmonary forward flow had a small drop at the beginning of HUT, it remained almost constant until the intermediate phase, and progressively decreased close to the end of the test; the fall was more rapid in HUT positive patients. Altogether the decrease of pulmonary venous flow was less pronounced compared to tricuspid forward flow reduction and resembled that of mitral forward flow (Table 5).

Discussion

Two-dimensional Echocardiography

The observed reduction of end-diastolic area of the two ventricles in both groups of subjects from the beginning of HUT, may be the consequence of the lowered venous return caused by the blood pooling in lower limbs and visceral veins [3]. The two sides of the heart show a different pattern of area change: while the right ventricle progressively reduces its loading throughout the test, the left ventricle maintains a more stable loading during early and intermediate steps of HUT, and its end-distolic area significantly falls down only at the onset of symptoms in HUT positive patients. End-systolic ventricular areas exhibited smaller variations during HUT so that FAC reduced in both ventricles, although the difference from the basal values was significant only in HUT positive patients at the onset of symptoms. Maybe FAC reduction is the mere consequence of the lowered ventricular loading that induces, by Starling mechanism, a decrease of ventricular contractility. In four HUT positive patients, just before the onset of symptoms, we observed a sharp increase of FAC followed soon by its reduction associated to bradycardia and syncope. This trend was previously described by Shalev [3] who hypothesized that neuromediated syncope was the consequence of vigorous ventricular contractions that stimulated myocardial mechanoreceptors, which provoked vasodilation and bradycardia by spinal integration. Such a trend was not reported by all the authors engaged in this topic; someone observed a progressive reduction [8], others documented a variable change [13, 14] in agreement with the present study. Maybe subjects with myocardial hypercontractility constitute a selected population, with high sensitivity to sympathetic stimulation elicited by carotid baroreceptors as a consequence of the lowered venous return, and secondary reduction of ventricular stroke volume. This hypothesis is reinforced by previous reports on stress-test. In fact, only few subjects develop bradycardia and hypotension under the action of sympathetic agents such as dobutamine [15].

Table 3. Doppler echocardiographic parameters of tricuspid and pulmonary flows during HUT (mean ± SD)

	SUPINE		*5 MIN*		*10 MIN*		*15 MIN*		*25 MIN*		*35 MIN*		*SYMPT*		*SYNC/END*	
	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)
VTI-E / VTI-A	3.2	3.3	2.1*	2.6*	1.8*	2.1*	1.6*	2.3*	1.3*	1.7*	1.2*	2.0*	1.1*	–	0.9*	1.9*
	±1.2	±0.9	±0.6	±0.7	±0.3	±0.4	±0.5	±0.4	±0.4	±0.5	±0.2	±0.4	±0.1	–	±0.3	±0.3
T-VTI / R-R	0.49	0.51	0.39*	0.44*	0.40*	0.45*	0.37*	0.43*	0.39*	0.41*	0.36*	0.39*	0.30*	–	0.25*	0.40*
(cm/ms)	±0.09	±0.05	±0.07	±0.07	±0.10	±0.05	±0.08	±0.06	±0.06	+0.08	±0.09	±0.03	±0.06	–	±0.11	±0.07
VTI-A / T-VTI	0.25	0.23	0.28	0.26	0.35*	0.29	0.37*	0.30*	0.44*	0.34*	0.47*	0.33*	0.46*	–	0.36*	0.36*
	±0.70	±0.06	±0.04	±0.07	±0.08	±0.04	±0.05	±0.05	±0.09	±0.08	±0.07	±0.04	±0.04	–	±0.08	+0.06
T-VTIpulm / R-R	0.81	0.85	0.83	0.88	0.80	0.84	0.78	0.82	0.74*	0.80	0.71*	0.80	0.65*	–	0.52*	0.78*
(cm/ms)	±0.05	±0.06	±0.09	±0.05	±0.10	±0.06	±0.04	±0.06	±0.05	±0.09	±0.06	±0.07	±0.10	–	±0.10	±0.05

(+), positive HUT; (−), negative HUT; Sympt, onset of symptoms; Sync/end, syncope or end of HUT; VTI-E, velocity-time integral of E wave; VTI-A, velocity-time integral of A wave; T-VTI, total velocity-time integral; R-R, square root of R-R interval of ECG; * $p < 0.05$ versus supine

Table 4. Doppler echocardiographic parameters of mitral and aortic flows during HUT (mean ± SD)

	SUPINE		*5 MIN*		*10 MIN*		*15 MIN*		*25 MIN*		*35 MIN*		*SYMPT*		*SYNC/END*	
	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)	(+)	(−)
VTI-E / VTI-A	2.4 ±0.60	2.4 ±0.09	1.8* ±0.08	1.8* ±0.07	2.2 ±0.06	2.1 ±0.08	2.3 ±0.08	1.9* ±0.04	2.2 ±0.09	1.8* ±0.07	2.0* ±0.06	2.1* ±0.03	1.3* ±0.07	– –	2.2 +0.12	2.0* ±0.09
T-VTI / R-R (cm/ms)	0.65 ±0.05	0.58 ±0.09	0.63 ±0.09	0.57 ±0.12	0.62 +0.05	0.58 ±0.05	0.62 ±0.08	0.57 ±0.06	0.56* ±0.09	0.54 ±0.09	0.54* ±0.07	0.52* ±0.07	0.48* ±0.09	– –	0.37* ±0.09	0.50* ±0.04
VTI-A / T-VTI (cm/ms)	0.29 ±0.06	0.28 ±0.04	0.36* ±0.08	0.36* ±0.07	0.32 ±0.06	0.32 ±0.08	0.30 ±0.07	0.35* ±0.05	0.31 ±0.10	0.35* ±0.08	0.33 ±0.07	0.32 ±0.04	0.41* ±0.12	– –	0.29 ±0.08	0.34* ±0.06
VTI aortic / R-R (cm/ms)	0.80 ±0.03	0.82 ±0.05	0.78 ±0.02	0.78 ±0.04	0.80 ±0.05	0.81 ±0.03	0.79 ±0.04	0.80 ±0.07	0.72* ±0.03	0.76 ±0.07	0.68* ±0.06	0.75* ±0.05	0.60* ±0.08	– –	0.48* ±0.08	0.76 ±0.09

(+), positive HUT; (−), negative HUT; Sympt, onset of symptoms; Sync/end, syncope or end of HUT; VTI-E, velocity-time integral of E wave; VTI-A, velocity-time integral of A wave; T-VTI, total velocity-time integral; R-R, square root of R-R interval of ECG; * $p < 0.05$ versus supine

Table 5. Percentage changes in echocardiographic and doppler parameters during HUT, with respect to clinostatism (mean ± SD)

	EDRVA		*EDLVA*		*RVFAC*		*LVFAC*		*T-VTI tric*		*T-VTI mitr*		*T-VTI pulm*	
	(+)	(–)	(+)	(–)	(+)	(–)	(+)	(–)	(+)	(–)	(+)	(–)	(+)	(–)
15 MINUTES	–27	–17	–4	–6	–8	–7	–2	–2	–24	–16	–5	–1	–3	–3
	±3.9	±4.1	±0.9	±0.4	±0.3	±0.5	±0.3	±0.5	±7	±8	±0.6	±0.3	±0.6	±0.2
SYNCOPE / END	–44	–32	–29	–14	–34	–22	–28	–11	–49*	–21	–43*	–13	–35*	–9
	±4.9	±4.1	±0.3	±0.5	±0.9	±0.7	±21	±6	±12	±6	±11	±2	±13	±0.3

(+), positive HUT; (–), negative HUT; * $p < 0.05$, (+) versus (–)

Since FAC was reduced at the onset of symptoms in the majority of subjects of the present study, we think that myocardial hypercontractility is not a necessary event in the pathophysiology of neuromediated syncope, but it simply appears as a collateral consequence of the reduction of left ventricle stroke volume.

Doppler-echocardiography

In agreement with previous reports [7], our results are characterized by a progressive reduction during HUT of the total atrioventricular forward flow with a decrease of early diastolic loading and a relative increase of late diastolic loading [7, 10]. The changes were different on the right and the left side of the heart. In fact, tricuspid flow decreased early and progressively, while mitral flow remained rather stable during early and intermediate phases of HUT and dropped quickly at the onset of symptoms in HUT positive patients. Pulmonary venous flow substantially paralleled mitral flow trend. Thus our results look to confirm the conclusions of Guazzi et al. [9] about the compensation of pulmonary venous flow to maintain left ventricular loading during HUT. Subjects are asymptomatic as long as the dislocation of blood from pulmonary veins to the left side of the heart is able to maintain adequate left ventricle loading. When pulmonary flow cannot compensate the reduced output of right ventricle, left ventricle loading and stroke volume drop and syncope develops. The variations of aortic flow we have observed during HUT are in agreement with this hypothesis. The change of E/A ratio in tricuspid and mitral flows during upright position have been previously described in normal individuals during orthostatism [16], as well as after application of negative pressure to inferior limbs [17]. The lowered atrial pressure and atrioventricular gradient are considered to be the main reasons for the reduction of early diastolic flow, thus total forward flow increasingly depends on atrial contraction. The compensation due to late diastolic active flow, appears to be more effective in HUT positive patients probably because in these subjects a stronger reduction of atrioventricular gradient occurs. Just before the onset of syncope we can observe a sort of atrial stunning, thus the active atrial flow drops and ventricular loading drops.

All these morphological and functional changes are present in HUT positive as well as in HUT negative individuals, but the degree and velocity of these variations are more elevated in the former. This observation is in agreement with the results of Yamanouchi et al. [8] who documented a faster decrease of left ventricle volume in patients developing syncope during HUT compared to controls. The authors concluded that this trend could reflect an impaired venous tone in these subjects.

Conclusions

From the results obtained in the present study we can draw the following conclusions:

- During HUT the venous return to the heart is diminished because pooling of blood occurs in the lower limbs and the splanchnic veins.

- Right ventricle loading is early and progressively impaired while in the left side of the heart a "lung compensation" occurs and a greater amount of blood is displaced from pulmonary veins to left atrium. Such a compensation is effective throughout the test in HUT negative subjects, while it is lost and becomes ineffective if the upright position is maintained in HUT positive patients. Thus cardiac output quickly drops and syncope develops.
- A progressive reduction of RVFAC was observed. In HUT positive patients LVFAC exhibited a slight decrease as long as the onset of syncope lasted, then this parameter showed a marked variability showing an increase as well as a decrease of its values.
- Venous return reduction appears to be the main cause of syncope with secondary neuromediated vasodilation and/or bradycardia, while the increase of left ventricle contractility appears to be a collateral event which arises only in a few subjects.

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CARDIAC PACING:
NEW AND CONTROVERSIAL INDICATIONS

Pacing from Unconventional Sites: Who, When and Why?

R. Cazzin, P. Golia, G. Di Fonzo and C. Lestuzzi

Introduction

Presently, the right ventricular apex is by far the preferred site for permanent ventricular pacing, because of the easy fixation of the lead and the low stimulation threshold.

According to several studies, apical stimulation may impair both diastolic and systolic left ventricular function [1-4]. Among the patients who undergo bicameral (DDD) permanent pacemaker implant, the abnormal ventricular activation due to apical stimulation probably has trivial effects in those with normal atrial and ventricular function. On the other hand, when the basic cardiac function is impaired, the negative effect of apical stimulation may be relevant and possibly affect clinical conditions.

The increasing interest in the hemodynamic effects of cardiac stimulation, following the studies on electrical therapy of severe dilated cardiomyopathy [5-7], again raised the question of the most useful pacing site.

It is well known, from the first experiences in cardiac pacing, that the right ventricle may be paced also in the outflow tract, and that epicardial pacing of the left ventricle may be advantageous as compared with traditional pacing [3, 8-10].

Right Ventricular Outflow Tract versus Apical Pacing

For optimal systolic and diastolic left ventricular function, a regular activation is necessary. Right ventricular apex pacing (RVAP) leads to abnormal activation with asyncronous ventricular contraction and relaxation, hypokinesia of interventricular septum and delayed activation of the left ventricle. Left ventricular function then worsens, and cardiac output is reduced as compared to atrial pacing with normal left ventricular activation [1-4, 11]. Together with altered systolic function, diastolic function worsens and the left ventricular relaxation velocity is reduced [12, 13].

Recent studies suggest that right ventricular outflow tract (RVOT) or high

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septum pacing might be preferable to RVAP, since it improves cardiac output and other hemodynamic parameters and apparently the improvement is more marked in patients with reduced cardiac function [14, 15].

Hemodynamic evaluation of RVOT versus RVAP pacing in animals with induced AV block shows a significant improvement of both systolic and diastolic function [16]. With RVOT pacing it is possible to obtain effects intermediate between those obtained during atrial stimulation with normal ventricular activation and those of RVAP pacing.

The most relevant experience about RVOT pacing has been recently published by Giudici et al. [17]. The study enrolled 89 patients with different indications to permanent stimulation. Several advantages of RVOT, as compared with RVAP pacing, were demonstrated:

- significant increase of cardiac output and cardiac index
- most evident improvement in patients with left ventricular dysfunction
- normal axis and shorter QRS duration at surface ECG

Pacing threshold is slightly higher in RVOT than in apical stimulation, but still within acceptable values.

The reliability and safety of RVOT pacing has been confirmed at long-term follow-up [18].

In our experience, RVOT is safe, with good pacing threshold and shortened QRS duration [19]. QRS width is even more reduced using multisite apex-septum pacing [19, 20]. Multisite pacing providing a rapid contraction of the ventricles with a narrower QRS, probably would produce a better stroke volume and cardiac output! Patients studied with cardiac output measurements during pacing in RVAP, RVOT and both right ventricular sites simultaneously, evidenced a reduction in QRS duration during both sites pacing that correlated significantly with the improvement of cardiac output [20]. Multisite (apex and outflow tract septum) pacing of the right ventricle, in patients with impaired left ventricular function, seems to induce an earlier activation of the left ventricle as compared to apical pacing [21].

Biventricular Stimulation

Encouraging results have been recently obtained using atrial-biventricular pacing (ABVP) in patients with dilated cardiomyopathy. Simultaneous activation of both ventricles showed a striking hemodynamic and clinical improvement in patients with advanced left ventricular dysfunction and conduction defects [22-27].

The mechanisms of this improvement are not yet fully understood. With advanced left bundle branch block (LBBB) and/or RVAP, there is a left ventricular activation delay which can disappear during ABVP. Nevertheless, the clinical relevance of bundle branch block is not clear, since the hemodynamic improvement during ABVP is not always associated with a shortening of QRS duration [22, 28]. Some authors suggested also that in patients with advanced dilated cardiomyopathy, LBBB, and long PQ interval, the conduction defect is not only a consequence

but a cause of cardiac dysfunction [29]. In these patients a bilateral bundle branch block would be present and the ventricle would be activated through a nodal-septal pathway with consequently very slow activation of ventricular mass and with a very low voltage (not detectable at surface ECG). In these particular patients, ABVP might improve cardiac function through the shortening of ventricular activation and new synchronization of both ventricles.

There are some technical difficulties to obtain ABVP, as regard left ventricular pacing. Formerly, it was obtained with an epicardial lead; more recently the left ventricle has been paced endocavitary through the coronary sinus [23, 30].

Conclusions

According to present knowledge and experience with cardiac stimulation from unconventional sites, this technique should not yet be considered as the first choice. Multicenter trials are needed, in order to confirm the favorable results of preliminary observations on a large number of selected patients.

Centers experienced in electrical treatment of cardiac failure might act following a randomized protocol of RVOT or multisite apical-septal stimulation, in selected patients who require maximum hemodynamic benefit.

Biventricular stimulation is presently on trial in a limited number of centers, mostly in France, and it is reserved to patients in end-stage heart failure. More recently, encouraging experiences on endocavitary biventricular pacing have been reported: the left ventricle is stimulated through the coronary sinus - great cardiac vein with usual ventricular leads. If the favorable effect of biventricular stimulation is confirmed, the procedure will probably be performed, at least in some patients, in a relatively simple and non-invasive way.

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Hypertrophic Obstructive Cardiomyopathy: Is DDD Pacing Really Useful?

J.C. Daubert, D. Pavin, H. Le Breton and D. Gras

For more than 30 years [1], it has been known that apical stimulation of the right ventricle with total ventricular capture can reduce or even abolish systolic obstruction in hypertrophic obstructive cardiomyopathy (HOCM) (Fig. 1). This effect probably results from the reversal of the ventricular activation sequence, which delays septal thickening and SAM occurrence, and reduces left ventricular hyperkinesia. However, ventricular capture can only be hemodynamically beneficial (increase in stroke volume and systolic arterial pressure) provided optimal ventricular filling is maintained through fully effective left atrial function. This dual prerequisite (full ventricular capture and optimal atrioventricular synchrony) explains why it took up until recent years [2] and the introduction of highly sophisticated dual-chamber pacemakers for it to claim any clinical benefit. However the clinical relevance of this new therapeutic approach still remains controversial.

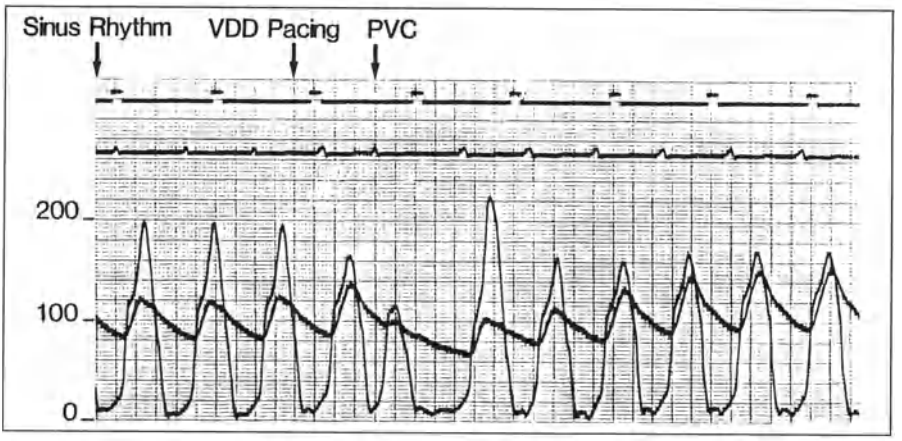

Fig. 1. Acute effect of VDD pacing on LVOT gradient and aortic pressure. As soon as pacing is switched "ON", the gradient decreases progressively until it is abolished. Aortic pressure increases proportionally. Note a paradoxical increase in LVOT gradient after a long cycle following a premature ventricular contraction. This can be explained by a transient AV dysynchronization due to the escape in VVI mode

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Results of Non-controlled Studies with Permanent DDD Pacing

Up until the past few months, the benefit of DDD pacing in hypertrophic obstructive cardiomyopathy could only be assessed from the open study results published during the last few years by essentially 5 centers [2-7], which currently represent a population of more than 200 patients with an average follow-up of 2 to 3 years. This preliminary experience only involved highly symptomatic patients (NYHA class II-IV) not responding or not tolerating maximal dose treatment (β-blockers, verapamil, amiodarone) and whose systolic obstruction (either constant or intermittent and provokable by the usual maneuvers) was clearly of sub-aortic location. In the initial experience a positive response to temporary DDD pacing was required to select responder patients prior to implant. But this prerequisite was rapidly abandoned when it was clearly demonstrated that acute phase response was not predictive of long-term effects [7].

Within that specific context, which is that of the usual indications for surgical treatment, permanent DDD pacing seems to provide nearly identical functional and hemodynamic benefit as surgery. On average, the LVOT gradient was reduced by 60%; in our own experience [7], where all efforts were made to optimize AV synchrony in each patient, the mean reduction was 80%. Gradient decrease was paralleled by a clear functional improvement. Nearly all patients gained 1 or 2 NYHA grades. Pooling the data from the 5 above mentioned centers showed that the mean NYHA class decreased from 3.2 before the implantation to 1.6 at the end of follow-up. Identical benefit was reported for chest pain with a complete or nearly complete relief in most patients, and for syncope and near-syncope. In the series from Bethesda [3, 4], the incidence of syncope was reduced from 47% before the implantation to 7% at the end of a mean follow-up period of 3 years.

The subjective benefit was paralleled by a significant increase in exercise tolerance. In the two studies which analyzed this parameter, the exercise time measured during comparative symptom limited exercise tests was increased by an average of 40% [2, 3].

But the most intriguing results, specific to pacing therapy, are perhaps the LV geometrical and functional modifications that may occur in some patients after a long phase (usually after 3 months) and which evoke "ventricular remodeling". The most obvious consequences is the "memory effect" of pacing. When the pacemaker is inhibited after a long period of continuous pacing, the gradient does not recur immediately (at its baseline value at least); when it recurs, the process is all the slower as the pacing period was longer. The observation made by several teams [4, 8] of a gradual decrease in thickness of the anterior septum and the LV antero-lateral wall bolsters the "remodeling" hypothesis. The increase in end-systolic volume without any parallel increase in end-diastolic volume, indicating that the effect is due to the reduced LV hyperkinesia, is also consistent with that hypothesis. Lastly, mitral regurgitation, when unrelated to major structural abnormalities of the valves and/or the sub-valvular apparatus, regresses in proportion with the gradient [9]. While fascinating, these very preliminary results have to be confirmed in prospective studies.

Results of the Controlled Studies

For the moment we only have the preliminary results of two randomized, crossover trials, the Mayo Clinic Study [10] and the European PIC (Pacing in Cardiomyopathy) Study [11]. The results of another American study, the M pathy study, are expected in late 1997.

In the Mayo Clinic Study [10], 21 patients, mean age 58, with severely symptomatic (NYHA class II-IV) and drug-refractory hypertrophic obstructive cardiomyopathy were included after baseline evaluation consisting of quality of life assessment (Minnesota questionnaire), two-dimensional and Doppler echocardiography, and cardiopulmonary exercise tests. Nineteen patients completed the protocol and underwent double-blind randomization to either DDD pacing for 3 months followed by back-up AAI pacing for 3 months, or the same study arms in reverse order. Results showed a significant reduction in LVOT gradient to 55 ± 38 mmHg after DDD pacing compared with baseline (76 ± 11 mmHg; $p < 0.05$) and with back-up AAI pacing (83 ± 59 mmHg; $p < 0.05$). Quality of life score and exercise duration were significantly improved from the baseline after DDD pacing (41.6 ± 25.9 vs 55.1 ± 23.7; $p < 0.05$ and 6.9 ± 2.2 min vs 5.7 ± 2.7 min, $p < 0.05$, respectively), but were not significantly different between the DDD arm and the back-up AAI arm. Peak oxygen consumption dit not significantly differ among the three periods. Finally 63% of patients had symptomatic improvement during the DDD period, but 42% also during the AAI period. Thirty-one percent did not experience any significant change in functional status and 1 patient had deterioration of symptoms during the DDD pacing period.

Similarly *the European PIC Study* [11] was a randomized, blind and crossover study, aimed at comparing the effect of DDD pacing and of no pacing (AAI 30) in patients with symptomatic HOCM refractory or intolerant to conventional drug treatment. But unlike the Mayo Clinic Study, the PIC Study was a multicenter trial and involved a larger number of patients ($n = 83$).

Inclusion criteria were (a) significant functional limitation (NYHA class II-III), related to dyspnea and/or angina, despite maximal tolerated drug treatment, (b) peak oxygen consumption less than 85% of the age predicted value during graded treadmill exercise test using a modified Bruce protocol and (c) permanent LVOT gradient ≥ 30 mmHg due to systolic obstruction of sub-aortic location. The patients were classified into two groups according to the acute hemodynamic response to temporary DDD pacing. Group A was defined by a decrease > 30% of LVOT gradient in comparison with baseline and group B if there was less or no gradient modification. Patients of group A and B were stratified by central randomization into two arms defining the sequence of therapies (Fig. 2). Randomization was active after the discharge tests where the apparently "optimal" AV delay was identified in each patient and pacemaker function verified. Patients were allocated to a 12-week period of active (DDD 30 bpm) or inactive (AAI 30 bpm) pacing mode. After 12 weeks the two patient arms were similarly assessed and their pacing modes inverted (crossover). After the second 12-week period the two groups were reassessed and finally, the pacing mode preferred by the patient was programmed

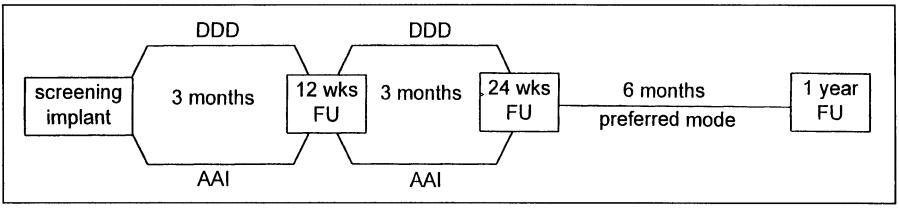

Fig. 2. Protocol design of the PIC study (see text)

for the long-term period (6 months). Each evaluation consisted of quality of life analysis (Karolinska questionnaire), cardiopulmonary exercise testing (symptom limited), 24-hour ambulatory ECG and Doppler echocardiography. All test documents were reanalyzed in central core laboratories.

Results showed a significant reduction in peak LVOT gradient to an average of 26.7 mmHg after DDD pacing compared with back-up AAI pacing (57.1 mmHg; $p < 0.0001$) and with baseline (73.6 mmHg; $p < 0.0001$). Identical evolution was observed whatever the order of randomization, DDD → AAI or AAI → DDD. Symptoms were assessed by clinical history and quality of life questionnaire. From the 28 patients in NYHA class III during the AAI backup period, 24 (84%) improved by one class or more with DDD pacing and no one deteriorated. From the 37 patients in NYHA class II during the AAI phase, 17 (46%) improved with DDD pacing, 19 remained unchanged and only one deteriorated. However when comparing with the baseline data at entry into the study, 20 patients reported some improvement although the pacemaker was inactivated (AAI 30). Scores of dyspnea and angina were similarly influenced with a significant improvement ($p = 0.001$) when the pacemaker was activated and conversely a significant deterioration when the device was inactivated (AAI 30). These subjective findings were further substantiated by the quality of life assessment. Compared with back-up AAI pacing, the DDD mode resulted in a significant improvement in scores of self-perceived symptomatology (dyspnea and chest pain), self-perceived health, self-autonomy, strenuous activity and alertness. However cognitive and sexual functionning as well as emotional state were not significantly affected by the pacing mode.

In the whole group there was no significant difference in exercise duration and in maximal oxygen uptake when comparing the end of the activated (DDD) period and the end of the inactivated (AAI) phase. However subgroup analysis demonstrated a significant improvement, on average by 21% ($p < 0.008$) in the more severely limited patients, those who had exercise tolerance < 10 minutes with inactivated pacemaker.

