Ronald W. F. Campbell Michiel J. Janse (Eds.)

Cardiac Arrhythmias: The Management of Atrial Fibrillation

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BASF Group

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With 23 Figures

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Preface

This publication contains the papers presented at a special Symposium on Atrial Fibrillation during the European Society of Cardiology 1991 meeting in Amsterdam, Holland. The scientific program was generously supported by Knoll Pharmaceuticals.

As is evident from these papers there is a renewed interest in atrial fibrillation which has fuelled fresh investigative activity. Professor Peter Schwartz, well known for his contribution to the understanding of the long QT syndrome, offers a comprehensive and challenging approach to the role of the autonomic system in atrial fibrillation. Dr. Maurits Allessie brings us up to date on the pioneering work that he and Professor Michiel Janse have undertaken on the basic electrophysiology of atrial fibrillation; in the process they have exposed new areas for therapeutic attack. Dr. Michael Franz has made important contributions to the field of ventricular electrocardiography through his elegant monophasic action potential (MAP) recordings. Using knowledge gained in that research, he now turns his attention to how MAP recordings can reveal more about the process of fibrillation and how the phenomenon of postrepolarization refractoriness may be an important therapeutic factor.

Class I drugs and the classification of these agents is a vexed issue which remains to be resolved. New approaches to characterizing the effect of these drugs abound in the current literature. Dr. Nawrath offers us a new perspective on this issue. Dr. Nattel follows with a detailed appraisal of the effects of class I agents on atrial myocardium – we often forget that our current concepts are based largely on drug effect defined in Purkinje tissue.

Dr. Kuck and Dr. Kerr then review the clinical therapeutic challenges of atrial fibrillation from a European and a North American stance respectively. Prevention of thromboembolic complications rightly features as important, as do new thera-

peutic approaches to preventing and/or controlling the fibrillation process. Class Ic drugs such as propafenone are emerging as important for this condition. Class III agents operating by quite different electrophysiological mechanisms also have much to offer.

Finally, Professor Campbell suggests how improved basic knowledge can be incorporated into everyday management of atrial fibrillation. An attack on the underlying etiological processes should not be overlooked, nor should calculation of the risk benefit of intervention.

These papers cannot cover all of the subject. They address topical new issues indicating what we know, what we don't know and which are the important things to find out about. There is food for thought for the basic scientist. For the practising clinician there is enough to prompt a reappraisal of current management of this most difficult of rhythms, atrial fibrillation.

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Paroxysmal Atrial Fibrillation and the Autonomic Nervous System

P. J. Schwartz

Introduction

The autonomic nervous system has profound influences on cardiac electrophysiology (Schwartz et al. 1978; Corr et al. 1986; Schwartz and Priori 1990), and alterations in sympathetic (Schwartz et al. 1978, 1984, 1991, 1992a; Yusuf and Teo 1991) and in vagal (Vanoli et al. 1991; Schwartz et al. 1992b) activity can either enhance or reduce the risk for ventricular fibrillation. At atrial level, these influences are possibly more complex and certainly not less important.

That vagal activity was capable of influencing atrial rhythm was already known before the end of the last century, as indicated clearly by the studies by McWilliam (1887), by Fischel (1897), and particularly the impressive study performed by Knoll (1897). These earlier studies provided the first evidence that elevated vagal activity was associated with a greater propensity for tachyarrhythmias.

On these foundations a large number of studies were performed, but for the considerable progress made in understanding the pathophysiology of atrial fibrillation and the neurogenic influences related to paroxysmal atrial fibrillation we owe much to the groups led by Allessie and Coumel respectively. Most of the data and concepts presented here originate from their studies and from the work by Rensma (1987).

I will briefly review the relationship between the autonomic nervous system, and particularly its vagal component, and atrial fibrillation. This will be preceded by considering the underlying electrophysiologic mechanisms.

Reentry and the Length of the Excitation Wave

As discussed in the Sicilian Gambit (The Task Force of the Working Group on Arrhythmias of the European Society of Cardiology 1991) the mechanism of atrial fibrillation is Na^+ channel-dependent reentry over a short excitable gap. The main factors involved in the initiation and per-

sistence of reentrant arrhythmias are the inhomogeneity in electrophysiologic properties, the length of the excitation wave, and the tissue mass (in the present case, the size of the atria).

In the normal atria, dispersion of refractoriness exists physiologically and is affected by heart rate and by autonomic activity. In clinical studies, Michelucci et al. (1982) have demonstrated that an increased asynchrony in the recovery of excitability is associated with increased vulnerability to paroxysmal atrial fibrillation.

Allessie and his associates have repeatedly stressed the importance of the length of the excitation wave in the occurrence of atrial fibrillation (Rensma et al. 1988), and have recently reviewed these concepts (Allessie et al. 1990). For the initiation and continuation of reentry in the classic ring-like structure described by Mayer (1906) and Mines (1913) two conditions must coexist: (1) a temporal conduction block and (2) the point of origin of the impulse must be excitable again when the new excitation wave arrives from the other side. The second condition requires that the length of the excitation wave, which is the distance travelled during the refractory period, is shorter than the pathway around the obstacle, thus leaving part of the circuit fully excitable (Lewis 1925). Because in normal atria the occurrence of large areas of conduction block is unlikely, a long wavelength will prevent the initiation of reentrant tachycardias. There are a host of reasons (Rensma 1987) to suppose that determination of the length of the excitation wave might be useful in the assessment of the probability of atrial fibrillation developing. As indicated in Fig. 1, the wavelength can be calculated by multiplying the functional refractory period by the conduction velocity. As a generalization, interventions which shorten the wavelength may be expected to favor the occurrence of reentrant arrhythmias, and the opposite may be expected of interventions that prolong the wavelength.

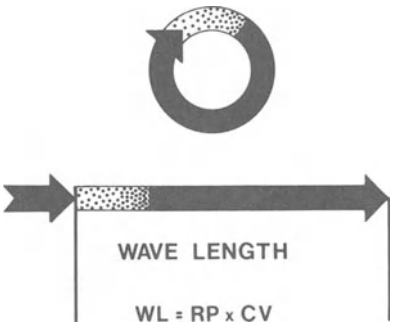


Fig. 1. Schematic drawing of a functionally determined reentrant circuit. The black area represents tissue which is in its unexcitable phase, whereas the dotted area indicates relatively refractory tissue. Because no excitable gap exists between head and tail of the excitation wave, the size of the circuit is determined by the wavelength (*WL*) of the impulse. *RP*, functional refractory period; *CV*, conduction velocity. (From Rensma 1987)

Wavelength and Cycle Length

Several clinical studies, based on programmed electrical stimulation, have reported that the atria become more susceptible to tachyarrhythmias whenever there is a high driving rate or the premature beats have a short coupling interval (Michelucci et al. 1982; Haft et al. 1968; Wyndham et al. 1977; Engel and Gonzales 1978; Watson and Josephson 1980; Simpson et al. 1982; Cosio et al. 1983).

In the conscious canine model for the study of atrial fibrillation developed by Rensma and associates (Rensma 1987; Rensma et al. 1988), the effect of regular pacing on the refractory period, on conduction velocity, and on wavelength was carefully studied. Figure 2 illustrates how shortening of the pacing interval from 350 to 200 ms had no significant effect on these three variables. However, a further decrease of the pacing in-

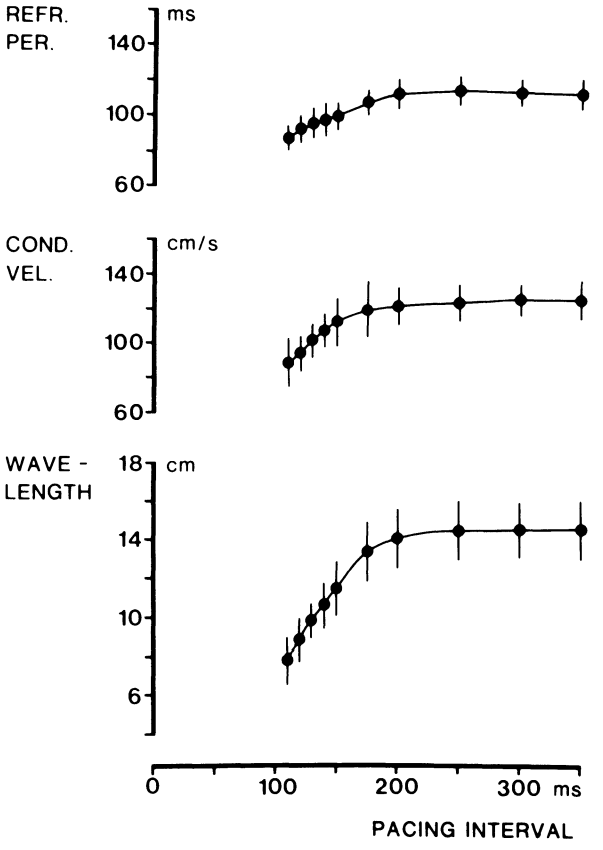


Fig. 2. Effect of the pacing interval on the wavelength of a regularly driven impulse as determined in the left part of Bachmann's bundle. The mean and standard deviation ($n = 13$) of the refractory period, conduction velocity and wavelength are plotted as a function of the pacing interval. (From Rensma et al. 1988)

terval caused a progressive decrease of both refractoriness (−22%) and conduction velocity (−30%), which resulted in a major shortening (−46%) in the wavelength.

This concept was further analyzed by exploring and quantifying the effects of varying the degree of prematurity of single premature beats during relatively slow (350 ms) and regular sinus rhythm. Figure 3 shows that premature beats with coupling interval longer than 250 ms did not alter either refractory period or conduction velocity. However, further shortening of the coupling interval resulted in a progressive shortening of the wavelength (−55%), secondary to a combined decrease in refractoriness (−30%) and conduction velocity (−35%). These changes in the electrophysiologic parameters have important counterparts in the generation of arrhythmias. Figure 4 shows the different type of arrhythmias that are induced according to the varying degree of prematurity. The left panel

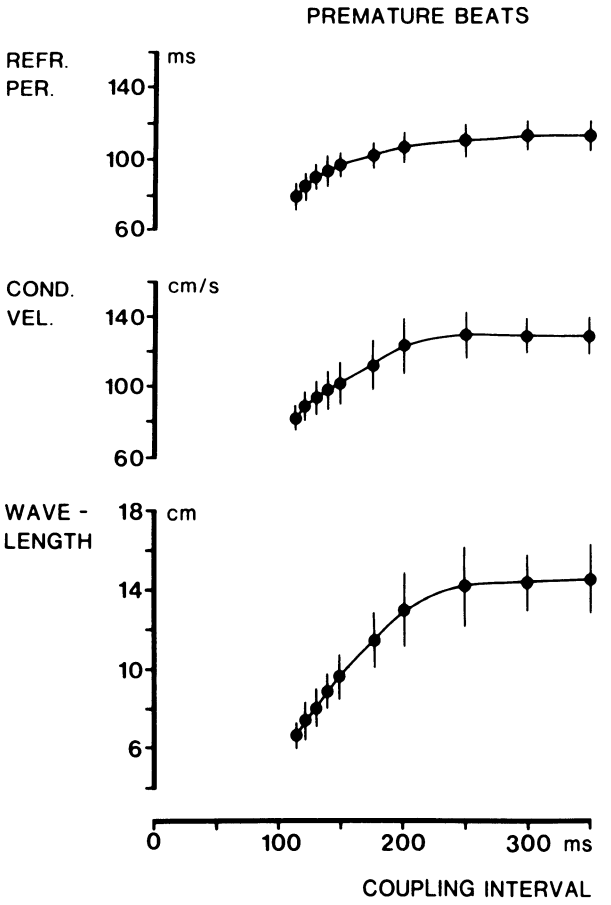


Fig. 3. Effect of the degree of prematurity of extrasystoles on refractory period, conduction velocity and wavelength. Mean values and standard deviation ($n = 18$), as measured in the left part of Bachmann's bundle, are plotted. (From Rensma et al. 1988)

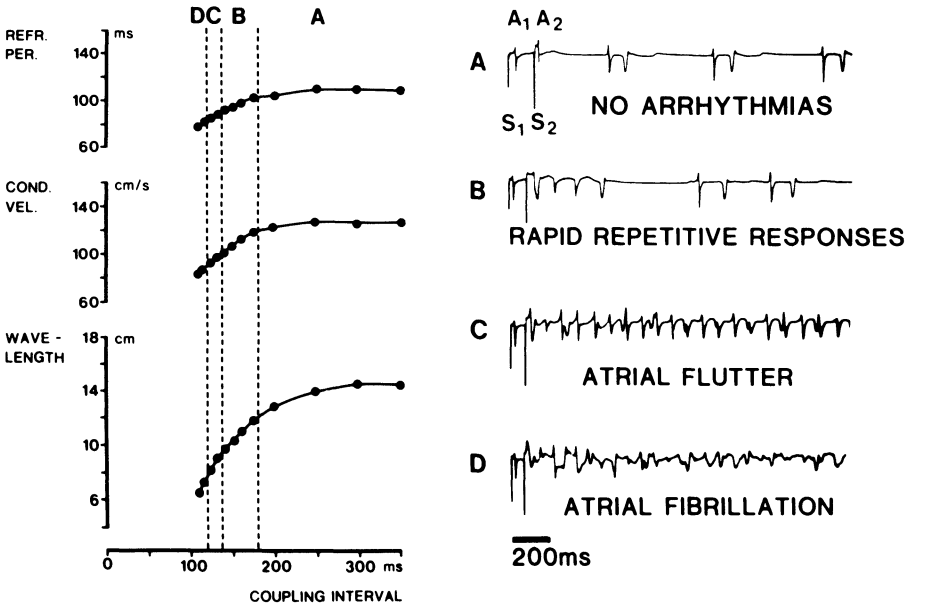


Fig. 4. Example of the atrial response to premature stimuli (S_2) elicited in the left part of Bachmann's bundle. (From Rensma et al. 1988)

shows the relationship between the coupling interval of premature impulses and refractory period, conduction velocity, and wavelength. The prematurity zones A through D in the left panel correspond to the tracings in the right panel. Premature stimuli with a long coupling interval (zone A) elicited only single premature responses (A_2). Moderately premature stimuli (zone B) were followed by a short series of rapid repetitive responses. Extrasystoles coupled even earlier (zone C) sometimes resulted in a bout of atrial flutter, whereas premature stimuli delivered immediately after the refractory period (zone D) frequently induced episodes of atrial fibrillation. These responses of increasing severity were coincident with gradual decreases in the values of refractory period, conduction velocity, and consequently of wavelength.

Thus, cycle length and wavelength are closely related and premature depolarizations favor the onset of atrial tachyarrhythmias in conjunction with parallel changes in the three measured variables; this did not allow conclusions as to which parameter is more closely related to susceptibility to atrial arrhythmias.

Autonomic Influences and Atrial Electrophysiology

The early observations identifying a relationship between vagal activity and atrial fibrillation failed to clarify whether these arrhythmias were automatic or reentrant in nature. It was a series of papers by Allessie and coworkers that suggested that vagal activity favored intra-atrial reentry by shortening atrial refractoriness (Allessie et al. 1977, 1984, 1985; Smeets et al. 1986). Subsequently, this group also investigated the effects of autonomic activity and of autonomic drugs on refractory period, conduction velocity, and length of the atrial excitation wave. Furthermore, they also studied how modulations of autonomic tone might influence dispersion of refractoriness, another potentially important factor in the initiation of reentrant arrhythmias.

Figure 5 illustrates not only the effects of acetylcholine and of atropine but also the effects of isoproterenol and of propranolol on the three parameters already studied under different conditions. At variance with the studies which employed variations in the cycle length, autonomic interventions were able to modify wavelength through a selective action on just one of the two critical factors, conduction velocity and refractory period. The administration of acetylcholine produced a 20%–30% shortening of the wavelength, due to a reduction of the refractory period without affecting conduction velocity. Muscarinic blockade by atropine had an opposite effect, from a qualitative point of view, and increased the wavelength by 15% secondary to a prolongation of the refractory period. By contrast, neither isoproterenol nor propranolol was able to modify these electrophysiologic parameters.

This study (Rensma et al. 1988) demonstrated that acetylcholine shortens the wavelength in the atrium by decreasing the refractory period without affecting conduction velocity. This finding is in complete agreement with the well-recognized arrhythmogenic effect of vagal stimulation at atrial level. On the other hand, beta-adrenergic stimulation and blockade did not modify the wavelength. This would seem to be in contrast with the occurrence of adrenergically-mediated atrial fibrillation in man. Rensma (1987) has postulated that this apparent discrepancy, which suggests that changes in the wavelength of the atrial impulse may not be importantly involved in this type of clinical atrial fibrillation, might reflect the fact that even modestly diseased atria are more sensitive to catecholamines which would initiate reentry by increasing the incidence of premature beats.

An important question is whether vagal activation might not only favor the onset but also increase the rate of atrial tachyarrhythmias. Figure 6 shows the effect of a brief infusion of acetylcholine on the beat-to-beat

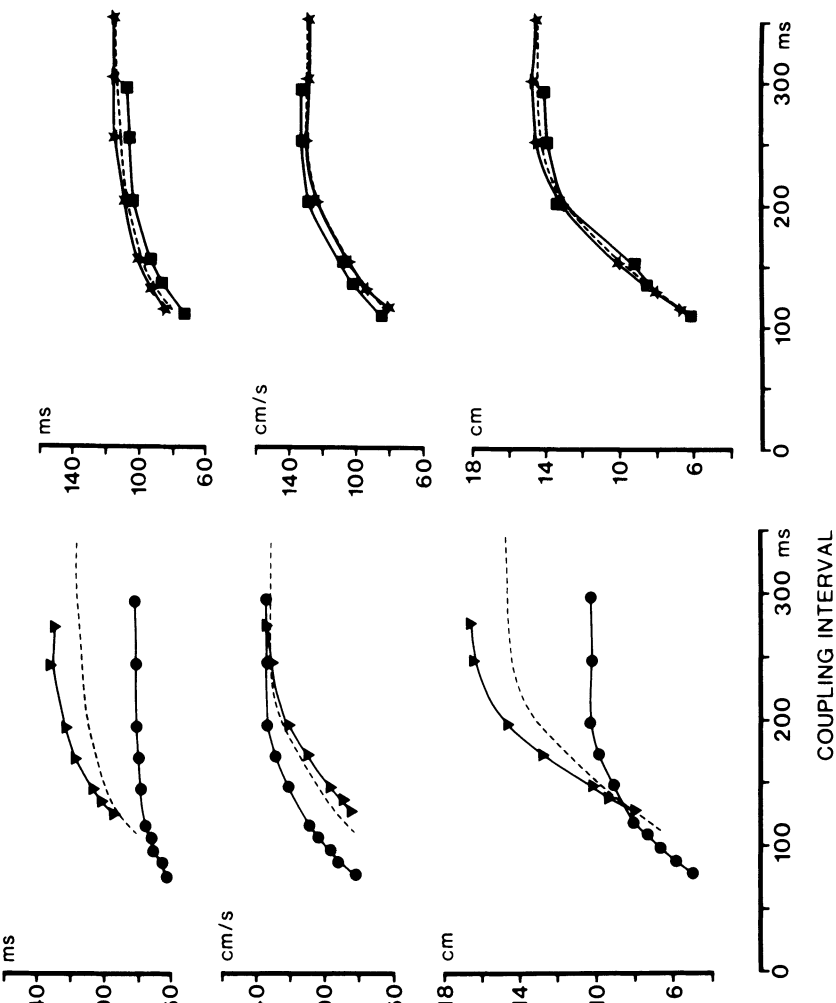


Fig. 5. Autonomic influence on atrial electrophysiological properties. Control values are represented by the interrupted line. The *left panel* shows the effects of acetylcholine (●) and atropine (▼) on the refractory period (RP), conduction velocity (CV) and wavelength (WL) of extrasystoles with varying prematurity, as measured in the left part of Bachmann's bundle. In the *right panel* the effects of isoproterenol (■) and propanolol (*) are shown. It is clear that both sympathomimetric and sympatholytic activity exerted a little effect on RP, CV and WL in the atrium. (From Rensma 1987)

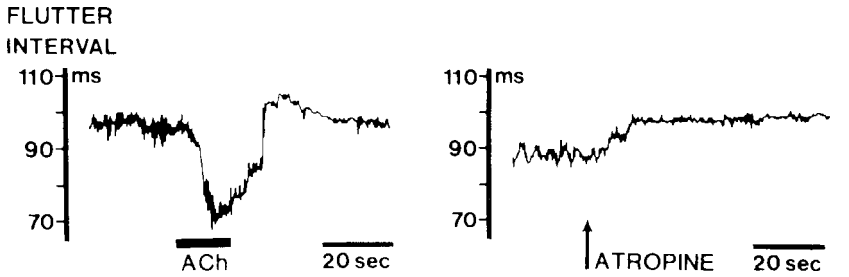


Fig. 6. The effects of acetylcholine (*left panel*) and atropine (*right panel*) on the beat-to-beat interval of atrial flutter. (From Rensma 1987)

interval of an episode of atrial flutter. This produced a transient decrease of flutter interval from approximately 96 to 70 ms. Muscarinic blockade by atropine had an opposite effect. This type of findings supports the concept that atrial flutter, in the experimental model used by Allessie and associates, is based on functional reentry of the leading circle type (Allessie et al. 1977).