Finally, the 41 patients randomized to DDD pacing first completed all the 12-week period, but after inactivation of the pacemaker (AAI 30), 14 (34%) returned prematurely to the clinic (mean delay = 26 days) because of severe deterioration in symptoms and self perceived health status. From the 41 patients randomized to AAI pacing first, 3 returned to hospital early because of no improvement in symptoms, but all patients completed the second crossover phase with the pacemaker active.

Therefore these preliminary results demonstrate that DDD pacing compared with the back-up AAI mode significantly improves symptoms (NYHA class and scores of self-perceived symptoms), quality of life, exercise tolerance (at least in the subgroup of severely limited patients) and hemodynamics (LVOT gradient) in patients with HOCM and symptoms refractory to conventional drug treatment. So DDD pacing can actually be considered as the only therapy to be validated in this indication. Other therapeutic approaches, drug treatment, surgery or chemical ablation, have never been evaluated in controlled studies.

Limitations of the Controlled Studies

One of the limitations of both the Mayo Clinic Study and the PIC Study was the lack of real pacemaker programming optimization in each patient before and during the crossover period. Similarly the drug regimen was kept unchanged. This limitation undoubtedly resulted in underestimation of the benefit from DDD pacing and from its combination with optimized drug therapy.

How to Optimize Benefit of Pacing Therapy?

Results of non-controlled and controlled studies strongly suggest that an optimal benefit of DDD pacing therapy can only be achieved if two complementary conditions are met at any time, first complete ventricular capture from the very apex of the right ventricle, and second, prevention of any alteration in left heart electromechanical AV synchrony in order to preserve a fully efficient left atrial contribution to ventricular filling.

In practice, two subgroups of patients are particularly at risk of impaired left atrial contribution during short AV delay DDD pacing. The first group consists of patients with short PR interval during spontaneous sinus rhythm. This situation is frequent in young patients and requires the programming of ultrashort values of AV delay to achieve the goal of complete and permanent ventricular capture. The second group is made up of patients who are usually older, with left atrial dilatation, atrial conduction defects and long interatrial conduction time resulting in a very delayed left atrial activation and contraction. Programming a short AV delay value in this particular situation results in a major risk of inducing a "DDD pacemaker syndrome" due to the loss of any left atrial contribution, the left atrial contraction occurring after the closure of the mitral valve by the ventricular systole. So we can easily understand why short AV delay DDD pacing may result in some patients in complete failure, or even more in paradoxical deterioration, due to a major alteration in mechanical AV synchrony in the left heart.

To better evaluate this question, we did a prospective study [12] on 34 consecutive patients, 15 males and 19 females, mean age 56 years (range 30-80). All patients were invalidated by symptoms (NYHA class II-IV) refractory to conventional medical treatment. A permanent LVOT gradient $\geq$ 30 mmHg was present in

every case. After the implantation of a DDD(R) pacemaker, patients underwent a 3-step protocol of AV synchrony optimization.

Step 1: programming of the apparently "optimal" AV delay. In a first approach, the "optimal" AV delay was defined as the longest programmable value ensuring complete ventricular capture (CVC) on both paced atrial cycles at rest and on sensed atrial cycles at rest and during exercise. CVC was defined by reference to VOO pacing regarding the maximal enlargement of the paced QRS complex. Algorithms of AV delay hysteresis and of rate-responsive AV delay were used in all cases to maintain CVC during exercise. This initial programming resulted in two different behaviors.

The LVOT gradient was acutely reduced by more than 50% in 19 patients (56%), and completely abolished in 9. An early and significant improvement in symptoms was observed in all of these "responder" patients. In this group, the "optimal" AV delay programming and identical drug regimen were maintained. The initially documented benefit remained remarkably stable over time in terms of both functional improvement and gradient reduction.

In the other 15 patients (44%), no change or only a minor decrease (on average 31%) in LVOT gradient was observed, and not one of these "non-responder patients" reported significant change in functional status.

Comparison of responder and non-responder patients (Table 1) showed that non responders were significantly younger, had significantly higher baseline gradient, and importantly presented with significantly shorter PR intervals during spontaneous sinus rhythm. Consequently the apparently "optimal" AV delay value was very short (43 ± 19 ms) in non-responder patients in comparison with responders (92 ± 20 ms; $p < 0.0001$).

Table 1. Comparative data at baseline in "responder" and "non-responder" patients to conventional DDD pacing with the apparently "optimal AV delay"

Patients	Responder n = 18	Non-responder n = 14	*p*
Age (Years)	65 ± 14	47 ± 14	0.013
Grdt (mmHg)	99 ± 34	135 ± 14	0.024
PR (ms)	143 ± 23	115 ± 15	0.015
AVD (ms)	92 ± 20	43 ± 19	0.0001

Grdt = maximal LVOT gradient
PR = PR interval
AVD = AV delay

Step 2: drug treatment optimization. The second step was an attempt to use drugs to prolong the AV conduction time in the subgroup of the initially non-responder patients. To achieve this objective, the maximal tolerated doses of cardiodepressor drugs (combination of β-blockers and verapamil in most cases) were given. Drug tolerance was obviously facilitated by the antibradycardia support in a majority of patients.

A significant prolongation of the PR interval could be obtained in 7 patients (46% of non-responder group) and permitted optimization of AV delay programming. In those 7 "drug responder" patients the gradient could be decreased by more than 50% and symptoms were significantly improved. However long-term benefit persisted in only 3 patients. Escape to drug treatment occurred in the other 4 patients after a time delay ranging from 2 months to 3 years, and required a move to step 3.

Step 3: AV junction catheter ablation. RF catheter ablation of the AV junction was proposed in 1994 [13] with the sole objective of optimizing AV synchrony in HOCM patients who did not respond to conventional DDD pacing despite optimized drug therapy (Fig. 3). Induction of complete heart block made it possible to program the truly optimal AV delay in each patient. In the prospective study (Fig. 4), 12 patients (35%) underwent RF ablation. The procedure was performed early after the implantation (from 1 day to 1 month) in 8 patients who did not respond in step 2 or did not tolerate increased drug regimen. In the other 4 patients, the time of ablation procedure was delayed up to 3 years and was indicated by escape to drug therapy.

At the end of this 3-step procedure of AV synchrony optimization, identical benefit in terms of symptoms improvement, LVOT gradient decrease and mitral

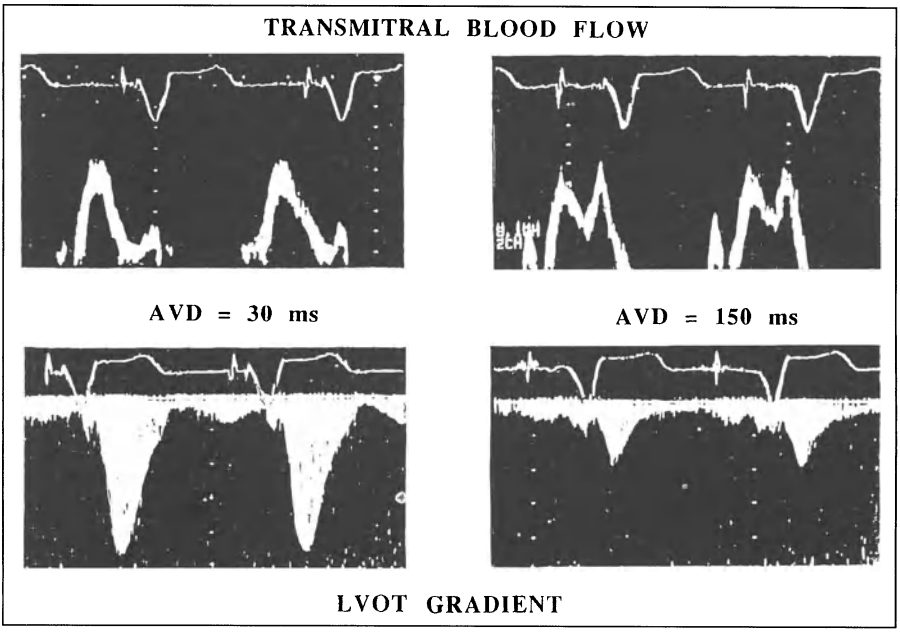

Fig. 3. Optimization of DDD pacing benefit after AV junction ablation. Before ablation, the spontaneous PR interval remains very short (100 ms) despite maximal tolerated doses of propranolol and verapamil. Complete ventricular capture could only be obtained after programming the AV delay at 30 ms. LVOT gradient was not reduced (80 mmHg) and transmitral flow showed a major alteration in left atrial contribution with a very delayed, short and low amplitude A wave. Induction of complete heart block allowed programming of a truly optimal AV delay of 150 ms. For the same degree of ventricular capture, the gradient was abolished and the mitral flow was nearly normalized with the evidence of a fully efficient left atrial contribution

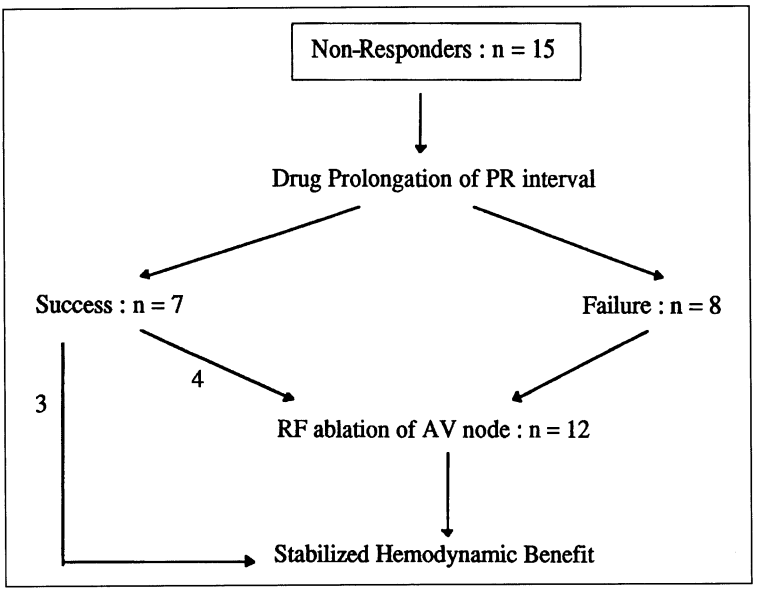

Fig. 4. Results of the procedure of AV synchrony optimization in the group of "non-responder" patients

regurgitation reduction (Fig. 5) was observed in the two subgroups of patients, those who where initially considered as "non-responder" and those who had an immediate positive response to DDD pacing. In both groups, the benefit remained remarkably stable during the whole follow-up (mean FU time = 44 ± 18 months).

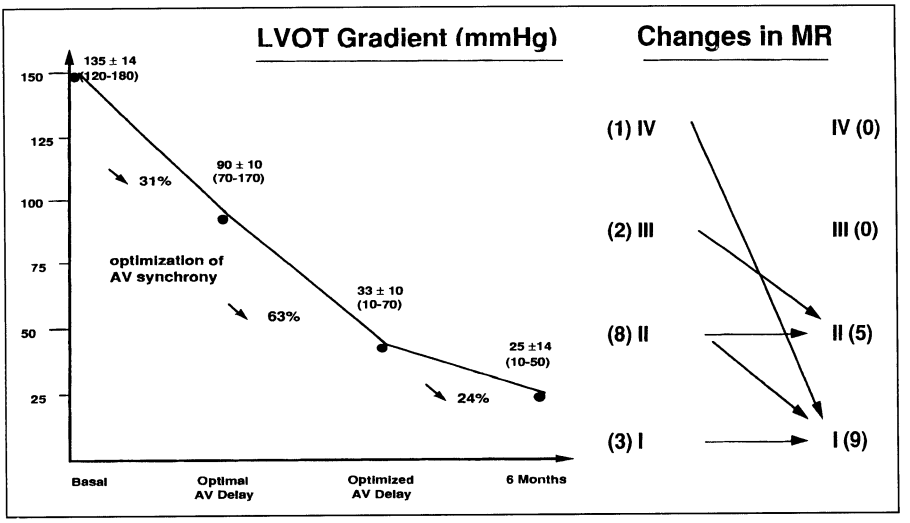

Fig. 5. Evolution of LVOT gradient and of mitral regurgitation grade in the group of initially "non-responder" patients ($n = 15$). Effect of AV synchrony optimization protocol

New Perspectives

New technical solutions will probably be available in the near future to optimize left atrial contribution in DDD paced patients while preserving intrinsic conduction. An alternative strategy to ablation could be provided by a new pacing system combining biatrial synchronous pacing and conventional DDD pacing in a triple-chamber pacemaker configuration [14]. The pacing system consists of three leads (Fig. 6). The right atrial lead is conventionally placed in the high right atrium. The left atrium is sensed and paced through the coronary sinus by using a specifically designed lead. The ventricular lead is positioned at the very apex of right ventricle. The two atrial leads are connected to a Y bifurcated adaptor in order to obtain a composite biatrial lead. The biatrial lead and the ventricular lead are connected to the atrial and ventricular ports of a DDD(R) pacemaker. A special algorithm of "atrial resynchronization" is loaded into the RAM memory of the device. With the algorithm programmed "ON", every atrial sensed event

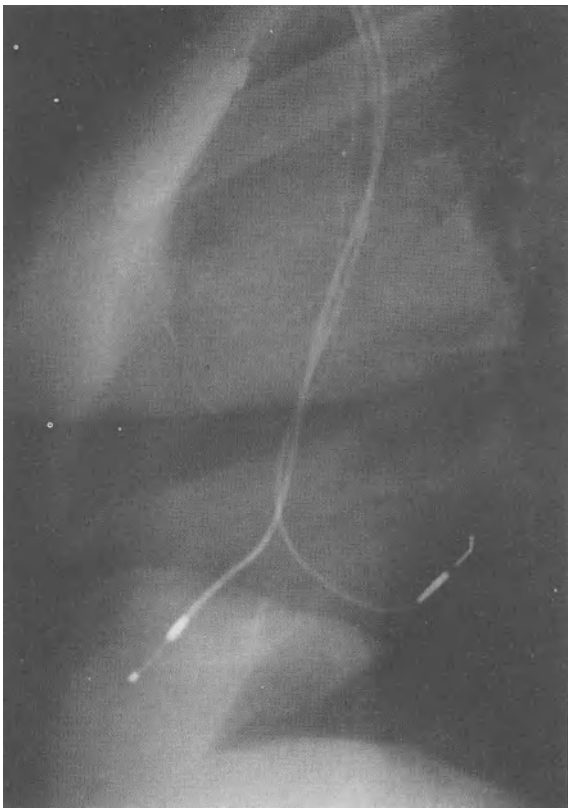

Fig. 6. "Triple-chamber" pacemaker. Chest X-ray in a sagittal view showing three transvenous leads placed in the high right atrium, in the mid part of the coronary sinus (to sense and to pace the left atrium), and at the very apex of the right ventricle

(sinus beat or right or left atrial extrasystole) immediately triggers biatrial pacing thus resulting in complete and permanent atrial resynchronization. In HOCM patients treated by DDD pacing, the aim of biatrial synchronous pacing is to advance the timing of the left atrial contraction by the time interval corresponding to the value of the interatrial conduction time in each patient. This makes it possible to program a very short AV delay ensuring CVC without impairing AV synchrony in the left heart. A privileged indication is for patients with atrial conduction defects and long interatrial conduction time who are at high risk of "DDD pacemaker syndrome". But this new pacing technique may significantly contribute to optimizing AV synchrony in all the patients who require a short AV delay programmed value for ensuring CVC. In our present experience, 16 unselected patients were implanted with this new pacing system. One week after the implantation, the value of mean LVOT gradient was only 22 ± 8 mmHg with the biatrial DDD mode compared to 45 ± 12 mmHg ($p < 0.01$) with the conventional DDD mode (Fig. 7) and to 77 ± 21 mmHg ($p < 0.001$) with the pacemaker inactive. After a mean follow-up of 11 months (range 3 - 24), no patient needed an increase in drug treatment. RF ablation of the AV junction was indicated in only 3 patients (19%) compared with 12 in the previous group of 34 patients ($p < 0.01$) implanted with a conventional DDD pacemaker. The indication for ablation was refractory atrial tachyarrhythmias in 2 of those 3 patients.

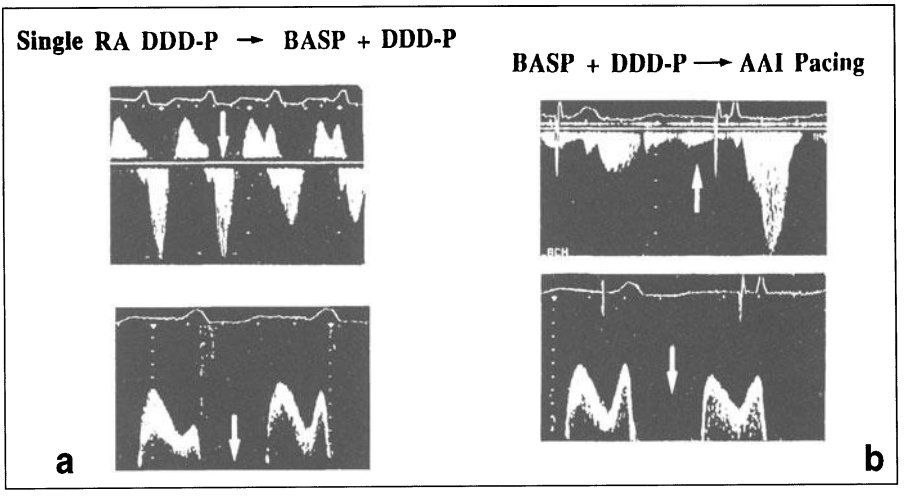

Fig. 7 a,b. Beneficial effect of biatrial synchronous DDD pacing in HOCM patients. Switching (arrow) form conventional (single RA) DDD pacing at the apparently "optimal" AV delay to biatrial synchronous (BASP) DDD pacing at the same AV delay, results in (**a**) the normalization of the transmitral flow with the reappearance of an efficient left atrial contribution and (**b**) a complementary decrease in LVOT gradient from 75 to 35 mmHg. Comparison between biatrial synchronous DDD pacing and AAI pacing at the same pacing rate shows that BASP does not alter left atrial contribution to LV filling

Conclusions and Interrogations

What conclusions are to be drawn from this early experience report? With probably equal results, DDD pacing differs from surgery by its simplicity and innocuity (the operative risk of myomectomy has been kept between 2% and 5% by the most efficient teams). It appears therefore reasonable to propose pacing directly, as a first alternative to medical treatment when the latter is ineffective or poorly tolerated. In our center, the only indications for surgery as a primary intent are for forms of cardiomyopathy accompanied by major organic mitral regurgitation, and as a secondary intent for the few cases of failure or secondary escape to pacing. However, beyond the short- and mid-term functional improvement, this novel therapeutical approach leaves many questions unanswered. One is: will results be sustained in the long term? Our observations of patients implanted over 5 years ago are very encouraging. Who are those patients who are most likely to benefit from ventricular remodeling and what is the magnitude of that phenomenon? Can pacing prevent hypertrophy from progressing, and thus alter the expression of the pathological phenotype in children and adolescents? Lastly, can pacing influence prognosis and in particular reduce the risk of sudden death? This constitutes a vast scope for clinical research with conclusions that are unlikely to be available before several years.

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Is There a Role for Left Ventricular Pacing in the Treatment of Congestive Heart Failure?

J.J. Blanc, Y. Etienne and M. Gilard

Background

Relations between cardiac pacing and heart failure have evolved with time. During the early years patients with chronic atrioventricular (AV) block not only had recurrent syncopes but also very often had more or less severe signs of congestive heart failure (CHF) and at that time treatment was limited to right ventricular pacing. These initial encouraging results in treating heart failure due to bradycardia were rapidly obviated by observations of initiation of CHF by VVI pacing, particularly in patients with sinus node disease. Signs of heart failure were integrated in the description of the pacemaker syndrome [1]. Dual-chamber pacing eliminated this side effect and pacing was again considered as a treatment for CHF not only in patients with chronic AV block but also in those with sinus node disease who may develop signs of heart failure when they are not adequately treated. It should be noted that in all these early observations CHF was not an indication for pacing per se but treated through the restoration of a «normal» ventricular rate.

A new period began in 1990 with the publication of the study of Hochleitner et al. [2]. In their initial study of 16 severely symptomatic patients, dual-chamber pacing with a short AV delay of 100 ms was used only for hemodynamic benefit and not for resolution of bradycardia. Short term follow-up revealed a marked symptomatic improvement in NYHA classification and an increase of ejection fraction (16.0% ± 8.4% to 25.6% ± 8.6% in one year). These initial results were *confirmed* by a second study after a longer follow-up [3]. These reports gave the impulse for further studies. Some were performed on an acute basis during a short period of pacing [4, 5], others examined the effects of dual-chamber pacing with short AV delay over long periods in patients with implanted pacemakers [6, 7]. Despite initial encouraging findings the results of these studies were controversial and Gold et al. in a double blind randomized trial of 12 patients with severe CHF observed no difference in functional classification or ejection fraction [8]. It should be noticed that despite these overall *negative* results a subset of patients benefited from physiological pacing in most series, and that the ventricular lead was positioned at the right ventricular apex in all cases.

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The *last period* was initiated by a case report of Cazeau et al. [9] in 1994: a 57-year-old man with end-stage cardiac failure due to dilated cardiomyopathy was dramatically improved by a four-chamber pacing system (biatrial and biventricular synchronous pacing). In 1996 the same group reported favorable outcome in a small series of patients with NYHA class IV using biventricular pacing. The left ventricular electrode was inserted either by transthoracic approach with a high mortality rate, or in few cases, through the coronary sinus [10] which resulted as a safer procedure.

Present Results

As the subject of left ventricular pacing is evolving very quickly it seems difficult to pin down the knowledge we have and the aim of this review is only to fix a moment in this evolution.

Acute Studies

Comparison between Left and Right Ventricular Pacing

We have undertaken an acute study to compare the right and left ventricular pacing in 9 patients with severe cardiac failure (7 men; mean age 65.8 ± 7.4 years). Their mean ejection fraction was 26% ± 6% and all the patients were in NYHA class IV despite an «optimal» pharmacological treatment, with a left bundle branch block (1 had a permanent pacemaker) and/or a long PR interval. Left ventricular pacing with a short AV delay of 100 ms induced in most patients a dramatic improvement in hemodynamic parameters when compared to right ventricular pacing [11].

Comparison between Right and Biventricular Pacing

In 8 patients with intraventricular conduction block (left bundle branch block with «large» QRS complex) Cazeau et al. [10] showed that acute biventricular pacing significantly improved cardiac index and wedge pressure when compared to baseline or right ventricular apical measurements. The same conclusion was drawn from our personal study [11].

Chronic Studies

As previously mentioned very few studies have been reported on long term results of left ventricular pacing. Cazeau et al. [10] published a preliminary series of 8 patients with end-stage cardiac failure. Four patients died (1 preoperative and 1 during intervention). The remaining 4 surviving patients had a marked symptomatic improvement (from NYHA class IV to class II).

Discussion

Acute Studies

Although the number of studies and patients is limited, the acute results of left ventricular pacing are very impressive with, in some patients, a decrease by more than 50% of the capillary wedge pressure and a complete disappearance of major V waves. This latter result might shed some light on the mechanism by which left ventricular pacing improves ventricular function: by decreasing mitral regurgitation, a frequent finding in patients with severe cardiac failure. However the mechanism is probably multifactorial including better sequence of activation between atria and ventricules. Up to now there is no solid data to substantiate the intellectually attractive concept that biventricular pacing gives better results than left ventricular pacing alone. Although this is a crucial question it is still far from being answered and the few questions that follow are just listed to give an idea of the large amount of work which now remains to be done in this field: Is acute testing useful for the selection of those patients who would benefit from left ventricular pacing? Is long PR interval and/or left bundle branch block mandatory? Is atrial fibrillation a contraindication?

Chronic Studies

Permanent left ventricular pacing raises a lot of problems.

Technical Issues

The left ventricular myocardium is stimulated only epicardially either by a screw-in lead or by a *usual* lead placed in a tributary vein of the coronary sinus. The former procedure seems easier but gives a higher proportion of side effects, the latter seems more difficult but safer. Improvement in technology, knowledge of anatomy and operative procedure will certainly favor the less *aggressive* method in the near future.

Conceptual Issues

The main issue is of course to demonstrate that left ventricular pacing alone or associated with right ventricular pacing is useful in patients with cardiac failure and better than right pacing alone with optimized AV delay. Such studies are not available, some are on the way but their results will be published probably in two years or more.

Conclusion

Left ventricular pacing in patients with severe cardiac failure is an appealing method and, if the preliminary results are confirmed, it may play a key role in the treatment of these patients as alternative methods are experimental (artificial heart), disappointing (cardiomyoplasty), or reserved to a very selected number of patients (transplantation). However before the method is widely accepted a lot of work still remains to be done.

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Mobitz Type I and First Degree AV Block: When to Permanently Pace?

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Permanent cardiac pacing has experienced an increase in indications, applications and numerous worldwide implantations. This has happened thanks to a constant technological advancement in hardware, available pacing mode choices, and an increasingly sophisticated multiprogrammability.

In 1984 the American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Sub-committee on Pacemaker Implantation) published the guidelines for permanent cardiac pacemaker implantation [1]. The Guidelines were revised in 1991 [2]. There are three main classes of patients, which may be summarized as follows:

- Class I. Conditions in which there is a general agreement that a permanent pacemaker should be implanted. This includes syncopal patients with complete heart block or prolonged sinus arrest and implies that the condition is chronic or recurrent but not due to drug toxicity, acute myocardial ischemia or infarction,or electrolyte imbalance.
- Class II. Conditions in which permanent pacemakers are frequently used but there is some divergence of opinion about whether they are needed.
- Class III. Conditions for which there is general agreement that pacemakers are not necessary.

The presence of symptoms related to bradyarrhythmia is fundamental to the ACC/AHA committee, because a better survival rate has not yet been shown for each pacing indication. Thus, the relief of symptoms becomes the therapeutic goal. The committee defines the symptoms as follows: "clinical manifestations that are directly attributable to the slow heart rate: transient dizziness, light headedness, near syncope or frank syncope as manifestations of transient cerebral ischemia, and more generalized symptoms such as marked exercise intolerance or frank congestive heart failure".

The ACC/AHA recommendations represent a guideline for physicians considering cardiac pacing as a treatment for their patients. There are, however, some areas where published data indicate that pacing should be more widely used as a first line therapy: long QT syndrome, obstructive hypertrophic cardiomyopathy,

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dilated cardiomyopathy with mitral and/or tricuspid valve insufficiency, neurally mediated syncope [3].

In patients with a markedly prolonged anterograde AV conduction, the close proximity of the atrial systole to the preceding ventricular systole produces the same hemodynamic consequences as continual retrograde ventriculoatrial conduction [4, 5]. The symptoms and signs associated with this pseudopacemaker syndrome [6] are multiple, subtle, and often quite non-specific [7].

Chirife et al. [8] reported a 40-year-old patient with first degree AV block (PR, 400 ms) and no evidence of organic heart disease who complained of dyspnea with minimal household chores. The patient became asymptomatic after implantation of a DDD pacemaker.

Subsequently Mabo et al. [9] also indicated that very long PR intervals can cause severe hemodynamic impairment. They reported data on eight patients with very long PR intervals (410 ± 45 ms) and severe symptoms on exercise (pacemaker syndrome without a pacemaker).The patients improved remarkably after the implant of a DDD pacemaker: the duration of exercise increased by 44%, cardiac output on exercise increased by 29%, and the mean PCWP decreased by 33%, all statistically significant changes.

Zornosa et al. [10] described three patients who developed long PR intervals with progressive PR prolongation at faster rates as complication of radiofrequency ablation of the AV junction. Low levels of activity induced inappropriate sinus tachycardia and fatigue. The symptoms resolved after placement of a dual-chamber pacemaker.

Kim et al. [11] described a patient with AV nodal reentrant tachycardia in whom radiofrequency ablation of slow pathway was attempted, with inadvertent damage to the fast pathway. The patient developed marked first degree atrioventricular block associated with symptoms mimicking pacemaker syndrome. A permanent dual-chamber pacemaker provided symptomatic relief.

Experimental studies since 1911 [12-15] showed that a properly timed, effective atrial contraction is necessary for optimal left ventricular systolic function by increasing left ventricular end-diastolic pressure while maintaining a low mean left atrial pressure. In 1995, Nishimura et al. [16] found that the reestablishment of the optimal mechanical atrial and ventricular synchrony by AV sequential pacing produced an increase in cardiac output. This effect was greatest in patients in whom atrial contraction occurred so prematurely that the atrial contribution to ventricular contraction was lost. The AV interval required to achieve this optimal AV synchrony varied from patient to patient.

Two other mechanisms are involved in the improvement induced by dual-chamber pacing.

First, in patients with long PR intervals and high diastolic pressures, there is an abbreviation of the diastolic filling period because the mitral valve closes prematurely when left ventricular pressure increases above left atrial pressure after premature atrial contraction and relaxation. A shorter AV interval lengthens the diastolic filling period by abolishing this premature valve closure [16].

Second, ventricular contraction following atrial contraction may be so delayed

in patients with a prolonged PQ interval that the reversed AV pressure gradient, in the absence of complete closure of the mitral valve, may bring about diastolic mitral regurgitation.

Abolition of this regurgitation has also been proposed as a mechanism by which dual-chamber pacing may improve the hemodynamic variables in long PQ intervals [17].

Levine [18] has suggested criteria to evaluate patients with first degree AV block and a very long PR interval who therefore need a permanent pacemaker. These include:

1) Holter monitor or exercise test showing that the P wave coincides with the ST-T wave of the previous conducted QRS complex. This should correlate with symptoms of dyspnea and fatigue.
2) Temporary DDD pacing with a more physiological AV interval to demonstrate improvement of symptoms and exercise tolerance.
3) Temporary atrial and ventricular pacing showing improved hemodynamics during DDD pacing with a shorter AV interval than during normal sinus rhythm with the first degree AV block. This can be achieved with either invasive or non-invasive monitoring (arterial line and Swan-Ganz catheter or echodoppler studies).

The implantable device should have a wide range of programmable AV intervals to optimize the mechanical AV relationship on the left side of the heart, and the AV interval should be rate adaptive on exercise [4].

In conclusion, first-degree AV block, once classified as a Class III indication for permanent pacing, can now be reconsidered under a new light thanks to recent reports which allow the physician to place the symptomatic form in Class II [4] or even Class I [7].

The two types of second-degree AV block were originally described by Wenckebach [19] and Hay [20] from analysis of the a-c interval of the jugular pulse. After the introduction of the ECG, these were classified by Mobitz [21] as types I (or Wenckebach AV block) and II. Wenckebach AV block is characterized on the surface ECG by progressive prolongation of the P-R interval until a P wave fails to conduct to the ventricle. In a typical Wenckebach arrangement, the degree of increment of the P-R interval decreases progressively, with most of the increment occurring between the first and second beat in the cycle. This would result in progressive shortening of R-R intervals. Wenckebach AV block may result from conduction delay and block in the AV node, the bundle of His, or the bundle branch-Purkinje system [22].

When the Wenckebach block is located in the AV node, a progressive prolongation of the A-H interval is recorded in the His bundle electrogram until an atrial electrogram is not followed by a His bundle deflection.

Wenckebach block in the His bundle is uncommon, occurring in approximately 9% of patients, and may be seen in the presence of a narrow or wide QRS complex. A His bundle recording is required to identify an intra-Hisian Wenckebach block. The recording usually shows a split His bundle potential with progressive lengthening of the interval between the two deflections before failure of transmission in the distal His bundle.

Wenckebach block distal to His bundle is manifested as either (a) progressive prolongation of the H-V interval until a sinus beat is blocked distal to the level of His bundle recording or, (b) progressive change of the QRS configuration from a normal to incomplete bundle branch block pattern and finally to a complete bundle branch block with progressive increase in the H-V interval.

The 1984-1991 recommendations of the joint ACC/AHA Task Force [1, 2] designated asymptomatic Mobitz type I atrioventricular block as a Class III indication for permanent pacing. Three studies were reported in support of this recommendation.

No patients with Mobitz type I atrioventricular block were described by Donoso et al. [23] in a review of 100 consecutive cases of Morgagni-Adams-Stokes syndrome treated over a period of 15 years from 1946 to 1961, at The Mount Sinai Hospital, New York.

In the study of Dhingra et al. [24] the His bundle electrograms were recorded in 15 patients with second-degree atrioventricular block and bundle branch block and these patients were prospectively followed. Although permanent pacing was indicated in three of the four patients with Mobitz type I AV block proximal to His bundle, the authors recommended that these patients should be paced only if symptoms developed.

Strasberg et al. [25] studied 56 patients with documented chronic second-degree atrioventricular nodal block proximal to His bundle. Nineteen of the patients (34%, mean follow-up 1395 days) had no organic heart disease, and 37 (66%, mean follow-up 1345 days) had organic heart disease. ECG demonstrated episo-des of type I second-degree block in all patients. They concluded: " Without complicating organic heart disease, chronic second-degree AV nodal block is usually benign. Most patients do not need permanent pacing, because of lack of progressive bradyarrhythmia or bradyarrhythmic symptoms. These patients can be reassured without need for prophylactic pacing and followed periodically.".

On the other hand, the British Pacing and Electrophysiology Group (BPEG) [26] recommended that even asymptomatic patients with second-degree atrioventricular block should be treated with a permanent pacemaker. This conclusion was based on the observations of Shaw et al. [27].

The authors reported 214 patients with a mean age of 72 years who were followed over a 14 year time period. Their patient population consisted of patients with permanent AV block, who were divided into three groups: type I block (77 patients), type II block (86 patients) and 2:1 or 3:1 block (51 patients). The five year survival was similar in all groups being 57%, 61%, and 53% in groups 1,2, and 3, respectively. The presence or absence of bundle branch block did not appear to influence prognosis. In particular, the three and five year survivals of the 47 patients in group 1 without bundle branch block (72% and 60% respectively) were similar to those of the patients in group 2 (70% and 61% respectively). In group 1 the survival at five years was 78% for paced subjects compared with 42% for unpaced subjects ($p < 0.01$), in group 2 the figures were 73% and 48% respectively ($p < 0.015$), and in group 3 they were 86% and 31% respectively ($p < 0.001$).

The significant prognostic advantage observed in paced patients led the authors to conclude that: "These results refute the benign reputation of chronic

Mobitz type I block and imply that patients with this condition should be considered for pacemaker implantation on similar criteria to those adopted for higher degrees of block".

Recently, Connelly and Steinhaus [28], on the basis of the different conclusions reached by the two national committees, proposed a ACC/AHA Task Force Class II indication for pacing and recommended that "one should consider permanent pacemaker implantation in patients with asymptomatic chronic Mobitz type I atrioventricular block, especially in older patients with structural heart disease".

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CARDIAC PACING:
DIFFERENT MODES OF STIMULATION

Chronotropic Incompetence: How to Diagnose and Treat It?

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During dynamic exercise the acceleration of ventricular rate, due to vagal withdrawal, is the most important contribution for increasing cardiac output according to the metabolic needs. The inability to adequately increase the heart rate in response to exercise is defined Atrial Chronotropic Incompetence (ACI).

In the majority of cases ACI may be expected to occur in evident or latent sinus node dysfunction, where the corrected sinus node recovery time is prolonged, even though it cannot be considered as equivalent or synonymous with Sick Sinus Syndrome (SSS). In fact, SSS can occur without ACI and conversely ACI can be observed in the absence of SSS [1]. ACI is often present after heart transplantation due to heart denervation, and also in patients without organic cardiopathy or disorders of impulse formation or conduction. An electrophysiological abnormality of the sinoatrial node, an excessive autonomic influence on the sinus node, or an idiopathic degenerative fibrosis of the sinus node have been noted in some cases.

Several investigations have suggested that a lower chronotropic response to exercise could be considered as a sign of silent myocardial ischemia even in the absence of ST-segment abnormalities [2-4].

Recently, there has been increasing interest in the knowledge of ACI because of the following factors:

1) ACI is often associated with symptoms such as dyspnea, angina, abnormal fatigue etc, sometimes particularly severe depending on the degree of ACI, the presence and type of associated organic cardiopathy and the cardiac rhythm allowing the effective ventricular rate adaptation (junctional or idioventricular rhythm);
2) ACI is related to a higher incidence of all-cause mortality and coronary heart disease events [3, 5];
3) sinus bradycardia and reduced heart rate increase during exercise are the most common factors influencing the occurrence of supraventricular tachyarrhythmias, especially when a SSS is present. In fact, sinus bradycardia may provoke an increased atrial vulnerability, a dispersion of action potential

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duration and refractoriness in the atrial fibers, frequent atrial premature complexes with the short-long cycle sequences, an atrial conduction block resulting in an asynchronism of activation in the two atria. All of these factors produce the electrophysiological conditions for a reentrant mechanism (slow conduction in the right atrium and retrograde activation in the left atrium). However, the excessive increase of catecholamine, related to relative bradycardia has been hypothesized to have a potential role in the induction of atrial fibrillation during exercise;

4) new pacing modalities, the sensor-driven rate modulated pacemakers, are now available which mimic the natural heart rate response to the metabolic needs of the patient [1].

Diagnosis

Sinus chronotropic response is a linear function of age and therefore lower in the elderly. The knowledge of the relationship between maximal heart rate during exercise and age allows the physician to provide the test is truly maximal. Moreover it must take into consideration the extreme variability in the mean heart rate values reached during exercise, about 15%-20% in comparison to the formula based on age [2-4]. Other factors influencing the heart rate response are resting heart rate, exercise capacity, physical fitness, presence of organic cardiopathy and cardiac function [3, 4, 6, 7].

Twenty-four-hour Holter monitoring does not allow significant correlation of heart rate variations during daily activities with the patient's real metabolic needs; in general the mean values of heart rate during Holter monitoring are lower than those during stress testing; so the evaluation of the presence and the degree of ACI usually requires treadmill or cycloergometer stress testing. If possible the measurement of VO2 allows us to establish that VO2 max and the anaerobic threshold are reached, thus avoiding problems deriving from unsatisfactory patient cooperation [8].

A stress test must be performed in the absence of drugs that may influence sinus node response, such as digoxin, β-blockers, verapamil, amiodarone and other antiarrhythmic drugs. In patients who need to take these drugs for long periods because of their clinical condition, the evaluation of the cardiac response during pharmacological treatment provides important clinical and therapeutical information.

The physiologic heart rate response during exercise includes:

1) an immediate acceleration of heart rate a few seconds after the beginning of the exercise;
2) a plateau during which heart rate is stable for constant efforts;
3) slow reduction of heart rate to basic values at the end of exercise.

Failure to achieve the maximal, predicted heart rate (MPHR, calculated by subtracting the age in years from 220) at peak exercise if truly maximal, is the major criterion to diagnose ACI. The response is considered abnormal if MPHR is lower than 75% on the basis of the following equation [9]:

$$\text{Percent. MPHR} = \frac{\text{Maximal Achieved Heart Rate}}{\text{Maximal Predicted Heart Rate}} \times 100$$

Additional criteria for the diagnosis of ACI are the following:
- lag in initiation of heart rate acceleration;
- abnormal prolongation of plateau phase with flatter trend of heart rate acceleration curve, important if it is considered at the final phase of the test rather than at the initial phase;
- faster reduction of heart rate at the end of exercise with presence of long sinus pauses that may be symptomatic;
- irregular trend of heart rate acceleration curve.

To avoid problems deriving from factors that may influence heart rate response (age, resting heart rate, exercise capacity) additional analyses include percent heart rate reserve (HRR) and percent metabolic reserve (MR) at any stage of exercise calculated by the following formulas:

$$\text{Percent HRR} = \frac{\text{HR stage} - \text{HR rest}}{\text{MPHR} - \text{HR rest}} \times 100$$

$$\text{Percent MR} = \frac{\text{METS stage} - 1}{\text{METS peak} - 1} \times 100$$

Percent HRR is then graphed against the percent MR for each stage of exercise and the ratio reflects the relationship between heart rate response and metabolic work during exercise. These parameters are more accurate than the heart rate acceleration to exercise alone and allow us to distinguish the effects of age, resting heart rate and physical fitness on the heart response to exercise. A low ratio implies an ACI.

The electrophysiologic study for the evaluation of the sinus node function by the measure of the corrected sinus node recovery time is performed only to establish the presence and the degree of a sinus node dysfunction; using antiarrhythmic drugs, such as flecainide, pentisomide or propafenone, allows us to unmask sinus node disease [10, 11].

Total pharmacological autonomic blockade is usually performed to distinguish sinus node dysfunction related to intrinsic involvement of the sinus node from autonomic influences.

Therapy

Pharmacological therapy (atropine, isoproterenol) can be used only temporarily for the treatment of symptomatic sinus bradycardia, but patients who require therapy for longer periods should be treated with permanent cardiac pacing.

Today a large number of new and sophisticated pacemakers is available for clinical use so that the cardiologist can choose the best solution for every patient not only to ensure the constant capture of the paced cardiac chamber and to support life, but also to improve the cardiac performance, to enhance the quality of life, and to prevent cardiac tachyarrhythmias as well [12-14].

A permanent atrial pacemaker (AAI), in presence of normal A-V conduction, or a dual-chamber pacemaker (DDD), instead of ventricular pacing (VVI), are indicated by certain physiological factors for their beneficial effects, such as:

1) preservation of A-V synchrony that improves hemodynamics and coronary flow; the loss of atrial systole is a well known possible cause of significant reduction of cardiac output, mainly in the presence of left ventricular dysfunction and/or valvulopathies;
2) avoidance of retroconduction of the impulses that may occur during ventricular pacing; the so-called "pacemaker syndrome" and the incidence of atrial fibrillation episodes, when the retroconducted impulses fall during the atrial vulnerable period, can be avoided;
3) prevention of supraventricular tachyarrhythmias and thromboembolic events by the correction of sinus bradycardia, the reduction of dispersion of the action potential duration and the refractory period in atrial fibers, and by the suppression of atrial premature contractions.

ACI renders AAI/DDD pacemakers incapable of increasing pacing rate on exercise and reduces the physiological nature of these pacing systems. The recent introduction of rate-adaptive units (AAIR/DDDR) has been hailed as a major step toward optimal management of ACI patients; in fact they constantly provide an adequate rate responsive pacing and a further increase of cardiac output during exercise [15, 16].

A theoretical concern associated with the use of AAIR/DDDR pacing modes is the issue of atrial competition and its potential for inducing AF that may occur in about 10%-15% of patients with permanent atrial or dual-chamber PMs. The potential for atrial competition and atrial arrhythmias, especially at faster sensor modulated rates, exists when the spontaneous P wave falls into the terminal portion of the Total Atrial Refractory Period (TARP) and it is not sensed; the following atrial stimulus occurring just before the atrial escape interval time expires, may potentially fall into the vulnerable period of atrial repolarization and result in AF. This phenomenon easily occurs when the TARP is prolonged to avoid retrograde conduction or when the maximum sensor modulated rate or the maximum tracking rate or the 2:1 block rate are programmed incorrectly [17, 18].

The presence of paroxysmal atrial tachyarrhythmias in the patient's clinical history has constituted up to now a contraindication to DDD or DDDR pacing to avoid atrial tracking and correspondingly rapid ventricular rates during atrial tachycardia.

For this instance the best solution is the use of dual-chamber PMs with automatic mode switching, a new function designed to protect patients from rapid ventricular rates during supraventricular tachyarrhythmias. It refers to a PM capability in detecting the presence of atrial tachycardia and, upon detection, in

changing the pacing modality to a non-tracking mode stopping the atrial synchronization. The switch is from DDD/DDDR or VDD/VDDR to DDI/DDIR or VVI/VVIR pacing modes according to the design or programmability. In this way the use of dual-chamber pacing may be extended to patients that have or should have recurrent paroxysmal atrial tachyarrhythmias because symptoms due to irregular and rapid ventricular rhythm and frequent time-consuming pacemaker reprogrammations may be avoided. Patients should have the benefits of physiologic DDD or DDDR pacing as long as possible because the PM reverts back to the previous pacing mode when the sinus rhythm is restored [19].

Conclusions

Analysis of the chronotropic response to exercise identifies appropriate or inappropriate response of sinus node during all levels of exercise. Relative bradycardia or failure of adequate heart rate response to exercise limit maximal oxygen uptake, cardiac performance and physical fitness.

For the evaluation of ACI easier methods reflecting the daily activities of patients rather than exercise-stress testing are expected.

Sensor rate modulated pacemakers are available to adapt heart rate response to the effective metabolic needs of ACI patients during exercise and to mimic the physiologic response of the heart during exercise. To optimize the beneficial effects of these devices the post-ventricular atrial refractory period, the A-V delay, the maximum tracking rate, as well as the sensor parameters must be carefully programmed.

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New Sensors for Pacing and Diagnostic Application: What Is Their Clinical Uselfulness?

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Modern cardiac pacemakers are capable of storing cardiac events on a long-term basis in their RAM. These data provide information on the pacemaker operation and on the patient's health status and can be retrieved during the follow-up visits. The diagnosis of atrial arrhythmias has become a reality that is reliable and clinically relevant. In rate-responsive pacing, additional information can be retrieved from the retrospective examination of the sensor activity, which provides the physician with a display of the patient's heart rate profiles during daily life. The diagnosis of chronotropic incompetence can be objectively validated, and the appropriateness of the sensor operation reliably verified. This may prompt reprogramming of the pacemaker to adjust the sensor-driven rates and better match the patient's needs. However, no device currently available is able to provide enough information to assist in the diagnosis of comorbidity.

Diagnosis and Correction of Chronotropic Incompetence

Chronotropic incompetence may be quite variable over time in a given patient and the results of a stress test performed for diagnostic purposes may not be reproducible. On the other hand, the pacemaker counters can memorize the number of sensed and paced beats. It is thus possible to roughly determine the need for rate-responsive pacing as a function of the patient's physical activities: an 80% rate of paced beats in an active patient indicates a probable chronotropic incompetence; the physician will draw the same conclusion if the curve of the last 24-hour mean heart rate, retrieved from the pacemaker and displayed on the programmer screen, is flat although the patient was engaged in sports or performed strenuous works during the same time period. These very simple findings may trigger a diagnostic evaluation that would not otherwise have been initiated. In addition, in some pacemakers, the sensor can be switched «on» though it remains inactive. The device, then, records the signal analyzed by the sensor but the rate-responsive function remains inactive. Heart rate curve and sensor-generated curve can be stored simultaneously by the pacemaker and analyzed

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retrospectively. It is then possible to compare the spontaneous variations of the heart rates against the sensor information which should reflect the intensity of exercise. However no function is available to automatically switch the mode to the rate-responsive pacing.

Once the sensor has been programmed to be active, several memory functions indicate the appropriateness of the sensor-driven rates. The same tools can be used, i.e., 24-hour heart rate curve, number of sensed versus paced beats, as well as rate histograms displaying how the pacemaker would have managed the patient's heart rate in the absence of spontaneous activity. These tables can only show that the sensor is excessively reactive, or the opposite. Today's pacemakers, however, can automatically adjust the rate profiles.

Features Automatically Controlled by the Sensor

Rate Profiles

In the past, all rate-responsive pacemakers had their settings programmed by the physician during follow-up visits according to patient's symptoms, Holter recordings or results of stress tests. However, the settings programmed initially may not be appropriate over time because of changes in the patient's health or activity level. This is particularly true in the case of pacemakers with a physiological sensor. The physiological parameter measured can behave differently if it has been modified by an associated disease. As an example, the QT interval can be prolonged by antiarrhythmic drugs which may modify its variations during exercise. Similarly, the evolution of pulmonary disease can influence the variations in the minute ventilation during exercise. It is thus essential for the pacemaker to adjust the relationship between sensor activity and exercise according to the variations of the measured parameter. A so-called autocalibration function is provided to adapt sensor-driven rates to patient's activities [1]. When a pacemaker records autocalibration curves, it is able to differentiate periods of heavy versus light physical activities. Consequently, the sensor information can be used to identify the resting periods. If the measured parameter does not vary from its resting state for a certain period of time or if its variability decreases compared to the variability measured during active periods, the pacemaker recognizes a rest period. These periods can then be accompanied by a decrease in the back-up rate [2]. As a consequence, the life of the pacemaker battery will be extended. This information, recorded in the RAM memory, may also show the preferential occurrence of arrhythmias at rest or during exercise, and guide physicians in their choice for antiarrhythmic therapy.

Automatic Output Adjustment

The battery size of pacemakers has decreased considerably in the last years. Consequently, when high pacing outputs are programmed, life expectancy is

much shorter. This has forced physicians to pay more attention to the setting of the pacing output in order to extend the battery life span as much as possible. The best system available today uses an automatic output adjustment which minimizes energy consumption while maintaining a safe margin. The Pacesetter company has already released the Microny/Regency DR + systems which has proved to be successful [3-6]. It is based on the sensing of a pacing induced depolarization gradient after a short blanking period. From time to time, the system decreases the pacing amplitude by steps of 0.3 V in the ventricle. Two consecutive captures indicate pacing efficacy, whereas two consecutive losses of capture lead to immediate increase in amplitude after 64 ms after every ineffective pacing spike. The pacing amplitude is automatically set to 0.6 V above that of the last effective amplitude step. A similar concept is being developed by most companies.

Diagnosis of Associated Diseases

If the sensor measures a physiological signal, it might be feasible to use the information in the diagnosis of associated diseases. Today, however, no pacemaker has this capability. Some commercially available systems incorporate technical features which might allow such function. The sensor of Ela Medical pacemakers measures minute ventilation. These devices also have a large RAM memory and external programs that can be downloaded into the RAM. One of these RAM programs can store the minute ventilation profile over the last 24 hours. From these curves, it is possible to distinguish rest from activity, or from awakening for example. It would theoretically be possible to dissociate the tidal volume from the respiratory rate curves to obtain reliable information on the patient's ventilatory profiles during daily life activities and during calibrated tests. However, this analysis requires more space in the RAM which is already crowded by many other memory functions.

Sorin Biomedica (Saluggia, Italy) has developed an original sensor measuring the cardiac peak endocardial acceleration (PEA) with a specific so-called BEST (Biomechanical Endocardial Sorin Transducer) lead connected to a rate-responsive pacemaker (Living device). Just behind the lead tip, a hermetic and rigid can contains an inertial mass connected to a piezo-electric quartz. The amplitude of the acceleration signals serves as a sensor of the cardiac inotropy. The sensor has a sensitivity of 5 mV/G and a frequency range of 0.05 Hz to 1 kHz. Preliminary experimental results have shown that the device does provide reliable information relative to the inotropic state in animals and in humans [7,8]. Over 60 experimental evaluations performed in 7 sheep showed that the mean PEA at baseline was 0.9 G (heart rate = 99 bpm) and increased to 1 G during AAI (170 bpm) and VVI pacing (160 bpm). During dobutamine infusion, the PEA value was 3.7 G at a heart rate of 168 bpm. In 15 patients, mean baseline PEA was 1.1 G and increased to 1.3 G during AAI pacing and 1.4 G during VVI pacing (heart rate = 140 bpm). Dobutamine infusion increased PEA to 3.7 G with a heart rate of 121 bpm. Thus far, the system has been used as a rate-responsive device. The clinical investiga-

tion of the implantable device (Best-Living) showed, in 54 patients with normal sinus node function, an excellent correlation between PEA variations and heart rate during 24-hour monitoring ($r = 0.67$, $p < 0.005$), with similar results obtained during calibrated stress tests.

Although this system can reliably drive the heart rate, it has also been tested for other purposes. When changing the AV delay setting from long to short values in patients with complete heart block, PEA decreases slightly and then increases when AVD becomes too short. This profile corresponds to the variations in first heart sound variations when altering AVD. The first heart sound and its vibrations increase when AV valves suddenly close as AVD becomes too short, AV valves being still widely opened at the onset of ventricular contraction. An automatic feature is included in the programme, randomly and temporarily programming various AVD settings and measuring PEA. The optimal AVD is obtained when PEA is at its minimum. With this function it has been possible to measure the optimal AVD after paced P at 204 ms and after sensed P at 150 ms at rest.

Another specific application was recently tested in vasovagal syncope. Some forms of this syndrome are characterized by a sharp increase in sympathetic activity, promoting stimulation of the ventricular C fibers leading to parasympathetic overcompensation with a sudden drop in arterial pressure and heart rate. If the inotropic stimulation that occurs during the increased sympathetic activity can be measured by a sensor of the contractile state of the heart, one could imagine the attenuation or suppression of the parasympathetic overreaction by a sensor-driven rate increase. This hypothesis was tested in a short-term study including 10 patients presenting with vasovagal syncope [9]. Peak endocardial acceleration was recorded continuously during upright tilt testing. The sensor detected a significant increase in myocardial contractility in 9 out of 10 patients in the minutes preceding the symptoms occurrence. Three patients were implanted with the new Best-Living system. Each patient had syncope during the head-up tilt in the DDD mode, but syncope was prevented in 2 patients and delayed in one patient in the DDDR mode [10]. Pacing rate rose from 70 to 112 bpm over 3 minutes. After a follow-up of 5 months, these patients have remained asymptomatic.