Along the same lines, Fig. 7 shows local recordings of atrial fibrillation in control condition and during administration of acetylcholine. The average length of the activation intervals was clearly shorter during

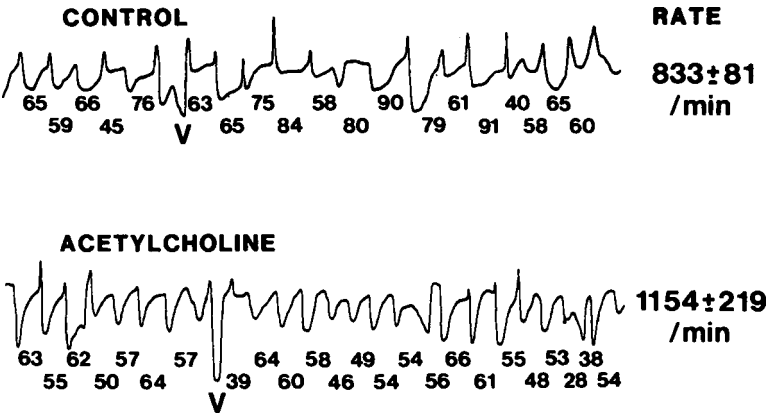


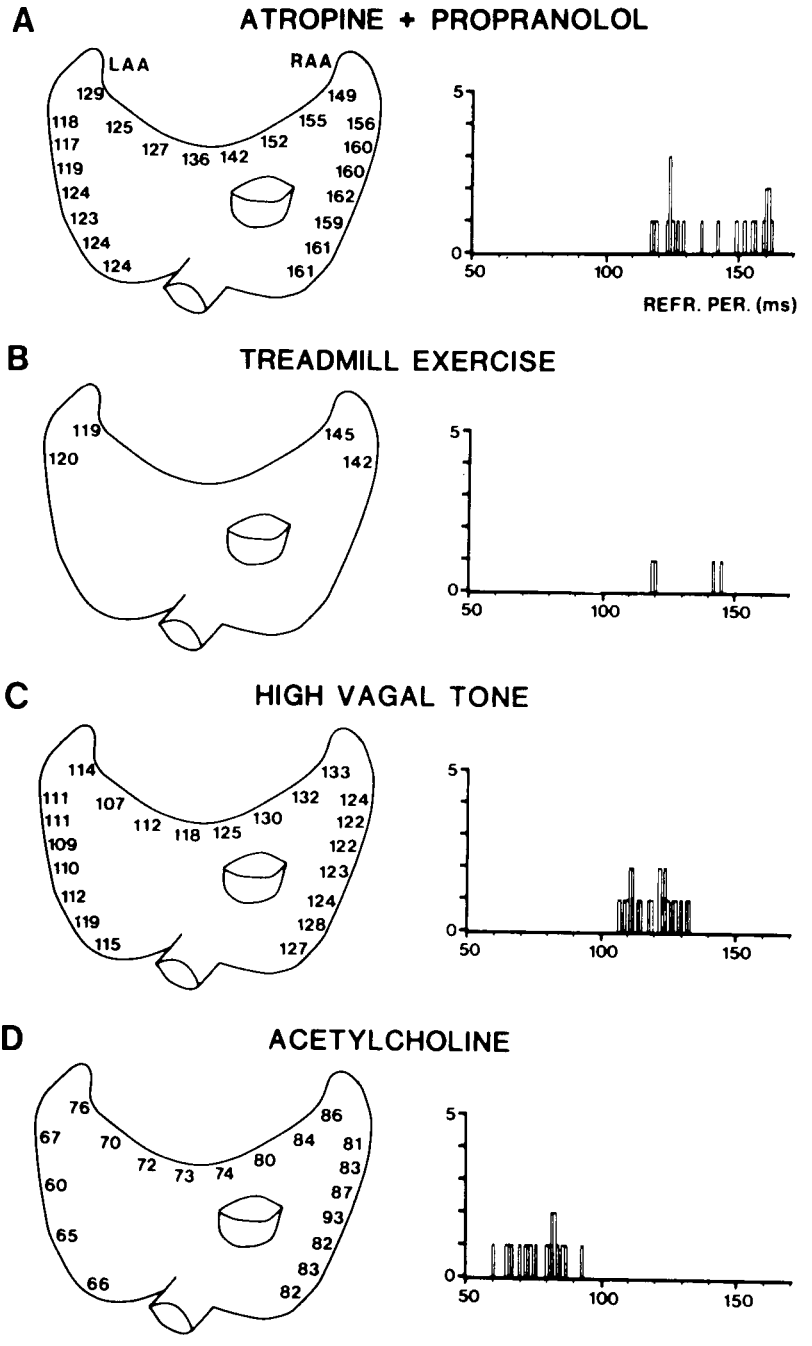
Fig. 7. Local recordings of atrial fibrillation under control conditions and during the administration of acetylcholine. The intervals (ms) between successive activations are given below the tracings. *V* denotes ventricular complex. In both situations, the varying shape and amplitude of electrograms and the irregularity of activation interval, which are characteristic of fibrillation, are easily visible. (From Rensma 1987)

acetylcholine, as the atrial fibrillation rate increased from 833±81 to 1154±219 activations (or "beats") per minute. This finding confirms previous reports by Rosenblueth (1953) and Farges (et al. 1977), and according to Rensma (1987) supports the concept that atrial fibrillation is based on multiple intramyocardial circuits. Indeed, the shortening of the refractory period and the higher number of reentering wavelets secondary to a shorter wavelength may increase the local activation rate.

Finally, in the chronic conscious animal model (Rensma 1987) the autonomic influence on the spatial dispersion of refractoriness was investigated, and the results are illustrated in Fig. 8. During complete autonomic blockade (panel A) the maximal difference between the right and left atrium reached its peak at 45 ms (162–117 ms). During treadmill exercise (panel B) the refractory period was shorter and maximal dispersion was less, 26 ms (145–119 ms). During sleep (panel C), used as an equivalent of high vagal tone, the refractory period was further shortened and the dispersion was again 26 ms (133–107 ms). Administration of acetylcholine (panel D) decreased markedly the refractory period, and the dispersion was 33 ms (60–93 ms). This decrease in spatial dispersion in refractory periods is due to the fact that the refractory period was reduced more markedly in areas with a long intrinsic refractory period (such as in the right atrium) than in areas with a shorter intrinsic refractory period (such as the left atrium). The actual decrease in the dispersion of refractoriness secondary to vagal activation indicates that it plays no role in the initiation of vagally induced atrial fibrillation. The Allessie group concluded this series of impressive studies by stating that the vagally dependent increased vulnerability to atrial fibrillation is entirely dependent on the shortening of the wavelength of the atrial impulse.

The Autonomic Nervous System and Clinical Atrial Fibrillation

Close examination of the clinical history of patients with paroxysmal atrial fibrillation coupled with the behavior of heart rate just prior to the onset of these episodes has been critically important for the recognition of the triggering role not only of vagal but also of sympathetic activation. We are largely indebted to Coumel and his associates for the current knowledge on this specific aspect of atrial tachyarrhythmias. Their views have been expressed in a series of articles and reviews (Coumel et al. 1978; Coumel and Leclereq 1983; Coumel 1990).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Vagally Mediated Atrial Fibrillation

This arrhythmia in its most typical presentation consists of a combination of atrial flutter and fibrillation. The onset of the arrhythmia is preceded by a progessive reduction in heart rate, an obvious marker of augmented vagal activity, and there is a further lengthening of the cardiac cycle just prior to the initiation of atrial fibrillation. Figure 9 represents an example of nocturnal paroxysmal atrial fibrillation. The large decrease in heart rate around 10 PM suggests that at this time the patient fell asleep. Two hours later atrial fibrillation started. The electrocardiogram in the few seconds immediately preceding the onset of atrial fibrillation show the presence of

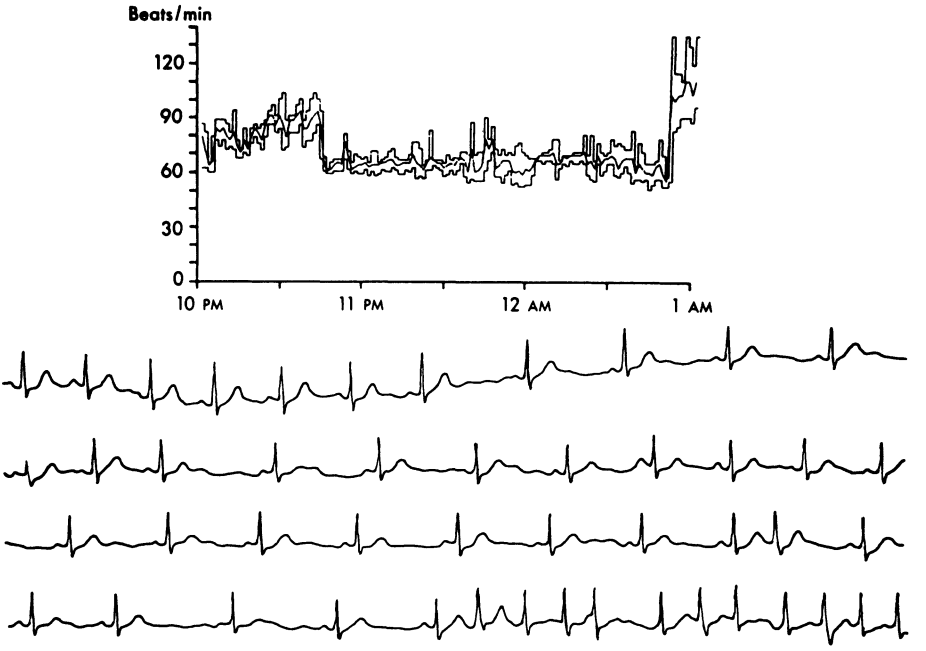


Fig. 9. Onset of a nocturnal paroxysmal atrial fibrillation in a patient. The upper panel shows the diagram of the heart rate. The lower panel shows the ECG tracing just prior to the onset of the atrial fibrillation. Note in the two top tracings the important beat-to-beat cycle length variations, and the presence of an atrial premature beat in the third tracing. (From Coumel and Leclercq 1983)

Fig. 8A–D. Dispersion of refractoriness in the atrium during different states of autonomic control as measured along Bachmann's bundle (n = 13 dogs) and in the free wall of the right (n = 10) and the left (n = 4) atrium. The numbers of the maps indicate the mean refractory period (RP) at the site during regular rhythm (300-ms interval). Next to the maps the related histograms of the distribution of local RP are given. In all situations there were only slight differences in RP in the free wall of the right and the left atrium, while a marked shortening of RP along Bachmann's bundle from right to left was found. (From Rensma et al. 1988)

irregularly occurring variations in cycle length (another marker of vagal activity) with an overall reduction in heart rate and with the occurrence (third tracing) of a premature atrial beat.

The relatively large population with this type of autonomically dependent atrial fibrillation encountered and studied by Coumel and associates has allowed a description of the main features of vagally mediated atrial fibrillation:

- Male predominance: M:F ratio 4:1
- Age of appearance: 40–50 years (25–60)
- Weekly episodes
- Occurrence at night: the attacks often end in the morning
- Favored by rest, alcohol, digestion (particularly after dinner)
- Mixed picture of atrial flutter and fibrillation
- Lack of tendency toward permanent atrial fibrillation
- Onset usually preceded by progressive bradycardia
- Vagal maneuvers of muscarinic stimulation may reproduce the episodes

The clinical history is often long. An interesting and important aspect is the lack of tendency for an evolution toward chronic atrial fibrillation. This arrhythmia is always regarded as idiopathic and is usually classified as "lone atrial fibrillation". The number of episodes varies widely and it often takes several years for the frequency of the attacks to increase from rare to almost daily. Most patients have weekly attacks that may last from a few minutes up to a few hours.

A most typical feature, which should alert the physician to this possible diagnosis, is the occurrence of the attacks at night. The patients wake up abruptly, often with a sensation of anguish or fear, and have to get up from the bed and move around. Within a variable amount of time, often related to the degree of physical exercise that the patient makes to hide his distress, the attacks end, and not infrequently this happens in the morning hours. These episodes seem to be favored by the digestive period, particularly after a large dinner expecially if there has been a generous alcohol intake (it may not be by chance that this pattern has been noted in Paris!).

From a therapeutic point of view most, but not all, of these patients do not do well when treated with beta-blockers. The best results have been obtained with amiodarone, probably because its blocking action on the K^+ (outward) repolarizing currents prevents the shortening of the action potential duration and hence the shortening of the refractory period. I recommend that, at the onset of the arrhythmia, these patients perform a hand-grip maneuver with any appropriate object easily available to them

(e.g., a hard tennis ball); the hand-grip reflex produces an immediate vagal withdrawal accompanied by a powerful sympathetic activation that may often terminate the attacks.

Finally, a new opening is suggested by a recent study by Yamaguchi et al. (1990). Using the methodology used by our group to identify post-myocardial infarction individuals at high risk for sudden cardiac death (Schwartz et al. 1988; La Rovere et al. 1988), they measured baroreflex sensitivity in patients with paroxysmal atrial fibrillation. Their population was unbalanced, with a predominance of adrenergically versus vagally mediated arrhythmias (perhaps reflecting the lesser inclination for gargantuan dinners in Japan!). Of 11 patients, eight had the adrenergically dependent type of paroxysmal atrial fibrillation with a typical onset on awakening in the morning. Their baroreflex sensitivity value was 3.2 ± 1.2 ms/mmHg; a strikingly low value (mean values for normal individuals are between around 8 and 15 ms/mmHg). One patient had the arrhythmia at rest, and his baroreflex sensitivity was 9.5 ms/mmHg. The most interesting finding comes from the two patients, admittedly a small number, with a classic vagally-mediated paroxysmal atrial fibrillation, whose attacks occurred whilst they were asleep. Their baroreflex sensitivity was extremely high, over 25 ms/mmHg. These preliminary but intriguing data raise a host of interesting possibilities. The association between vagally mediated paroxysmal atrial fibrillation and an index of very powerful vagal reflexes certainly fits well with our understanding of atrial electrophysiology and of the clinical manifestations of this cardiac arrhythmia.

Adrenergically Mediated Atrial Fibrillation

Less frequently, the analysis of Holter recordings suggests that initiation of the arrhythmia is associated with an increase in sympathetic activity. The distinguishing features of this second type of paroxysmal atrial fibrillation related to the autonomic nervous system are the following:

- Much less frequently observed
- Includes some cases of hyperthyroidism and of pheochromocytoma
- Frequency accompanied by polyuria
- Episodes almost exclusively during the daytime (particularly in the morning), or during exercise or emotional stress
- Arrhythmia onset coincides with a definite value of sinus node frequency
- Responsive to beta-blockade

Patients with hyperthyroidism and with pheochromocytoma not surprisingly have a relatively high incidence of adrenergically mediated atrial fibrillation. It is interesting that the onset of the episode is usually related not only to a nonspecific increase in heart rate but to the attainment of a specific (for each patient) heart rate. This specific rate is in most individuals close to 90 beats per minute, and the repeated analysis of Holter tapes is useful in demonstrating this point. This arrhythmia is often reproduced by beta-adrenergic agonists. The therapy is, of course, based either on beta-adrenergic blocking agents or on sodium channel blockers with beta-blocking activity, such as propafenone (Rensma et al. 1988).

Conclusion

The autonomic nervous system plays a critical role not only in ventricular but in some supraventricular arrhythmias as well; paroxysmal atrial fibrillation is a prime example. Understanding the complex relationship between muscarinic and adrenergic stimulation and the most critically important electrophysiologic parameters, such as the atrial wavelength, provides insights into the mechanisms underlying several types of this troublesome arrhythmia and may help choose targeted therapy. Recent data also suggest that autonomic responses may be of use in the identification of patients more susceptible to autonomically related paroxysmal atrial fibrillation.

Acknowledgements. I wish to express my gratitude to Drs. Maurits Allessie, Philippe Coumel and Pieter Rensma for having provided me with a large amount of precious information concerning their studies on atrial fibrillation and for having given me the authorization to use it in a very liberal way. I am also greatly indebted to Dr. Iwao Yamaguchi for having provided me with data on his ongoing study. I am very grateful to my mother for special help. I wish to thank Ms. Pinuccia De Tomasi for her care in the preparation of the manuscript.

References

Allessie MA, Bonke FIM, Schopman FJG (1977) Circus movement in rabbit atrial muscle as a mechanism of tachycardia: III. The "leading circle" concept: a new model of circus movement in cardiac tissue without the involvement of an anatomic obstacle. Circ Res 41:9–18

Allessie MA, Lammers WJEP, Bonke FIM, Hollen J (1984) Intra-atrial reentry as a mechanism for atrial flutter induced by acetylcholine and rapid pacing in the dog. Circulation 70:123–135

Allessie MA, Lammers WJEP, Bonke FIM, Hollen J (1985) Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J (eds) Cardiac electrophysiology and arrhythmias. Grune and Stratton, Orlando, pp 265–275

Allessie MA, Rensma PL, Brugada J, Smeets JLRM, Penn OC, Kirchhof CJHS (1990) Pathophysiology of atrial fibrillation. In: Zipes DP, Jalife J (eds) Cardiac electrophysiology. From cell to bedside. Saunders, Philadelphia, pp 548–559

Corr PB, Yamada KA, Witkowski FX (1986) Mechanisms controlling cardiac autonomic function and their relation to arrhythmogenesis. In: Fozzard HA, Haber E, Jennings RB, Katz AM, Morgan HE (eds) The heart and cardiovascular system, vol II. Raven, New York, pp 1343–1403

Cosio FG, Palacios J, Vidal JM, Cocina EG, Gomez-Sanches MA, Tamargo L (1983) Electrophysiologic studies in atrial fibrillation. Slow conduction of premature impulses: a possible manifestation of the background for reentry. Am J Cardiol 51:122–130

Coumel P (1990) Role of the autonomic nervous system in paroxysmal atrial fibrillation. In: Touboul P, Waldo AL (eds) Atrial arrhythmias. Current concepts and management. Mosby Year Book, St. Louis, pp 248–261

Coumel P, Leclercq JF (1983) Role of the autonomic nervous system in the genesis of clinical arrhythmias. In: Rosenbaum E (ed) Frontiers of cardiac electrophysiology. Nijhoff, Boston, pp 552–581

Coumel P et al. (1978) Syndrome d'arythmie auriculaire d'origine vagale. Arch Mal Coeur 71:645–656

Engel TR, Gonzales Adel C (1978) Effects of digitalis on atrial vulnerability. Am J Cardiol 42:570–576

Farges JP, Ollagnier M, Faucon G (1977) Influence of acetylcholine, isoproterenol, quinidine and ouabaine on effective refractory periods of atrial and ventricular myocardium in the dog. Arch Int Pharmacodyn 227:206–219

Fischel R (1897) Über Tonusaenderungen und die anderen graphisch an den vier Abteilungen des Saeugethierherzens bei elektrischer Reizung desselben zu ermittelnden Erscheinungen. Arch Exp Pathol Pharmacol 38:228–248

Haft JI, Lau SH, Stein E, Kosowsky BD, Damato AN (1968) Atrial fibrillation produced by atrial stimulation. Circulation 37:70–74

Knoll PH (1897) Ueer die Wirkungen des Herzvagus bei Warmbluetern. Arch Physiol 67:587–614

La Rovere MT, Specchia G, Mortara A, Schwartz PJ (1988) Baroreflex sensitivity, clinical correlates and cardiovascular mortality among patients with a first myocardial infarction. A prospective study. Circulation 78:816–824

Lewis T (1925) The mechanism and graphic registration of the heart beat, 3rd edn. Shaw, London

Mayer AG (1906) Rhythmical pulsation in scyphomedusae. Carnegie Institution Publication No 47

McWilliam JA (1887) Fibrillar contraction of the heart. J Physiol 83:296–310

Michelucci A, Padeletti L, Fradella GA (1982) Atrial refractoriness and spontaneous or induced atrial fibrillation. Acta Cardiol 37:333–344

Mines GR (1913) On dynamic equilibrium in the heart. J Physiol 46:349–383

Rensma PL (1987) Atrial arrhythmias and measurement of the wavelength in a chronic dog model. Doctoral thesis, Limburg University, Maastricht

Rensma PL, Allessie MA, Lammers WJEP, Bonke FIM, Schalij MJ (1988) Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res 62:395–410

Rosenblueth A (1953) The mechanism of auricular flutter and auricular fibrillation. Circulation 7:612–619

Schwartz PJ, Priori SG (1990) Sympathetic nervous system and cardiac arrhytmias. In: Zipes DP, Jalife J (eds) Cardiac electrophysiology. From cell to bedside. Saunders, Philadelphia, pp 330–343

Schwartz PJ, Brown AM, Malliani A, Zanchetti A (eds) (1978) Neural mechanisms in cardiac arrhythmias. Raven, New York, p 442