An active field of investigation concerns the determination of tolerance of tachyarrhythmias. If a tachyarrhythmia is poorly tolerated, one might expect its association with a decrease in contractility index. This parameter could serve as a criterion for the choice of an immediate aggressive therapy in the event of a poorly tolerated sustained ventricular tachycardia (VT), versus antitachycardia pacing if well tolerated. Although underway, these investigations remain preliminary due to the small number of patients studied so far. However, several recordings have already shown a decrease in PEA amplitude after close-coupled PVCs, and the disappearance of the signal during episodes of nonsustained VT, suggesting that PEA may be useful in this application.

The use of PEA in cardiomyopathies is of great interest. No commercially available sensor can reliably evaluate the long-term effects of various pacing configurations or different programming settings on hemodynamics. Time has come to test PEA amplitude variations in hypertrophic obstructive cardiomyopathy. In

this disorder, programming of the proper AV delay is critical to successfully reverse the ventricular mechanical activation sequence, reduce the left intra-ventricular pressure gradient and allow completion of ventricular filling. However, the shortest AV delay setting available in the Living pacemaker is 60 ms, which might be too long in this indication unless a His bundle ablation has been performed.

In dilated cardiomyopathy, there is growing interest in multisite pacing to optimize the ventricular activation sequence frequently distorted by conduction disturbances secondary to the underlying disease. Once the system is implanted, the main difficulty consists in programming the optimal rates and AV intervals. PEA measurements may assist in these difficult choices. The problem of connections between pulse generator and leads, and the impossibility to program shorter AV intervals than 60 ms will persist, however.

It is also conceivable that this device will provide information pertaining to the patient's underlying heart disease and its evolution. This implies the extension of the RAM and subsequent calculations in order to show «inotropism profiles». These hopes are supported by new indications for pacing, based strictly on hemodynamic considerations, i.e., hypertrophic obstructive cardiomyopathy, dilated cardiomyopathy, or after heart transplant, for example.

With respect to heart transplantation, Shreier found a highly significant correlation between ventricular evoked responses and grading of histological rejection in endomyocardial biopsy specimens [11, 12]. Ventricular evoked potentials proved to be significantly more reliable than measurement of electrogram characteristics. The assessment of ventricular evoked response in heart transplant recipients could be of great help in the long-term follow-up of graft rejection.

Sensor Information and Arrhythmia Diagnosis

Measurements by a sensor can serve to discriminate normal sinus rate accelerations from atrial tachyarrhythmias. In Vitatron devices, the sensor is used to calculate a mean «physiological rate» and define a physiological band the width of which equals the physiological rate plus 15 bpm. If the atrial rate is above this physiological band, the pacemaker diagnoses an atrial tachyarrhythmia and triggers the automatic mode switch (DDIR functioning) to avoid inappropriate ventricular rate acceleration. A similar algorithm has been developed by Intermedics in the Marathon device with a programmable band width. This system behaves reliably on the condition that the sensor operates properly. This means that if the sensor is not reactive enough, a normal sharp sinus acceleration can be interpreted as an arrhythmia with subsequent inappropriate mode switch. Another drawback is the absence of mode switch in the event of an atrial arrhythmia at a rate within the physiological band, for instance during exercise.

Another concept consists in keeping the mean parameter values in the pacemaker memory. As soon as the atrial rate exceeds the «normal rate» plus a programmable margin, the pacemaker switches to the single chamber mode.

Conclusions

Nowadays, the information provided by sensors is useful to diagnose chronotropic incompetence and verify the appropriate adjustment of the sensor activity to the patient's requirements. Manufacturers and physicians must undoubtedly learn much about the different sensors available to broaden their diagnostic use. An expansion of RAM is needed to develop new algorithms and reach this objective. If one wants to use sensors to diagnose comorbidity, specific algorithms using existing sensors, or new physiologic sensors will need to be developed. Physicians will have to learn the interpretation of these new data which will undoubtedly become available within the next decade.

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Single Lead DDD Stimulation: Is It a Real Progress?

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Introduction

Although the benefits of dual (DDD) over single (VVI) chamber pacing have been demonstrated in hemodyamics, exercise capacity, quality of life and reduced complications in patients with atrioventricular block and sick sinus syndrome; a considerable number of such patients still receive single-chamber ventricular pacemakers, mostly because of the lower cost and easier implantation of such pacing systems. An interesting alternative to DDD(R) pacemakers is offered by single lead VDD(R) pacing system, where atrial sensing and ventricular pacing are incorporated in the same lead, which provides the benefits of A-V synchronous pacing with a system as easy to implant as a VVI pacemaker.

Since the early 1980s, many studies [1] have shown that the atrial signal can be sensed for ventricular tracking with a single lead system, and a variety of atrial electrode arrays have been developed and tested for that purpose. Obviously, the major limitation for single-lead VDD systems is the lack of ability to pace the atrium, which limits the use of this systems to patients with isolated AV conduction disturbances.

Therefore, a single-lead DDD system, with atrial floating electrodes, was developed. However, this mode of pacing was limited by high atrial capture thresholds and by complex electrode geometry.

In order to evaluate the feasibility of pacing the atrium through a new stimulation methodology, which uses two floating atrial ring electrodes on a single A-V lead and overlapping biphasic pulses of opposite polarity (OLBI system), a multicenter, prospective study was performed in Italy.

Material and Methods

In 25 Italian implant centers a population of 74 patients, 47 male and 27 female, with a mean age of 74.9 ± 8.7 years (range: 49-90), all with symptomatic A-V

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block and without evidence of sinus node dysfunction, were implanted with 64 cardiac pacemakers (PM) Biotronik mod. DROMOS SL M7 and 10 PM mod. EIKOS SLD, both equipped with same capability to perform OLBI atrial pacing. All PM were connected to Biotronik single A-V leads mod. SL 60, with 1.0 cm atrial dipole spacing, passive fixation and an Iridium fractal coating on the surface of all electrodes. An A-V distance of 13 cm was used in 81% of patients and of 15 cm in the remaining 19%.

Implantation of the lead was made following the standard procedure of a single-lead VDD system. Atrial lead position was only selected in terms of sensing characteristics. Atrial pacing thresholds (APT) were not measured during implantation. APT and parasitic phrenic nerve stimulation (PNS) threshold were assessed at 1 week before discharge, and at 1 and 3 months after implant. Follow-up data also discriminate results by sex and by orientation of the stimulation vector (i.e. if PM was implanted in the left or right side of the chest). Data were collected in various body positions (supine, sitting, lying, right and left decubitus) and a 24 h Holter recording was performed at the third-month follow-up.

Results

The position of the floating dipole inside the atrial chamber, assessed by X-ray fluoroscopy, was very high (exit of superior vena cava) in 2.7%, medium-high in 50%, medium in 39.2% and medium-low in 8.1% of cases. The position was apparently stable without significant changes during the entire follow-up.

The mean values of APT, (at 0.5 ms), measured in the supine position, were: 2.53 ± 0.82 V at 1 week, 2.57 ± 0.63 V at 1 month and 2.52 ± 0.47 V at 3 months. No APT values were observed above the output limit (4.8 V). The stability of APT over time demonstrates the corresponding stability of dipole position and absence of tissue reactions due to the floating condition.

In supine position PNS (at pulse amplitudes <4.8 V and 0.5 ms) was observed in 12% of patients at 1 week, in 20% at 1 month and in 19% at 3 months. The reason why more patients show sensitivity to PNS at 1 and 3 months may be attributed to the progressive anatomical settlement of the lead inside the atrium which moves the field vector into the proximity of the phrenic nerve. In all cases PNS threshold voltage was higher than APT.

Measured mean values of floating atrial sensing (AS) were: 1.96 ± 0.81 mV at 1 week, 1.86 ± 0.92 mV at 1 month and 1.84 ± 0.83 mV at 3 months. P wave undersensing was never detected during follow-up.

Constancy of pacing was investigated in terms of postural changes. During this test, APT detected in supine condition was increased by 50% and then the patient was asked to take different body positions. Results are shown in Table 1.

This test was limited in time and performed when (at the first and third month) the vascular and endocardial endothelization around the lead was still underway. The dipole was quite free to float inside the atrial chamber, its spatial position changing as it is affected by respiration and gravitational force. This justifies the observed variation of capture at atrial level.

Table 1. Patient body positions versus constancy of atrial pacing

	Constancy of pacing (% of pts)			
Postural position	95%-100%	50%-95%	< 50%	No Pace
Sitting	81	17	2	0
Lying	81	17	2	0
Left decubitus	56	33	9	2
Right decubitus	61	30	9	0

During Holter monitoring patients were paced in DDD mode at a rate of 5 to 10 bpm higher than patient sinus rate at rest. The system showed good performance with constant atrial pacing (over the 95%) at rest condition. Regular inhibition by spontaneous atrial activity was observed when patient chronotropic competence exceeded PM basic rate. Few undersensing phenomena were observed during night time, probably induced by postural changes, but they were limited in time and no related symptomatic consequences were reported by the patients.

When male and female patients are considered and compared as separate groups, the collected data reveals the following. Statistical differences in APT are not significant (t-test); the mean values (male vs female) were respectively: 2.66 ± 0.85 V vs 2.32 ± 0.71 V at 1 week, 2.54 ± 0.67 V vs 2.62 ± 0.54 V at 1 month and 2.50 ± 0.54 V vs 2.58 ± 0.38 V at 3 months. A substantial stability of values was detected in both groups.

Significant differences between the two groups were observed in PNS sensitivity. Male patients vs female patients showed PNS (at supine position and pulse amplitudes < 4.8 V and 0.5 ms) respectively: 5% vs 24% at 1 week and 13% vs 33% at 3 months. Probably for anatomic or physiological reason, females seem to have a more excitable phrenic nerve.

The mean values of AS, shown by the two groups, were respectively: 1.96 ± 0.98 mV vs 2.02 ± 0.76 mV at 1 week, 1.82 ± 1.05 mV vs 1.81 ± 0.88 mV at 1 month and 2.01 ± 0.97 mV vs 1.87 ± 0.73 mV at 3 months. Also in this case values were stable and no statistically significant difference between the two groups was observed.

The position in which the PM case is implanted, left or right side of the chest, will drastically change the anatomical area influenced by field vectors, this on deductive basis. If the PM is implanted in the right pectoral area, the field strength will affect tissues of right atrium free wall more, while, when the PM is implanted in left pectoral area, the vector will interact more with tissues of septal wall between atria. Theoretically, values measured in the two conditions described above must be different.

In the patient population examined, 37 PM were implanted in left and 37 in right pectoral position. Mean APT (left vs right at 0.5 ms) measured was respectively: 2.25 ± 0.68 V vs 2.77 ± 0.87 V at 1 week, 2.53 ± 0.56 V vs 2.61 ± 0.69 V at 1 month and 2.48 ± 0.65 V vs 2.59 ± 0.54 V at 3 months. The only difference was detected at 1 week after implant and was not statistically significant. The discrep-

ancy may be attributed to a progressive anatomic spatial repositioning of the atrial portion of the lead, which compensates the forces acting during atrial systole and diastole. In other words it means that, in a short period of time (about 1 month) the lead, free of constrictive links, will keep its optimal atrial shape, independent of the way of access and by atrial dynamic.

The same behavior was shown by PNS. Left vs right implant showed a PNS sensitivity (at supine position and pulse amplitudes < 4.8 V) of respectively: 8% vs 13.5% at 1 week and 13.5% vs 13.5% at 3 months. This means that leads implanted through the right access immediately acquire their optimal atrial position while leads implanted through the left access need some time (1 to 3 months) to reach the same condition.

AS does not show any significant statistical difference between the two access conditions, both at 1 week and 3 months after implant.

Discussion

It is well established [1] that single-lead VDD pacing is a physiologic, reliable and easy mode of pacing to use. However, since no atrial pacing is provided, this system should only be implanted in rate-competent patients with normal sinus node function. Hence, the development of a single-lead DDD system would represent a significant advance in cardiac pacing.

It has been demonstrated that single-lead DDD pacing is possible, but it is limited by unacceptably high APT using conventional bipolar and unipolar approach of stimulation. Even if energy expenditure is not considered, atrial pacing using high energy stimulation via floating atrial electrodes may lead to PNS. In fact, PNS occurs when the electric field strength outside the atrial wall, where the phrenic nerve is located, is still sufficiently high to determine the parasitic nerve stimulation.

Recently, a new pacing method, using two simultaneous unipolar biphasic pulses of opposite polarity (OLBI waveform) delivered via two atrial floating ring electrodes, has been shown to reduce APT by increasing the current density in the atrial endocardium. Furthermore, by reducing the distance between isoelectric potential lines, this waveform was found to reduce the incidence of diaphragmatic pacing in animals. In fact the OLBI method allows the generation of an intense field strength in proximity of the floating dipole and inside atrial wall. Outside the heart, the field strength becomes significantly lower. Moreover, the field is oriented on a plane containing dipole and PM case. All this limits the spread of the field and consequently the possibility to induce PNS.

Several clinical studies [2-11] have demonstrated the feasibility of pacing the atrium using OLBI stimulation. In all these studies, made in different clinical centers, comparable APTs in the range of 2.19-2.7 V have been observed. Similarly, they have demonstrated that the effects of change in posture are negligible with OLBI stimulation, since there are no significant variations in APT. Furthermore, a stable APT, allowing reliable floating pacing, was observed during the entire follow-up period (6 months).

The performed Holter recordings proved atrial capture over the long term during follow-up. In these studies [2-11] OLBI pacing mode offered a higher safety margin between diaphragmatic and atrial pacing thresholds compared with either bipolar or unipolar pacing in all atrial locations. However, despite the significant reduction in APT and improvement in the safety margin of OLBI waveform to avoid PNS, a relevant population of patients, ranging from 12% to 36%, experienced PNS at atrial output of 4.8 V or lower, especially in upright position.

Preliminary clinical results, collected in the Italian multicenter study, confirm the encouraging results obtained in previous studies. The OLBI system allows reliable DDD pacing, without PNS during daily activity, in more than 80% of patients. Capture losses occur more frequently when the patient is supine in lateral decubitus position. The phrenic nerve seems to be less excitable in males than in females for reasons unknown. Leads implanted by right access kept a stable position in atrium immediately, while those implanted by left access required more time to stabilize.

In conclusion, all initial results suggest that single-lead DDD pacing is possible. The OLBI system, using atrial floating ring electrodes in a modified VDD pulse generator, demonstrates its reliability giving stable back-up atrial pacing in patients with complete or advanced A-V block and sporadic chronotropic incompetence, and it may, therefore, be an alternative mode of pacing in future primary single-lead DDD systems.

Further evaluation is required to assess the safety of permanent atrial pacing with the OLBI system in the short and long term, mainly because PNS remains an important clinical problem in a considerable number of patients.

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What Is the Real Usefulness of the AutoCapture Function?

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Introduction

AutoCapture™ (Pacesetter Inc., St.Jude Medical Co., Sylmar, CA, USA) is a programmable function incorporated in the Pacesetter Microny™ and Regency™ SSI/R pacemakers, which provides for the automatic ventricular capture verification, the increase in output voltage in the presence of transient loss of capture and threshold searching, with adjustment of output settings, when the device is connected to a Membrane™ bipolar ventricular lead.

AutoCapture™ Algorithm

The AutoCapture™ algorithm includes the automatic capture confirmation of each ventricular paced complex by monitoring the Evoked Response (ER) associated with the cardiac depolarization resulting from the output stimulus. Monitoring starts after a 15 ms blanking period and continues until 62 ms after the output pulse. Detection of the ER within this window confirms capture, and normal ventricular pacing follows. If an ER is not detected within this window, a high output backup pulse of 4.5 V is delivered at the end of the 62 ms interval. After two consecutive noncapture episodes, the system automatically steps up the programmed output and performs a stimulation threshold search. The stimulation threshold is also systematically performed every eight hours even if no episodes of repeated noncapture have been detected or by simply applying a magnet over the pacemaker (Fig. 1). When the threshold search is completed, the system automatically sets the output to 0.3 V above the capture threshold value, i.e. the lowest output level that results in two consecutive captures, holding the pulse duration constant.

Polarization is a phenomenon that occurs at the tip of the lead when the device delivers a stimulus. It plays a very negative role as it interferes with detection of the heart muscle's depolarization, i.e. ER. With AutoCapture™ it is absolutely neces-

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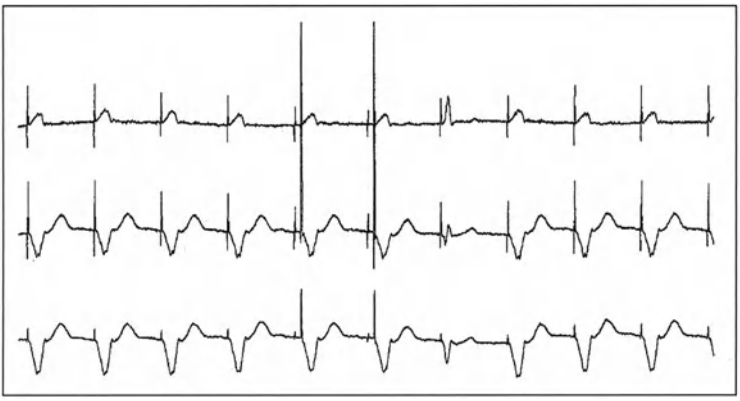

Fig. 1. ECG tracing with stimulation threshold performed by applying a magnet on the device

sary to use leads with sufficiently low polarization such as Membrane™ leads.

The evolution of the stimulation threshold over time can be monitored by the above mentioned pacemakers at different sampling intervals, ranging from two seconds to 12 hours. The "freeze" mode can be selected which interrupts the data collection when 256 samples have been acquired and the data is stored until retrieved by the physician at the follow-up visit (Fig. 2). If "freeze" is not activat-

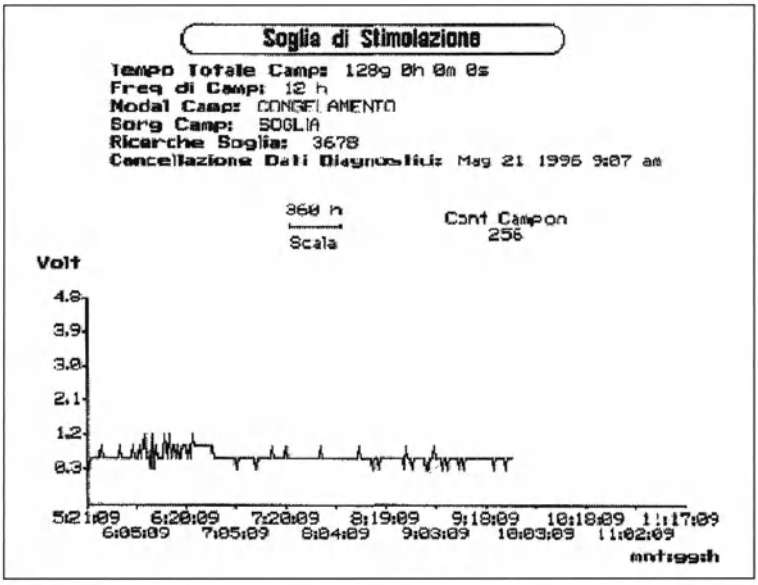

Fig. 2. Example of stimulation threshold vs. time graph when the freeze mode is activated. The sampling rate is 12h, therefore the maximum data collection time is 18 weeks, a time-frame which covers the known threshold changes after implant

ed, the system will delete the oldest data while storing the most recent measurements. The QRS and ER sensitivity tests can be performed by the APS™ II mod. 3004 programmer using the 3201C software [1, 2].

AutoCapture™ Data Collection

The PACEMATE study [2], performed by 19 Italian centers, was designed to evaluate the pacing threshold characteristics of the Membrane™ 1400T and 1401T leads over a protracted period of time, utilizing the AutoCapture™ function built-in the Microny™ SR+ pulse generator. Fifty-four patients were enrolled in the study and followed using the diagnostic capabilities provided by the pacemaker.

The graph in Figure 3 displays the capture threshold mean values recorded automatically by the pacemaker at the time of each follow-up (days) at a pulse width of 0.49 ms. The Membrane™ series of leads either with (1401T) or without steroid impregnation (1400T), provided very low capture thresholds at six months postimplant and beyond which, in combination with AutoCapture™, should allow the system to function safely with a very low safety margin. Also ER amplitude threshold mean values, graphically displayed in Figure 4, maintain excellent values over time assuring the continuous appropriate sensing for the operation of AutoCapture™.

Several short, medium and long-term clinical experiences with AutoCapture™ have been reported [3-9]. All the data collected confirmed the proper functioning of this feature with regard to the algorithm, the ER amplitude stability and sensing. In no cases have problems arisen that have put the patient at risk. In those few cases where the device had not stimulated at the optimal amplitude, the amplitude has been too high. Two causes have been recognized, one being that the native cardiac rhythm was so similar to the pacemaker's basic rate that many fusion

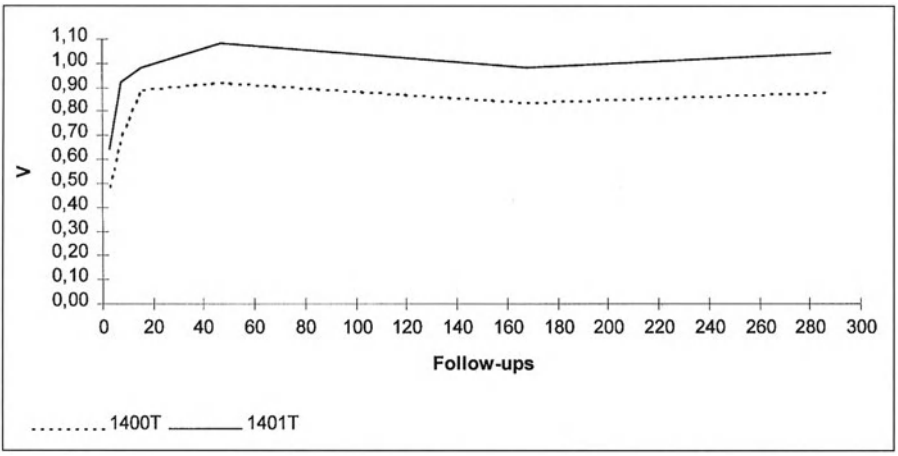

Fig. 3. AUTOCAPTURE pacing threshold at 0.49 ms (AT)

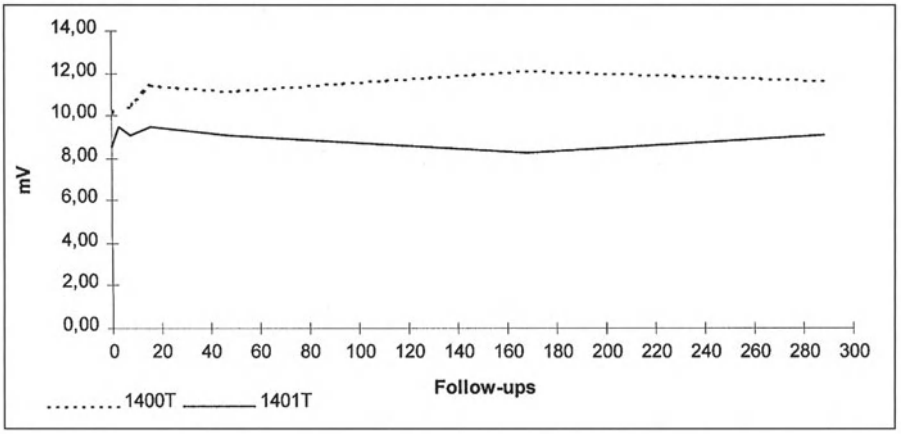

Fig. 4. Evoked response amplitude

beats occurred, the other that the sensing was incorrectly programmed and spontaneous heartbeats were not detected. In both cases it has been possible to rectify the trouble by programming basic rate and sensitivity, respectively.

Clinical Utility of AutoCapture™

Acute thresholds cannot be used to predict chronic values for any given patient and thresholds changes as a function of implant time, thus some patients require long periods before they can be considered to be stable [10]. In addition, physiological changes during the patient's daily activities, such as electrolyte balance and common cardiac drugs may influence thresholds [11-14].

Pacemakers must always deliver stimuli able to assure effective pacing, in spite of the dynamic behaviour of thresholds, in order to avoid the risk of loss of capture. To overcome this trouble a margin of safety of 1.5-2.0:1 with respect to the voltage threshold has been recommended [15, 16]. There are two potentially adverse effects of this practice. The first is an excessive battery current drain, which shortens the pacemaker longevity if the daily fluctuations are not programmed. The second is that in rare patients, the capture threshold may exceed the programmed output, resulting in loss of capture [10]. The automatic monitoring of capture threshold and the output adjustment on a beat-by-beat basis eliminates the need for programming of arbitrary safety margins, assuring truly safe and effective pacing over time while maximizing the service life of the pacemaker power source for the actual requirements of patients [2, 5, 7, 17].

On the other hand, pacemaker longevity is still important. The consequence of AutoCapture™ is that the device consumes less energy. This makes it possible to produce normal-size pacemakers such as the Regency™ (18.5 g) with an extremely long life span with the advantage that many patients will never need to undergo more

than one implantation, or very small-size pacemakers such as the Microny™ (12.8 g and an expected life-time of 7-10 years) with remarkable practical benefits for many patients. In addition, more and more automatic functions are required from a modern pacemaker, and the energy savings obtained with AutoCapture™ will increase their capabilities without the need to increase their size.

Again, in very aged patients, patients suffering from serious diseases or disabilities, patients living far from the pacemaker clinic and patients who generally have difficulties to undergo the scheduled pacemaker check, Autocapture™ may provide safe and effective pacing for years without any regular follow-up. Autocapture™ also represents a great advantage for physicians at the time of the follow-up. Sensing measurements of both native cardiac activity and ER is unfortunately unavoidable, but are carried out automatically by the programmer. After that, a quick look at the curve that shows how the threshold value has varied lately, is sufficient to know that the automatic function is working properly.

Conclusions

AutoCapture™ allows the implanted system to perform at very low output settings, thus reducing the battery current drain and increasing the projected longevity of the pacemaker, while assuring patient safety by maintaining effective cardiac stimulation, and removing concerns of transient rises in capture threshold. This capability has been considered *the most desirable feature of a smart pacemaker* in the past [18]. Currently, AutoCapture™ works only in the ventricle and has been proved to work properly only in conjunction with a bipolar Membrane™ lead, but hardware and software for new systems have been developed for the atrial ER detection, unipolar o bipolar ER detection, pacing and sensing, all of which are independently programmable [19].

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CARDIAC PACING: OTHER ISSUES

Pacemaker and ICD Infections: How to Manage Them?