Schwartz PJ, Billman GE, Stone HL (1984) Autonomic mechanisms in ventricular fibrillation induced by myocardial ischemia during exercise in dogs with a healed myocardial infarction. An experimental preparation for sudden cardiac death. Circulation 69:780–790

Schwartz PJ, Vanoli E, Stramba-Badiale M, De Ferrari GM, Billman GE, Foreman RD (1988) Autonomic mechanisms and sudden death. New insights from the analysis of baroreceptor reflexes in conscious dogs with and without a myocardial infarction. Circulation 78:969–973

Schwartz PJ, Locati E, Moss AJ, Crampton RS, Trazzi R, Ruberti U (1991) Left cardiac sympathetic denervation in the therapy of the congenital long QT syndrome: a world-wide report. Circulation 84:503–511

Schwartz PJ, Motolese M, Pollavini G, Malliani A, Ruberti U, Trazzi R, Bartorelli C, Zanchetti A, Lotto A, Italian Sudden Death Prevention Group (1992a) Prevention of sudden cardiac death after a first myocardial infarction by pharmacological or surgical antiadrenergic interventions. J Cardiovasc Electrophysiol 3:2–16

Schwartz PJ, La Rovere MT, Vanoli E (1992b) Autonomic nervous system and sudden cardiac death. Circulation 85 [Suppl I]:I77–I91

Simpson JR, Foster JR, Gettes LS (1982) Atrial excitability and conduction in patients with interatrial conduction defects. Am J Cardiol 50:1331–1337

Smeets JLRM, Allessie MA, Lammers WJEP, Bonke FIM, Hollen J (1986) The wavelength of the cardiac impulse and reentrant arrhythmias in isolated rabbit atrium. Circ Res 58:96–108

The Task Force of the Working Group on Arrhythmias of the European Society of Cardiology: Bigger TJ Jr, Breithardt G, Brown AM, Camm AJ, Carmeliet E, Fozzard HA, Hoffman BF, Janse MJ, Lazzara R, Mugelli A, Myerburg RJ, Roden DM, Rosen MR, Schwartz PJ, Strauss HC, Woosley RL, Zaza A (1991) The Sicilian Gambit. A new approach to the classification of antiarrhythmic drugs based on their actions on arrhythmogenic mechanisms. Eur Heart J 12:1112–1131; Circulation 84:1831–1851

Vanoli E, De Ferrari GM, Stramba-Badiale M, Hull SS Jr, Foreman RD, Schwartz PJ (1991) Vagal stimulation and prevention of sudden death in conscious dogs with a healed myocardial infarction. Circ Res 68:1471–1481

Watson RM, Josephson ME (1980) Atrial flutter: I. Electrophysiologic substrates and modes of initiation and termination. Am J Cardiol 45:732–741

Wyndham CRC, Amat-Y-Leon F, Wu D, Denes P, Dhingra R, Simpson R, Rosen KM (1977) Effects of cycle length on atrial vulnerability. Circulation 55:260–267

Yamaguchi I, Kurihara T, Maeda H, Sugishita Y (1990) Baroreflex sensitivity of patients with paroxismal atrial fibrillation. Circulation 82 [Suppl III]:III-57

Yusuf S, Teo KK (1991) Approaches to prevention of sudden death: need for fundamental reevaluation. J Cardiovasc Electrophysiol 2 [Suppl]:S233–S239

Atrial Fibrillation: Is Our Electrophysiological Understanding on the Right Wavelength?

M. A. Allessie and M. J. Janse

The Multiple Wavelet Hypothesis

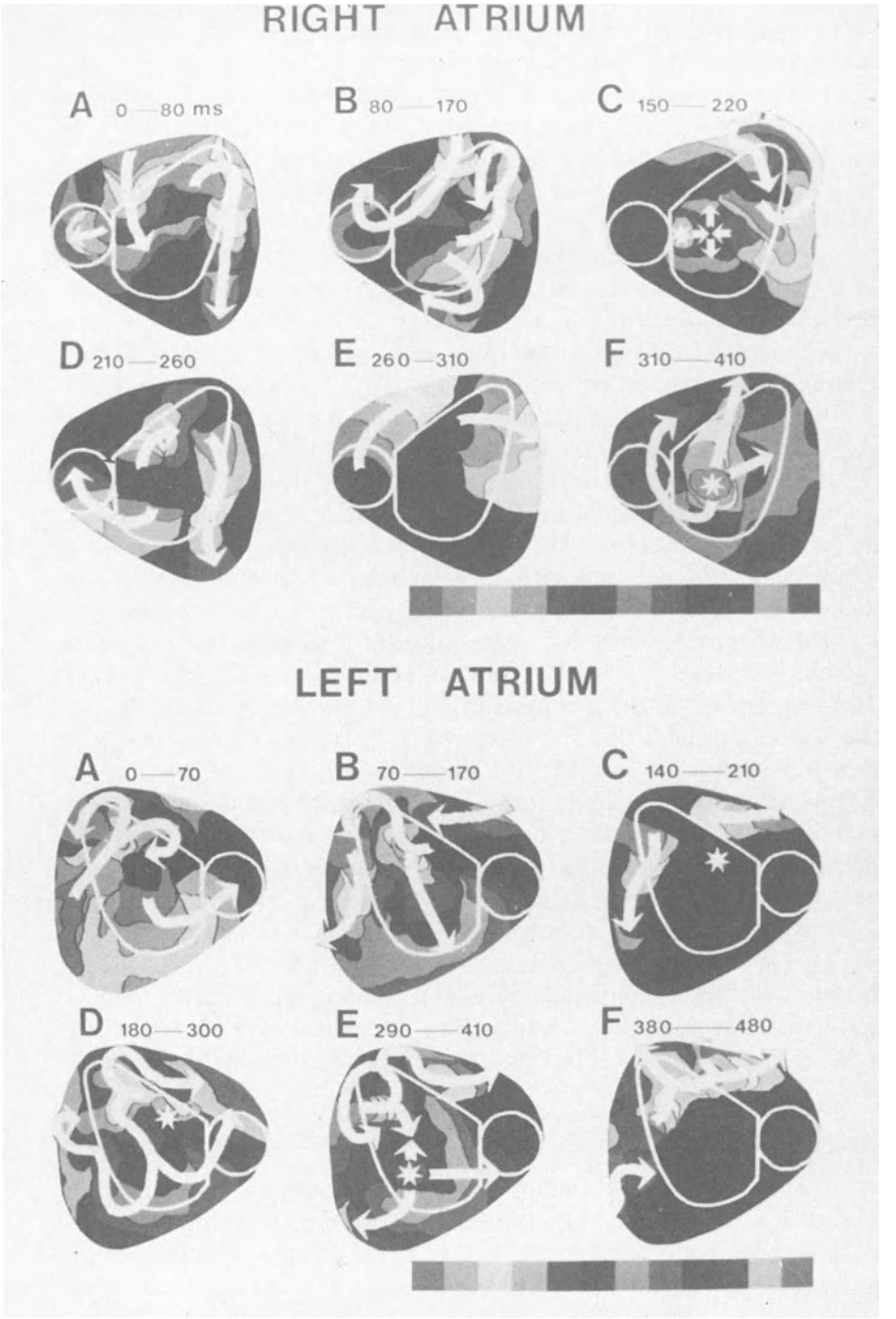
Experimental atrial fibrillation can be induced in various ways. Rapid stimulation of the atrium, especially when combined with vagal stimulation, and local application of aconitine both produce atrial fibrillation with the same characteristics as far as rate and irregularity are concerned (Garrey 1914; Scherf 1947; Moe and Abildskov 1959). Yet the mechanisms underlying the two arrhythmias are completely different. When atrial fibrillation is induced by rapidly stimulating an atrial appendage and the appendage is clamped off, fibrillation ceases in the appendage but continues in the rest of the atrium (Garrey 1914; Moe and Abildskov 1959). When after application of aconitine to an appendage this structure is clamped off, sinus rhythm is restored in the rest of the atrium while the clamped-off appendage shows a fast regular tachycardia (Moe and Abildskov 1959). In this case, the arrhythmia is due to a focus that discharges so rapidly that uniform excitation of the atrium is no longer possible. This kind of fibrillation is best described as "fibrillatory conduction" where at multiple and varying sites rate-dependent arcs of conduction block develop (Allessie et al. 1985). To explain the mechanism of the other type, best called true fibrillation, Moe and Abildskov (1959) formulated the multiple wavelet hypothesis. The key element of this hypothesis is that the

"wave front becomes fractionated as it divides about islets or strands of refractory tissue, and each of the daughter wavelets may now be considered as independent offspring. Such a wavelet may accelerate or decelerate as it encounters tissue in a more or less advanced state of recovery. It may divide again or combine with a neighbour; it may be expected to fluctuate in size and change in direction. Its course, though determined by the excitability or refractoriness of surrounding tissue, would appear to be as random as Brownian motion. Fully developed fibrillation would then be a state in which many such randomly wandering wavelets coexist. The likelihood of persistence of this process should depend upon the number of wavelets present. If the number is large, there is little chance that all elements will fall into phase (i.e., be refractory or excitable simultaneously), but if the number is small, there is a considerable probability that they may fuse and permit resumption of sinus rhythm. The average number, in turn, will depend upon the atrial mass, the mean duration of the refractory period, and the mean conduction velocity."

At the time this hypothesis was formulated, simultaneous recording from a sufficient number of sites in the atria to document the complex excitation pattern was impossible, and Moe (1962) wrote that "direct test of the hypothesis is difficult, if not impossible in living tissue". Moe and associates (1964) developed a computer model with, as key feature, a nonhomogeneous distribution of refractory periods to simulate atrial fibrillation. Premature stimulation of sites with short refractory periods initiated a rapid, irregular rhythm, which was sustained by "irregular drifting eddies which varied in position and size". The number of wavelets varied between 23 and 40. The arrhythmia could be terminated by prolonging the refractory period.

Some 25 years later, when equipment became available to record simultaneously from multiple atrial sites, Moe's hypothesis could be tested directly (Allessie et al. 1985). To this end, two solid egg-shaped multielectrodes were inserted into the cavities of right and left atria of isolated, Langendorff perfused dog hearts. Each egg electrode contained 480 recording electrodes equally spaced on the surface at interelectrode distance of 3 mm. At the side of the interatrial septum, the eggs were flattened to better fit the shape of the atrial cavities. Simultaneous recordings could be made from 192 electrodes. In Fig. 1, the patterns of excitation of right and left atrium are shown during atrial fibrillation induced by rapid pacing in the presence of acetylcholine in the perfusion fluid. To visualize the endocardial surface, a virtual cut was made in the inferior atrium from the AV ring to the tip of the appendage and the lateral and medial walls were unfolded. Within the two-dimensional plane thus obtained, the outline of the egg electrode was drawn, together with the circular flattened part of the electrode facing the interatrial septum. In Fig. 1, two time windows of about 0.5 s are shown. The upper six panels depict the activation sequence of the right atrium, the lower six panels that of the left atrium, recorded a few minutes later during stable atrial fibrillation. A gray scale was used to indicate isochronic areas activated within the same 10-ms interval; arrows indicate general spread of excitation. At time zero (upper panel A), which was arbitrarily chosen, three independent waves of depolarization

Fig. 1. Consecutive activation maps covering the spread of activation in the right and left atrium during half a second of stable atrial fibrillation in the canine heart. The recordings of right and left atrium were not made simultaneously and therefore cannot be time-aligned. The endocardial activation is plotted in a two-dimensional plane by making a virtual cut in the interior atrium from the AV ring to the tip of the appendage and unfolding the lateral and medial atrial walls. The propagation of the impulse is visualized by gray-scaled isochrones of 10 ms. The general direction of wavelets is indicated by *white arrows*. *Asterisks* indicate sites of origin of "new" impulses coming from the other atrium. See text for further details


RIGHT ATRIUM
A 0—80 ms
B 80—170
C 150—220
D 210—260
E 260—310
F 310—410
LEFT ATRIUM
A 0—70
B 70—170
C 140—210
D 180—300
E 290—410
F 380—480

are present in the right atrium. One wave travels down the septum and is extinguished at time 30 at the AV junction (smallest arrow). The other two waves travel originally in opposite directions and collide at time 20. One of the waves makes a 180° turn and continues as a narrow wavelet in the free wall of the right atrium until it dies out at the atrioventricular ring at time 80. In panel B, starting at time 80, the large depolarization wave present at the end of panel A is split into three separate wavefronts. One of these (arrow turning counterclockwise in panel B) succeeded in reexciting the lateral wall of the appendage which was activated only 70 ms before by another activation wave (the long narrow wavelet in panel A). We have here an example of reexcitation by a different wavefront than the original one, a phenomenon which is typical for reentry during fibrillation.

However, reexcitation by the same wavefront can occur as well: after exciting the lateral wall of the appendage, the impulse made a full 360° turn in the anterior part of the free lateral wall, leading to the creation of a closed local circuit. This reentrant wave continued for another revolution in panel C (upper right arrow), but size and location had changed. Panel C shows two other phenomena. First, at time 180, a new impulse appears at the site of the asterisk. This impulse probably represents endocardial breakthrough of a wave originating in the left atrium. The second phenomenon is indicated by the four small arrows. Here we can see what happens when two narrow wavelets collide. Instead of mutual extinction, which is seen when two broad wavefronts collide, we see a "clash-and-go" phenomenon, where the two wavelets collide and then travel on, making a 90° turn. In panel D three wavelets are present, in panel E only two. Both these wavefronts die out. The left wave, coming from the septum, was caught in the medial wall and found itself enclosed by the atrioventricular border at the left, the oncoming other wavefront and refractory tissue at the right. The right wave was extinguished because continuation around the appendage was rendered impossible by the approaching other wave, while propagation along the lateral wall in a posterior direction was blocked by refractoriness of the tissue. The disappearance of the wandering wavelets in the right atrium did not result in termination of the arrhythmia. Less than 30 ms after the waves had died out, a new impulse (asterisk in panel F) appeared, most likely an offspring from a left atrial wavefront.

Detailed analysis of such activation patterns revealed several characteristics of atrial fibrillation:

1. Although circulating excitation of the "leading-circle" type (Allessie et al. 1977) can occur, it is exceptional that an impulse follows the same circular route more than once. Rather, reentry as the basis for fibrillation means reexcitation of a given area that had already been excited

before by another wavefront. This has been called "random reentry" by Hoffman and Rosen (1981).

2. Conduction velocity of the wavelets varies between 20 and 90 cm/s.
3. Wavelets can be as narrow as a few millimeters, but broad wavefronts propagating uniformly over large segments of atrial tissue occur as well.
4. Each wavelet exists for only a short time, not longer than a few hundred milliseconds. Extinction of a wavelet can be caused by fusion or collision with another wavelet, by reaching the border of the atria, or by meeting refractory tissue. New wavelets can be formed by division of a wave at a local area of conduction block, or by an offspring of a wave travelling toward the other atrium.
5. The critical number of wandering wavelets for perpetuation of fibrillation is between three and six. In any chamber, an average of three wavelets is present, with a maximum of four and a minimum of zero. With an average of three simultaneously present wavelets the chance for all wavelets ceasing to exist is rather high, but with an average of six (three in each atrium), fibrillation does not terminate spontaneously. When the concentration of acetylcholine in the perfusion medium is reduced, resulting in a prolongation of refractoriness and a prolongation of the wavelength (vide infra), the number of wavelengths gradually decreases to three or less and the arrhythmia terminates.

Whereas experiments such as described above clearly provide evidence that random reentry causes atrial fibrillation, it must be emphasized that various other mechanisms could in principle also give rise to the electrocardiographic pattern of fibrillation. The definition of fibrillation is a descriptive one, based on the electrocardiogramm, and usually includes characteristics such as rapidity and irregularity and the inability to distinguish individual QRS complexes (ventricular fibrillation) or P waves (atrial fibrillation). Electrophysiological mechanisms other than random reentry which could produce such ECG characteristics are: (a) A single wandering reentrant circuit. In the ventricles, this has been shown to occur in acutely ischaemic myocardium where a single reentrant circuit that changed size and location from beat to beat produced extracellular potentials that were indistinguishable from fibrillation caused by random reentry (Janse et al. 1980). In the atria, this possibility is also suggested by maps made from both canine and human atria during atrial fibrillation (Cox et al. 1991). (b) A single rapid focus (automatic, triggered or "micro" reentrant) with fibrillatory conduction, where because of inhomogeneities in refractoriness not all parts of the tissue are able to follow the rapid rate, and rate-dependent arcs of conduction block develop that change in size and loca-

tion. (c) Two independent foci at fixed sites with different intrinsic rates of discharge ("parasystolic fibrillation"). (d) Combination of a single focus and a single reentrant circuit.

The Wavelength Concept

For sustained reentry, all cells in the reentrant circuit must have recovered their excitability before being reexcited. This can only occur if the path length of the reentrant circuit is greater than the wavelength of the propagating impulse, which is given by the product of conduction velocity and refractory period. If wavelength is short, because of a short refractory period, slow conduction or both, more reentrant wavelets can be present in a given tissue mass, and therefore the likelihood for fibrillation will be increased. In the normal dog, there is a close relationship between wavelength and the occurrence of induced atrial arrhythmias (Rensma et al. 1988). In conscious dogs in which multiple electrodes for stimulation and recording had been attached to both atria, refractory periods and conduction velocity were measured. To change wavelength, a number of agents (acetylcholine, propafenone, lidocaine, ouabain, quinidine, sotalol) were administered and refractory period duration, conduction velocity and their product were correlated with the induction of atrial arrhythmias by single premature stimuli. In all 19 dogs, atrial arrhythmias, including atrial fibrillation, could be induced. Although at shorter refractory periods a relatively high incidence of atrial fibrillation was observed, prolongation of the refractory period did not always prevent atrial fibrillation. In fact, the predictive value of refractory period duration alone or conduction velocity alone for induction of arrhythmias was poor. Figure 2 shows the correlation between the induction of atrial fibrillation (and the instances when no arrhythmias could be induced) and refractory period, conduction velocity and wavelength of the provoking premature impulse. The critical wavelength where atrial arrhythmias (repetitive responses or atrial flutter) started to be induced was 12 cm, and the critical wavelength for atrial fibrillation was 8 cm. Because of the variety of drugs administered, values for conduction velocity and refractory period varied widely. Atrial fibrillation could be induced over a wide range of refractory periods (50–150 ms) and conduction velocities (50–140 cm/s). For each of these parameters there is a wide overlap between the population of "no arrhythmias" and atrial fibrillation. When, however, wavelength was used as a criterion, there was a clear separation between the two populations.

These findings suggest that it might be useful to describe part of the properties of antiarrhythmic drugs in terms of wavelength. It must be em-

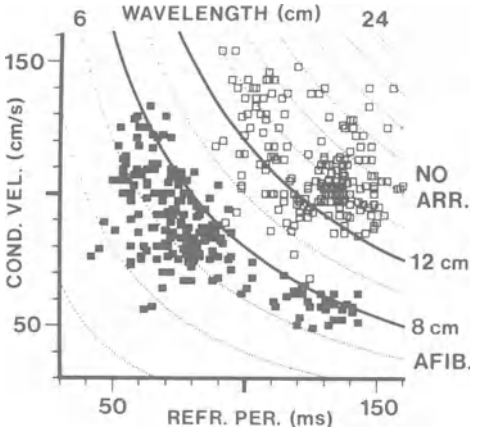


Fig. 2. Relation between induction of atrial fibrillation and refractory period, conduction velocity and wavelength of the initiating premature beat. Because wavelength is the product of refractory period and conduction velocity "iso-wavelength" curves are drawn at 8 cm and 12 cm. Because of the effects of a wide variety of administered drugs, a wide range of refractory periods and conduction velocities was achieved. Different responses to premature stimulation, i.e., either no arrhythmias (*NO ARR.*) or atrial fibrillation (*AFIB.*) were obtained over a wide range of conduction velocities and refractory periods. However, wavelength discriminated well between the two types of response

phasized, however, that these results are valid for normal dog atria, in which it may be supposed that electrophysiological characteristics are fairly homogeneous throughout the atrial tissue. In diseased atria, with possibly an inhomogeneous distribution of refractory periods and conduction velocity, there may not be a single wavelength, but varying wavelengths at different sites. In such atria, it may not be as easy to demonstrate a similar relationship between wavelength and arrhythmogenesis.

Electrophysiological Abnormalities of Atria Prone to Fibrillation

Several electrophysiological abnormalities have been reported to be associated with atrial fibrillation. Transmembrane potentials have been recorded from tissue obtained from fibrillating human atria, and it was found that resting membrane potential levels were significantly reduced compared to resting membrane potentials of cells from nonfibrillating atria (Rosen et al. 1982). This would imply that, because of the reduced upstroke velocity of the action potential as a consequence of the low resting membrane potential level, conduction velocity would be decreased, which, as discussed above, would promote reentry by decreasing wavelength. It is not known whether resting membrane potential varies in different parts of fibrillating atria.

Attuel and associates (1982) were the first to describe an intriguing abnormality in patients vulnerable to atrial fibrillation. In these patients there was no or hardly any adaptation of the atrial refractory period to changes in heart rate. At the most rapid rates investigated (cycle lengths in the order of 350–400 ms) the range of refractory periods was similar to that of normal patients (approximately 160–250 ms). Upon slowing of the heart rate, however, no prolongation of the refractory period was observed, so that at cycle lengths between 800 and 1000 ms, the refractory periods of the patients prone to atrial fibrillation were much shorter than those of normals. These findings were largely confirmed in a later study, in which action potentials were recorded from isolated pieces of atrial tissue at different pacing rates (Le Heuzey et al. 1989). Importantly, dispersion of action potential duration was much greater in the atrial fibrillation group than in the control group, indicating that in atria prone to fibrillate, dispersion in recovery of excitability is increased.

The classical method of determining refractory period duration is to deliver a premature stimulus S_2 after every eigth or tenth basic stimulus S_1 during a regularly driven rhythm and to vary the coupling interval until the shortest S_1S_2 is found at which S_2 results is a propagated response. To determine refractory periods at multiple sites is a very time-consuming procedure. The average interval between local activations during both atrial fibrillation (Lammers et al. 1986) and ventricular fibrillation (Opthof et al. 1991) has been used as an index for local refractoriness. This is based on the concept, supported by microelectrode recordings, that during fibrillation cells are reexcited as soon as their refractory period ends by one of the many wandering wavelets. Recording local electrograms simultaneously at many sites during fibrillation allows assessment of spatial dispersion in "refractoriness" in a very short time. The correlation between fibrillation interval at various sites and refractory period duration measured after defibrillation at the same sites by the classical S_1S_2 method was very good for both atrial and ventricular fibrillation (Lammers et al. 1986; Opthof et al. 1991). A difference between shortest and longest fibrillation interval of some 15 ms corresponded to a difference in refractory period duration at a regularly driven rhythm (cycle length 350 ms) of 35–40 ms. The fibrillation interval should be regarded as an index of the shortest possible refractory period.

In a population of patients undergoing cardiac surgery, atrial fibrillation was induced by premature stimulation in a group who had never had atrial fibrillation and a group with paroxysmal atrial fibrillation, and fibrillation intervals were determined at 30 atrial sites in each patient. In the atrial fibrillation group, the average fibrillation interval was 25 ms shorter than in the control group and the spatial dispersion in fibrillation

intervals were three times larger (Ramdat Misier et al. 1990). These findings support those of earlier studies, and indicate that as far as refractoriness is concerned, atria of patients with spontaneous atrial fibrillation are inhomogeneous. The wavelength concept is still valid, but there is no single value for wavelength in such atria.

Summary

The experimental evidence obtained from both animal and human studies indicates that atrial fibrillation is generally due to random reentry caused by multiple reentrant wavelets. Other mechanisms, however, such as a single wandering reentrant circuit or a focal mechanism, may also cause atrial fibrillation. Electrophysiological abnormalities of atria prone to fibrillation include short refractory periods, failure to adapt the refractory period duration to changes in heart rate, low resting potentials and a large dispersion in action potential duration and refractoriness. Short wavelengths predispose to atrial fibrillation, but in inhomogeneous tissue it is difficult to determine the critical wavelength.

References

Allessie MA, Lammers WJEP, Bonke FIM, Hollen J (1985) Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. In: Zipes DP, Jalife J (eds) Cardiac electrophysiology and arrhythmias. Grune and Stratton, Orlando, pp 265–275

Attuel P, Childers R, Cauchemez B, Poveda J, Mugica J, Coumel P (1982) Failure in rate adaptation of the atrial refractory period: its relationship to vulnerability. Int J Cardiol 2:179–197

Cox JL, Canavan TE, Schuessler RB, Cair ME, Lindsay BD, Stone C, Smith PK, Corr PB, Boineau JP (1991) The surgical treatment of atrial fibrillation: II. Intraoperative electrophysiologic mapping and description of the electrophysiologic basis of atrial flutter and fibrillation. J Thorac Cardiovasc Surg 101:406–426

Garrey WE (1914) The nature of fibrillary contraction of the heart. Its relation to tissue mass and form. Am J Physiol 33:397–414

Janse MJ, van Capelle FJL, Morsink H, Kléber AG, Wilms-Schopman FJG, Cardinal R, Naumann d'Alnoncourt C, Durrer D (1980) Flow of "injury" current and pattern of excitation during early ventricular arrhythmias in acute regional myocardial ischemia in isolated porcine and canine hearts. Circ Res 47:151–165

Lammers WJEP, Allessie MA, Rensma PL, Schalij MJ (1986) The use of fibrillation cycle length to determine spatial dispersion in electrophysiological properties and to characterize the underlying mechanism of fibrillation. New Trends Arrhyt 2:109–112

Le Heuzey JY, Boutjdir M, Gagey S, Lavergne T, Guise L (1989) Cellular aspects of atrial vulnerability. In: Attuel P, Coumel P, Janse MJ (eds) The atrium in health and disease. Futura, Mount Kisco, pp 81–94

Moe GK (1962) On the multiple wavelet hypothesis of atrial fibrillation. Arch Int Pharmacodyn Ther 140:183–188

Moe GK, Abildskov JA (1959) Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. Am Heart J 58:59–70

Moe GK, Rheinboldt WC, Abildskov JA (1964) A computer model of atrial fibrillation. Am Heart J 67:200–220

Opthof T, Ramdat Misier AR, Coronel R, Vermeulen JT, Verberne HJ, Frank RGJ, Moulijn AC, van Capelle FJL, Janse MJ (1991) Dispersion in refractoriness in canine ventricular myocardium: effects of sympathetic stimulation. Circ Res 68:1204–1215

Ramdat Misier A, Opthof T, van Hemel N, Defauw J, Kingma H, de Bakker J, Janse M (1990) Dispersion in "refractoriness" in patients with recurrent paroxysmal atrial fibrillation. Eur Heart J 11 [Suppl]:238

Rensma PL, Allessie MA, Lammers WJEP, Bonke FIM, Schalij MJ (1988) Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res 69:395–410

Rosen MR, Bowman FO, Mary-Rabine L (1982) Atrial fibrillation: the relationship between cellular electrophysiologic and clinical data. In: Kulbertus HE, Olsson SB, Schlepper M (eds) Atrial fibrillation. Hässle, Mölndal, pp 62–69

The Contribution of Monophasic Action Potential Recordings to the Understanding of Atrial Fibrillation

M. R. Franz and B. Koller

Introduction

Atrial fibrillation is a common arrhythmia with significant clinical impact. Despite newer advances in arrhythmia treatment such as arrhythmia surgery and catheter ablation, atrial fibrillation remains a domain for pharmacologic therapy. Although many clinical variables predisposing to atrial fibrillation have been determined (e.g., enlarged atrial size and hyperthyroidism), the electrophysiologic mechanisms leading to atrial fibrillation, its termination and its recurrence are little understood. This has made it difficult to apply pharmacologic therapy on a scientific basis.

In the basic laboratory, cellular electrophysiologic properties can be assessed directly by measuring the transmembrane action potential with an intracellular microelectrode. The transmembrane action potential has been very useful in identifying antiarrhythmic drug effects on the action potential characteristics and how these effects may suppress arrhythmias. However, the microelectrode technique cannot be employed in the beating human heart. The body surface electrocardiogram, on the other hand, often is too insensitive to measure local electrophysiologic changes and drug effects at the myocardial level.

To close the gap between basic and clinical electrophysiology, we have developed a contact electrode catheter which allows recording in the human heart of so-called monophasic action potentials (MAPs; Franz 1983). These MAPs have been shown to accurately reflect the onset, duration and configuration of transmembrane action potentials of adjacent myocardial cells (Franz et al. 1986), thus making it possible to study basic cellular events in the human heart.

MAP Catheter Design

The design of the contact electrode MAP catheter (EP Technologies, Inc., Mountain View, California) and its validation have been described in detail previously (Franz et al. 1986, 1989). Briefly, this catheter features two non-polarizable electrodes, one forming the tip of the catheter while the other

is located 5 mm proximal to the catheter tip. The tip electrode records the MAP from an area of approximately 2–3 mm while the proximal electrode serves as a reference. The catheter also has embedded in its tip a second electrode pair consisting of platinum electrodes wich are mounted opposite each other halfway between the tip and the proximal MAP recording electrodes. These electrodes are used for pacing. The distance between the catheter tip and the pacing electrodes is 2 mm, making the pacing and recording sites almost identical. The MAP signals are amplified with a high input impedance, direct-current coupled, differential preamplifier (Model 1001, EP Technologies, Inc.) with a frequency response of 0–5000 Hz.

Because this catheter allows both MAP recording and pacing, measurements of action potential duration (APD) and effective refractory period (ERP) can be made simultaneously and at the same site (Franz et al. 1989). An extrastimulus of twice diastolic current strength is delivered repeatedly after every 20 steady-state basic drive stimuli, with the extrastimulus coupling interval being shortened by 5-ms decrements until refractoriness occurs. This defines the ERP, which can be compared directly with the APD, commonly measured at the level of 90% repolarization (APD90).

We have reported previously that there is a very close correlation between APD and ERP in the human myocardium (Franz and Lee 1991). This correlation is constant over a large range of steady-state cylce lengths such that cycle length-dependent changes in APD and ERP parallel each other. Because of the close correlation between APD and ERP, the wavelength of excitation can be assumed to be similar to the wavelength of refractoriness. Wavelength determinations based on the APD are more convenient because the APD can be measured on a beat-by-beat basis and does not require repeated extrastimuli as is necessary for the ERP determination. We will see, however, that there are conditions in which the APD and ERP differ from each other, especially during antiarrhythmic drug treatment.

Definition of Electrophysiologic Intervals by MAP Recordings

Because the MAP catheter not only detects local activation but also records the entire repolarization time course with high accuracy, it can be used to measure electrophysiologic intervals not available with conventional electrode catheters. This is demonstrated in Fig. 1, which shows two simultaneously recorded right atrial MAPs, a His bundle electrogram and several surface ECG leads. First, we can measure the APD, in this example at 90% repolarization (APD90). Second, the diastolic interval (DI) be-

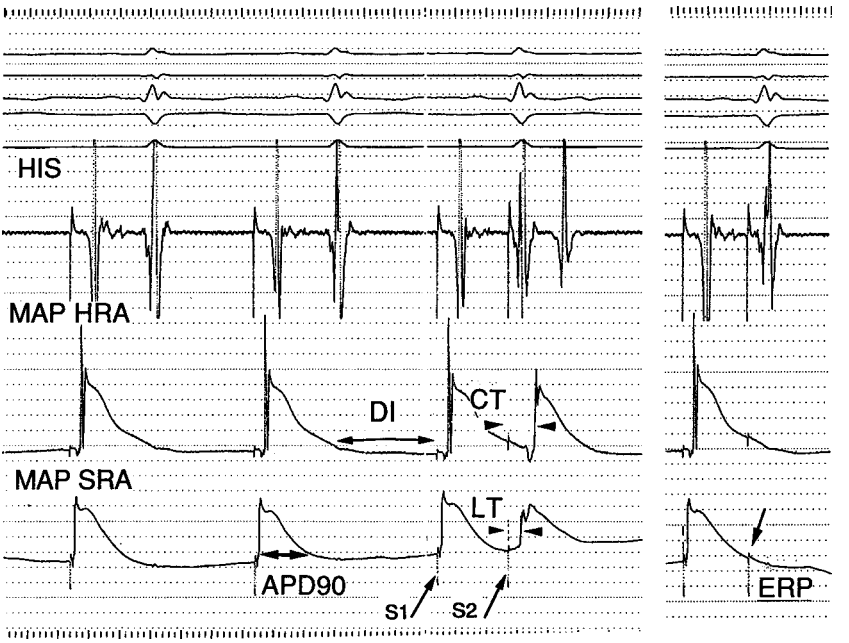


Fig. 1. Two recorded monophasic action potentials (*MAP*), one from the high right atrium (*HRA*), the other from the septal right atrium (*SRA*), recorded simultaneously with several surface ECG tracings and a HIS bundle electrogram. Action potential duration was measured at the level of 90% repolarization (*APD90*). The interval between the conclusion of APD90 and the beginning of the next action potential was designated as the diastolic interval (*DI*). The SRA tracing shows simultaneous determination of APD90 and refractoriness (*ERP*). The time interval from the stimulus artifact (*S1, S2*) to the local MAP upstroke was designated as the local stimulus-response latency (*LT*), and the interval between the upstroke of the two MAPs as the conduction time (*CT*)

tween one action potential and the next can be measured and has significance for identifying the rhythm abnormality, as shown below. Third, through simultaneous pacing we can determine the ERP at the MAP recording site. This allows us to establish the relationship between repolarization and excitability or the ERP/APD ratio at the same site. The ERP/APD ratio, as will be shown below, is important for identifying antiarrhythmic drug effects. Fourth, by recording MAPs from two separate sites simultaneously, the conduction time (CT) between the two sites can be measured. If the distance (d) between the two sites is known, the conduction velocity (CV) can be calculated as CT/d = CV. The MAP recording also distinguishes between local stimulus-response latency (the time from the stimulus artifact to the local MAP upstroke) and conduction time between the two sites (the interval between the two MAP upstrokes). Final-

ly, by calculating the product of conduction velocity and APD or ERP, we can determine the wavelength of excitation or refractoriness, respectively (Smeets et al. 1986).

MAP Recordings During Atrial Tachyarrhythmias

In the first part of this study, we used MAP recordings to help describe the features of atrial fibrillation and what distinguishes it from other tachyarrhythmias. In the second part, we used the MAP catheter to examine the conditions that might lead to atrial fibrillation as well as conditions that favor its suppression or prevent its recurrence.

MAP recordings reveal distinct differences between atrial tachycardia, flutter and fibrillation, even under circumstances in which the surface ECG may be unreliable in differentiating these different types of arrhythmias. Figure 2 shows MAP recordings during three different types of arrhythmia – ectopic atrial tachycardia, atrial flutter and atrial fibrillation. During atrial tachycardia, the MAP shows a regular and repeating waveform with characteristics very similar to that during sinus rhythm. Despite the fast rate, repolarization is always complete between successive depolarizations, so that they are separated from each by a distinct DI. In atrial flutter, the MAP recordings are still regular and of consistent morphology, but they follow each other directly with no obvious DI between successive potentials. In contrast, during atrial fibrillation, the MAP pattern is totally irregular. The depolarization phase is markedly slowed, distorted and reaches variable magnitudes. Also in contrast to atrial tachycardia and flutter, during atrial fibrillation the potential does not return to its normal diastolic level but is interrupted by the subsequent depolarization at various degrees of incomplete repolarization, giving the MAPs the appearance of "riding" on each other. These irregularities in the MAP pattern may reflect, in part, the interdigitation of multiple wavelets and in part variability in the threshold of excitability within the small area of cells from which the MAP is recorded. Thus, in atrial fibrillation there seems to be a continuum of repolarization and depolarization, with subsequent depolarizations occurring as soon as the tissue recovers from absolute refractoriness. This is in keeping with the observation that overdrive pacing is not possible during atrial fibrillation (lack of excitable gap), while during atrial tachycardia and atrial flutter it is usually possible to capture the atrial myocardium. The salient features of the three types of atrial tachyarrhythmias are compared in Table 1.

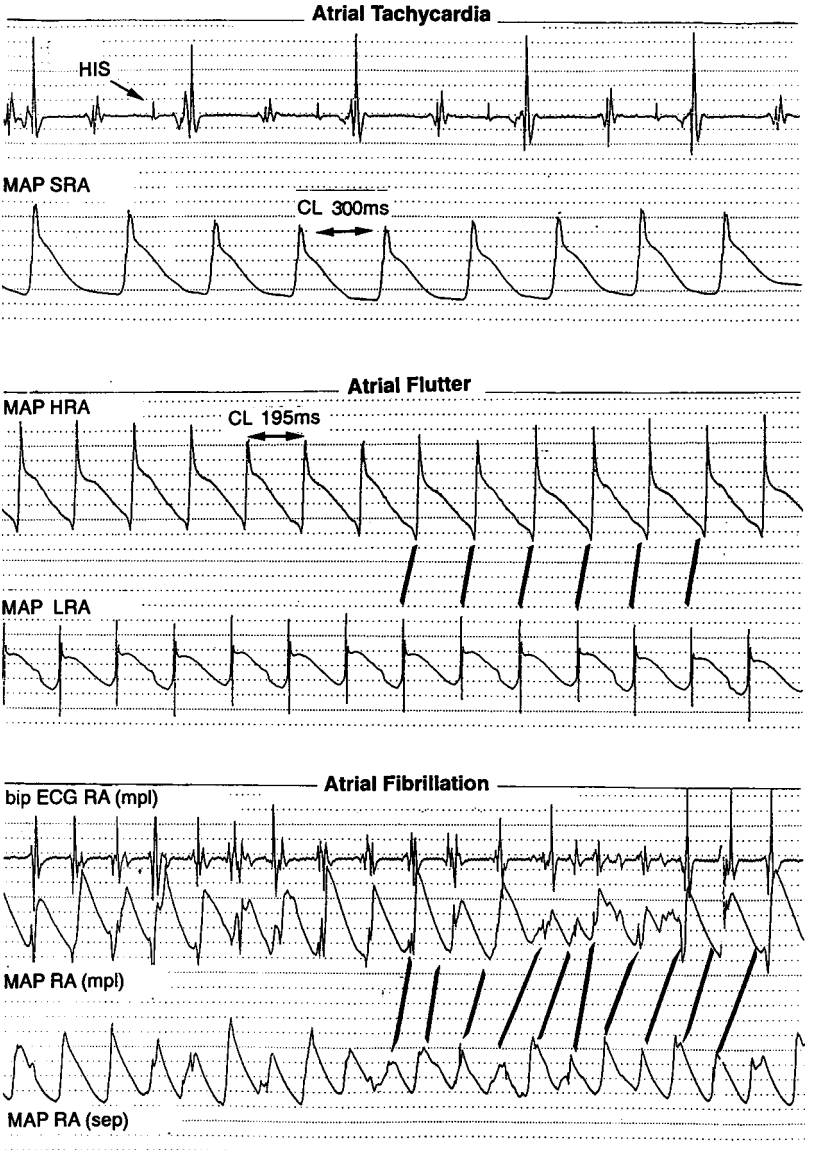


Fig. 2. Original MAP recordings during ectopic atrial tachycardia (*upper panel*), atrial flutter (*middle panel*) and atrial fibrillation (*lower panel*). In the atrial tachycardia recording, a conventional tripolar catheter was placed in HIS-bundle position (*HIS*) and a monophasic action potential (*MAP*) catheter in septal right atrium (*SRA*) position. During atrial flutter, two MAP tracings, one at the high right atrium (*HRA*) and one at the low right atrium (*LRA*), were recorded . During atrial fibrillation, one MAP catheter was placed at the septal right atrium (*RA sep*), the other at a mediposterolateral position of the right atrium (*RA mpl*). A bipolar ECG (*bip ECG*) was recorded at the latter site

Table 1. MAP distinction of atrial tachyarrhythmias

	Tachycardia	Flutter	Fibrillation
Cycle length	Regular	Regular	Irregular
Leading wavefront	Steady	Steady	Changing
Diastolic interval	Present	Very short	Absent
Morphology	Regular	Regular	Irregular
Take-off potential	Phase 4	End phase 3	Different levels of phase 3
Excitable gap	Present	Present	Absent

Effects of Antiarrhythmic Drugs on Repolarization and Refractoriness

Because of the dependence of excitability on repolarization, drug-induced prolongation of APD always results in at least a comparable increase in ERP. On the other hand, drugs may prolong ERP without increasing APD, thus causing an increase in the ERP/APD ratio (Franz and Costard 1988; Costard et al. 1989; Campbell 1983). The increase in the ERP/APD ratio has been linked directly to the antiarrhythmic efficacy of the drugs, based on the rationale that ERP prolongation relative to APD provides a "window" of *postrepolarization refractoriness* that prevents the occurrence of early premature beats and rapid ventricular tachycardias (Rosen 1976).

Electrophysiologic Factors Promoting Atrial Fibrillation

Allessie et al. (1990) have demonstrated that atrial fibrillation involves the simultaneous existence of several small wavelets. Therefore, in order to induce atrial fibrillation, we must have shorter than normal wavelengths of excitation (or refractoriness). We will now see how MAP recordings can help us to detect electrophysiologic factors that either predispose to or trigger atrial fibrillation. Once these mechanisms are better understood, we may be able to apply antiarrhythmic drugs more specifically to prevent atrial fibrillation from recurring.

Predisposing Factors: Action Potential Duration and Its Dispersion

Olsson et al. (1971) measured the duration of monophasic action potentials in a group of patients with atrial fibrillation shortly after electrical cardioversion. They found that patients who did not have recurrences of atrial fibrillation during a 3-month follow-up period all had APDs com-

parable to those in control patients who never had atrial fibrillation. In contrast, patients who relapsed into atrial fibrillation within a few weeks after cardioversion had significantly shorter APDs. These interesting data underscore the importance of APD, and thus of a sufficiently long wavelength, for the protection against arrhythmias.