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Introduction

Among the complications associated with the wide use of implanted cardiac pacemakers, the incidence of infection of the pacing system is reported to occur in 0% to 19% of the patients [1]. Signs and symptoms of infection in the generator pocket are most frequently observed, while septicemia is a less frequent but life-threatening event [2, 3]. Infections occurring after implantation of an implantable cardioverter-defibrillator (ICD) are an even more dangerous condition, and it is reported with an incidence of 2%-7% [4-7]. ICD devices have much in common with implanted pacemakers. Both systems consist of electrodes and a pulse generator, and are manufactured using the same materials. Thus it seems reasonable to apply the lessons learned from permanent pacemakers to defibrillator implants.

Once the infection involving an implanted pacemaker or an ICD device has been diagnosed, several strategies can be carried out: (a) conservative treatment, including systemic antibiotics, debridement of the generator pocket and insertion of an irrigation system, (b) partial removal of the system (pulse generator only) in addition to the measures taken with conservative treatment, (c) complete removal of the pacing or defibrillating system, usually in conjunction with the conservative measures.

Some successful treatments of cardiac pacemaker infections have been achieved using local debridement and irrigation systems, supported by administration of antibiotics [8-11]. However, local infections of the pacing systems can later cause serious complications such as septicemia, superior vena cava syndrome or venous obstruction, and are associated with a high rate of new surgical treatments [12]. We agree with most authors that in the presence of a resistant infection all the pacemaker hardware should be removed [13, 14]; this is particularly the case for patients with septicemia related to the pacing system.

Infections are one of the most serious complications in patients with an implanted ICD and particular emphasis should be placed on prevention of this event. Strict adherence to asepsis and a meticulous surgical technique are essen-

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tial. Identification of risk factors in each individual patient allows a patient-tailored treatment policy that may add to infection prevention. Complete removal of the system is the most successful treatment when an implant infection occurs [15]. However, there are difficulties with this approach, particularly with the old implanted transthoracic systems. The inflammatory response and tissue ingrowth of the patches into the myocardium can lead to serious complications during removal of the ICD system, such as damage to the myocardium, the coronary vessels or the coronary artery bypass grafts. For these reasons, in patients with epicardial patches, some authors have reported a successful management by using aggressive local debridement, closed irrigation of the generator pocket and culture specific antibiotic therapy [16, 17]. We believe, however, that most infections of transvenous cardioverter defibrillators can be managed like infections of implanted cardiac pacemaker systems.

In the past, removal of chronic pacing leads has been performed by direct traction or by attaching weights via a pulley system [18, 19] and applying traction for several hours. The results were discouraging and many complications related to these procedures have been reported, including arrhythmias with shock caused by invagination of the right ventricular wall, as shown by fluoroscopy [20], ventricular fibrillation [21], avulsion of a tricuspid valve leaflet [22], lethal hemopericardium due to a tear in the right ventricular apex after an excessively forceful traction [23]. Recently a fatal case of myocardial rupture at the atrial lead site after prolonged (24 hours) external traction has been described [24].

The only alternative approach was cardiosurgical removal; this has been effectively applied [25-27], but it often requires median sternotomy and cardiopulmonary bypass, that are both major risks for elderly patients as they may have concomitant important diseases. Therefore, now most authors agree that this approach should be applied to unsuccessful cases of nonthoracotomy procedures or in case of contraindications to transvenous removal, such as the presence of vegetations attached to the pacing leads, detected by transesophageal echocardiography.

The availability of new systems allowing transvenous removal of electrodes has changed the management of paced patients with signs and symptoms of infection. In fact, in view of the high effectiveness and relative safety [28, 29] of these techniques, all otherwise intractable infections of pacing systems represent an indication to total removal of pacemakers and pacing leads. The same consideration is valid for patients with infection of transvenous cardioverter-defibrillator systems.

We will report the experience we had in the management of these patients since transvenous removal techniques have become available. Most patients were referred to us after ineffective conservative treatment attempts, as removal of the pacing or defibrillating leads had been previously advised from the referring centers in absence of alternatives.

Materials and Methods

From December 1989 to April 1997, 174 patients affected by infection of the pacing or defibrillating system were referred to us from many Italian Centers in order to undergo transvenous extraction of the pacing system. The pacing or defibrillating leads to be removed were 277 (Table 1).

Table 1. Patient characteristics

	N° patients	men/women	mean age years	(range)
Local infection	97	66/31	67.2	(17 - 88)
Septicemia	77	51/26	68.1	(32 - 88)
Total	174	117/57	67.6	(17 - 88)

The population was subdivided into two groups: 1) patients with local infection and 2) patients affected by septicemia.

The local infection group (Group 1) consisted of 97 patients (66 men and 31 women, mean age 67.22 years, range 17-88). Infections were diagnosed after positive local culture or thanks to clear clinical signs in 50 patients, while in the remaining patients the infection was suspected because of skin erosion or pocket exposure or, often, just because these patients had undergone many attempts at conservative procedures. A total of 155 leads needed to be removed and had been implanted for a mean period of 64.9 months (range 4-252). There were 148 pacing leads: 97 ventricular and 51 atrial leads. One atrial and 1 ventricular lead were intravascular. There were 7 defibrillating leads (4 ventricular, 1 atrial intravascular and 2 caval leads) that had been implanted for a mean period of 48 months in 4 patients with a mean age of 54.3 years (range 49-64).

Clinical and laboratory findings of septicemia were observed in all the 77 patients (51 men, 26 women, mean age 68.14 years, range 32-88) of Group 2. The leads considered for extraction were 122; they had been implanted for a mean period of 63.62 months (range 1-245). The pacing leads to be removed were 119, 82 ventricular and 37 atrial; 3 atrial and 10 ventricular leads were intravascular. The defibrillating leads were 3, 2 ventricular and 1 caval, which had been implanted for a mean period of 11.67 months (range 11-13) in 2 men with a mean age of 43 years.

In all procedures, when possible, we performed, first of all, a continuous manual traction up to 5 minutes, by applying a force up to 250 g, in order to extract the lead avoiding, on the other hand, irreversible damage due to excessive coil lengthening.

If this attempt proved ineffective, instrumental traction was carried out by using all the tools of the transvenous Cook Pacemaker Corporation (CPC) system. In addition, more intravascular instruments, such as Catchers and Lassos by Osypka, were used when necessary.

A standard approach via insertion vein was performed in the case of exposed leads, while an intravascular approach based on the use of a transvenous workstation was used in case of intravascular leads. Both techniques were used in a combined approach under particular conditions.

A careful physical examination, laboratory tests and echocardiographic examination were performed in all patients before the procedure; transesophageal echocardiogram was used to evaluate the presence of vegetation on the leads or cardiac valves, particularly in patients affected by septicemia.

All removal procedures were performed under local anesthesia with continuous ECG, fluoroscopic and radial blood pressure monitoring. Transvenous back up pacing was almost always used, as well as echocardiographic evaluation before and after the procedure; cardiosurgical standby was also ensured.

Surgical extraction was carried out in septicemic patients after unsuccessful manual and instrumental traction.

After the procedure, patients were admitted to the cardiac care unit for at least 24 hours, and any vital sign was closely monitored; a blood sample, ECG recording, chest X-ray and echocardiogram were obtained the following day.

Results

Transvenous extraction was defined as a non-feasible procedure when evidence of serious lead deterioration or previous attempts at repairing or removing the lead made use of the available tools impossible. In 8 pacing leads (2.9%: 4 exposed and 2 intravascular ventricular leads, plus 2 intravascular atrial leads), implanted in 5 patients of Group 1 and in 2 patients of Group 2, the procedure was defined as non-feasible due to the above mentioned conditions.

In the patients affected by local infection (Group 1) the removal procedure was performed on 149 leads. Manual traction was effective in 17 of the 147 exposed leads (11.5%) implanted for a short mean period (18.4 months, range 4-80). The instrumental traction allowed complete removal of 119 leads. Three leads (2%) were considered to have been partially removed because it was impossible to extract the tip and the distal part of the coil. The procedure was unsuccessful on 10 leads (6.7%). All the defibrillating leads were successfully extracted. In conclusion, the procedure was effective in 91.3% of the leads of Group 1 (Fig. 1).

In Group 2 patients, the procedure was performed on 120 leads. Manual traction was effective in 14 of the 107 exposed leads (13.1%). In 92 leads the instrumental procedure was effective; all the 3 defibrillating leads were removed. Fourteen leads (11.66%) were not removed despite an aggressive approach; all these patients were referred to cardiosurgery. In conclusion, we removed 106 leads (88.33%) in this group (Fig. 2).

Taking both groups into consideration, the mean success rate of the tecnique was 89.96%.

No lethal complication related to the procedure was observed in our experience. In 2 patients (Group 2) cardiac tamponade occurred requiring urgent tho-

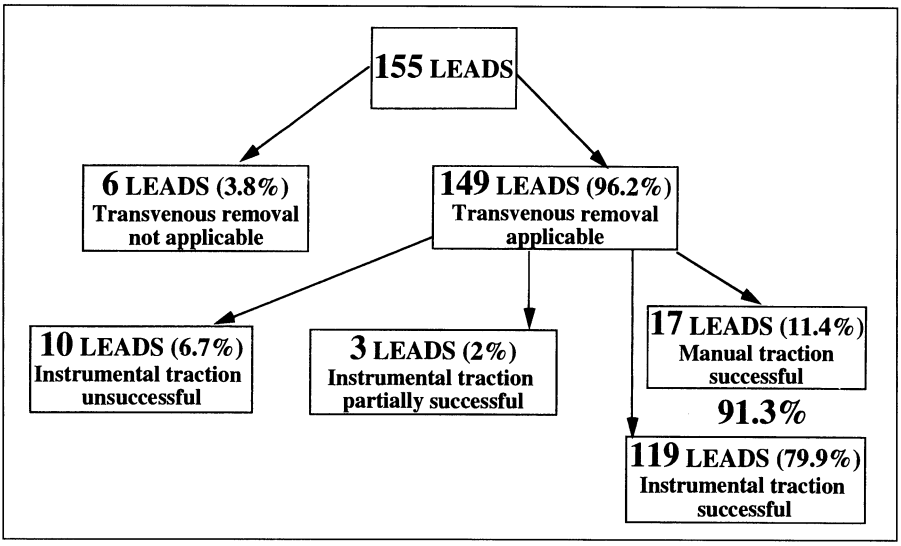

Fig. 1. Results of lead removal from patients with local infection (group 1). The total success rate was 91.3%

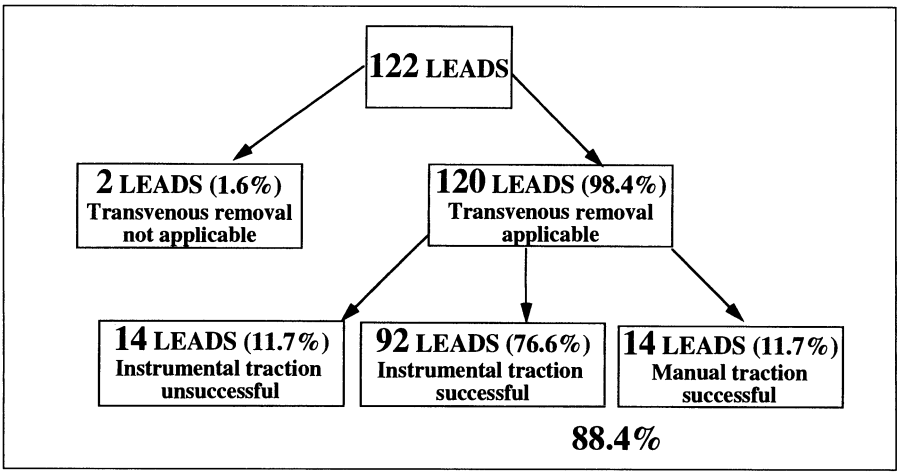

Fig. 2. Results of lead removal from patients with septicemia (group 2). The total success rate was 88.4%

racotomy. In one case a tear in the lateral wall of the right atrium was produced by the Dotter basket, during an attempt at removal of an intravascular ventricular electrode. The other case occurred after the removal of a ventricular pacing lead in which a very strong traction was performed with the locking stylet, while countertraction with the dilator sheaths had not been possible because of strong adherences to the ventricular wall. In 2 patients pulmonary embolism (in one

Table 2. Lead characteristics

	N° leads	Pacing leads ventricle/ atrium	Defibrillating leads ventricle/ atrium/SVC	mean pacing period months	(range)
Local Infection	155	97 <> 51	4 <> 1 <> 2	64.9	(4 - 252)
Septicemia	122	82 <> 37	2 <> - <> 1	63.6	(1 - 245)
Total	277	179 <> 88	6 <> 1 <> 3	64.4	(1 - 252)

case complicated by ventricular fibrillation) occurred within 2 hours after the procedure. In 3 patients apparently unmotivated ventricular fibrillation occurred within 24 hours after the procedure. Three patients developed signs and symptoms of subclavian vein thrombosis, requiring anticoagulant therapy. Transient hypotension requiring medical treatment was observed in 58 patients. All these complications were successfully treated.

Three patients suffering from longstanding septicemia (1 to 6 months) died suddenly later after a successful extraction; cardiac lesions related to the procedures were excluded by the morphologic examinations performed and the exitus was related to the infective disease. In a patient affected by endocardial cushions defect and cor pulmonale, fatal right ventricular failure developed 2 days after a successful procedure.

During follow-up, all patients of the septicemia group were asymptomatic. In many of the unsuccessful cases of Group 2, local infection is still an unsolved problem. One patient has voluntarily chosen to undergo surgical removal.

Discussion

Indications to the removal of the pacing systems have been affected up today by the absence of an effective treatment different from cardiosurgical removal. Before the development of transvenous lead extraction systems, manual or weighted traction was used with poor effectiveness and a high rate of complications. On the other hand, medical treatment of infections is usually ineffective in the presence of a prosthesis. Reintervention and local care of the infection of the wound and the pacemaker pocket is usually just a temporary solution to the problem. This situation led to a conservative management policy and reduced indications to removal. Therefore indications to removal of the chronic pacing leads have been currently limited to case of life-threatening complications, such as septicemia.

Recently, much interest has been focused on the new techniques for transvenous removal, which have been shown to be highly effective and relatively safe

[30-32]. The availability of these techniques must lead to a critical review of the management of pacemaker and defibrillating systems infections and to the extension of indications to removal.

In our opinion, and in accordance with many authors, the presence of pocket infection or generator exposure must also be considered as a serious complication requiring explantation of the entire pacing system, including the transvenous leads. In case of skin erosion without exposure, it is possible to try with a local wound care. However, though this method has been occasionally reported to be successful, it often leads to failure.

The same approach must be applied to transvenous ICD systems. The infection of cardioverter-defibrillator systems brings many concerns; there are no suitable alternatives to the ICD in almost all patients, and total explantation usually must be followed by reimplantation of another entire system. The removal of epicardial patches is associated with many possible complications and the treatment of such patients must be carefully tailored.

Our experience with transvenous removal techniques confirms that manual traction allows removal of just a few leads, particularly those that have been implanted recently and at a time when fibrous entrapment was less tenacious. It is possible to obtain better results by applying a stronger traction force, but this is often associated with irreversible lead damage, which makes instrumental traction inapplicable, when necessary. Remarkably, none of the ventricular or atrial defibrillator leads were removed manually.

Instrumental traction was highly effective, and allowed limiting elective surgical procedures to a few unsuccessful cases from the septicemia group. In this group, that had mandatory indications, we observed major complications because a very aggressive procedure with a strong traction and countertraction was carried out; the presence of a cardiosurgical standby allowed emergency thoracotomy to repair the lesions.

Despite the lead design and the greater possibility of exposed coil binding to the endothelium, all defibrillating leads were removed by instrumental traction. However, this result must take into account our previous extensive experience with pacing leads.

The deaths reported in the septicemia group were not related to the procedure, as shown by the chest X-ray, echocardiogram, and the absolute absence of signs and symptoms of mechanical impairment. The impossibility to treat ventricular fibrillation was probably due to an involvement of the cardiac muscle in the infective process. Ventricular fibrillation had occurred in one patient during hospitalization before the removal procedure. Another patient affected by longstanding septicemia, without a documented cardiac disease, died suddenly while waiting for hospital admission. These observations confirmed that longstanding septicemia is a very dangerous disease, which requires aggressive antibiotic therapy and, as soon as possible, total removal of the pacing or defibrillating system.

In conclusion, the techniques available today for transvenous removal of the pacing and defibrillating leads are very effective in the treatment of infective complications, and must be considered as a first choice therapy.

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Cellular Phones and Pacemakers: How Do They Interact?

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Introduction

Non-ionizing radiation is emitted by different types of equipment such as microwave ovens, high-voltage electrical lines, cellular phones, etc. This kind of radiation (electromagnetic waves) can also cause interference. Many electronic medical devices such as pacemakers (PM) can malfunction as a consequence of electromagnetic interference (EMI) [1-5].

EMI is spread by different modes such as (a) electrical lines or cables, (b) electrostatic induction, or (c) electromagnetic radiation.

Interference usually affects electrical equipment by penetrating through the cables or by irradiation. These electrical disturbances can be distinguished from necessary and unavoidable interference. Implantable devices for controlling hypokinetic and/or hyperkinetic arrhythmias are widespread. Their exposure to numerous sources of electromagnetic fields can give rise to possible malfunction. PMs are made up of electronic circuits which can be affected by electromagnetic fields in a negative way. Presently, these devices are protected from most of electromagnetic sources.

Cellular phones have become the most recent concern [6-11]. Cardiologists should decide soon what to do in order to restrict use of cellular phones by PM-dependent patients. The effects of EMI on PMs are based on several physical factors such as the strength of external signal, the distance between the signal and the PM, the frequency range, modulation type and immunity level of the PM. The outcome of the effect of EMI on the PM can be pacing inhibition by triggering of a ventricular pacing rhythm that is more rapid with VDD and DDD PMs, or asynchronous pacing, or other pacing modes [12-14].

The aim of this study was to evaluate the possible negative effects of environmental electromagnetic radiation on PM, which increase the possible health risk for patients due to PM malfunction.

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Methods

Electromagnetic Compatibility Test Laboratory (anechoic chamber)

Electromagnetic compatibility is the capability of a device, piece of equipment or system to operate satisfactorily in its own electromagnetic environment, without generating unacceptable electromagnetic disturbances for other equipment. Since January 1st 1996, in compliance with EEC directive 89/336, Italian law requires that only those products for which the aforementioned capability has been verified be sold. Compatibility will be certified by means of a special EMC trademark. In the railway sector the electromagnetic compatibility problem is created by the coexistence of high power equipment which generates noise with lower power devices performing vital functions. In order to facilitate the study of electromagnetic compatibility problems and certify the equipment it manufactures, Ansaldo Trasporti (Naples Research Center) has set up a laboratory in compliance with the following standards: IEC 801-3, EN 55022, MIL-STD 461C RS03 (up to 1 GHz), FS-IS 402, CISPR-16, ENV50141, EN1000-4-2, EN1000-4-4, EN1000-4-5. The laboratory has SINAI accreditation n° 0124.

Description of the Laboratory

- *Screneed chambers*
Semi-anechoic chamber. Attenuation to MIL-STD-285 (range 14 KHz-10GHz), maximum dimensions for tested object h = 1900, l = 2200, d = 600 mm. Pyramlid absorbers in compliance with specifications (Fig. 1): ASMT-D-1692-74 and NRL Report N 8093. Control room: attenuation to MIL STD 285 (range 14 KHz-10 GHz)
- *Control and computation system*
The system comprises the following components: control and data processing system, management software. The software installed enables test operations to be performed manually or completely automatically. In addition to controlling the antenna generation and control and computation system, the software acquires test data and the incoming data from the equipment being tested (ET). A data base can be created for use during the preparation of test reports.
- *Antenna generation and amplification system*
This subsystem is used to generate electric fields up to a maximum intensity of 40 V/m in the 10 kHz-1 GHz frequency range. A synthesized RF generator ensures the frequency coverage required, while the external modulator easily fulfills normal modulation requirements. The RF power level needed to generate electric fields of the required intensity is ensured by two amplifiers which deliver 1000 W in the 10 kHz to 220 MHz range, and 100 W in the 100 to 1000 MHz range, respectively. The strength of the electrical field generated can be measured by means of isotropic detectors and displayed in the control room by the field repeated. The simultaneous use of two sensors allows monitoring of the uniformity of the electrical field in the test area. Instrumentation is equipped with IEEE 488 ports for controlling the data processing system during automatic testing. Conducted susceptibility and conducted/radiated emission tests are performed.

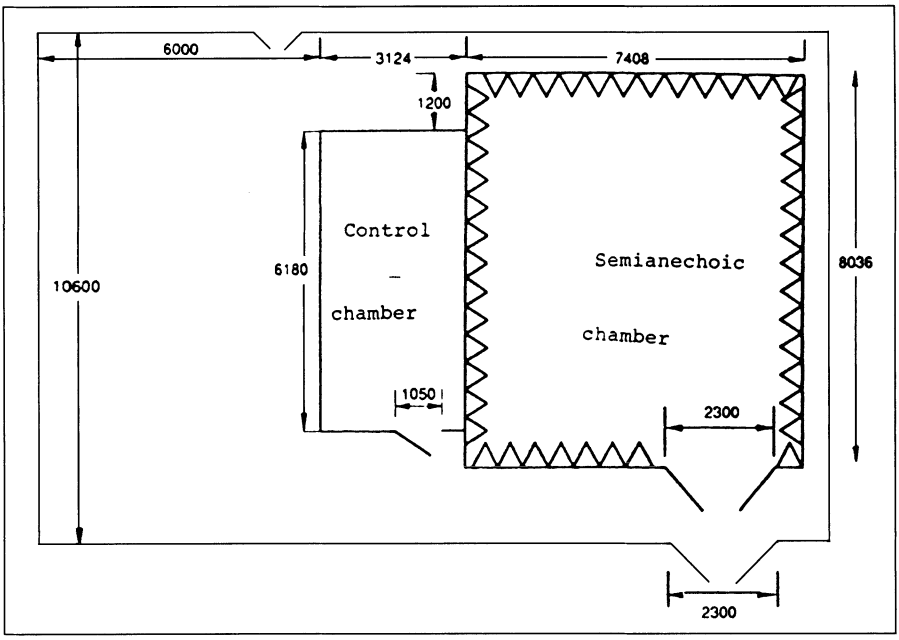

Fig. 1. The EMC Laboratory

- *Closed circuit television and intercom system*
The TVCC and intercom system makes it possible to check correct operation of the equipment or malfunctions which may arise during EMC testing.

Cellular Phone Technology

Presently, almost all cellular phones in the USA use a simple analogue frequency modulation technology. In analogue systems, messages are transmitted by amplitude or frequency variation of continuous radio waves. Digital systems transmit messages as rapid pulse train. Two kinds of digital technology have been introduced in the USA: Code Division Multiple Access (CDMA) and Time Division Multiple Access (TDMA). Actually, the European standard is the Global Standard for Mobile Communication (GSM) which utilizes TDMA technology. The power of cellular phones varies from 0.02 to 2 W. With digital technology the maximum power delivered can reach 8 W.

Technological Features of ETACS

ETACS cellular phones operate in a frequency range from 872 to 950 MHz; NMT 900 from 890 to 960 MHz; AMPS from 824 to 894 MHz. Power level can vary from 0.006 to 0.6 W.

Technological Features of GSM

GSM operates on different standards. GSM cellular phones operate in a frequency range from 890 to 915 MHz and from 930 to 960 MHz.

Power level can vary from 1 to 2 W.

First Test

The first study evaluated the effects of magnetic field with damped wave form motion in the anechoic chamber on 4 single chamber PMs (VVI): Opus RM (Elamedical) (test a), Reflex 8220 (Telectronics) (test b), Meta (Medtronic) (test c), Optima MPT (Telectronics) (test d). PMs were set on standard activity function by a remote control device that monitored PMs before, during, and after test. PMs were tested in an anechoic chamber at one meter above the ground in a horizontal and vertical position in order to simulate patient posture. PMs were connected to the monitor of a Biotronik PM 30 parameter controller by means of a 5.8 m long shielded cable. Firstly, PMs were immersed in a magnetic field with damped wave form motion at variable current amplitudes (400 impulse/s, from 10-15-20-30-40-50-60-80 Voltage/control, current range 100 A. Then, with electromagnetic fields ranging from 30-220 MHz and 220-1000 MHz. The susceptibility was demonstrated at 70÷80 voltage/control.

Second Test

The PM was lodged inside and outside a trolley-bus equipped with an electrical operating device of medium power. Preventive internal electromagnetic specifications of the vehicle permitted to reveal the most risky positions, where the PM was then positioned. Moreover, PMs received electromagnetic field interference produced by walkie-talkies used as a communication system among traveling and ground personnel. We tried to demonstrate a relationship between well-known conditions of the environmental EM pollution and device malfunction.
Phase 1: inside the trolley-bus
Phase 2: outside the trolley-bus, 3 m away from the bipolar line center.
Phase 3: inside the trolley-bus with interference caused by walkie-talkie.

The PM was placed in different points as shown in Figure 2.
a) R = 1.50 m from ground = points A, B, C, D, E, F, G.
b) h = 2.50 m (under roof) = points A', B', C', D', E', F', G'.
Point A indicates the position next to the driver and the passenger exit zone.
Point B indicates the low voltage electrical panel.
Point C is near high voltage box on the inverter side.
Point D indicates the high voltage box, inductive side.
Point E represents the trolley effect connected to the bipolar line of input line and passenger lounge.
Point F is the passenger entrance.
Point G indicates the lateral panel of the display.

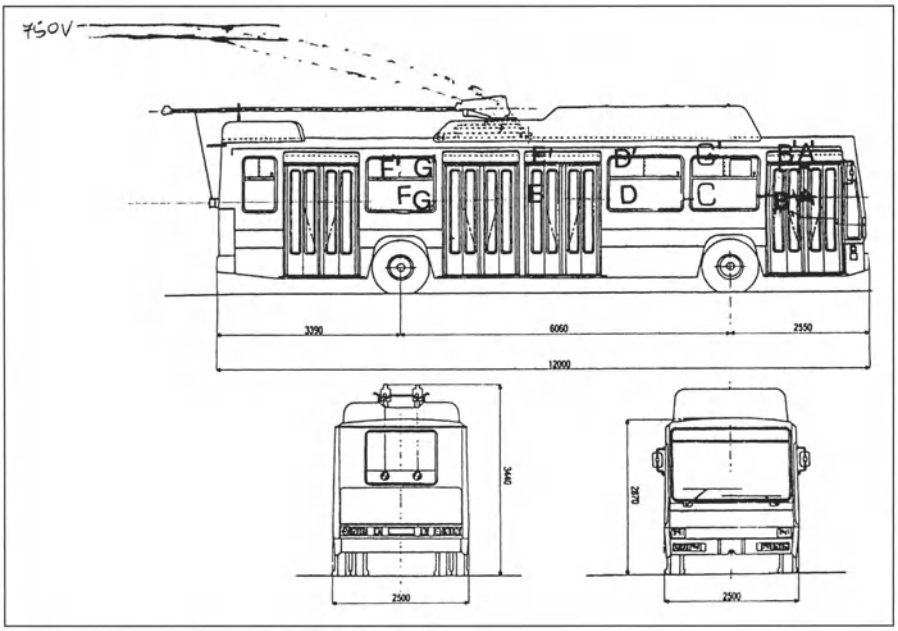

Fig. 2. Positionning of pacemaker within the trolley-bus

In phase 1, all the tests were performed in the following configurations (with 750 V input or diesel engine switched on):
a) stopped vehicle
b) vehicle at constant velocity
c) vehicle during rapid acceleration
d) vehicle during acceleration on a ramp
e) vehicle during smooth breaking
f) vehicle during sudden breaking
g) vehicle in reverse drive.