We compard APDs measured at different right atrial sites in patients with normal sinus rhythm and patients who were cardioverted from atrial fibrillation. Patients prone to atrial fibrillation exhibited marked differences in APD between different atrial sites. On average, patients with recurrent atrial fibrillation had significantly greater heterogeneity (or dispersion) of atrial APDs during sinus rhythm than the control group.

Thus, it would make sense to treat atrial fibrillation with drugs that prolong the action potential. However, it may be equally important to achieve a more uniform distribution of APD across the atrium.

How Does Premature Stimulation Trigger Atrial Fibrillation?

Figure 3 (upper panel) shows how an extrastimulus initiates an atrial tachyarrhythmia and how the MAP recordings, obtained from two different right atrial sites, may provide clues for the mechanism of induction. When the premature extrastimulus is introduced so early that it encroaches on the repolarization phase of the preceding action potential but still produces a propagated response, we can observe two important changes. The first is that the APD of the premature response is shorter than that of the regularly paced beat. The second is that the CT between the two recording sites is increased. A lengthening of CT is equivalent to a slowing of CV; hence both the APD decrease and the increase in CT (decrease in CV) contribute to a shortening of the wavelength of excitation. It is likely that this wavelength shortening initiates the tachycardia.

The same extrastimulus protocol was repeated after administration of procainamide (Fig. 3, lower panel). Procainamide prolonged the APD and in addition increased the ERP beyond the APD (postrepolarization refractoriness). As a result, the earliest premature response that could be elicited by an extrastimulus showed much less APD shortening and also much less conduction slowing than before. Under these conditions, atrial fibrillation was not inducible; the patient remained in sinus rhythm.

Increases in the ERP and therefore in the wavelength of refractoriness can also be achieved by drugs which do not prolong the APD (Liem et al. 1987). As shown in Fig. 4a, propafenone has little effect on the atrial APD but produces pronounced postrepolarization refractoriness. The postrepolarization refractoriness increased as the pacing cycle length was decreased;

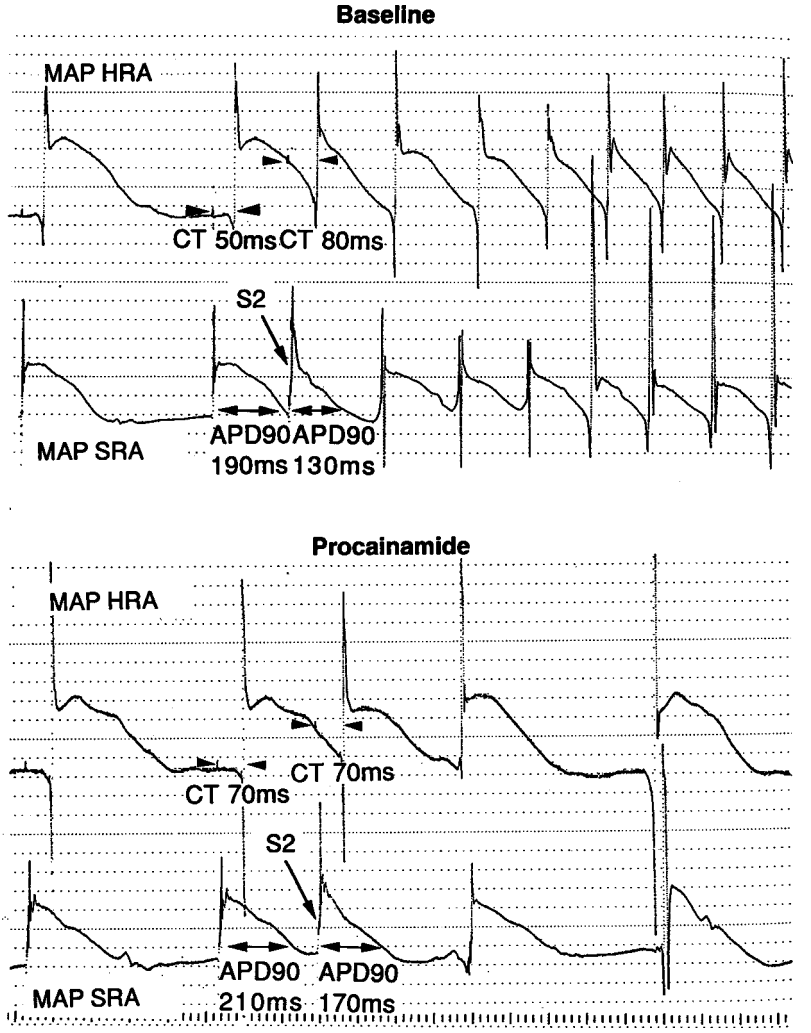


Fig. 3. *Upper panel:* Initiation of an atrial tachycardia in an MAP recording by inducing an extrastimulus (*S2*) at the septal right atrium (*SRA*) which is followed by the atrial tachycardia. *Lower panel:* Failure to induce an atrial tachycardia after procainamide. (See text for further explanations)

in other words, propafenone's effect on postrepolarization refractoriness exhibited rate or use dependence (Hondeghem 1987). As a result, the shortest pacing cycle length that still resulted in one-to-one capture was 350 ms. Faster pacing rates resulted in intermittent local unresponsiveness (or local conduction block), sometimes with the characteristics of a Wenckebach's periodicity. It is quite interesting that such rate-dependent local

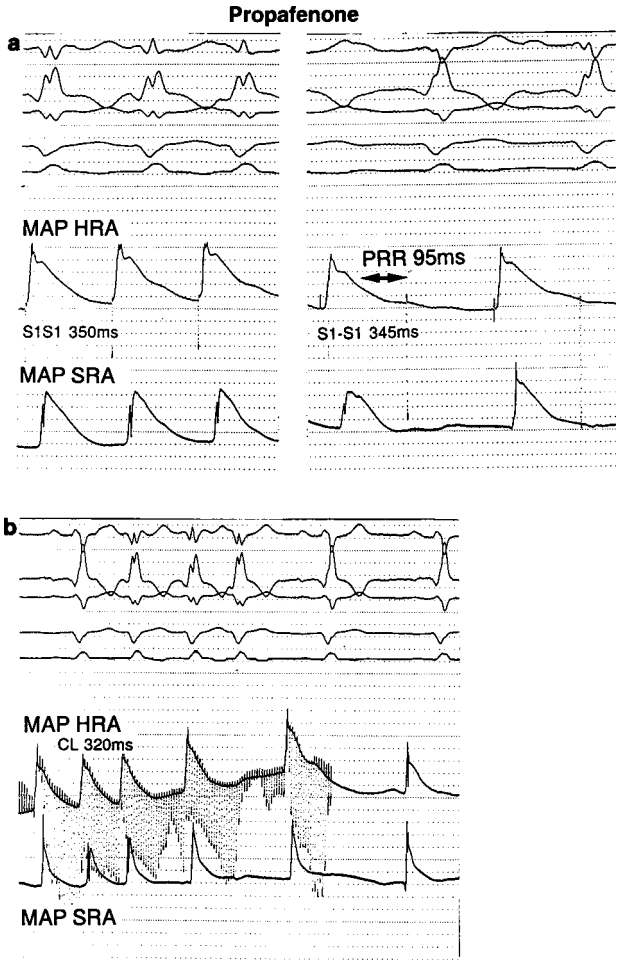


Fig. 4. **a** Simultaneous recording and pacing in the high right atrium (*HRA*) after administration of propafenone. A second MAP was recorded from the septal right atrium (*SRA*). A pacing cycle length (*SIS1*) of 350 ms resulted in one-to-one capture. Faster pacing rates resulted in intermittent local unresponsiveness, due to postrepolarization refractoriness (*PRR*). **b** High-frequency burst stimulation resulted in the shortest cycle length (*CL*) of 320 ms. Atrial fibrillation was not inducible

block can be observed in the atrial myocardium itself and not just in the atrioventricular node. This local block is most dramatically illustrated by the recordings in Fig. 4b, where we attempted to fibrillate the atria by high-frequency burst stimulation. As seen, the atrial myocardium remains refractory to the electrical stimuli for quite some time after repolarization,

a finding which could never be seen in drug-free myocardium. Thus, even during this aggressive electrical stimulation, atrial fibrillation could not be induced.

Mechanisms of Preventing Atrial Fibrillation

Figure 5 summarizes the effect of premature stimulation on the APD, CV, and the wavelength of excitation. As the extrastimulus is brought in more and more prematurely, there is a rapid and progressive shortening of the atrial wavelength, due to both shortening of APD and slowing in CV. In-

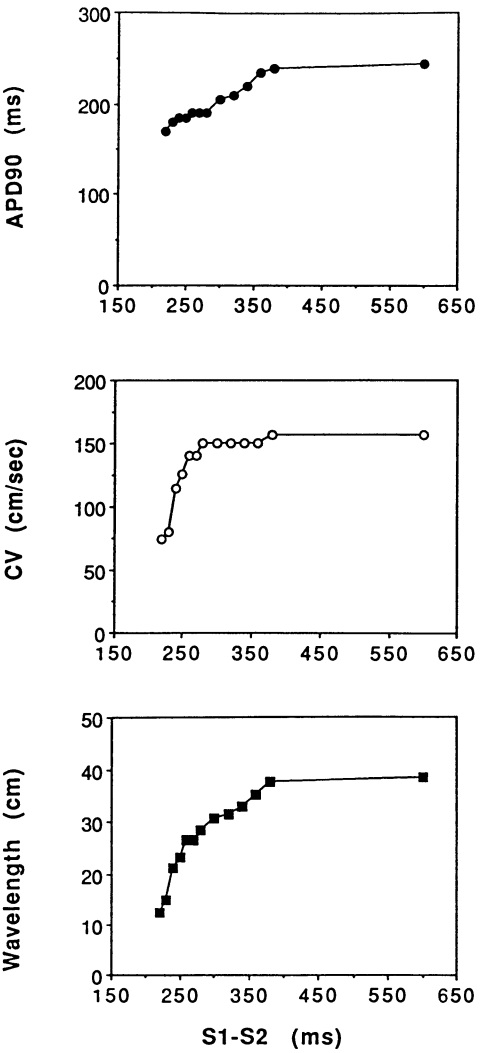


Fig. 5. Effect of premature stimulation (*S1–S2*) on the action potential duration at 90% repolarization (*APD90*), conduction velocity (*CV*) and the wavelength of excitation. As prematurity is increased, the atrial wavelength shortens due to shortening of APD90 and slowing in CV

Table 2. Effect of antiarrhythmic drugs on atrial electrophysiology

	CT	APD	ERP	ERP/APD
Procainamide	↑	↑	↑	–
Amiodarone	↑	↑↑	↑↑	↑
Propafenone	↑↑	–	↑↑	↑↑[a]

[a] ↑↑ ERP/APD = postrepolarization refractoriness

duction of atrial fibrillation or flutter was most commonly observed when the wavelength had shortened by more than 50%. According to these findings, we would like the antiarrhythmic drug to prevent such excessive wavelength shortening. This could be achieved by either APD prolongation or by producing postrepolarization refractoriness. The latter seems to be a particularly promising approach since postrepolarization refractoriness hinders the premature impulse from encroaching on the repolarization phase of the previous action potential. By keeping the premature impulse at a safe distance from the preceding action potential the untoward effect of conduction slowing, which occurs during incomplete repolarization, is avoided. The effects of common antiarrhythmic drugs on the three variables are compared in Table 2.

Summary and Conclusion

Monophasic action potentials can be safely and easily recorded from human atrial myocardium and can provide significant information about the type of atrial tachyarrhythmia and into mechanisms of their induction and therapy. The following specific electrophysiologic information can be gained from atrial MAP recordings:

1. Distinction of atrial fibrillation from other atrial tachyarrhythmias (flutter, ectopic tachycardia).
2. Synchronicity vs asynchronicity of activation and repolarization at different sites.
3. Better definition of intervals: activation, repolarization, diastolic intervals, latency and conduction times.
4. Relationship between APD and ERP (or wavelength of excitation and refractoriness).
5. Drug effects on the wavelength of excitability and refractoriness.
6. Mechanisms of drug efficacy in atrial fibrillation (e.g., drug-induced changes in ERP/APD ratio, postrepolarization refractoriness and local block).

Thus, MAP recordings are an important adjunct in clinical studies concerned with the nature, mechanism and treatment of atrial tachyarrhythmias.

References

Allessie MA, Rensma PL, Brugada J, Smeets JLRM, Penn O, Kirchhof CJHJ (1990) Pathophysiology of atrial fibrillation. In: Zipes DP, Jalife J (eds) Cardia electrophysiology – from cell to bedside. Saunders, Philadelphia, pp 548–559

Campbell TJ (1983) Kinetics of onset of rate-dependent effects of Class I antiarrhythmic drugs are important in determining their effects on refractoriness in guinea-pig ventricle, and provide a theoretical basis for their subclassification. Cardiovasc Res 17:344

Costard A, Liem LB, Franz MR (1989) Rate dependent effect of quinidine, mexiletine, and their combination on postrepolarization refractoriness in vivo. J Cardiovasc Pharmacol 14:810

Franz MR (1983) Long-term recording of monophasic action potential from human endocardium. Am J Cardiol 51:1629

Franz MR, Costard A (1988) Frequency-dependent effects of quinidine on the relationship between action potential duration and refractoriness in the canine heart in situ. Circulation 77:1177

Franz MR, Lee HC (1991) Relation between repolarisation and refractoriness in the human ventricle: cycle length dependence and effect of Procainamide. J Am Coll Cardiol

Franz MR, Burkhoff D, Spurgeon H et al. (1986) In vitro validation of a new cardiac catheter technique for recording monophasic action potentials. Eur Heart J 7:34

Franz MR, Chin MC, Sharkey HR, Scheinman MM (1989) A new combination catheter for measurement of both action potential duration and refractory period at closely adjacent myocardial sites in vivo. PACE 12:187

Hondeghem LM (1987) Antiarrhythmic agents: modulated receptor applications. Circulation 75:514

Liem LB, Clay DA, Franz MR, Swerdlow CD (1987) Electrophysiology and anti-arrhythmic efficacy of intravenous pirmenol in patients with sustained ventricular tachyarrhythmias. Am Heart J 113:1390

Olsson BS, Cotoi S, Varnauskas E (1971) Monophasic action potential and sinus rhythm stability after conversion of atrial fibrillation. Acta Med Scand 190:381

Rosen MR (1976) Effects of pharmacological agents on mechanisms responsible for reentry. In: Kulbertus HE (ed) Reentrant arrhythmias: mechanisms and treatment. University Park Press, Baltimore, pp 283–294

Smeets JLRM, Allessie MA, Lammers WJEP et al. (1986) The wavelength of the cardiac impulse and reentrant arrhythmias in isolated rabbit atrium. Circ Res 58:96–106

Class I Antiarrhythmic Drug Effects: What Is the Basis for Subgroups Ia, Ib and Ic in Human Heart Muscle?

H. Nawrath, U. Jahnel, J. Rupp, H. Oelert, and P. Satter

Introduction

Thanks to refined electrophysiological techniques, great progress has been made in understanding the cellular mechanisms of cardiac arrhythmias and the action of antiarrhythmic drugs. Nevertheless, the application of clinically useful substances in patients has remained mostly empirical. The great number of available antifibrillatory agents, however, calls for a rational basis to distinguish among the various antiarrhythmic drug actions, under both experimental and clinical conditions. A practical approach to meet these requirements was introduced more than two decades ago (Vaughan Williams 1970). The classification of Vaughan Williams, updated at intervals (Vaughan Williams 1980, 1981, 1984, 1991), defines four classes of antiarrhythmic drug actions on the basis of the electrophysiological effects of each substance on isolated heart tissue preparations, as determined by measurements of transmembrane potentials using conventional microelectrode techniques. Class I drugs, such as quinidine, share the property of depressing phase zero of the action potential by their ability to decrease the membrane conductance for Na^+. Class II agents, such as propranolol, are characterized by their β-adrenoceptor blocking effects. Class III substances, such as amiodarone, selectively prolong the action potential duration (APD), probably by an inhibiting effect on K^+ channels, whereas class IV drugs, such as verapamil, selectively inhibit Ca^{++} channels. The classification scheme by Vaughan Williams is now widely accepted, although its impact on the differential therapy of arrhythmias has remained relatively poor.

The majority of agents found effective in the treatment of cardiac arrhythmias are Na^+ channel blocking agents (class I antiarrhythmic drugs). Unfortunately, the actions of drugs that might be antiarrhythmic for patients are only poorly predicted by this classification. Class I antiarrhythmic drugs comprise a very large number of compounds with widely disparate chemical structures and clinical electrophysiological properties. Therefore, in recent years, a subclassification of drugs with class I action has been proposed (Singh and Hauswirth 1974; Harrison 1985). One obvious difference among the putative subgroups was that the APD was dif-

ferently affected. In class Ia, typified by quinidine, APD was prolonged, in class Ib, typified by lidocaine, ADP was shortened and in class Ic, typified by flecainide, APD was virtually unchanged.

Three substances belonging to class Ic (flecainide, encainide and moricizine) were included in the Cardiac Arrhythmia Suppression Trial (CAST). These drugs were chosen for their ability to suppress ventricular arrhythmias with tolerable side effects in the Cardiac Arrhythmia Pilot Study (CAPS Investigators 1988). CAST was designed to find out whether or not antiarrhythmic drugs which were able to suppress premature ventricular depolarizations (PVD) could reduce the incidence of sudden cardiac death in patients with PVD after myocardial infarction. It transpired that the mortality was more than twice as high in the group of patients treated with encainide or flecainide as in the group receiving placebo (CAST Investigators 1989). CAST was continued with moricizine after slight modifications of the protocol (CAST II), but halted recently when it became clear that moricizine also did not decrease mortality.

On theoretical grounds, the repolarization phase of the cardiac action potential may create problems in the analysis of antiarrhythmic drug actions. This difficulty is related to the fact that the repolarization phase of the cardiac action potential is brought about not only by the ion fluxes of K^+ but also of Na^+ and Ca^{++}. The discrete balance of ionic currents during depolarization in cardiac tissues derived from different species or different parts of the heart may produce inconsistent results with respect to the effects of antiarrhythmic drugs in human heart muscle. And "in this field, the only important target is man" (Vaughan Williams 1989). We have investigated the effects of several class I antiarrhythmic drugs on the action potential of human ventricular heart muscle obtained at cardiac surgery. For comparison, control experiments were performed in atrial and ventricular preparations from guinea pig hearts.

Methods

Preparations, Solutions and Experimental Setup

Human papillary muscle samples were obtained from patients undergoing open heart surgery. In the present study, 40 ventricular preparations from 27 patients (19 female, 8 male) were used. Their age ranged from 3 to 71 years. The patient population, the premedication and the procedures for isolating and further handling of human ventricular heart muscle in vitro have been described in detail in previous publications (Eckel et al. 1982; Jakob et al. 1988). In short, immediately after excision the samples were

placed in cool (4 °C) preoxygenated Tyrode's solution (pH 7.4) and carried to the laboratory. The time between excision and the beginning of laboratory processing was about 90 min. In the laboratory, the papillary muscles were transferred to a dissection chamber containing Tyrode's solution and cut into thin preparations such that as far as possible the muscle fibres ran parallel to the length of the strip.

Guinea pigs of either sex weighing 300–600 g were stunned and bled from the carotid arteries. The hearts were removed, immersed in warmed and oxygenated Tyrode's solution and suitable left atrial trabeculae and right papillary muscles were dissected from the heart.

The Tyrode's solution had the following composition (mmol/l): NaCl 136.9, KCl 5.4, $CaCl_2$ 1.8, $MgCl_2$ 1.05, NaH_2PO_4 0.42, $NaHCO_3$ 11.9, glucose 5.6 and was equilibrated with 95% O_2 and 5% CO_2 at 37 °C (pH 7.4). The preparations were mounted horizontally in a 2-ml organ bath which was built into a perspex block that also contained a main reservoir of 100 ml Tyrode's solution. Communication between the two compartments was provided by connection pores through which the fluids were driven by gas (95% O_2 and 5% CO_2). The preparations were fixed in the organ bath to keep the muscle length as constant as possible. One end of the preparation was positioned between two platinum electrodes and the other end connected to an inductive force displacement transducer via a stainless steel wire.

Experimental Protocol and Recordings

The preparations were electrically driven at 1 Hz by rectangular pulses of 0.1–1 ms duration at 10% above threshold using a Grass stimulator (model S44) in combination with an isolation unit. The preparations were allowed to stabilize for at least 120 min. The effects of drugs were investigated by exposure either to single or to cumulatively increasing concentrations, achieved by adding drugs to the main Tyrode's reservoir, and increasing the concentration after the establishment of a stable response.

Force of contraction (F_c) was recorded at the apex of the preload active tension curve via the inductive force displacement transducer in conjunction with a Hellige frequency carrier preamplifier. The transmembrane potential was detected intracellularly by the use of 10 to 20-MΩ glass microelectrodes filled with KCl 3 mol/l. The signals were led off by means of a voltage follower with input capacitance compensation. For the determination of maximal upstroke velocity of the action potential, dV/dt was obtained by analogue differentiation. Transmembrane potential, dV/dt and tension were displayed on a cathode ray oscilloscope and stored on floppy

disks in conjunction with a digital storage system (Nicolet 310). Data were evaluated for peak F_c, APD at 20% and 90% of repolarization (APD_{20} and APD_{90}) and maximal upstroke velocity (dV/dt_{max}). For determination of the frequency dependence of the drugs, the frequency of stimulation was varied between 0.01 Hz and 3 Hz. Recovery from use-dependent block was assessed by determination of dV/dt_{max} of the first action potential after increasing periods of rest from 1 to 60 s. The time course of the recovery process was found to fit a single exponential term with a time constant τ_{rec}, denoting the time required to restore dV/dt_{max} to 1/e (equals 36.7%). All values were obtained by computerized analysis of the original data using an IBM-compatible desk computer. In addition figures were plotted using a Hewlett-Packard model 7475 A.

Results

Measurements of Action Potential and Force of Contraction

Effects of Quinidine

The APD effects of quinidine (10 µmol/l) were inconsistent; both prolongation and shortening were observed (Fig. 1 a). In other experiments (not shown), APD was prolonged at lower concentrations (below 10 µmol/l) and shortened at higher concentrations (higher than 10 µmol/l): In yet other situations, APD was first prolonged and then shortened at intermediate concentrations of quinidine (around 10 µmol/l). Quinidine always depressed dV/dt_{max} of phase 0 of the action potential in this preparation of human ventricular heart muscle. One part of the block was tonic, the other part frequency-dependent (Fig. 1 b), as was described more than three decades ago by Johnson and McKinnon (1957) in guinea pig heart muscle. These results with quinidine led us to assume that the influence of antiarrhythmic drugs on dV/dt_{max} in human heart muscle might correspond with the findings in different animal preparations, but that the effects on APD might be different or more complicated. As a consequence, the effects of antiarrhythmic drugs on APD in animal preparations should not be extrapolated immediately to man and, more importantly, should not be taken as clear-cut evidence to classify a drug action with respect to the putative subgroups Ia, Ib and Ic. This consideration prompted us to investigate the effects of flecainide, propafenone and moricizine (commonly grouped into class Ic) in human ventricular heart muscle.

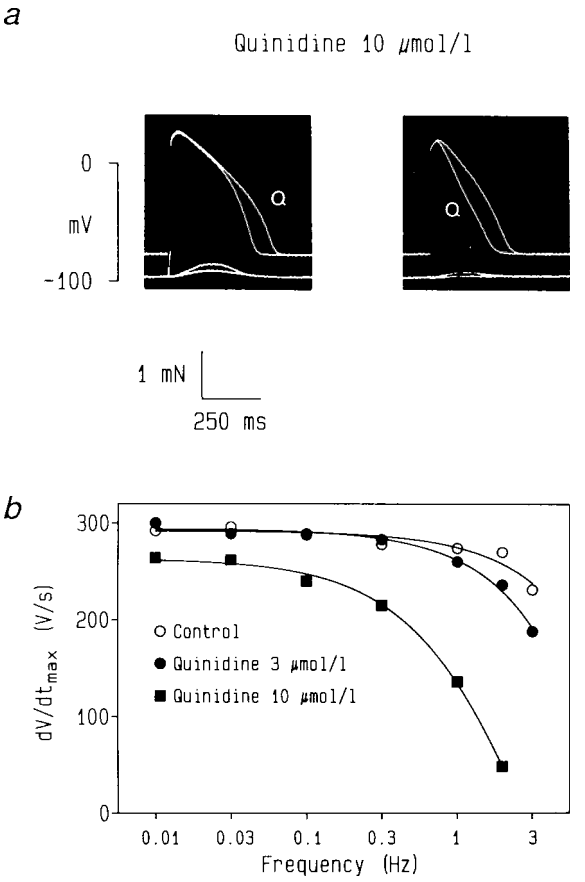


Fig. 1 a, b. Effects of quinidine in human ventricular heart muscle. **a** Original recordings of action potential (*upper traces*) and force of contraction (F_C, *lower traces*) under control conditions and in the presence of quinidine 10 µmol/l (*Q*) were superimposed. Records were obtained from two different preparations dissected from the same heart. APD was increased in the recording depicted on the left side, whereas an decrease in APD was observed in the other preparation. F_C was decreased in both preparations. **b** Influence of frequency of stimulation on dV/dt_{max} obtained under control conditions and in the presence of quinidine. Under control conditions, only at high frequencies of stimulation was a decrease in dV/dt_{max} observed (frequency-dependent block). The depressive effect on dV/dt_{max} was enhanced in the presence of quinidine 3 µmol/l. Note that quinidine 10 µmol/l caused an additonal decrease in dV/dt_{max} even at low frequencies of stimulation (tonic block)

Effects of Propafenone, Flecainide and Moricizine

Propafenone, flecainide and moricizine diminished APD and dV/dt_{max} in a concentration-dependent manner (Fig. 2a–c). Prolongation of APD, as seen occasionally or transiently in the presence of quinidine, was never ob-

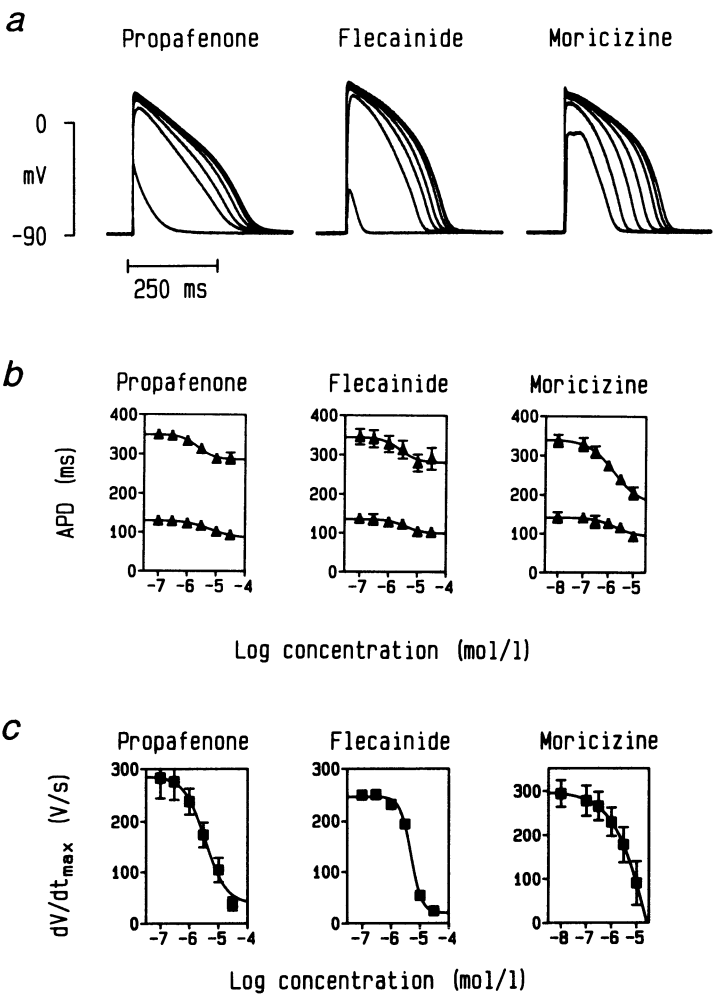


Fig. 2a–c. Influence of propafenone, flecainide and moricizine on action potentials (AP) obtained from human ventricular heart muscle. **a** Original recordings of AP revealed that all drugs caused a concentration-dependent decrease in APD without changing resting membrane potential. **b, c** Influence on APD_{90} (**b**, *upper values*), APD_{20} (**b**, *lower values*) and dV/dt_{max} (**c**) in the presence of increasing concentrations of the drugs. Data represent means ±SEM of three to six preparations

served with propafenone, flecainide or moricizine. The effects of the drugs were observed in concentrations between 0.1 and 30 μmol/l. No significant differences in potency could be established among the substances. At concentrations higher than 10–30 μmol/l, dV/dt_{max} was almost completely depressed; no action potentials were elicited under these conditions. The effects of the drugs developed continuously and reached a steady state

within 30–60 min. The equilibrium of drug effects was reached more quickly with higher than with lower concentrations. In control experiments, no significant changes of action potential parameters were detected during the observation period of 3–4 h. Within this time, complete concentration-response relationships were obtained in one preparation by cumulatively increasing the drug concentrations. Microelectrode impalements were usually stable throughout the experiment so that all action potential recordings were derived from one individual cell.

In a second series of experiments, the effects of propafenone, flecainide and moricizine, each at a concentration of 3 μmol/l, were investigated at stimulation frequencies between 0.01 and 3.0 Hz (not shown). All drugs were virtually ineffective at low driving rates; significant effects on APD and dV/dt_{max} occurred at frequencies between 1.0 and 3.0 Hz. At frequencies higher than 3.0 Hz, the preparations failed to respond regularly to the electrical stimuli.

Measurement of the Time Constant of Recovery from Frequency-Dependent Block of dV/dt_{max}

The effects of quinidine, propafenone, flecainide and moricizine on dV/dt_{max} were more pronounced at higher than at lower stimulation frequencies (frequency-dependent block of sodium channels). Depending on the period of rest, at any given frequency the effects of the drugs on dV/dt_{max} develop with a characteristic time course (use-dependent block). The recovery from frequency-dependent block can be observed after varying periods of rest when the stimulation is resumed. Both the development of and the recovery from use- and frequency-dependent block have typical time constants, τ_{on} and τ_{rec} respectively, the former being dependent and the latter being independent of the drug concentrations (Campbell 1983). We therefore chose to investigate τ_{rec} in more detail both in human and in guinea pig heart muscle.

Figure 3a schematically illustrates the experimental procedure for the determination of τ_{rec}. The preparations were driven at 1.0 Hz in the presence of either propafenone, flecainide or moricizine. When steady-state effects were reached, the stimulation was stopped and resumed after increasing periods of rest. In each train, dV/dt_{max} of the first action potential was determined (indicated by the arrows). The inset in Fig. 3a shows that the recovery from frequency-dependent block follows a monoexponential time course. Under control conditions, τ_{rec} is in the range of 50–100 ms (not shown). Therefore, fully recovered values of dV/dt_{max} are observed almost immediately after the determination of each

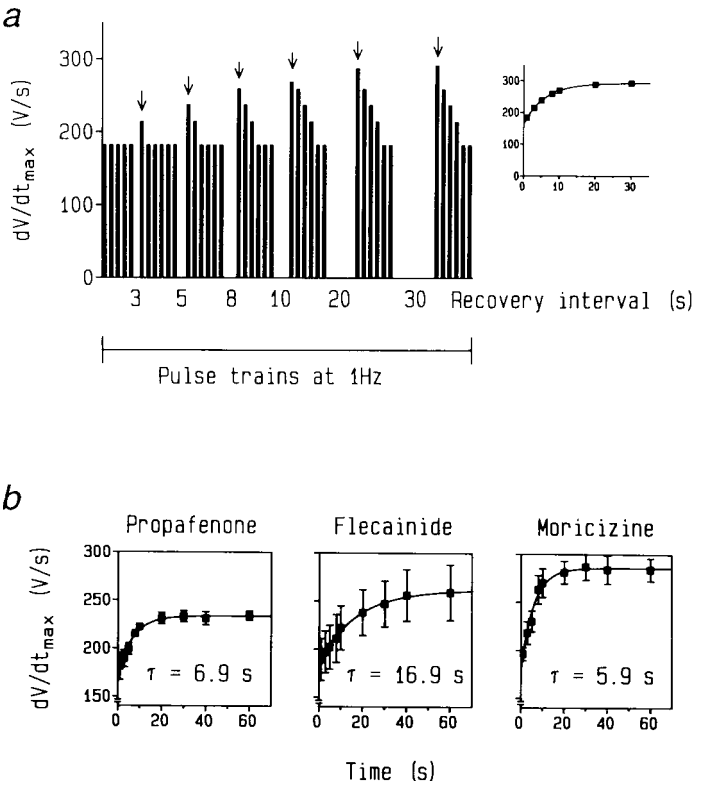


Fig. 3 a, b. Determination of time constants for recovery from frequency-dependent block (τ_{rec}). **a** Illustration of the experimental procedure for calculation of τ_{rec}. For further details see text. **b** Influence of propafenone 3 μmol/l, flecainide 3 μmol/l and moricizine 3 μmol/l on τ_{rec} in human ventricular heart muscle. Data represent means ±SEM of three or four preparations. Note the longer τ_{rec} in the presence of flecainide

individual action potential. Antiarrhythmic drugs can profoundly alter τ_{rec}. In the presence of propafenone and moricizine τ_{rec} was prolonged to 6.9 s and 5.9 s respectively, whereas in the presence of flecainide τ_{rec} was 16.9 s (Fig. 3 b). The effects of quinidine were comparable to those of propafenone and moricizine. In the presence of quinidine τ_{rec} was 7.3 s in the human ventricle and 6.7 s in the guinea pig ventricle (Fig. 4).

In the last series of experiments, we investigated the effects of quinidine, propafenone, flecainide and moricizine in the guinea pig atrium and in the guinea pig ventricle. A summary of all results, with reference to the results in human ventricular heart muscle, is given in Table 1. The drugs prolonged τ_{rec} differently, but to a similar degree in each tissue. The different values of τ_{rec} represent, therefore, quantitatively different drug actions rather than differences in the response of various tissues. A selec-

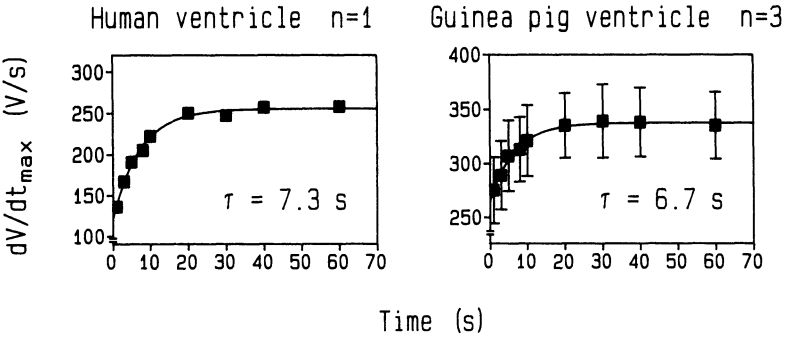


Fig. 4. Comparison of τ_{rec} in the presence of quinidine 10 μmol/l in human ventricular heart muscle (*left*) and guinea pig ventricular muscle (*right*). Almost identical values of τ_{rec} were obtained in the two tissues

Table 1. Time constant of recovery from frequency-dependent block in guinea pig and human heart muscle

	Quinidine	Propafenone	Flecainide	Moricizine
Guinea pig atrium	8.6 s	4.6 s	16.6 s	11.1 s
Guinea pig ventricle	6.7 s	5.4 s	19.8 s	7.8 s
Human ventricle	7.3 s	6.9 s	16.9 s	5.9 s

tion of previously published data in different animal tissues reveals similar results (Table 2). Quinidine and propafenone prolonged τ_{rec} to about 5 s except in the study by Kohlhardt and Seifert (1980), where propafenone prolonged τ_{rec} to 15.5 s. We could not reproduce this result in the same tissue under our experimental conditions. In all studies, τ_{rec} was prolonged to about 15 s by flecainide.

Discussion

By definition, class I antiarrhythmic drugs share the property of restricting the fast Na^+ inward current during phase 0 (fast depolarization phase) of the cardiac action potential, thereby decreasing the conduction velocity of the cardiac impulse. In most studies on antiarrhythmic drugs in isolated tissues, the maximum rate of depolarization (dV/dt_{max}) of phase 0 is taken as an indirect measure of the fast sodium current. Although there are theoretical difficulties with this approach, it has provided a useful tool in describing the effects of antiarrhythmic agents and in understanding the basic mechanisms of antifibrillatory drug actions.

Table 2. Time constants of recovery from frequency-dependent block in various animal tissues

Drug	Time constant	Publication
Quinidine	4.7 s	Grant et al. 1982
	4.0 s	Langenfeld et al. 1990
	5.7 s	Kodama et al. 1990
Propafenone	15.5 s	Kohlhardt and Seifert 1980
	4.4 s	Thompson et al. 1988
	5.4 s	Rouet et al. 1989
Flecainide	15.5 s	Campbell 1983
	15.5 s	Vaughan Williams 1984
	16.4 s	Delpon et al. 1991

The majority of drugs found to be effective in the treatment of arrhythmias are Na^+ channel blocking agents. Unfortunately, the effect of drugs that might be antiarrhythmic for patients are only poorly predicted by this classification. The greatest impact for the use of antiarrhythmic drugs in patients has come recently from the CAST, which made clear that the treatment of patients after myocardial infarction with one of several drugs belonging to class Ic (flecainide, encainide or moricizine) can increase the risk of sudden arrhythmic death (CAST Investigators 1989). It is not safe to extrapolate from these studies that all drugs belonging to class Ic necessarily increase the risk of sudden cardiac death. Alternatively, the possibility that drugs which do not belong to class Ic may also increase mortality after myocardial infarction should not be excluded. At this stage, the benefits and the risks of antiarrhythmic agents cannot be inferred from any classification scheme. Rather, a decision pro or contra a particular drug for clinical applications can be reached only by individual clinical trials.

Nevertheless, it seems desirable to rely on a classification scheme of drug actions which predicts the effects of a particular substance both under in vitro and in vivo conditions. Our study has shown that the subclassification of class I antiarrhythmic drugs into subgroups Ia, Ib and Ic may yield different results in different animal preparations. This became obvious when the effects of drugs on the repolarization phase were taken as an index for the membership of subgroup Ia, Ib or Ic. In human ventricular heart muscle, quinidine either prolonged or shortened APD, depending on the drug concentration and/or exposure time. In this case, it is difficult to decide whether quinidine belongs to subgroup Ia or Ib. Propafenone, flecainide and moricizine all diminished APD in a concen-

tration-dependent manner. It would then seem logical to assign these substances to class Ib; this conflicts, however, with most experimental studies in tissues other than from man.

In recent years, an alternative way of subgrouping antiarrhythmic drug actions has been suggested (Campbell 1989). According to this subclassification, antiarrhythmic drugs belonging to class I can be subgrouped into classes Ia, Ib and Ic by their different effects on the kinetics of onset and the recovery from frequency-dependent block of Na^+ channels. Based on block of Na^+ channels, members of class Ib have fast onset of block and fast recovery from block (below 1 s). By contrast, agents in class Ic are characterized by a slow onset of and a slow recovery from block (around 15 s). Class Ia agents have intermediate kinetics of block development and recovery.

In our experiments on human ventricular heart muscle, the rate constant of recovery from frequency-dependent block (τ_{rec}) was about 17 s with flecainide but about three times shorter with both propafenone and moricizine. Interestingly, no species or tissue differences were found with respect to τ_{rec}. Quinidine was found to induce intermediate values of τ_{rec} in the guinea pig atrium, the guinea pig ventricle and the human ventricle. Propafenone induced somewhat lower values than quinidine in all tissues. The action of moricizine resembled that of quinidine, while flecainide was characterized by longer time constants.

Conclusions

The following conclusions can be drawn from our experiments in ventricular heart muscle:

1. The duration of the action potential, as affected by antiarrhythmic drugs, is not a reliable parameter for assigning individual substances into class Ia, Ib or Ic.
2. A more reliable classification parameter is the rate of recovery from frequency-dependent block of Na^+ channels, τ_{rec}. This parameter was independent of the species or the particular heart tissue investigated and of the drug concentration.
3. On the basis of our τ_{rec} measurements, flecainide belongs to subclass Ic, whereas propafenone and moricizine would more appropriately be grouped in group Ia.

   In constrast to lidocaine (τ_{rec} around 300 ms), antifibrillatory agents which are characterized by a τ_{rec} of 5 or 15 s, would be expected to exert significant effects on the impulse propagation at normal heart

rates. It remains uncertain, therefore, whether a subclassification into subgroups with long (around 15 s) and intermediate (around 5 s) values of τ_{rec} is of clinical significance.