In phase 2, the PM was placed in a fixed position 1.50 m above the ground and 3 m away from center of the bipolar line, in the following conditions:
a) stopped vehicle
b) vehicle at constant velocity
c) vehicle during rapid acceleration
d) vehicle during sudden breaking.
In phase 3, the PM was positioned inside the vehicle, vertically and 1.50 m above the ground, in the following conditions:
a) PM in different points
b) Irradiation by a portable radio, with transmitting and receiving frequencies of 158.825 MHz and 163.425 MHz, respectively, and a power of 1.5 W, placed in different sides:

- perpendicularly to PM and direct to radio-bridge;
- perpendicularly to PM and direct to PM up to a 50 cm distance from the PM susceptibility was evidenced up to 40 cm;
- oblique to PM.
c) Vehicle operating as shown in the points A-F.

Results

First test: PM parameters did not change between 200 and 1000 MHz. However, we observed temporary malfunctions on all 4 PMs tested, with temporary VOO setting at the programmed rate. In two PMs we observed temporary pacing inhibition.
From 30 to 220 MHz of EM field the results were:
- test a: horizontal PM = not susceptible;
  vertical PM = influenced at 44.03 MHz, (amplitude (A), 0.99; duration (W), K; frequency (F), K)
- test b: horizontal PM = not susceptible;
  vertical PM = influenced at 51.33 MHz (temporary inhibition), and 87.85 MHz (A, 0.73; W, 1.34; F, 94.9)
- test c: horizontal PM = not susceptible;
  vertical PM = influenced at 47.54 MHz, 51.33, and 87.85 MHz (A,0.80; W, K; F, K);
- test d: horizontal PM = not susceptible;
  vertical PM = influenced at 40.78, 81.36, 87.85, and 119.43 MHz (temporary inhibition at 51.33 MHz).

A frequency range between 220 and 1000 MHz with frontal and lateral antenna with 5 V/m and 10 V/m fields in AM modulation and pulse modulation any kind of susceptibility was observed on PMs tested.

Second test: Our measurements showed PM malfunction as follows:
- phase 1: only in source sites (transient VOO pacing)
- phase 3: only a certain distance, temporary inhibition and one 2,3,6 irreversible inhibition (test d).

Concerning the phase 2 no changes of PM program features were observed.

Discussion

PMs with unshielded and untwisted leads are much more heavily affected by EMI than PMs with twisted leads and a grounded shield. In fact in the test results analysis, test a, we have only a susceptibility frequency at 44.03 MHz using a shielded twisted cable, with a grounded shield, compared to many susceptibility frequencies obtained using a non-grounded shield. Thus, to increase the immunity level of PMs to the interference, a dedicated cable design should be considered a priority.

Our in vitro results show that operating ETACS cellular phones do not interfere with PMs. As a matter of fact, we did not observe any malfunction when irradiating PMs with frequencies in the 220-1000 MHz range. The same is true for cellular phones with analogue standards. This study shows some discrepancies due to inadequate correlation between our experimental models and the real situation encountered in an implanted PM. However, many authors [2, 4, 7] consider in vitro testing as being much more useful, both because the tests are carried out without harming the patients, and PMs can be tested before being put on the market. In addition, some conditions can not be reproduced in vivo, such as the situation of a failed call. In this phase the cellular phone sends a signal of repeated impulses sited in the connection-phase of with the base station without any thrill. This signal, according to Barbaro et al. [14] caused PM inhibition of up to 20 seconds with GSM phones. However, it is clear that more information and long-term evaluation is needed in order to correctly inform PM dependent patients that cellular phones could be potentially harmful.

EMI is a well-known and long recognized problem that can interfere with implanted electronic medical devices. In particular the ICD patient may need to be counseled on avoiding EAS devices, just as avoidance of other sources of EMI has become routine. Labeling sources of EMI, such as EAS devices, should also be considered. Since EAS devices operate by a variety of methods, further clinical testing of specific models should be done to determine which of these EAS devices can interact with specific models of PM. While our patients did not clinically suffer from this inappropriate PM firing, the potential for harm to patients is clear enough to warrant further study in order to fully define the nature of this risk.

In conclusion, in PM dependent patients a dedicated follow-up for the possible interference provoked by different EMI is needed.

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PROGRESS IN NON-PHARMACOLOGICAL TREATMENT OF CARDIAC ARRHYTHMIAS

Which Patients with Dilated Cardiomyopathy May Really Benefit from Dual-chamber Pacing?

S. ROMANO, M. PAGANI, P. MONTANARI AND ISSC GROUP

Congestive heart failure is one of the leading causes of morbidity and mortality in our country. In most patients, signs and symptoms of heart failure are the result of an enlarged, poorly contractile left ventricle. Therapy has been directed toward lowering pre-load, reducing after-load, improving contractility and interfering with the detrimental neurohumoral mechanisms activated in heart failure. In 1990, dual-chamber pacing was proposed as a therapeutic alternative for relief of symptoms in patients with dilated cardiomyopathy and severe heart failure who were unresponsive to the optimal medical therapy [1]. Initial reports have demonstrated a subjective abatement in symptoms as well as an objective increase in ejection fraction and cardiac output in patients undergoing dual-chamber pacing with short atrioventricular (AV) intervals [2, 3]. Subsequently these results were partially confirmed [4] or completely contradicted [5, 6], probably because the results were derived from observational studies with small, heterogeneous patient populations. In addition, it is unknown whether all subjects with left ventricular systolic disfunction respond to dual-chamber pacing or whether the beneficial effect is limited to a select subgroup of patients. The hemodynamic mechanisms of this "electrical" therapy may be resumed in three main physiopathologic statements:

1) The reduction of mitral regurgitation. Sequential pacing with short AV interval leads to an activated atrium during the expulsive stage of the left ventricle, thus determining the reduction of the ventriculoatrial gradient, the diastolic mitral regurgitation and the early mitral valve closure [1, 7].
2) A better utilization of the Frank-Starling mechanism obtained by restoring the atrioventricular synchronization [8].
3) A better sequence of the activation-relaxation induced by sequential pacing compared with that realized by the normal conduction pathways [3, 4, 9]. This mechanism may reduce the apical activation delay, that it's very pronounced in dilated hearts, and, consequently, the wall stress.

From these previous statements it appears evident that only a small, select group of patients may benefit from DDD pacing with shortened AV delay.

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The ISSC Study

The "Italian Study on Stimulation in Cardiomyopathy" (ISSC) provided the enrollment of a large number of patients affected by chronic heart failure due to coronary artery disease, idiopathic dilated cardiomyopathy or hypertensive cardiomyopathy with a left ventricular ejection fraction < 25% and a mitral regurgitation time > 50% of the R-R interval, who were followed for 2 years [10-11].

The randomization created 2 groups of patients: subjects with optimal pharmacological therapy and patients with the same therapy associated with sequential pacing with shortened optimized AV interval. The optimized AV interval was defined as the specific programmed AV delay which resulted in the minimal mitral regurgitation time that did not reduce the cardiac output during paced ventricular rhythm. We associated to the paced group enrolled for the ISSC, a group of paced patients with the same clinical and hemodynamic enrollment characteristics but not randomized, reaching a total of 26 subjects, and then evaluated the clinical and hemodynamic outcome in 4 subsets: patients with an echocardiographic pattern of altered relaxation rappresented by an E/A ratio < 1 at echo-doppler curve (group 1) versus subjects with a restrictive pattern represented by an E/A ratio > 2 (group 2); patients with a PR interval ≥ 200 ms (group 3) versus patients with a PR interval < 200 ms (group 4).

Twenty-one patients of groups 1 (11 patients) and 2 (10 patients) reached the 1-month follow-up and 12 (7 patients of group 1) reached the 6-month follow-up, while groups 3 (11 patients) and 4 (9 patients) were analyzed only at the 6-month follow-up; the subjects with an E/A ratio between 1 and 2 were not considered. In Table 1 it appears that in group 1 the arterial blood pressure deteriorated significantly while NYHA functional class, energy and activity scores are equally and significantly improved at the 1-month follow-up. The echocardiographic parameters, except left atrium diameter, diastolic left ventricular diameter and cardiac output, were significantly improved.

In group 2 (Table 1) none of the clinical and echocardiographic data improved significantly. In Table 2 (6-month follow-up) it appears that in group 1 the arterial

Table 1. Clinical and hemodynamic outcome for groups 1 and 2 at 1 month follow-up

Group 1 - Altered Relaxation Pattern (E/A < 1) (11 pts)

Data	Pre-impl	1st Month	P
ABP (mmHg)	134 ± 21	122 ± 12	<0.02
NYHA	3.1 ± 0.4	2.5 ± 0.5	<0.02
LAD (mm)	50.3 ± 5.7	49.6 ± 7.2	NS
LVSD (mm)	63.8 ± 7.6	61.4 ± 8.8	<0.05
LVDD (mm)	71.7 ± 7.3	71 ± 8.1	NS
FS (%)	11.9 ± 3.1	14.6 ± 5.3	<0.05
EF (%)	23.3 ± 5.1	26.9 ± 7.4	<0.05
CO (l/m)	3.8 ± 1.3	4.1 ± 1.3	NS
MRT (ms)	440 ± 57	390 ± 53	<0.03
LVFT (ms)	326 ± 143	401 ± 209	<0.05
ES	4.1 ± 0.9	5.2 ± 1.0	<0.02
AS	4.0 ± 0.7	4.9 ± 0.7	<0.04

Cont. Table 1.

Group 2- Restrictive Pattern (E/A > 2) (10 pts)

Data	Pre-impl	1st Month	P
ABP (mmHg)	121 ± 28	110 ± 14	NS
NYHA	3.2 ± 0.4	3.1 ± 0.3	NS
LAD (mm)	48.1 ± 6	46.5 ± 4.7	NS
LVSD (mm)	59.7 ± 11.9	58.9 ± 11.5	NS
LVDD (mm)	71.7 ± 12.2	71.7 ± 11	NS
FS (%)	16.7 ± 5.1	17.5 ± 5.1	NS
EF (%)	22.6 ± 7.3	23.7 ± 8.6	NS
CO (l/m)	3.4 ± 0.9	3.7 ± 1.1	NS
MRT (ms)	391 ± 77	389 ± 51	NS
LVFT (ms)	377 ± 118	383 ± 103	NS
ES	4.4 ± 0.8	4.6 ± 0.8	NS
AS	4.3 ± 0.6	4.7 ± 0.9	NS

ABP, arterial blood pressure; NYHA, New York Heart Association functional class; LAD, left atrial diameter; LVSD, left ventricular systolic diameter; LVDD, left ventricular diastolic diameter; FS, fractional shortening; EF, ejection fraction; CO, cardiac out put; MRT, mitral regurgitation time; LVFT, left ventricular filling time; ES, energy score; AS, activity score

Table 2. Clinical and hemodynamic outcome for groups 1 and 2 at 6-month follow-up

Group 1 - Altered Relaxation Pattern (E/A < 1) (7 pts)

Data	Pre-impl	6th Month	P
ABP (mmHg)	136 ± 22	128 ± 10	NS
NYHA	3.1 ± 0.3	2.5 ± 0.7	NS
LAD (mm)	51.6 ± 5.6	50.0 ± 7.4	NS
LVSD (mm)	63.9 ± 6.3	60.7 ± 4.1	<0.05
LVDD (mm)	72.6 ± 6.7	72.4 ± 6.3	NS
FS (%)	10.9 ± 0.7	15.1 ± 3.1	<0.05
EF (%)	24.0 ± 3.3	29.5 ± 5.2	<0.05
CO (l/m)	4.0 ± 1.3	4.0 ± 0.8	NS
MRT (ms)	420 ± 45	349 ± 53	<0.03
LVFT (ms)	280 ± 158	358 ± 113	<0.05
ES	3.5 ± 0.5	5.7 ± 1.2	<0.05
AS	3.7 ± 0.4	5.2 ± 1.2	NS

Group 2- Restrictive Pattern (E/A > 2) (5 pts)

Data	Pre-impl	6th Month	P
ABP (mmHg)	109 ± 17	116 ± 13	NS
NYHA	3.4 ± 0.5	3.0 ± 0.7	NS
LAD (mm)	42.3 ± 2.5	44.0 ± 1.7	NS
LVSD (mm)	62.0 ± 16.1	60.0 ± 11.4	NS
LVDD (mm)	74.7 ± 17.1	72.3 ± 11	NS
FS (%)	17.4 ± 3.0	16.9 ± 2.6	NS
EF (%)	26.3 ± 9.1	29.7 ± 4.7	NS
CO (l/m)	3.8 ± 0.9	3.5 ± 1.2	NS

Cont. Table 2.

Data	Pre-impl	6th Month	P
MRT (ms)	405 ± 84	409 ± 30	NS
LVFT (ms)	353 ± 170	429 ± 118	NS
ES	4.4 ± 1.1	4.4 ± 1.3	NS
AS	4.6 ± 0.8	4.4 ± 1.5	NS

ABP, arterial blood pressure; NYHA, New York Heart Association functional class; LAD, left atrial diameter; LVSD, left ventricular systolic diameter; LVDD, left ventricular diastolic diameter; FS, fractional shortening; EF, ejection fraction; CO, cardiac out put; MRT, mitral regurgitation time; LVFT, left ventricular filling time; ES, energy score; AS, activity score

blood pressure deteriorated too, but not significantly, and that the NYHA functional class and the activity score improved too, but not significantly; the outcome of the other echocardiographic data was like the first-month follow-up.

No significant improvement in the clinical and echocardiographic parameters was found in group 2 at the 6-month follow-up (Table 2).

As illustrated in Table 3, we did not find any significant improvement in the group 3 patients (PR ≥ 200 ms) except for the systolic left ventricular diameter and the mitral regurgitation time. The group 4 patients showed a significant improvement in all the data except the arterial blood pressure, the NYHA functional class and the diastolic left ventricular diameter (Table 3).

Table 3. Clinical and hemodynamic outcome for groups 3 and 4 at 6-month follow-up

Group 3 - PR Interval ≥ 200 ms (11 pts)			
Data	Pre-impl	6th Month	P
ABP (mmHg)	121 ± 11	125 ± 13	NS
NYHA	3.1 ± 0.6	2.8 ± 0.7	NS
LAD (mm)	45.5 ± 5.1	45.7 ± 5.3	NS
LVSD (mm)	61.8 ± 11.2	58.0 ± 8.9	<0.05
LVDD (mm)	72.9 ± 13.3	70.2 ± 9.8	NS
FS (%)	14.9 ± 4.5	17.0 ± 4.0	NS
EF (%)	23.1 ± 5.4	25.0 ± 6.3	NS
CO (l/m)	3.6 ± 1.3	3.5 ± 1.8	NS
MRT (ms)	460 ± 82	406 ± 66	<0.05
LVFT (ms)	274 ± 158	337 ± 134	NS
ES	4.4 ± 1.5	5.1 ± 1.6	NS
AS	4.5 ± 1.1	4.9 ± 1.7	NS
Group 4 - PR Interval ≤ 200 ms (11 pts)			
Data	Pre-impl	6th Month	P
ABP (mmHg)	135 ± 19	132 ± 10	NS
NYHA	3.1 ± 0.6	2.4 ± 0.7	NS
LAD (mm)	51.0 ± 6.0	48 ± 7.0	<0.05
LVSD (mm)	64.6 ± 5.1	61.7 ± 4.8	<0.01

Cont. Table 3.

Data	Pre-impl	6th Month	P
LVDD (mm)	73.1 ± 5.6	72.4 ± 6.0	NS
FS (%)	10.8 ± 1.8	14.1 ± 2.1	<0.01
EF (%)	24.2 ± 3.4	32.4 ± 4.8	<0.01
CO (l/m)	4.1 ± 0.4	4.3 ± 0.5	<0.02
MRT (ms)	409 ± 50	375 ± 38	<0.05
LVFT (ms)	358 ± 87	470 ± 108	<0.02
ES	3.8 ± 0.7	5.6 ± 1.1	<0.02
AS	4.0 ± 0.8	5.5 ± 0.8	<0.05

ABP, arterial blood pressure; NYHA, New York Heart Association functional class; LAD, left atrial diameter; LVSD, left ventricular systolic diameter; LVDD, left ventricular diastolic diameter; FS, fractional shortening; EF, ejection fraction; CO, cardiac out put; MRT, mitral regurgitation time; LVFT, left ventricular filling time; ES, energy score; AS, activity score

Discussion

The effect of dual-chamber pacing in end-stage dilated cardiomyopathy was first reported by Hochleitner et al. [1] without determining any precise mechanism of action. The beneficial effects of this "electrical" therapy were explained by different hemodynamic mechanisms. Some authors [2] considered the reduction of ventriculoatrial regurgitation obtained by shortening the AV delay as the determining factor, others [3-4] pointed out the modification of pre-load or the optimization of the mechanical atrioventricular synchrony. However, from some studies it appeared evident that only a select group of patients might benefit from pacing therapy [2, 4, 12]. Our data suggest that an optimized, programmed AV interval may reduce mitral incompetence, probably by a better synchronization between atrial and ventricular systole, allowing a more prolonged time for ventricular filling, as suggested by Nishimura [4, 11]. The normal pattern of the left ventricular filling is altered in congestive heart failure [13]. Early in heart failure the amount and rate of the early filling are reduced, and the relative importance of the filling during atrial contraction is enhanced. This has been attributed to a slowing of the rate of the left ventricular relaxation rappresented by an E/A ratio < 1 at echo-doppler curve. Only at this time of the heart failure can optimal synchronization of the atrioventricular systole be favorable. When, later in the course of the disease, the stiffness of the left atrium and ventricle, represented by an E/A ratio > 2, is established, optimal atrioventricular synchronization becomes less important, and a shortening of the programmed AV interval might be dangerous. Nishimura, furthermore, found a beneficial effect of the DDD stimulation only in those subjects with a prolonged PR interval [4]. In these patients the atrial contraction is so early as to lose the "atrial kick", so that by restoring the normal synchronization between atrial and ventricular systole we could obtain an improvement of the cardiac output. Our data do not confirm these statements. In our study we obtain beneficial effects only in the group of patients with normal PR

interval (group 4). It is not easy to explain these results. We think that the sole explanation may be that in group 4 we had more than 50% of patients with an echocardiographic pattern of altered relaxation and only 12% with a restrictive pattern, the remaining patients having an E/A ratio between 1 and 2, while in group 3 (PR ≥ 200 ms) the two echocardiographic patterns evaluated were both present in 25% of the patients. If the situation of the altered relaxation has a great influence on the outcome of this therapy, it might alter the results in the groups of patients evaluated for the PR interval.

Conclusions

Our data are still incomplete, and do not allow us to answer the initial question in a demonstrable way. From our results we could outline a profile of the kind of patient suitable to benefit from sequential pacing with shortened AV interval. This patient might have a severe, drug-resistant, congestive heart failure, with an echocardiographic pattern of altered relaxation with an E/A ratio < 1. The importance of the PR interval is not clear. We hesitate to draw many conclusions from our results because they were obtained from a small sample and contrast with many previous studies. Certainly we feel we can discourage the use of this therapy in patients in which the pharmacological therapy is still effective and an echocardiographic restrictive pattern or an atrial paralysis are present.

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Atrial Flutter Ablation: Long-Term Results with Standard Approach after Eight Years of Experience

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Introduction

In the last 10 years there have been important advances in the understanding of atrial flutter mechanisms, that have led to new therapies aimed at circuit ablation. Mapping and entrainment studies have established that common flutter (FL) is due to a large reentry circuit in the right atrium, encircling superior and inferior vena cava in a "counterclockwise" direction (down the anterior wall, up the septal wall). A less common form of FL, usually producing positive looking waves in the inferior leads, is due to reentry in the same circuit in the opposite ("clockwise") direction [1]. The crista terminalis is thought to play a crucial role in both cases, by blocking transverse conduction between the venae cavae orifices, on the bases of anisotropic conduction, and other anatomic obstacles, such as the Eustachian ridge, may be important to direct activation in other areas [2].

After some initial attempts with direct current (DC) shocks, generally delivered over areas with fragmented electrograms [3], radiofrequency ablation has established itself as the treatment of choice [4]. This less aggressive therapy is directed at critical isthmuses in the circuit, all located in the low right atrium (RA). Linear ablation between tricuspid valve and inferior vena cava, tricuspid valve and eustachian ridge and tricuspid valve and coronary sinus ostium, can interrupt flutter and prevent its recurrence in many cases. However, there are some remaining questions about the long-term outcome of flutter ablation therapy. On one hand, there has been concern about recurrence rate, especially in early reports, but more importantly, a high incidence of atrial fibrillation has been reported by some authors during follow-up, casting a shadow over long-term prognosis.

The first oral report of successful radiofrequency (RF) flutter ablation was made in 1991 [5], and the first written report in 1992 [6]. Since then significant experience has been accumulated [7-13], including long-term follow-up, and allowing a better perspective of the therapeutic value.

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Pathogenesis of Atrial Flutter

Mapping, entrainment and RF ablation have clearly established the anatomic basis of the reentrant circuits producing flutter in the right atrium [1], however, *in most cases we still don't know what the actual cause of flutter is.* In the case of surgically produced atrial scars [14-16], the pathological substrate is clear. However, in common flutter, we find reentry around normal structures, i.e. the venae cavae and the crista terminalis (Fig. 1 and 2). Even in the presence of surgical scars, the incidence of scar flutter is very small, compared to the large number of patients undergoing cardiac surgery.

Most studies of atrial arrhythmias have considered flutter and fibrillation as a common entity, and we have no specific information on such basic issues as atrial size, muscle structure, or specific diseases underlying flutter. Experimental studies suggest that a combination of a short refractory period and/or slow conduction velocity (short wavelength) underlies both flutter and fibrillation, but wavelength would be shorter in fibrillation than flutter [17]. However, experimental flutter studied in this way does not necessarily have the same mechanism as clinical flutter; it needs an enhanced vagal tone to occur, and it has a functional basis, so that circuits can be localized any place in the atria [18]. In patients with paroxysmal flutter and fibrillation, electrophysiologic studies have shown a trend

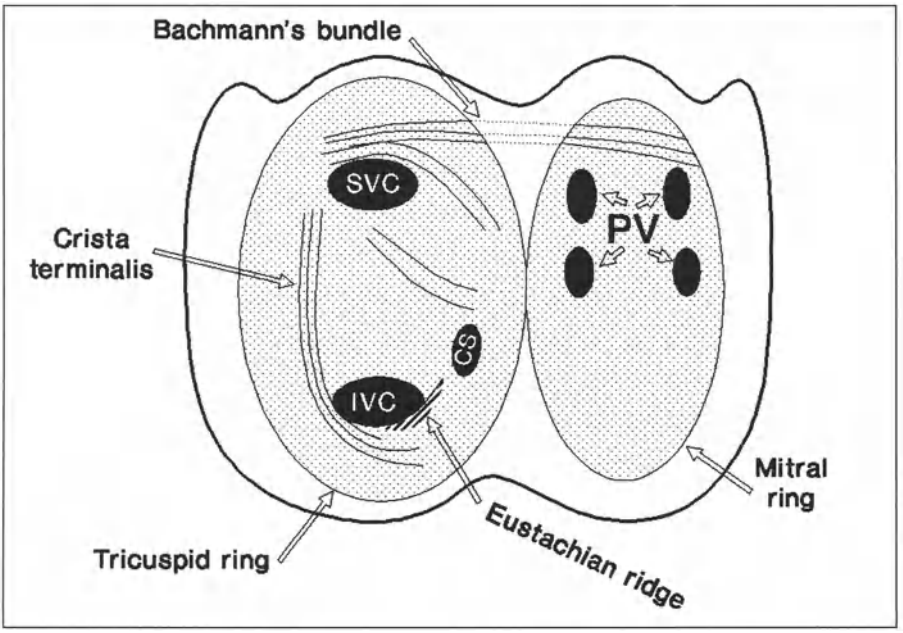

Fig. 1. Schematic representation of the atria in a left anterior oblique view, from the mitral and tricuspid rings. The endocardium is shaded, and the direction of the main muscle bundles is shown. CS, coronary sinus ostium; IVC, inferior vena cava; PV, pulmonary vein orifices; SVC, superior vena cava

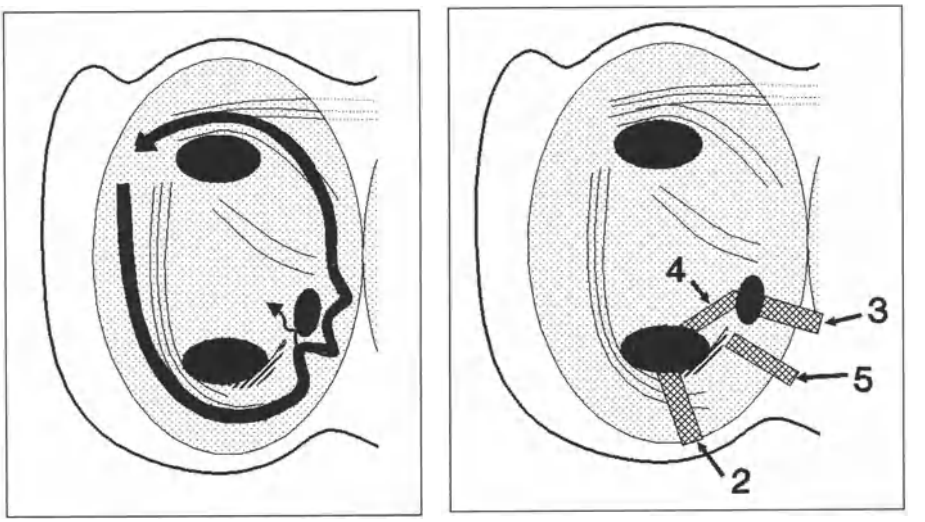

Fig. 2 a, b. (a) Schematic representation of reentrant activation in common flutter, on the same atrial representation used in Figure 1. A *bold arrow* marks the main activation pathway and the winding course suggests slow conduction. A *small arrow* between the Eustachian ridge and the coronary sinus ostium marks the alternative pathway present in some cases. (b) Targets for common or clockwise flutter ablation. *2*, Inferior vena cava-tricuspid isthmus. *3*, Coronary sinus ostium-tricuspid ring isthmus. *4*, Coronary sinus ostium-inferior vena cava isthmus. *5*, Tricuspid ring-eustachian ridge isthmus. All points in targets 2, 3 and 5 would meet also the condition of producing concealed entrainment and return pauses equal to flutter cycle length, but in some patients target *4* would be outside the circuit

toward short refractory periods and slow conduction of premature impulses [19, 20], but without significant differences between both arrhythmias.