References

Campbell TJ (1983) Importance of physico-chemical properties in determining the kinetics of the effects of class I antiarrhythmic drugs on maximum rate of depolarization in guinea-pig ventricle. Br J Pharmacol 80:33–40

Campbell TJ (1989) Subclassification of class I antiarrhythmic drugs. In: Vaughan Williams EM (ed) Antiarrhythmic drugs. Springer, Berlin Heidelberg New York, pp 135–155 (Handbook of experimental pharmacology, vol 89)

CAPS Investigators (1988) Effects of encainide, flecainide, imipramine and moricizine on ventricular arrhythmias during the year after myocardial infarction. Am J Cardiol 61:501–506

CAST Investigators (1989) Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 321:406–412

Delpon E, Valenzuela C, Tamargo J (1991) Electrophysiological effects of the combination of mexiletine and flecainide in guinea-pig ventricular fibres. Br J Pharmacol 103:1411–1416

Eckel L, Gristwood RW, Nawrath H, Owen DAA, Satter P (1982) Inotropic and electrophysiological effects of histamine on human ventricular heart muscle. J Physiol 330:111–123

Grant AO, Trantham JL, Brown KK, Strauss HC (1982) pH-dependent effects of quinidine on the kinetics of dV/dt_{max} in guinea-pig ventricular myocardium. Circ Res 50:210–217

Harrison DC (1985) Anti-arrhythmic drug classification: new science and practical applications. Am J Cardiol 56:185–190

Jakob H, Nawrath H, Rupp J (1988) Adrenoceptor-mediated changes of action potential and force of contraction in human isolated ventricular heart muscle. Br J Pharmacol 94:584–590

Johnson EA, McKinnon MG (1957) The differential effect of quinidine and pyrilamine on the myocardial action potential at various rates of stimulation. J Pharmacol Exp Ther 120:460–468

Kodama I, Honjo H, Kamiya K, Toyama J (1990) Two types of sodium channel block by class-I antiarrhythmic drugs studied by using V_{max} of action potential in single ventricular myocytes. J Mol Cell Cardiol 22:1–12

Kohlhardt M, Seifert C (1980) Inhibition of V_{max} of the action potential by propafenone and its voltage-, time- and pH-dependence in mammalian ventricular myocardium. Naunyn Schmiedebergs Arch Pharmacol 315:55–62

Langenfeld H, Weirich J, Köhler C, Kochsiek K (1990) Comparative analysis of the action of class I antiarrhythmic drugs (lidocaine, quinidine, and prajmaline) in rabbit atrial and ventricular myocardium. J Cardiovasc Pharmacol 15:338–345

Rouet R, Libersa CC, Broly F, Caron JF, Adamantidis MM, Honore E, Wajman A, Dupuis BA (1989) Comparative electrophysiological effects of propafenone, 5-hydroxy-propafenone, and *N*-despropylpropafenone on guinea pig ventricular muscle fibers. J Cardiovasc Pharmacol 14:577–584

Singh BN, Hauswirth D (1974) Comparative mechanisms of action of antiarrhythmic drugs. Am Heart J 87:367–382

Thompson KA, Iansmith DHS, Siddoway LA, Woosley RL, Roden DM (1988) Potent electrophysiologic effects of the major metabolites of propafenone in canine Purkinje fibers. J Pharmacol Exp Ther 244:950–955

Vaughan Williams EM (1970) Classification of anti-arrhythmic drugs. In: Sandoe E, Flensted-Jensen E, Olesen KH (eds) Symposium on cardiac arrhythmias. Astra, Södertälje, pp 449–472

Vaughan Williams EM (1980) Antiarrhythmic action. Academic, London

Vaughan Williams EM (1981) Classification of antiarrhythmic drugs. In: Szekeres L (ed) Pharmacology of antiarrhythmic drugs. Pergamon, Oxford, pp 125–150

Vaughan Williams EM (1984) A classification of antiarrhythmic actions reassessed after a decade of new drugs. J Clin Pharmacol 24:129–147

Vaughan Williams EM (1989) Classification of antiarrhythmic actions. In: Vaughan Williams EM (ed) Antiarrhythmic drugs. Springer, Berlin Heidelberg New York, pp 45–67 (Handbook of experimental pharmacology, vol 89)

Vaughan Williams EM (1991) Significance of classifying antiarrhythmic actions since the cardiac arrhythmia suppression trial. J Clin Pharmacol 31:123–135

Class I Drug Effects on the Atrium

S. Nattel, B. Fermini, Z. Wang, and G. O'Hara

Introduction

Class I drugs have been used to treat atrial reentrant arrhythmias since Lewis (1922) first described the ability of quinidine to terminate atrial fibrillation. There is, however, increasing knowledge about the effects of other class I agents in the management of atrial fibrillation. In addition, the effects of these agents on atrial action potentials and their in vivo actions have been characterized and are appropriate to review in considering how the management of atrial fibrillation may be improved.

Effects of Class Ia and Ib Agents in Atrial Fibrillation

Class Ia compounds such as quinidine – procainamide (Halpern et al. 1980) and disopyramide (Hartel et al. 1974) – have been found to be effective in the treatment of atrial fibrillation. Class Ib agents such as lidocaine, mexiletine, and tocainide have not been extensively tested in the treatment of atrial fibrillation, primarily because of a clinical impression that they have little efficacy for such arrhythmias. The ability of class Ia drugs to terminate and prevent atrial fibrillation has been related to their tendency to increase atrial refractoriness (Hoffman et al. 1975). Increases in refractory period are well known to antagonize reentrant mechanisms by promoting block in potential reentry circuits.

Actions of Class Ic Agents in Atrial Fibrillation

Class Ic agents are a group of compounds introduced in the treatment of cardiac arrhythmias in the 1980s. Their actions are characterized by important conduction slowing with little effect on refractory periods (Vaughan Williams 1984). Such a spectrum of action should, if anything, increase the likelihood of reentry, which is favoured by slow conduction and short refractory periods. Surprisingly, class Ic agents like propafenone (Marchlinski 1988) and flecainide (Suttorp et al. 1990) have been found to be

effective in treating atrial fibrillation and preventing recurrences, particularly when the arrhythmia is of recent onset. In comparison with class Ia agents, class Ic compounds have proved to be as effective as quinidine (Borgeat et al. 1986) and, at least in one study, more effective than disopyramide (Rasmussen et al. 1988). These clinical observations suggest either that our appreciation of class I drug action is incomplete or that we do not understand atrial fibrillation and its determinants as well as we think we do.

Effects of Class Ia and Ib Compounds on Atrial Action Potentials

Quinidine (Nawrath 1981; Vaughan Williams 1958; West and Amory 1960) and procainamide (Hordof et al. 1976) increase atrial action potential duration (APD) and decrease the rate of voltage rise during phase 0 (V_{max}). Such properties would account for these drug's ability to increase refractory period and slow conduction in atrial tissue (Hoffman et al. 1975). Class Ib agents like lidocaine (Singh and Vaughan Williams 1971) and mexiletine (Yamaguchi et al. 1979) have little effect on atrial APD consistent with their relative inefficacy in treating reentrant atrial arrhythmias.

Effects of Class Ic Compounds on Atrial Action Potentials

There is little information in the literature about the effects of class Ic agents on atrial action potentials. Flecainide increases atrial APD by about 10% – 20% in rabbit tissue (Ikeda et al. 1985). and by a similar amount in human atrial specimens (Le Grand et al. 1990; Wang et al. 1990). We were not able to find reports of microelectrode studies of the actions of other class Ic agents on atrial tissues.

The Possible Role of Rate-Dependent Actions of Ic Compounds on Atrial Action Potentials

The actions of antiarrhythmic drugs on APD be strongly influenced by heart rate (Nattel and Zeng 1984). We have examined the rate-dependent actions of flecainide on atrial action potentials of various species using quinidine as a comparison drug (Wang et al. 1990a). We found that quinidine's actions on APD were attenuated as activation rate increased, while flecainide's were enhanced. Some important differences in responses were noted among species. Human tissue was more sensitive to drug ac-

tion, requiring half to one third the concentration needed in dogs to achieve the same effect. Furthermore, the rate dependence of drug action was steeper in human tissues, although the pattern of rate dependence was qualitatively similar for all species tested.

Figure 1 shows the relationship between drug action and cycle length for changes in APD to 95% repolarization (APD_{95}) and refractory period in human atria. Both variables normally decrease as cycle length shortens, an adaptive phenomenon termed "accomodation". Flecainide attenuates rate-related accommodation, thus increasing APD_{95} and refractoriness to a greater extent as cycle length decreases (i.e., activation rate increases). Quinidine, on the other hand, has opposite rate-dependent actions, and its effects are greatest at slower rates. One possible explanation, then, of flecainide's action in atrial fibrillation is that at the rapid atrial rates characteristic of this arrhythmia flecainide substantially increases APD and refractory period, leading to arrhythmia termination.

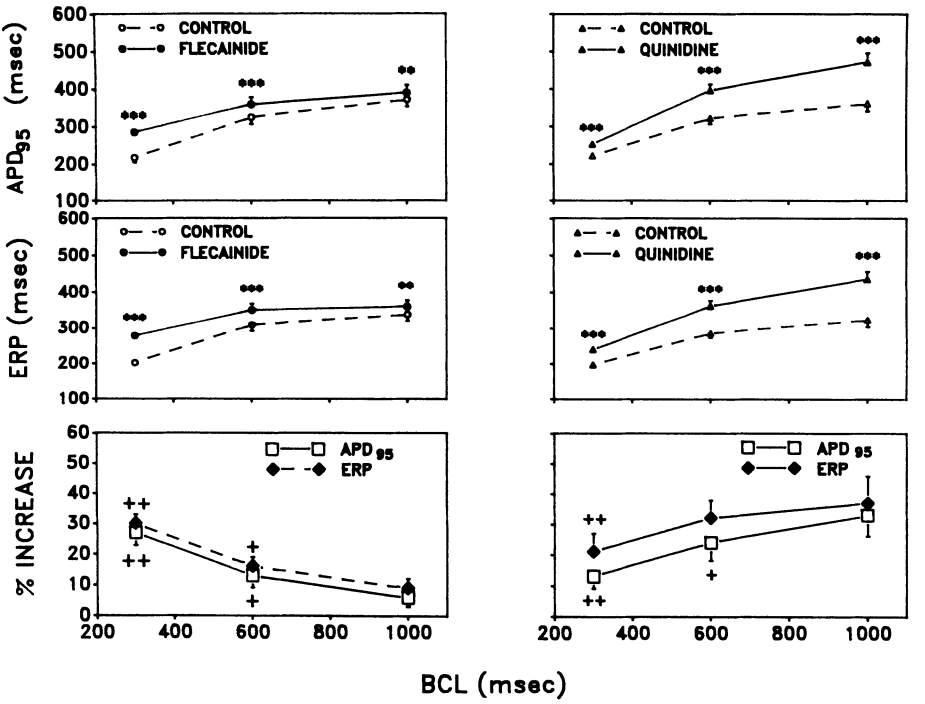


Fig. 1. Changes in action potential duration (*APD*) and refractory period (*ERP*) produced in human atrial tissues by flecainide and quinidine (2.25 μM for each). Percent changes are shown in the bottom graphs. All values are mean ±SE. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ vs control at the same basic cycle length (*BCL*); $^{+}p<0.05$, $^{++}p<0.01$ compared to effect on the same variable at *BCL* 1000 ms

Our results differ from those of Le Grand et al. (1990), who did not observe an enhancement of flecainide's effects on human atrial ADP_{90} by faster rates. The difference may be partly related to the drug concentrations used. We studied flecainide at a concentration of 0.9 mg/l, at the upper end of the therapeutic range, while Le Grand et al. examined a concentration of 0.2 mg/l, because their tissues became inexcitable at higher concentrations. Mean flecainide concentrations at the time of termination of atrial fibrillation averaged 0.53 mg/l in one clinical series (Suttorp et al. 1990).

In Vivo Effects of Class Ic Compounds on Atrial Refractoriness and APD

To further assess the role of the rate-dependent properties of class Ic drugs on atrial tissues in vivo, we have been studying the changes in atrial refractoriness produced by flecainide and propafenone. To date, our results indicate that both compounds are capable of producing the type of tachycardia-dependent increases in refractoriness that would be predicted from our previous in vitro work. In the case of flecainide, we have also evaluated changes in atrial APD using monophasic action potential recordings. As shown in Fig. 2, flecainide causes rate-related increases in APD (as measured to 90% repolarization). These changes are dose-dependent, and occur at drug concentrations relevant to the drug's clinical effects. Based on our previous in vitro observations suggesting that flecainide was at least twice as potent in human as in dog atrium (Wang et al. 1990a), we estimate that the actions of dose 2 in the dog (mean concentration 0.9 mg/l) should

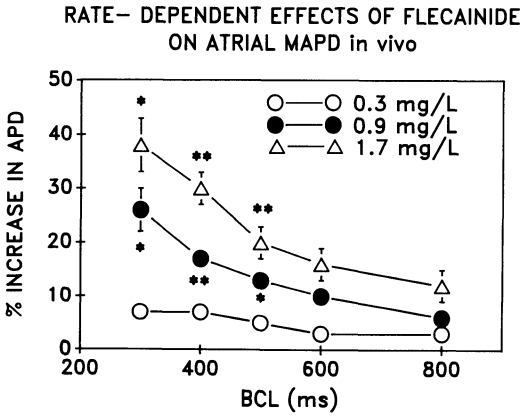


Fig. 2. Effects of flecainide on APD measured to 90% repolarization with monophasic action potential (Franz type) catheters in anesthetized dogs. $*p<0.05$, $**p<0.01$ vs effect at basic cycle length (*BCL*) 800 ms. All values are mean±SE. Where error bar is not seen, it is smaller than the symbol for mean

be similar to that of flecainide at the time of atrial fibrillation conversion in man (Suttorp et al. 1990). Changes in refractoriness were qualitatively similar to those in APD.

In Vivo Effects of Class Ic Compounds in Experimental Atrial Fibrillation

In order to try to relate the above findings to class Ic drug actions in atrial fibrillation, we have been working with vagally induced atrial fibrillation in the dog. When bilateral vagal stimulation is applied at 10 Hz and supramaximal voltage, a brief burst of atrial stimulation results in atrial fibrillation which is sustained until vagal stimulation is stopped. Flecainide and propafenone reproducibly terminate atrial fibrillation in this model. As expected based on its cellular actions, flecainide causes rate-dependent increases in atrial refractoriness. While the drug also produces tachycardia-dependent conduction slowing, changes in refractoriness predominate. The results, as determined by epicardial mapping with 56–112 atrial electrodes, is that flecainide decreases the number of reentry zones in the fibrillating atria until the arrhythmia can no longer sustain itself (Wang et al. 1980b). We have observed qualitatively similar phenomena with propafenone, but our experiments with the latter compound are still preliminary.

Kirchhof et al. (1991) studied the effects in canine atrial fibrillation of an experimental class Ic compound, ORG 7797. They also noted a rate-dependent increase in refractory period with the compound, but this action was offset by equally important drug-induced conduction slowing. Nonetheless, the compound showed clear antifibrillatory properties. They attributed the latter properties to the ability of the drug to slow the rate of activation during atrial fibrillation. Since rapid activation shortens APD and refractory period, a decrease in atrial rate during fibrillation indirectly increases the refractory period and tends to make the fibrillation unstable.

Possible Mechanisms of Atrial Antifibrillatory Actions of Class Ic Compounds

The data presented above suggest three possible mechanisms of the beneficial clinical actions of class Ic drugs in the treatment of atrial fibrillation. First, Le Grand's data suggests the possibility of a quinidine-like action at low drug concentrations. Second, our observations indicate that, at least for some class Ic agents, atrial repolarization may be delayed selectively

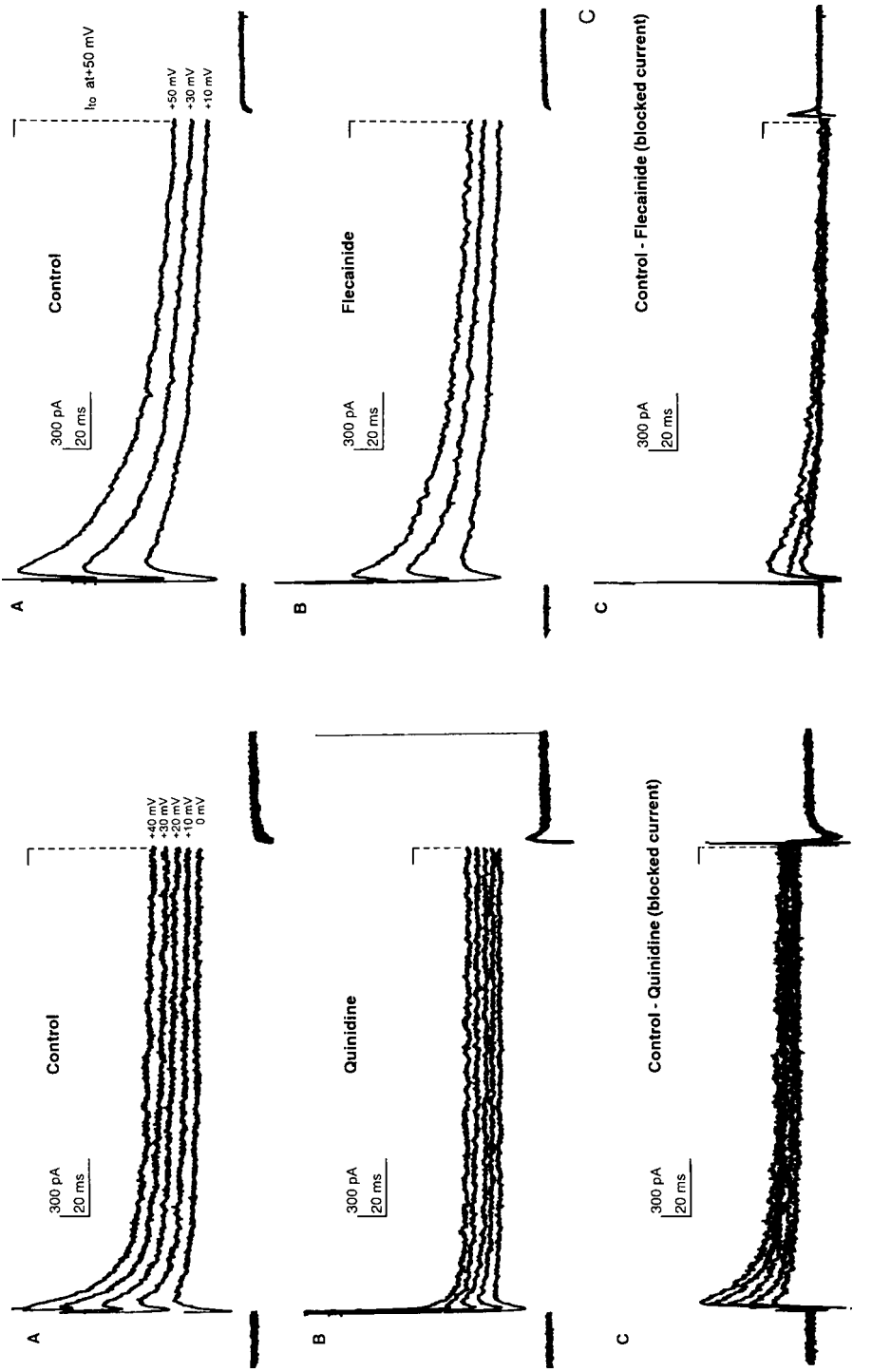
at rapid rates, leading to termination of atrial fibrillation. Finally, Kirchhof's studies suggest that slowing atrial rate during fibrillation may, under some circumstances, exert an antifibrillatory action by limiting the minimum wavelength (shortest path length of reentry) possible. Some or all of these mechanisms may play a role, depending on the properties of the drug, the arrhythmia, and the drug concentration. Further studies in man are likely to elucidate which mechanisms are operative in various circumstances.

Ionic Mechanisms Underlying Repolarization Effects of Class Ic Compounds

The rate-dependent APD prolongation that we have observed with flecainide is theoretically a highly desirable property. One of the major limitations of class Ia and class III compounds that increase APD is that their actions are generally bradycardia-dependent (Nattel and Zeng 1984; Roden and Hoffman 1985; Hondeghem and Synders 1990). Consequently, they increase APD more at resting heart rates than during tachyarrhythmias. While this does not prevent clinical efficacy, it causes a propensity to produce early afterdepolarizations and torsades des pointes ventricular tachyarrhythmias, particularly in the presence of bradycardia (Jackman et al. 1988). If the ionic mechanism of tachycardia-dependent APD prolongation could be identified, and drugs developed which have only this property, an important therapeutic advances might result.

We have begun to assess the ionic mechanisms by which flecainide and quinidine alter repolarization. Figure 3 shows the effects of flecainide and quinidine at equimolar concentrations (15 μM) on the transient outward current (I_{to}) in canine atrial myocytes. This current is prominent in atrial tissues of a variety of species, including man (Shibata et al. 1989), and is believed to play an important role in atrial repolarization. As seen in the figure, the current is activated during depolarization and then spontaneously inactivates. The availability of the current then recovers in a time-dependent fashion. As a result, the magnitude of I_{to} tends to decrease at rapid rates. As shown in Fig. 3, quinidine is a much more potent blocker of I_{to} than flecainide. This property may contribute to quinidine's bradycardia-dependent action, since I_{to} is expected to be substantially larger at slower rates.

Fig. 3. Effects of quinidine and flecainide (15 μ*M* for both) on I_{to} in rabbit atrial myocytes. Voltage steps were from −60 mV to 0, 10, 20, 30, and 40 mV for quinidine (*left*) and from −60 mV to 10, 30, and 50 mV for flecainide (*right*). Control currents are at the top, currents in the presence of drug in the middle, and subtracted (i.e., drug-blocked) currents at the bottom. Note the larger effect of quinidine than of equimolar flecainide


A
Control
300 pA
20 ms
+40 mV
+30 mV
+20 mV
+10 mV
0 mV
B
Quinidine
300 pA
20 ms
C
Control - Quinidine (blocked current)
300 pA
20 ms
A
Control
300 pA
20 ms
I_{to} at+50 mV
+50 mV
+30 mV
+10 mV
B
Flecainide
300 pA
20 ms
C
Control - Flecainide (blocked current)
300 pA
20 ms

On the other hand, flecainide is capable of blocking another potassium current, I_k (Follmer and Colatsky 1990), which also plays an important role in repolarization of a variety of cardiac tissues (Colatsky et al. 1990). Unlike I_{to}, I_k does not inactivate, and tends to be greater at faster rates. We have acquired preliminary data which sugest that flecainide blocks I_k more selectively than does quinidine. This may explain, at least in part, flecainide's ability to cause tachycardia-dependent APD prolongation, but much work remains to be done before the ionic mechanisms of APD accommodation and drug actions are fully elucidated.