Anisotropic conduction is considered an important factor in flutter. The structure of the crista terminalis, a thick bundle of parallel fibers, would seem enough to promote preferential conduction longitudinally (craniocaudally or caudocranially), while slowing or blocking conduction transversely, only on the basis of intercellular resistivity [21] (Fig. 1 and 2). Additional factors can accentuate anisotropy, such as end-to-end disposition of the gap junctions [22], and a specific ion channel predominance in cell membranes [23]. However, we again have no evidence that the crista, or its cell disposition are different in flutter than in normal rhythm or atrial fibrillation.

The presence and location of a slow conduction zone has been matter of debate. The recording of long conduction intervals between the lateral RA and the coronary sinus in flutter, compared to sinus rhythm [24], has been widely accepted as proof of the presence of an area of slow conduction in the flutter circuit. However, the length of the conduction path was never measured, and this concept has been questioned [25]. Some authors have localized an area of slow conduction in the low lateral right atrium [26], others in the inferior vena cava-tricuspid isthmus area [6, 9]. Other evidence points at the presence of areas of

slow conduction at the base of Koch's triangle, around the coronary sinus ostium [27, 28] (Fig. 2), where atrial myocardium is very thin, and contains fibers converging from multiple directions in crossing patterns [29]. Longitudinal periannular fibers, present around the tricuspid annulus, are also absent in this area, so that anisotropy may again be a significant factor determining local conduction velocity. At any rate, once again there is nothing to prove that, even if there is slow conduction in this or other parts of the flutter circuit, this is not due simply to anisotropy, given the abnormal, circular sequence of activation.

The inevitable conclusion of this review is that, even if ablation can interrupt the flutter circuit and thus prevent recurrence of the arrhythmia, this does not mean that it eliminates abnormal tissues which are the electrophysiologic or pathologic substrate. Flutter ablation only alters the anatomic structure that makes a particular reentry circuit possible, therefore, the term "cure" may not be applicable to atrial flutter ablation, as it is to accessory pathway ablation. However, there have been recent reports of flutter triggering atrial fibrillation in some patients [30], and if we put this together with its potential electrical remodeling effect [31], flutter ablation may have a beneficial impact beyond mere interruption of the arrhythmia.

Clinical Correlates

We have treated 62 flutter patients with radiofrequency ablation since March 1990. The clinical arrhythmia was common flutter in 59 and positive-wave (clockwise) flutter in 3. There was associated atypical flutter, due to reentry around a surgical scar in 6, and 7 had previously documented episodes of atrial fibrillation. As in other series, there was a clear male sex predominance (81%) and there was no uniform disease background (Table 1). The heart was normal in 14 (22.6%), there was a history of chronic obstructive lung disease in 10 (16%) and coronary artery disease in 9 (14.5%). Arterial hypertension, valvular heart disease and bradycardia-tachycardia syndrome were diagnosed in 4 (6.5%) each. Dilated cardiomyopathy was present in 5 (8%), and this is an interesting group, because in 2 patients cardiac size and function normalized after flutter ablation. There were hypertrophic cardiomyopathy and a small interatrial septal defect in one case each.

Another interesting group was that of patients having undergone cardiac surgery, because these tended to have multiple reentry circuits. This group includes 4 atrial septal defects, 1 ventricular septal defect, 1 case of Ebstein's anomaly operated for Wolff-Parkinson-White syndrome, and a right ventricular myxoma with residual tricuspid insufficiency. All of these 6 patients had common flutter and another flutter due to reentry around a lateral wall surgical scar. Two more patients had had surgery for right and left atrial myxoma respectively, 1 had surgical ablation of a posteroseptal accessory pathway and several others had coronary or valvular disease surgery, but none of these had reentry around surgical scars.

Similarly to the experience of other groups the larger single group of patients in our series had an apparently normal heart. However, the impression at the time

Table 1. Associated diseases in 62 consecutive patients with common or clockwise flutter, undergoing ablation between 1990 and 1997

	Number	%
Total series	62	100
Male	50	80.6
Female	12	19.4
Associated Heart Disease		
No heart disease	14	22.6
Chronic lung disease	10	16.1
Coronary disease	9	14.5
Dilated cardiomyopathy	5	8.1
Valvular heart disease	4	6.5
Sick Sinus Syndrome	4	6.5
Systemic hypertension	4	6.5
Post ASD repair	4	6.5
Post myxoma resection	4	6.5
Post VSD repair	1	1.6
Post WPW surgery	1	1.6
Hypert. cardiomyopathy	1	1.6
Small ASD	1	1.6

ASD, atrial septal defect; VSD, ventricular septal defect; WPW, Wolff-Parkinson-White syndrome

of RFA was that the right atrium was significantly dilated in most cases. If one considers the cases with bronchopulmonary disease, valvular heart disease, congenital left-to-right shunts or surgically induced tricuspid insufficiency, it would appear that right atrial overload could be a significant factor in flutter pathogenesis. It has been observed that patients with paroxysmal atrial flutter may have more right atrial dilation than those with paroxysmal fibrillation [32]. It should be noted that we are including in this review only patients having right atrial reentry circuits, and that this excludes around 15%-20% of atrial tachycardias within the flutter rate range [33] that are due to left atrial circuits, because the structure of these is not well known.

Natural History of Atrial Flutter

When we try to compare the long-term results of flutter ablation with its spontaneous evolution, it becomes clear that there is little information on flutter natural history. The literature contains reports on "atrial flutter and fibrillation" [34] but the possibility of flutter ablation demands a clear distinction between these arrhythmias, even though they may have similar clinical correlates. It is not known how many patients have both arrhythmias at one time or another, or why some patients only have either flutter or fibrillation.

Recently published work by Crijns et al. [35] sheds some light on the matter. These authors followed 50 patients with flutter with a higher prevalence of coro-

nary artery disease (38%) than our patients, but an almost identical proportion of lone flutter (28%). Ninety-six patients were successfully cardioverted with DC shock, then followed without antiarrhythmic drugs. There was a recurrence rate of 53% at 1 year, and 58% at 5 years, without any further antiarrhythmic treatment. When flutter recurred new cardioversion was attempted (1-6 cardioversions with a median of 2), and drugs were given. With this strategy 90% of patients maintained sinus rhythm after 5 years. It is interesting that no atrial fibrillation is reported in this group of patients during follow-up, perhaps because of a careful selection, excluding any fibrillation episodes prior to entering the study. This study indicates that a single cardioversion may be effective enough for 40% of the patients, but also, and very importantly, that atrial fibrillation does not necessarily occur in patients with flutter, even after several years of evolution.

The Experience with Radiofrequency Ablation

Flutter Interruption and Inducibility

Since the description of the anatomic bases of the circuit, multiple groups have reported successful ablation, defined by flutter interruption and non-inducibility at the end of the procedure [6-13]. Ablation targets have been (Fig. 2):

1. Points of the low right atrium producing concealed entrainment with a variable interval between stimulus and negative deflection on the ECG flutter wave [6, 9]
2. The inferior vena cava-tricuspid ring isthmus [7, 8, 10-12]
3. The coronary sinus ostium-tricuspid valve isthmus [10, 36]
4. The coronary sinus ostium inferior vena cava isthmus (mostly complementary with n. 2) [10, 36], and most recently,
5. The tricuspid ring-eustachian ridge isthmus [36].

Success rate has been 85%-95% in terms of flutter interruption, but slightly less if the endpoint was non-inducibility. Most groups now seem to favor an anatomic approach, complemented with timing the electrograms at the ablation target in the frame of septal and anterior wall activation [4, 7, 8], or with the relatively flat segment of the common flutter wave [10]. The use of larger electrode tips (8-10 mm length) with a power source delivering > 50 W may be more effective, decreasing the number of applications and duration of the procedure [9, 11, 37], but no comparative data are available. Notably the complication rate has been extremely low. The most significant problem has been an occasional incidence of atrioventricular block while making applications around the coronary sinus ostium [12]. Other authors have noted ventricular slowing with applications in the same area [10]. Pain may be a problem, especially when radiofrequency is delivered in the inferior vena cava, but generally it is well controlled with light sedation. Hemopericardium has not been reported.

The Problem of Flutter Recurrence

A recurrence rate of 20%-30% has been the rule after 3-12 month follow-up (Table 1). In a very long-term follow-up we observed most recurrences within the first 2 months after ablation, but some late recurrences brought the total rate to > 40% after 2 years [4]. Philippon et al. [11] reported a lower recurrence rate (9.4%), but their patient selection for ablation did not require previous recurrence after ablation and resistance to antiarrhythmic drugs. These results are not comparable to those of Crijns et al., described above [35], because most patients in ablation series had recurrent flutter, after cardioversion and antiarrhythmic drugs. In our and other authors' experience, recurrent flutter was generally the same common or clockwise flutter treated initially, and a second ablation was successful in almost all cases. This suggested that incomplete ablation of the critical isthmus was the problem, and raised questions on the value of flutter inducibility as an endpoint. The reproducibility of flutter induction has never been tested. A few patients with recurrent flutter were treated successfully with antiarrhythmic drugs that were ineffective before radiofrequency ablation.

Testing for conduction block across the inferior vena cava-tricuspid isthmus area as the endpoint seems to improve recurrence rates (Fig. 3). Patients without

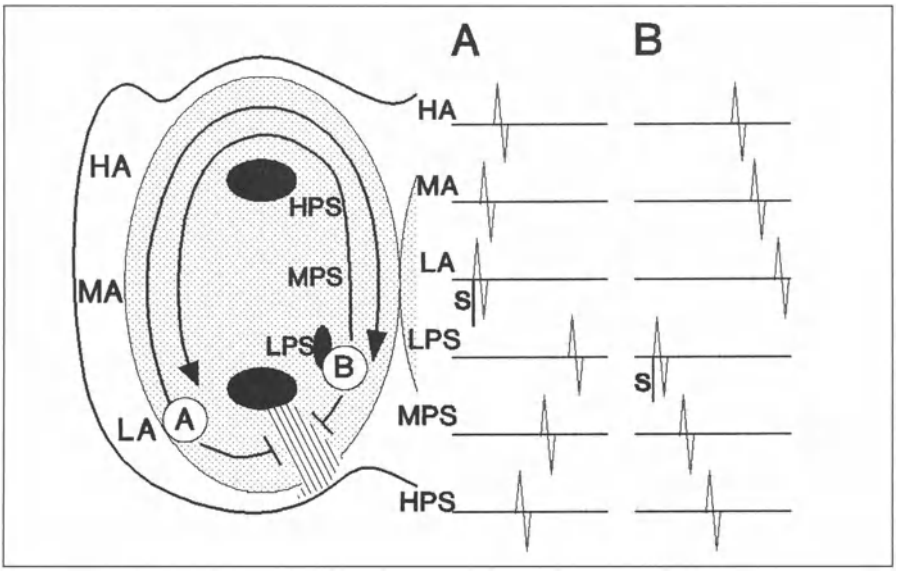

Fig. 3. Schematic representation of atrial activation after complete block of the inferior vena cava-tricuspid isthmus. The drawing on the left shows pacing sites on the low anterior (*A*) and low septal wall (*B*). The ablation (block) line is shaded. *Curved arrows* mark direction of activation, producing the (schematic) electrogram sequences shown on the right. Recordings are, from top to bottom: HA, high anterior; MA, mid anterior; LA, low anterior; LPS, low-posterior septum; MPS, mid-posterior septum; HPS, high-posterior septum. Note that pacing either side of the blocked isthmus activation reaches the high right atrium before descending the opposite atrial wall (from [44])

demonstrable conduction through the inferior vena cava-tricuspid isthmus after ablation, have a recurrence rate around 10%, while in those not showing complete, bi-directional isthmus block, recurrence rate may be ≥ 40% [38-40]. However, complete isthmus block may not be attained in all cases, and this strategy may still be met with recurrence rates of 20% in the long-term [41].

In our experience with 62 cases since 1990, recurrence rate was 58% with follow-up at 1 year in the 24 cases performed before 1995, when non-inducibility was the main endpoint (in the initial cases interruption was the only endpoint). In the 38 patients ablated since 1995, using mainly isthmus block as the endpoint, recurrence rate has been 13% ($p < 0.001$). Follow-up is shorter in the latter group, but the difference is still significant when only those patients followed for more than 3 months are considered (10.5% after 1995, 58.3% before, $p < 0.001$), and most recurrences occur in the first month after ablation. Recurrence rate was not related to the presence of associated organic heart disease.

The Problem of Atrial Fibrillation

The incidence of atrial fibrillation or other atrial arrhythmias, such as atypical flutter after ablation is of concern. Since early in the radiofrequency ablation experience an incidence of paroxysmal, or even permanent atrial fibrillation has been noted during follow-up, which is variable, but reaches 20%-35% [8, 10, 11, 13, 42]. Some of the patients had had documented episodes of fibrillation before flutter ablation, but in others it was documented for the first time after ablation. Philippon et al. [11] described several factors predictive of an incidence of atrial fibrillation, including previous history, organic heart disease, inducible sustained fibrillation after ablation, and a large number of antiarrhythmic drug failures prior to ablation.

We have followed 61 of our patients for 1-96 months (22.8 ± 19.8) (Table 2), and atrial fibrillation occurred in 39%, but there was a significant difference between the 24 patients treated before 1995 (71% incidence of atrial fibrillation) and the 38 treated since then (18%, $p < 0.001$). This difference can be explained by several factors, including patient selection, length of follow-up, and improved ablation techniques, however the difference remained significant when patients with a follow-up less than 6 month were excluded (71% incidence before 1995, 16% after, $p < 0.001$). The incidence of atrial fibrillation was higher in patients with flutter recurrence post-ablation (68%) vs no recurrence (27%, $p < 0.01$), but was not significantly higher in the 7 patients with previously documented episodes (57%) than in the 55 without (36%). The incidence of atrial fibrillation during follow-up was 35.7% in 14 patients with normal hearts, vs 39.5% in 48 patients with associated disease (p = NS). A history of heart failure was not significantly related to the incidence of post-ablation fibrillation either (46% of 13 patients with vs 37% of 49 patients without, p = NS).

In our series 67% of patients were in sinus rhythm up to the end of 7-year follow-up. Thirty-one percent were on antiarrhythmic drugs (12 with atrial fibrillation, 6 without). Five patients received AAI or DDD pacemakers for sick sinus syndrome and 3 patients underwent AV nodal ablation.

Table 2. Ablation success (flutter interruption), isthmus block, flutter recurrence and incidence of atrial fibrillation post ablation reported in the literature and our presently reported experience

Reference	Year	N. cases	% Success interruption	Isthmus Block	Follow-up (months)	Flutter recurrence	Atrial fibrillation
Kirkorian et al [8]	1994	22	86	—	13 ± 8	9%	27%
Fischer et al [10]	1995	80	90	—	20 ± 8	17%	20%
Philippon et al [11]	1995	59	90	—	13.2 ± 6.6		
Poty et al [38]	1995	12	100	11	9 ± 3	8%	—
Cauchemez et al [40]	1996	20	80	no/part 6	8 ± 2	43%	—
				comp 14		8%	—
Poty et al [39]	1996	44	100	comp 43	12.1 ± 5.5	9%	39%
Schartzman et al [41]	1996	35	100	part/comp	12 (act)	20%	—
Movsowitz et al [42]	1996	32	100	—	8.6 ± 5.2	16%	34%
Saxon et al [13]	1996	51	88	—	5.5 ± 1.9	22%	12%
Our series	1990-94	24	96	—	37.9 ± 23.3	58%	42%
Our series	1995-97	38	100	89%	13.7 ± 9.4	13%	8%

part, partial; comp, complete

Prognosis of Scar Flutter

We have ablated atypical flutter circuits, rotating around surgical RA scars in 6 patients that also had common or clockwise flutter. Three had had closure of an atrial septal defect, 1 of a ventricular septal defect, 1 surgery for right ventricular myxoma, and one surgical ablation of accessory pathways in the context of Ebstein's anomaly. In some patients scar flutter was well documented clinically, but in others it was only recognized during the electrophysiologic study leading to ablation. All 6 scar flutters were ablated successfully after 1-2 procedures, and none have recurred, even though common flutter did recur in 2 of the patients, needing another ablation procedure. This experience includes relatively simple heart disease, and is comparable to the early experience by Lesh et al. [9]. Delimitation of circuit anatomy, and critical isthmuses for ablation is much more difficult in patients with surgical correction of complex heart disease, such as transposition or tricuspid atresia (Mustard, Senning or Fontan procedures), and recurrences are also more common in this group [14-16].

Conclusions

Radiofrequency ablation of a critical isthmus in the low right atrium is very successful for flutter interruption, and with the appropriate endpoints recurrence rate is low. Recurrences can be successfully treated with new ablation, and in some other patients can be treated successfully with previously ineffective drugs. Development of better catheter designs and/or energy sources, may still improve the results of the procedure.

Further study is necessary on the effect of earlier flutter ablation on the late incidence of atrial fibrillation. If flutter and fibrillation have a similar pathologic and electrophysiologic background, then flutter ablation may simply modify the clinical manifestations of a process necessarily abutting to atrial fibrillation sooner or later. On the other hand, if these arrhythmias have significant differences, flutter ablation may change the natural history, by preventing the cardiomyopathic changes due to persistent tachycardia, both at the atrial and ventricular level [43], and perhaps preventing electrical remodeling leading to further arrhythmogenic changes in atrial myocardium.

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Is the Evaluation of Heart Rate Variability Before ICD Discharge Useful to Understand the Mechanisms of Sudden Cardiac Death?

F. Lombardi[1], M. Marzagalli[2] and A. De Rosa[3] for the HRV-ICD Italian Study Group[4]

The role of the autonomic nervous system in facilitating the occurrence of malignant ventricular arrhythmias is supported by several experimental and clinical observations [1]. In different animal models it has been demonstrated that sympathetic activation, particularly during acute myocardial ischemia, may alter cardiac electrical properties and increase electrical instability [1-3]. In the clinical setting, indirect signs of sympathetic activation such an increase in heart rate, are frequently observed in the minutes preceding the onset of ventricular tachycardia or fibrillation [4].

More recently attention has been paid to evaluate the role of the autonomic nervous system in patients with malignant ventricular arrhythmias in whom an implantable cardioverter-defibrillator was implanted as a non-pharmacological treatment to prevent arrhythmic death.

In these patients it has been possible to document the circadian distribution of the detected and treated arrhythmic events, to perform a correct analysis of the type of arrhythmias by analyzing the stored electrogram, and to study the mechanisms of onset of the detected arrhythmias [5-7]. Most of the available data indicate the presence of a circadian distribution of the arrhythmic events which are more frequent in the early morning hours and seem to parallel the well known day-night pattern of variation of autonomic modulation of sinus node. Moreover, the observed increase in heart rate, and the reduction of the coupling between sinus cycles and ectopic beats in the minutes preceding ventricular tachycardia or fibrillation, can be interpreted as a further indication of a critical trigger role of sympathetic activation.

The possibility of activating a storage function in some implantable cardioverter-defibrillators offers a new potentiality of analyzing the time series of RR intervals preceding the detected arrhythmic event.

Interest for this type of study derives from the numerous observations [8-11] which have indicated that time and frequency domain analysis of heart rate variability is a noninvasive technique capable of providing relevant information on the autonomic modulation of sinus node. The basic assumption is that the con-

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[4]The list of the partecipating centers is indicated in the appendix

tinuous beat-to-beat oscillations which characterize heart period even during resting controlled conditions are the result of a complex interaction between sympathetic and vagal efferent neural activities and sinus node responsiveness [7-11]. Thus, the identification and quantification of the most important oscillatory components can provide information on the neural mechanisms largely responsible for such a rhythm.

It is generally recognised [8-11] that during short term recordings two major oscillatory components characterize 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 normalized 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 ratio between LF and HF has been proposed and utilized as an index of sympatho-vagal balance [8-11].

An increase in LF and in LF/HF ratio has been reported in most clinical conditions associated with a shift of sympatho-vagal balance toward a sympathetic activation and a reduced vagal tone as in the acute and post-acute phase of an uncomplicated myocardial infarction [12], in congestive heart failure or in patients with mild to moderate essential hypertension [11]. On the contrary, LF/HF values smaller than 2 and a predominant HF component have been reported in clinical conditions characterized by a vagal predominance [11].

Thus, the time series which can be extracted by the storage function of Micro Jewel devices at the time of clinical control, can be used to analyze heart rate variability in the minutes before the onset of the detected ventricular tachycardia or fibrillation.

There are however several critical aspects which have to be taken into consideration to perform an appropriate analysis of heart rate variability, and to obtain appropriate information on autonomic modulation of sinus node.

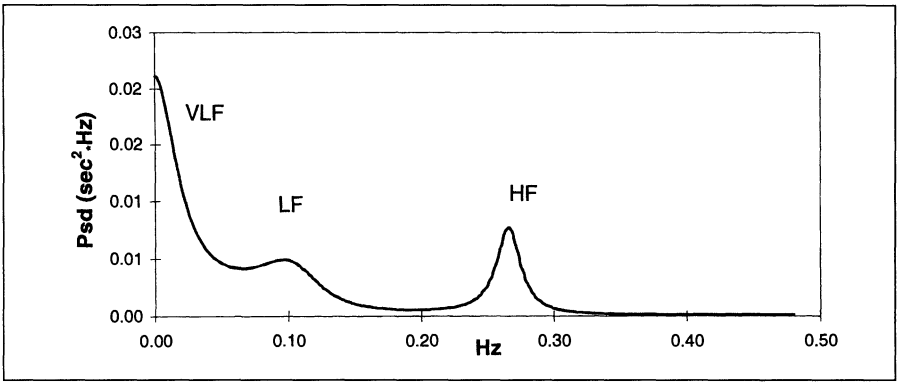

Fig. 1. Spectral analysis of heart rate variability during resting controlled conditions in a normal subject. Two major components at low (LF) and high (HF) frequency are well detectable

First of all, as indicated in Figure 2, it is necessary to perform a careful evaluation of the storage data which contain about 2000 RR intervals before the detected arrhythmic event. Abrupt changes in RR interval duration, likely due to premature ventricular or atrial contractions are present in the final part of the tachogram, immediately before the onset of the detected ventricular tachycardia. In the presence of such irregularities the time series is not stationary and an appropriate analysis of heart rate variability and a valid estimation of power spectrum are hindered. Moreover, no editing of the data can be performed without interfering with the original signal. Thus, the analysis must be performed on a shorter segment that is free of artefacts such as, for example, from cycle N°500 to cycle N°800.

Figure 3 illustrates the autospectrum derived by the analysis of the selected time series.

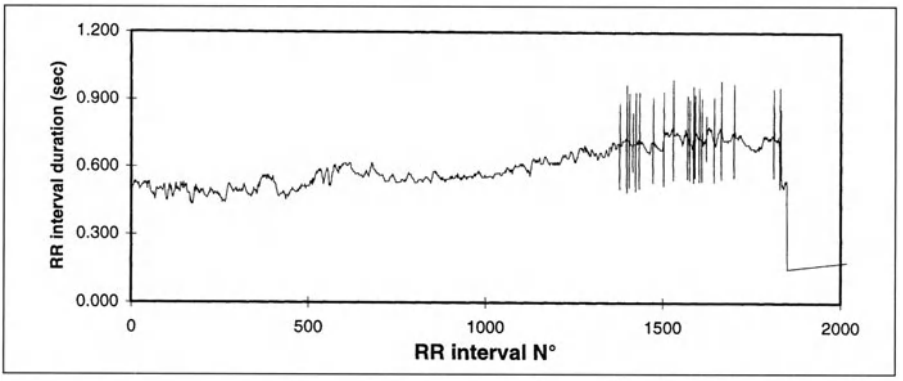

Fig. 2. RR interval time series extracted from the storage function of Micro Jewel N° 7223. Abrupt changes in RR interval duration between cycles 1300-1700 are likely to be due to premature ventricular contractions. The beginning of the detected arrhythmic event is indicated by the drastic reduction in RR interval duration

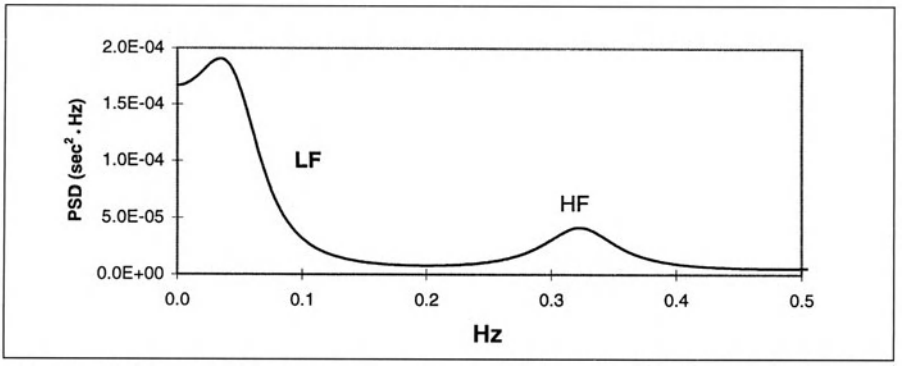

Fig. 3. Spectral analysis of heart rate variability in the minutes preceding the onset of detected ventricular tachycardia. See text for details

As indicated by the vertical scale, RR variance is very small and markedly reduced in comparison to that observed in the autospectrum of a normal subject depicted in Figure 1. However, also in this patient are two major components at low (LF) and high (HF) frequency clearly detectable. In this example the absolute and normalized power of LF is largely predominant over HF. The LF/HF ratio is 4:3. Both data are consistent with a shift of sympatho-vagal balance toward a sympathetic predominance and a reduced vagal modulation of sinus node: an autonomic imbalance which increases cardiac electrical instability and favors the occurrence of malignant ventricular arrhythmias.

It is our opinion that the analysis of heart rate variability in the minutes preceding the occurrence of malignant ventricular arrhythmias might provide some insight into the recognition of some of the arrhythmogenic mechanisms underlying ventricular tachycardia and fibrillation.

Evidence in support of a critical arrhythmogenic role of the autonomic nervous system in altering cardiac electrical properties and favoring the onset of malignant ventricular arrhythmias is already available. However, the definition of a consistent pattern of sympathetic activation in the minutes preceding the detected arrhythmic events which can vary from ventricular tachycardia to ventricular fibrillation is not as clear. It is possible that the autonomic nervous system plays a more relevant role on a reentrant arrhythmogenic substrate leading to sustained ventricular tachycardia than on the arrhythmogenic mechanisms leading to ventricular fibrillation. Moreover sympathetic activation may be further enhanced by the presence of premature ventricular contractions and by the occurrence of short-long cycle sequences which are associated with a surge of sympathetic efferent discharge directed to the heart.

This approach could also provide information about the effects of antiarrhythmic treatment on autonomic modulation of sinus node, which appears critical in relation to the growing number of controversial reports describing the possible beneficial effects of pharmacological antiarrhythmic treatment.

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Is QRS Duration a Reliable Parameter in Discriminating between Supraventricular and Ventricular Arrhythmias?

M. Fromer

Introduction

Automatic implantable cardioverter defibrillators (ICDs) are designed to detect and terminate ventricular tachyarrhythmias. Ideally, they do so with a high specificity and sensitivity. Actual ICD technology with detection based mainly on rate provides high sensitivity but moderate specificity. This means that ICD therapy can be initiated by rapid supraventricular tachyarrhythmias. These inappropriate therapies consist either of antitachycardia pacing, cardioversion or defibrillation. Antitachycardia pacing for a supraventricular tachycardia can induce ventricular tachyarrhythmias; in the worse case, this can ultimately lead to arrhythmic death [1]. It is recognized by many publications that inappropriate therapy imposes serious limitations to ICD therapy due to the discomfort associated as well as to the possible serious proarrhythmic consequences [2-7, 11].

It follows that inappropriate therapies are an important limitation of some types of ICDs. Indications for ICD therapy include today patients with sustained but not rapid ventricular tachycardia [8, 9]. This kind of tachycardia is treated mainly by overdrive pacing. The chance in case of overlap of low-rate ventricular tachycardia with sinus tachycardia or other supraventricular tachyarrhythmias has increased. However, when an ICD is used only to terminate ventricular flutter or ventricular fibrillation, the risk for misclassification is quite low. To avoid therapies for supraventricular rhythms, additional detection algorithms such as sudden onset, sustained high rate, rate stability and *QRS width* are provided. These options are programmable for the ventricular tachycardia detection window only.

The number of inappropriate therapies can be assessed either using the arrhythmia history given by the patient or by analysis of the memory readouts related to the device interaction. Patient histories are not reliable, because tachycardias, that are hemodynamically well tolerated and terminated by antitachycardia pacing, are frequently not perceived. However, the patient who experienced a cardioversion or defibrillation shock while he was exercising will prompt the physician to scan for inappropriate therapies. Assistance to sort out inappropri-

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ate from appropriate therapies is available by the data retrievable from the memory of the ICD. The information retrievable from the device is time and date of device therapy, the recorded RR-cycle length, the classification of the recorded events, the type of therapy given and the RR-intervals after therapy. In addition, the intracardiac R-wave is displayed (Fig. 1). All this information can be printed out. Technical data such as delivered energy, impedance and therapy sequences are available as well. Analysis of local electrogram in order to assess whether the rhythm is of ventricular or supraventricular origin may be of help, but is not an easy task. It is better to prevent inappropriate therapies than to care retrospectively about appropriateness.

Inappropriate Therapies

The term inappropriate therapy may define therapies delivered for any event sensed and misclassified as VT or VF. This may include therefore oversensing of T-waves, myopotentials, external signals, p-waves, pacing artifacts, etc. For the purpose of this article inappropriate therapy is defined as a therapy delivered for supraventricular tachycardias, most frequently atrial fibrillation and sinus tachycardia. Ventricular rate may increase dramatically during atrial fibrillation due to the adrenergic stimulation provoked by pain, by device discharge or other sympathetic stimuli. Grimm et al. reported that in 22% of 241 patients supraventricular tachycardias prompted inappropriate therapies [6]. In their study first, second and third generation devices were pooled. Only ICD discharges documented by EKG strip, intracardiac recordings and Holter monitoring were included in the study. In our European multicenter study there was evidence of inappropriate therapy delivery in 10 patients out of 60 [4].

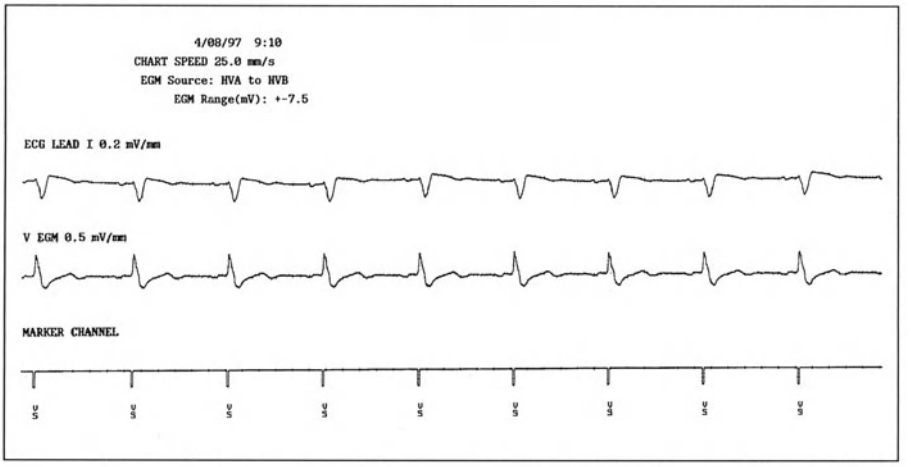

Fig. 1. Shown is a rhythm tracing during sinus rhythm. Represented are one surface ECG lead (lead I), a recording of the telemetered intracardiac electrogram and the marker channel®. The QRS complex shows an intraventricular conduction delay

QRS Width

One of the means to prevent device therapies for supraventricular tachycardias is to add the QRS width detection criterion. The QRS width criterion can be implemented only for ventricular tachycardia detection. QRS is usually narrow in supraventricular tachycardia but large for impulses not conducted via the specific conduction system. QRS width measures only depolarization, which is more reproducible than repolarization. QRS width measurements are implemented in the Medtronic Jewel model 7218 PCD and 7223 PCD. QRS width measurements are based on a width threshold and slew threshold (Figg. 2-4). The slew threshold is used to determine the onset and offset of the R-wave. The time between the two points defines the QRS width. To classify it as normal or wide the comparison with the normal QRS of an individual is needed. Sensing in Medtronic ICDs has been reviewed recently by W. Olson [10].

The physician activates QRS width measurement in the detection window. This is done during sinus rhythm or induced tachycardia. Slew threshold and QRS width threshold are adapted in such a way to obtain width duration measurements within a small range. This is possible in the majority of patients.

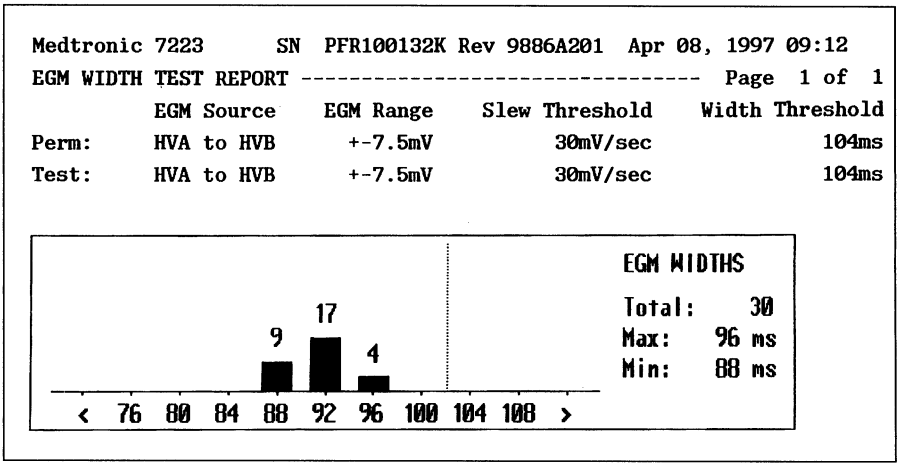

Fig. 2. This figure represents the EGM width test report as provided by the Medtronic MicroJewel® 7223 PCD device. Same patient as for Fig. 1. The R-wave width is the result of a far-field measurement. The width measurement during sinus rhythm ranges from 88 to 96 ms. The jitters is within 12 ms. For ventricular tachycardia detection, the QRS width has been programmed to 104 ms

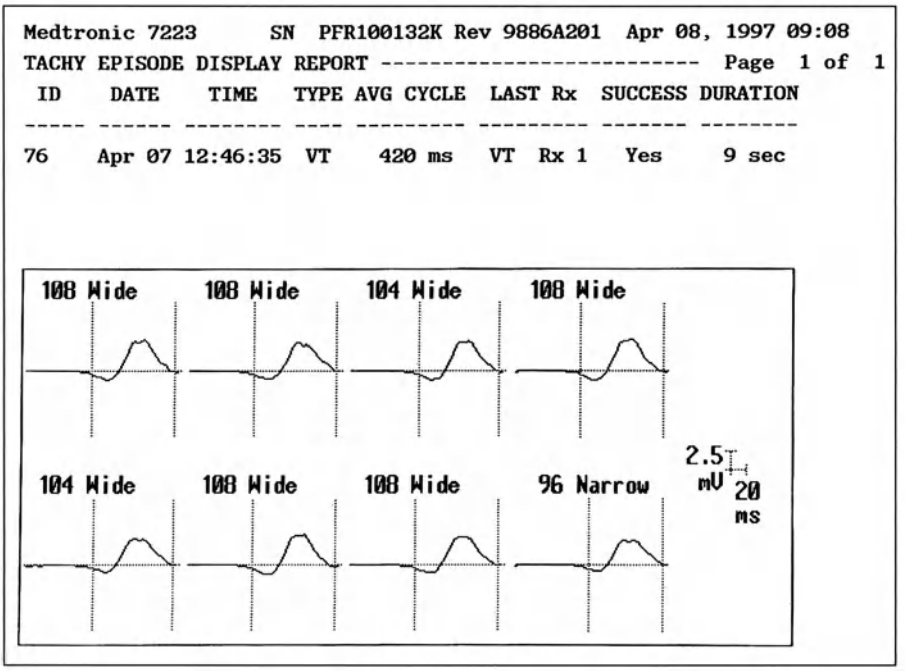

Fig. 3. Displayed is the plot of the QRS width as measured and recorded during a spontaneous ventricular tachycardia and retrieved during follow-up visit. Same patient as in preceding figures. Shown are the onset and offset of the recorded R-waves. The QRS duration ranges from 104 to 108 ms. The last beat represents a sinus beat with a plotted QRS width duration of 96 ms, 12 ms smaller than the complexes during ventricular tachycardia

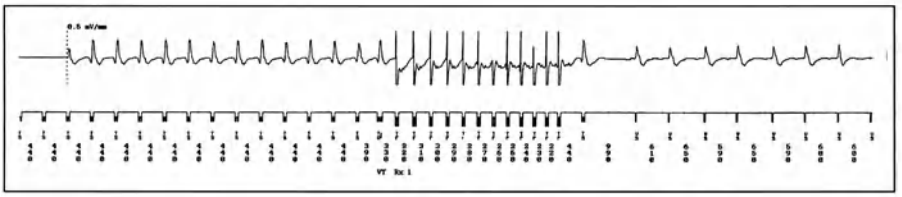

Fig. 4. This figure represents a printout of a spontaneous tachycardia episode as recorded by the device and retrieved from the device memory. Same patient as in preceding figures. Represented are the intracardiac R-wave electrogram and the marker channel. The categorization of the detected event is given by the annotation "TS" (tachycardia sense) and the cycle length of the recorded RR-intervals are given. The tachycardia is stopped by an overdrive ramp pacing with 12 stimuli and decrements of 10 ms

Recommendations to Program the QRS Width Criterion

According to the company's recommendations, the slew rate is set to 36 mV/s. The QRS width is measured first during sinus rhythm and then at rest for a mini-

mum of 30 beats. The jitters should be less than 12 ms. The QRS width is programmed + 4 ms to the measured maximum QRS width.

Clinical Results of QRS Width Criterion

At its best, a good VT detection criterion has a 100% sensitivity and specificity. For the QRS width criterion, this would mean rejection of all supraventricular tachycardia (specificity) and detection of all ventricular tachycardia (sensitivity).

The Medtronic company has undertaken a clinical investigation of the QRS width criterion using Jewel model 7218 PCD. Worldwide, the first 7218 PCD was implanted in our center. In this study, the criterion could be programmed to the "passive" or "on" mode. In the passive mode, the QRS width measurements and criterion decisions were stored, but the criterion was not applied during detection. Therefore, no therapies were withheld based on QRS width criterion. Based on described recommendations, the physicians selected a slew threshold in mV/s and a width threshold in ms. For the study purposes, QRS width criterion was measured in sinus rhythm as well as during induced ventricular tachycardia. Their ability to discriminate supraventricular from ventricular tachycardia was tested during follow-up. Results of the 7218 Jewel study were published by Medtronic Company in August 20, 1996. This study groups 52 centers involving 586 patients. The results showed an observed relative sensitivity of 98% and an incremental specificity of 83%.

Currently, on the initiative of Dr. Jung, in Bonn, a prospective multicenter study is being undertaken where patients are randomized between active and passive mode of the QRS width criterion. A quality of life assessment is being done. It can already be anticipated that a criterion improves specificity without compromising sensitivity.

Conclusions

The QRS width criterion is a valuable tool to reduce the incidence of inappropriate therapies. It has been shown that the performance with respect to sensitivity and specificity is good. The addition of the QRS width criterion represents an important step in improving the safety of device therapy as well as comfort for patients.

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Which Patients Are Good Candidates for Ventricular Tachycardia Ablation Today?

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The occurrence of ventricular tachycardia (VT) may be caused by a variety of mechanisms, whose understanding has recently been enhanced by the increasing use of catheter ablation as a curative approach for this type of arrhythmia.

This approach was initially used with ventricular tachycardias originating from structurally normal hearts – so called idiopathic VTs; due to the mostly favorable long term results, RF catheter ablation is now an established form of treatment for these VT.

Right Ventricular Outflow Tract Ventricular Tachycardia (RVOT-VT)

RVOT-VT is a rather frequently encountered type of VT, occurring in normal hearts, although evidence has been provided showing that a minor form of right ventricular cardiomyopathy (or dysplasia?) [1] can be documented in these patients. Due to its poor responsiveness to antiarrhythmic drug therapy, this type of VT often becomes a clinical problem leading to severe palpitations and, not infrequently, to syncope due to the fast rate.

In the electrophysiology laboratory, the inducibility of RVOT-VT is not uniform, and frequently the administration of isoproterenol is required; endocardial activation mapping is performed to record earliest activity, either on the septal side or on the right ventricular outflow tract free wall, usually in the range of -20/30 ms [2]. Exact pacemapping is frequently used to assess the proper ablation site, and, according to some authors, this might constitute the technique of choice [3].

The early report of one casualty following cardiac tamponade due to rupture of the ventricular free wall, called for prudence and has led towards a conservative approach in this type of tachycardia.

More recently, however, due to the increased experience and to the availability of temperature controlled systems, catheter ablation is performed with more confidence in this type of VT; not only in patients with sustained syncopal arrhythmias, but also in those presenting with disabilitating symptoms due to

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the high number of isolated premature ventricular beats or unsustained incessant ventricular tachycardia.

Idiopathic Left Ventricular Tachycardia (ILVT)

A less frequently encountered type of idiopathic VT originating from the left ventricule, is the so-called fascicular VT or Belhassen VT, characterized by a distinct ECG pattern of right bundle branch block (RBBB), an extremely superior axis, and "narrow" (0.12-0.14 s) QRS ventricular tachycardia. For this reason, and because of the prompt response to the intravenous administration of verapamil, the arrhythmia is frequently misdiagnosed as a supraventricular tachycardia with RBB aberracy; the extreme left axis deviation, however, and the presence of ventriculoatrial dissociation are clues for a correct diagnosis. The most frequently reported symptom is palpitation; syncope is a rare complaint, due to the lower average rate of this VT, with respect to RVOT-VT [4].

Although the long term prophylaxis with verapamil or β-blockers is effective in many cases, there is a substantial number of patients in whom the arrhythmia is drug refractory. As indicated by its acronym, ILVT is believed to be supported by a reentry circuit involving at least a part of the left posterior fascicle.

The rate of inducibility of ILVT is 80%-90%, this number including the standard ventricular stimulation protocol, but frequently also the use of atrial incremental pacing or the administration of isoproterenol.

During VT, the recording of a small, distinct, high frequency potential (P potential) preceding the local electrogram by 20-30 ms guides the choice of an effective ablation site; this is usually located in the postero-inferior wall of the left ventricle [5]. Early termination of VT during energy delivery is usually successful; persistent induction of VT with minor changes in surface ECG morphology, better appreciated in leads V2-V3, may occasionally occur and has been reported [6].

These minor forms of pleomorphism have been related to different exit sites of the Purkinje network to the endocardium and require multiple RF applications to achieve complete success. The procedure is, on the whole, highly effective and no significant complications have been reported; it can therefore be considered not only in patients with drug-refractory arrhythmia, but also in younger patients as an alternative to lifelong antiarrhythmic treatment.

Postinfarction Ventricular Tachycardia

The occurrence of ventricular tachycardia in patients with structural heart disease carries an adverse prognostic significance in many cases. In these settings, therefore, the indication for catheter ablation is less straightforward as compared to patients with idiopathic VT.

VT in the setting of chronic coronary disease is by far the most frequently occurring type of sustained ventricular arrhythmia. The role of catheter ablation

in the management of this type of VT is not uniformly defined: while the technique has proven to be effective in terminating VT and in preventing its subsequent reinduction [7], major concerns remain about the long term effectiveness of the procedure in preventing recurrences of the original tachycardia or other life-threatening arrhythmias, due to limited size of the catheter-induced lesion, compared to the extension of the arrhythmogenic substrate.

Furthermore, the possible application of this technique is not well defined, since many investigators feel that only a minority of patients suffering from postinfarction recurrent VT might benefit from RF catheter ablation, because of the need for hemodinamic tolerability of the induced arrhythmia [8, 9].

To address these issues, our experience in the treatment of post-infarction VT by catheter ablation is reported in the following paragraphs.

Patients and Methods

Between January of 1993 and March of 1997, 112 patients were admitted to the Arrhythmia Unit of our Center for evaluation of recurrent drug-refractory sustained VT late after myocardial infarction.

Patients were considered eligible for RF catheter ablation (RFCA) according to the following criteria:

- inducibility, or spontaneous occurrence, of at least one morphology of hemodynamically sustained VT tolerated (systolic arterial pressure <80 mmHg);
- absence of thrombi in the left ventricle;
- lack of indication for coronary angioplasty or bypass grafting or left ventricular aneurysmectomy.

Accordingly, 51/112 patients (45% of the study population) meeting the aforementioned criteria underwent RFCA. The mean age was 63 years (range 42-82); the mean interval between the last myocardial infarction and the time of the procedure was 11 years (range 2 months to 32 years). The mean left ventricular ejection fraction was 36% (range 17%-67%). At the onset of their history of VT, 14 patients (27%) presented syncope. A poorly tolerated fast VT was documented in all, requiring external cardioversion; cardiac arrest with ventricular fibrillation was documented in 3 more patients (6%); acute heart failure, severe hypotension, dizziness or palpitations were complaints made by all. Incessant VT was present in 10 patients (19%), and iterative (< 12 hours a day) in 5 patients (10%). Nine patients had a cardioverter-defibrillator implant (4 months-3 years) before undergoing the procedure.

All patients had undergone extensive antiarrhythmic drug testing, including amiodarone (alone or in combination with β-blockers or Class I drugs), sotalol, metoprolol, propafenon, mexiletine, alone or in combination, all of which had failed to prevent VT recurrences.

Ablation Procedure

The procedure was performed under mild sedation (morphine+diazepam I.V. boluses) during continuous monitoring of the arterial blood pressure and oxygen

saturation. Preliminary coronary angiography and left ventricular angiography were performed in all patients. Multipolar catheters were placed in the right atrium and right ventricle; the ablation catheter was introduced in the left ventricle through a retrograde transaortic approach.

Preliminary left ventricle mapping was performed during sinus rhythm to identify regions with low amplitude fragmented electrograms, thus allowing a gross localization of the infarcted area; subsequently left ventricle stimulation was performed searching for sites allowing a long stimulus-QRS interval with a 12 lead configuration exactly matching the spontaneous VT. Programmed stimulation was then undertaken from the right ventricular apex and from different left ventricular locations.

The following criteria were used to localize the ablation site:
- recording of early diastolic activity (preceding the surface QRS during VT by < 70 msec);
- isolated diastolic potentials;
- possibility of concealed entrainment with stimulus-QRS intervals compatible with the potential-QRS interval recorded during VT on the selected site.

RF was delivered under thermal control, presetting the catheter tip temperature at 60 °C; pulse duration was 1 min if the tachycardia was interrupted within 10 s; if not, energy delivery was discontinued within 10-15 s. After VT termination, reinduction attempts were made with the same protocol used in the baseline.

Ventricular Tachycardia Induction

One hundred and fourteen episodes of stable monomorphic VT were induced in 51 patients, 9 of them requiring multiple procedures; the mean cycle was 386±75 ms (range 270-580). One type of VT had been previously documented and could be induced in 21 patients; in the remaining 30 (59%), multiple morphologies had occurred spontaneously or were induced (range 2-6 per patient).

In 19/30 patients with multiple VTs induced, there were only minor differences (< 40 ms) in the tachycardia cycle length among the different morphologies; in the remaining 11 patients, the differences among cycle of the various morphologies was > 100 ms, and 5 of them also had poorly tolerated VTs.

Acute Results

The success of the procedure was defined by the following:
- early interruption during RF energy delivery (within 10 s);
- prevention of reinduction of any sustained VT.

Termination was achieved in 88/114 VT episodes (77%), in 20/21 patients (95%) with one VT, in 26/30 (86%) with multiple morphologies. The success rate for patients was higher than that for VT episodes, because 9 of them underwent multiple procedures.

Twelve out of 88 (13%) of the acutely terminated VTs remained consistently reinducible.

Of the acute failures 1 patient underwent subsequent map guided endocardial resection, and 5 had a cardioverter-defibrillator implanted.

Long Term Results

After hospital discharge, patients were followed regularly at 3-6 month intervals in the outpatient clinic. Antiarrhythmic therapy (amiodarone) was mantained in 37 patients (72%); the need for this was based upon the patient history (cardiac arrest or multiple VTs) and the degree of ventricular disfunction.

At a mean follow-up of 21±10 months (range 2-50), 12 patients (23%; 4 patients defined as partial success) had arrhythmic recurrences; 3 of them died from intractable heart failure due to incessant VT; 2 had appropriate implantable cardioverter defibrillator (ICD) interventions; 4, who already had ICD implanted at the time of ablation, still had sporadic recurrences (2-4/year); their frequency, however, was significantly diminished with respect to the months preceding the procedure. Among the patients with ICD implanted due to ablation failure or to inducibility of faster and hemodynamically untolerated tachycardias, 3 had arrhythmia recurrences; one of them, who had presented with incessant VT, experienced 3 recurrences over three years.

Conclusions

On the basis of the hemodynamic tolerability to the induced VT, RFCA was attempted in 45% of a consecutive series of patients evaluated for drug refractory arrhythmia. These data suggest that the role of this technique in the treatment of post-infarction VT is all but marginal. In our view, therefore, RFCA can be considered as a first choice approach for the treatment of drug-refractory VT before considering antiarrhythmic surgery or ICD implant.

One interesting point when considering the natural history of the arrhythmia is that in about one third of the patients undergoing RFCA the presenting arrhythmia was syncopal VT or ventricular fibrillation; long term antiarrhythmic treatment may have contributed to the more frequent recurrence of slower and better tolerated arrhythmias. On the other hand, a spontaneous evolution of the arrhythmic substrate is increasingly recognized in patients with ICD implanted for ventricular fibrillation or fast VT, presenting, at a interval of years, with slower incessant tachycardia.

A source of concern about the long term effects of RFCA on post-infarction VT is that, unlike for other type of arrhythmias, ischemic heart disease may lead to the onset of de novo arrhythmias, thus limiting the long term benefits of the procedure. However, this phenomenon did not occur in our patients.

Episodes of VT recurred in patients after failure of the ablation; in patients with partial success with persistent inducibility of faster arrhythmias, in whom a ICD was subsequently implanted, the recurrent VT had the same cycle as those induced after the procedure. No patient died suddenly; three died from

intractable heart failure due to incessant VT.

The overall success rate of the procedure is about 80% with 70% of the patients still on antiarrhythmic treatment. Although this may be a satisfactory result, further refinements of the tecnique may be sought in the following fields.

- Enhanced mapping of hemodinamically unstable VT, by a multielectrode array non contact electrode catheter [10].
- Feasibility of rapid endocardial mapping and ablation of fast VT by means of multielectrode recording system has been shown in animal models [11].
- In a minority of cases the deep or epicardial location of a critical area within the reentry circuit may cause failure of the procedure [12]. The role of epicardial mapping using the venous system to define an epicardial location is currently being investigated; while this approach appears safe and feasible in the majority of cases, its limitations are due to the fact that only a small part of the epicardial surface is covered by the venous system. Direct epicardial mapping from the pericardial space is also under investigation [13].
- Ablation of deep intramural or epicardial sites may be now achieved by the use of cooled systems; however, the risk of cardiac perforation is enhanced by these catheters.

Bundle Branch Reentry Ventricular Tachycardia (BBR-VT)

Although its mechanism is related specifically to disease of the intraventricular conduction system, BBR-VT occurs mainly in patients with dilated cardiomyopathy, either primary, or due to other types of heart disease [14]. Presenting symptoms are usually ominous (syncope or cardiac arrest), because of the high ventricular rate of this VT. The arrhythmia, however, can be very frequently induced by programmed stimulation, and the involvement of the branches or the fascicles can be recognized by adequate recording by catheters positioned over the His bundle or the branches.

The success rate of RF catheter ablation in this setting is very high, due to the focal nature of the substrate [15]. However in this clinical setting other types of ventricular arrhythmia can be associated with the macro-reentrant circuit of the BBR-VT, thus limiting survival in many of this patients and worsening the prognosis. Even though BBR-VT is curable by RF ablation catheter, patients with dilated cardiomyopathy may still be at risk for other ventricular arrhythmias, and additional antiarrhythmic therapy or ICD may be frequently needed.

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