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References

Borgeat A, Goy JJ, Maendly R, Kaufmann U, Grbic M, Sigwart U (1986) Flecainide versus quinidine for conversion of atrial fibrillation to sinus rhythm. Am J Cardiol 58:496–498

Colatsky TJ, Follmer CH, Starmer FC (1990) Channel specificity in antiarrhythmic drug action. Mechanism of potassium channel block and its role in suppressing and aggravating cardiac arrhythmias. Circulation 82:2235–2242

Follmer CH, Colatsky TJ (1990) Block of delayed rectifier potassium current, I_k, by flecainide and E-4031 in cat ventricular myocytes. Circulation 82:289–293

Halpern SW, Ellrodt G, Singh BN, Mandel WJ (1980) Efficacy of intravenous procainamide infusion in coverting atrial fibrillation to sinus rhythm: relation to left atrial size. Br Heart J 44:589–595

Hartel G, Louhija A, Konttinen A (1974) Disopyramide in the preservation of recurrence of atrial fibrillation after electroconversion. Clin Pharmacol Ther 15:551–555

Hoffman BF, Rosen MR, Wit AL (1975) Electrophysiology and pharmacology of cardiac arrhythmias: VII. Cardiac effects of quinidine and procaine amide B. Am Heart J 90:117–122

Hondeghem LM, Synders DJ (1990) Class III antiarrhythmic agents have a lot of potential but a long way to go: reduced effectiveness and dangers of reverse use dependence. Circulation 81:686–690

Hordof AJ, Edie RE, Malm JR, Hoffman BF, Rosen MR (1976) Electrophysiologic properties and response to pharmacologic agents of fibers from diseased human atria. Circulation 54:774–779

Ikeda N, Singh BN, Davis LD, Hauswirth O (1985) Effects of flecainide on the electrophysiologic properties of isolated canine and rabbit myocardial fibers. J Am Coll Cardiol 5:303–310

Jackman WM, Friday KJ, Anderson JL, Aliot EM, Clark M et al. (1988) The long QT syndromes: a critical review, new clinical observations and a unifying hypothesis. Prog Cardiovasc Dis 31:115–172

Kirchhof C, Wijffels JB, Brugada J, Planellas J, Allessie M (1991) Mode of action of a new class IC drug (ORG 7797) against atrial fibrillation in conscious dogs. J Cardiovasc Pharmacol 17:116–124

Le Grand B, Le Heuzey JY, Perier P, Peronneau P, Lavergne T, Hatem S, Guize L (1990) Cellular electrophysiological effects of flecainide on human atrial fibres. Cardiovasc Res 24:232–238

Lewis T (1992) The value of quinidine in cases of auricular fibrillation and methods of studying the clinical reaction. Am J Med Sci 163:781–794

Marchlinski FE (1988) Propafenone: new therapy for a tough, old arrhythmia. J Am Coll Cardiol 12:1012–1014

Nattel S, Zeng FD (1984) Frequency-dependent effects of antiarrhythmic drugs on action potential duration and refractoriness of canine cardiac Purkinje fibers. J Pharmacol Exp Ther 229:283–291

Nawrath H (1981) Action potential, membrane currents and force of contraction in mammalian heart muscle treated with quinidine. J Pharmacol Exp Ther 216:176–182

Rasmussen K, Andersen A, Abrahamsen AM, Overskeid K, Bathen J (1988) Flecainide versus disopyramide in maintaining sinus rhythm following conversion of chronic atrial fibrillation. Eur Heart J 9[suppl]:I–52 (abstr)

Rensma PL, Allessie MA, Lammers WJEP, Bonke FIM, Schalij MJ (1988) Length of excitation wave and susceptibility to reentrant atrial arrhythmias in normal conscious dogs. Circ Res 62:395–410

Roden DM, Hoffman BF (1985) Action potential prolongation and induction of abormal automaticity by low quinidine concentrations in canine Purkinje fibers. Circ Res 56:857–867

Shibata EF, Drury T, Refsum H, Aldrete V, Giles W (1989) Contributions of a transient outward current to repolarization in human atrium. Am J Physiol 26:H1773–H1781

Suttorp MJ, Kingma HJ, Jessurun ER, Lie-A-Huen L, van Hemel NM, Lie KI (1990) The value of Class IC antiarrhythmic drugs for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. J Am Coll Cardiol 16:1722–1727

Vaughan Williams EM (1958) The mode of action of quinidine on isolated rabbit atria interpreted from intracellular potential records. Br J Pharmacol 13:276–287

Vaughan Williams EM (1971) Effect of altering potassium concentration on the action of lidocaine and diphenylhydantoin on rabbit atrial and ventricular muscle. Circ Res 29:286–295

Vaughan Williams EM (1984) A classification of antiarrhythmic actions reassessed after a decade of new drugs. J Clin Pharmacol 24:129–147

Wang Z, Pelletier CL, Talajic M, Nattel S (1990a) Effects of flecainide and quinidine on human atrial action potentials. Role of rate-dependence and comparisons with guinea pig, rabbit, and dog tissues. Circulation 82:274–283

Wang Z, Villemaire C, Pagé P, Nattel S (1990b) Mechanism of flecainide's beneficial actions in experimental atrial fibrillation. Circulation 82:III–98

West TC, Amory DW (1960) Single fibre recording of the effects of quinidine at atrial and pacemaker sites in the isolated right atrium of the rabbit. J Pharmacol Exp Ther 130:183–193

Yamaguchi I, Singh BN, Mandel WJ (1979) Electrophsiological actions of mexiletine on isolated rabbit atria and canine ventricular muscle and Purkinje fibres. Cardiovasc Res 13:288–296

Atrial Fibrillation: A European Perspective

K.-H. Kuck and S. Gursoy

Introduction

With the introduction of ablative techniques, although we are now able to offer a permanent cure for a variety of arrhythmias, the management of atrial fibrillation remains a frustrating challenge. The conversion and maintenance of sinus rhythm is the initial step when treating the patient presenting with new-onset atrial fibrillation. If this cannot be achieved and the arrhythmia becomes chronic, the main goal changes to the control of the ventricular response and the prevention of thromboembolic events.

Conversion to and Maintenance of Sinus Rhythm

Antiarrhythmic drugs remain the first line of treatment in the management of atrial fibrillation. Although the Cardiac Arrhythmia Suppression Trial (CAST) dealt only with patients with ventricular arrhythmias, it also threw shadows on the use of antiarrhythmic agents in general. The recent report by the CAST investigators underlined the increased mortality in the encainide- and flecainide-treated subgroups (Echt et al. 1991). And although not published at the time of preparation of this manuscript, the moricizine arm of the CAST has also been terminated because of a similar trend towards increased mortality in this final part of the CAST. Despite all this bad publicity, many studies analyzing the efficacy of the new generation of antiarrhythmics (mainly the new class I drugs such as encainide, flecainide and propafenone and the class III drugs such as sotalol and amiodarone) for acute and maintenance therapy of a variety of supraventricular arrhythmias have continued to emerge. As a rule, the overall safety of any antiarrhythmic agent should be weighed up very carefully before instituting any form of therapy, and it remains to be determined in many patient populations, such as those with supraventricular arrhythmias.

Following the CAST, a very impressive meta-analysis of six randomized, double-blind, placebo-controlled studies examining the efficacy of quinidine in maintaining sinus rhythm in patients with atrial fibrillation

was published by Coplen et al. (1990). Although quinidine was much superior to control in maintaining sinus rhythm at 3, 6 and 12 months, the total mortality rate was also three times higher in the quinidine group. The validity of this analysis remains to be determined, as the limitations of such studies are well known. Therefore, as a minimum these data cannot and should not be extrapolated to other agents.

As a counterpart to the Coplen study, Pritchett and Wilkinson (1991) compared the mortality associated with the use of flecainide and encainide in patients with supra-ventricular arrhythmias (information obtained from the data bases of the respective pharmaceutical companies) with the mortality in a population referred to a research arrhythmia clinic. No significant differences were found in the 6-year survival of these two groups.

Another recent study by Juul-Moller et al. (1990) compared sotalol 80 or 160 mg bid to slow-release quinidine 600 mg bid. Although efficacy was similar at 6 months, sotalol was better tolerated, with fewer side effects and fewer patient withdrawals from therapy. In addition, among the patients who had recurrences while on therapy, the ventricular response to atrial fibrillation was better controlled in the group treated with sotalol.

Two other studies investigating flecainide deserve attention. Pritchett et al. (1991), reporting the results of the dose-response study by the Flecainide Supraventricular Tachycardia Group, found flecainide to be effective at the highest dose used (150 mg bid) in 86% of regular tachycardias and in 61% of cases of atrial flutter and fibrillation). A linear dose-response curve was observed. Pietersen and Helleman (1991), reporting for the Danish-Norwegian Flecainide Multicenter Study Group investigating the prevention of atrial flutter and fibrillation, reported similar results, with 50% suppression at 3 months of therapy (dose of 150 mg bid).

Prevention of Thromboembolis

Thromboembolic complications remain a major factor in patients with atrial fibrillation. Three important prospective large scale studies have addressed this issue in patients without valvular heart disease, but the results are still far from resolving all the issues. The Copenhagen AFASAK study (Petersen et al. 1989) was a single-center study in which patients with non-valvular chronic atrial fibrillation were randomly assigned to warfarin (to achieve a prothrombin time ratio of 1.5–1.9), aspirin (75 mg qd) or placebo and were followed up for 11 months. The primary end points of this study were ischemic stroke, transient ischemic attack or systemic embolism. The mean patient age was 74 years; half of the patients had a

history of heart failure, and one fourth had had a myocardial infarction. This study showed a clear reduction in end points in the warfarin group but failed to show any benefit from aspirin.

The SPAF study (Stroke Prevention in Atrial Fibrillation Investigators 1991) was a multicenter study which also randomized patients with chronic nonvalvular atrial fibrillation to warfarin (prothrombin time ratio of 1.3 – 1.8), aspirin (325 mg qd), or placebo. The end points were ischemic stroke and systemic embolism. As an age over 75 years rendered a patient ineligible for warfarin, the mean age for the warfarin group was 65 years compared with 68 years in the aspirin and placebo groups. Aspirin and warfarin both were effective in reducing the end points, but the magnitude of reduction in events by warfarin vs aspirin could not be compared.

Finally, the BAATAF (Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990) was also a multicenter study in which patients with nonvalvular atrial fibrillation were assigned to warfarin (prothrombin time ratio of 1.3 – 1.5) or to the control group (46% of these patients were taking aspirin). The primary end point was ischemic stroke. Again, the risk reduction with warfarin was significant. This study also showed that low-dose warfarin could be effective.

The AFASAK and SPAF trials also evaluated aspirin, and the former reported minimal benefit while the latter reported a significant benefit with aspirin. There were major differences between the two trials. The dose os aspirin was lower (75 mg vs 325 mg) and the mean patient age higher in the AFASAK trial. Furthermore, half the patients in the AFASAK study had a history of congestive failure, compared with only about one in five in the SPAF trial. Finally, no benefit from aspirin in patients over 75 years of age was observed in the SPAF trial.

Hopefully, SPAF II and two ongoing European trials will clarify the role of aspirin in the prevention of thromboembolic events associated with atrial fibrillation.

AV Nodal Ablation and Surgery for Atrial Fibrillation

In a large group of patients with atrial fibrillation, conversion to and maintenance of sinus rhyhtm remains impossible. Our main efforts are then directed at the control of the ventricular response. This is a palliative measure, and chronotropic incompetence, unmasked only with exercise, can still be present despite an adequate control of resting heart rate. In this subset, ablation of the AV node using radiofrequency current energy followed by the implantation of a rate-responsive pacemaker offers an effective alternative. The studies by Jackman et al. (1991) and Langberg et

al. (1991) show comparable and impressive results. Catheter technology continues to improve, and the availability of large-tip ablation catheters has increased the success rate for radiofrequency ablation of the AV node to over 90%. In the occasional patients in whom the ablation proves to be unsuccessful from the right ventricle, the AV junction can be ablated using the left ventricular approach, as reported by Sousa et al. (1991). As revealed by the Direct Current Catheter Ablation Registry and as outlined again by Rosenqvist et al. (1990), the risk associated with direct current ablation, although small, is prohibitive and includes sudden death. Direct current ablation should therefore be reserved for resistant patients in whom attempts at radiofrequency ablation have failed.

Two types of surgical approach are currently taken in the treatment of atrial fibrillation. Cox et al. (1991) recently reported the background of and their experience with the "maze" procedure, where incisions are placed on the atria to interrupt the reentrant circuits and to direct the sinus impulse to the AV node. Leitch et al. (1991) have reported their experience with the "corridor" operation, in which a strip of septal atrium between the sinus and AV nodes is isolated from the rest of the atrial tissue. Although both techniques restore sinus nodal chronotropy, one advantage of the Maze operation might be the maintenance of AV synchrony and preservation of atrial contraction. One noteworthy finding in both series was the high incidence of patients requiring a pacemaker following the surgery due to sinus node disease (two of seven for the Maze operation, four of nine for the Corridor operation). Finally, although Cox et al. anticoagulate their patients for only 3 months following surgery, the issue of chronic anticoagulation for these individuals remains unclear.

Conclusion

Despite recent advances in electrophysiology, atrial fibrillation remains a difficult management problem. The new advances to date represent but the tip of the iceberg; already the future prospects for controlling atrial fibrillation appear very bright.

References

Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators (1990) The effects of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. N Engl J Med 323:1505–1511

Coplen SE, Antman AM, Berlin JA, Hewitt P, Chalmers TC (1990) Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion. A meta-analysis of randomized control trials. Circulation 82:1106–1116

Cox JL, Schuessler RB, D'Agostino HJ, Stone LM, Chang BC, Cain ME, Corr PB, Boineau JP (1991) The surgical treatment of atrial fibrillation: III. Development of a definitive surgical procedure. J Thorac Cardiovasc Surg 101:569–583

Echt DS, Liebson PR, Mitchell B, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene L, Huther ML, Richardson DW, CAST investigators (1991) Mortality and morbidity in patients receiving encainide, flecainide, or placebo. N Engl J Med 324:781–788

Jackman WM, Wang X, Friday KJ, Fitzgerald DM, Roman C, Moulton K, Margolis PD, Bowman AJ, Kuck KH, Nacarelli GV, Ptiha JV, Dyer J, Lazzara R (1991) Catheter ablation of atrioventricular junction using radiofrequency current in 17 patients. Comparison of standard and large-tip catheter electrodes. Circulation 83:1562–1576

Juul-Moller S, Edvardson N, Rehnqvist-Ahlberg N (1990) Sotalol versus quinidine for the maintenance of sinus rhythm after direct current conversion of atrial fibrillation. Circulation 82:1932–1939

Langberg JJ, Chin M, Schamp DJ, Lee MA, Goldberger J, Pederson DN, Oeff M, Lesh MD, Griffin JC, Scheinman MM (1991) Ablation of the atrioventricular junction with radiofrequency current energy using a new electrode catheter. Am J Cardiol 67:142–147

Leitch JW, Klein G, Yee R, Guiraudon G (1991) Sinus node-atrioventricular isolation: long-term results with the corridor operation for atrial fibrillation. J Am Coll Cardiol 17:970–975

Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B (1989) Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation: the Copenhagen AFASAK study. Lancet 1:175–179

Pietersen AH, Helleman H (for the Danish-Norwegian Flecainide Study Group) (1991) Am J Cardiol 67:713–717

Pritchett ELC, Wilkinson WE (1991) Mortality in patients treated with flecainide and encainide for supraventricular arrhythmias. Am J Cardiol 67:976–980

Pritchett ELC, DaTorre SD, Platt ML, McCarville SE, Hougham AJ (for the Flecainide Supraventricular Tachycardia Group) (1991) J Am Coll Cardiol 17:297–303

Rosenqvist M, Lee MA, Moulinier L, Sprigberg MJ, Abbott JA, Wu J, Langberg JJ, Griffin JC, Sheinman MM (1990) Long-term follow-up of patients after transcatheter direct current ablation of the atrioventricular junction. J Am Coll Cardiol 16:1467–1474

Stroke Prevention in Atrial Fibrillation Investigators (1991) Stroke Prevention in Atrial Fibrillation Study: final results. Circulation 84:527–539

Sousa J, El-Atassi R, Rosenheck S, Calkins H, Langberg J, Morady F (1991) Radiofrequency ablation of the atrioventricular junction from the left ventricle. Circulation 84:567–571

Trends in Management of Atrial Fibrillation

C. R. Kerr, J. A. Yeung-Lai-Wah, and R. A. Leather

Introduction

Atrial fibrillation is the commonest sustained arrhythmia, increasing in frequency with patient age and occurring in approximately 5% of individuals over the age of 65 (Peterson and Godtfredsen 1984; Kerr and Chung 1985). The arrhythmia may impart increased risk of peripheral embolization and has been shown in population studies to be associated with increased mortality (Wolf et al. 1978; Gajewski and Singer 1981). However, the major challenge to the physician remains the control of symptoms resulting from atrial fibrillation: disabling palpitations, decreased exercise tolerance, and exacerbation of congestive heart failure or underlying coronary artery disease. Prevention of atrial fibrillation with quinidine and slowing of the ventricular response during atrial fibrillation with digoxin have been the mainstays of treatment since the 1920s (Lewis 1925), and remain the commonest forms of therapy. However, recent pharmacological and non-pharmacological developments are leading to gradual changes in these conventional approaches.

Pharmacological Treatment

Drug therapy in atrial fibrillation has two goals: the control of ventricular rate during atrial fibrillation and the termination of the episode and subsequent prevention of recurrent episodes of atrial fibrillation. Before commencing therapy, the goals of treatment in the individual case should be carefully delineated and the risk/benefit ratio of antiarrhythmic drug treatment should always be considered.

Should Atrial Fibrillation Be Treated?

The overwhelming indication for treatment of atrial fibrillation is the presence of symptoms. If the patient is found to be in chronic atrial fibrillation and is asymptomatic, there is no firm indication for attempting cardioversion. The main concerns with chronic atrial fibrillation are the

risk of embolization and a chronic uncontrolled rate. Consideration should be given to anticoagulation, and the risk and benefits of this should be carefully weighed up (Peterson et al. 1989; Stroke Prevention in Atrial Fibrillation Study Group 1990). A chronic rapid ventricular response can lead to rate-related cardiomyopathy and may result in subtle symptoms such as fatigue and exercise intolerance. Thus, patients with chronic atrial fibrillation should have monitoring of their rate and, if necessary, rate control should be implemented.

There is no evidence that conversion to sinus rhythm and maintenance with antiarrhythmic drugs improves survival or reduces the risk of embolic events. In fact, no study has shown improvement of mortality in patients converted and maintained in sinus rhythm, and a recent meta-analysis of controlled studies in which quinidine was compared to placebo following cardioversion showed no improvement and possibly slightly increased mortality with quinidine (Coplen et al. 1990).

Thus, patients with chronic atrial fibrillation or recurrent asymptomatic atrial fibrillation should primarily be treated for rate control and prevention of embolic events to avoid the risks, expense, and inconvenience of chronic antiarrhythmic drug therapy.

Rate Control

Rate control in atrial fibrillation is required either in the acute setting, in new-onset atrial fibrillation, or in the long-term setting, in patients with chronic atrial fibrillation. The traditional medication for rate control has been digoxin, and this frequently achieves satisfactory rate control, particularly in the resting state. However, patients frequently enjoy satisfactory rate control at rest and yet when minimally active have an excessive acceleration of the ventricular rate. It is not uncommon for a patient to complain of exercise intolerance and be found to have a well controlled rate at rest but a rate in excess of 150 beats per minute with standing and minimal exertion. Thus, patients with atrial fibrillation should have the response of their rate to exercise assessed. Frequently beta-blocking drugs or verapamil are more effective than digoxin in controlling this rate.

Non-pharmacological means of rate control have recently become available and will be discussed below.

Prevention of Recurrent Atrial Fibrillation

Because of frequent severe symptoms of atrial fibrillation, prevention by antiarrhythmic drugs is often required. Quinidine has been the mainstay

of drug treatment and remains the best-selling antiarrhythmic drug in North America. However, the frequent side effects force discontinuation of this drug in approximately one third of patients, and in many others the drug is ineffective.

A large number of newer antiarrhythmic drugs have been developed over the past decade and they are making gradual inroads in the treatment of atrial fibrillation. Other class Ia antiarrhythmic drugs such as procainamide and dysopyramide share a similar efficacy with that of quinidine.

Trends recently have been away from class Ia antiarrhythmic drugs to class Ic and class III antiarrhythmic drugs.

Class Ic Drugs

Propafenone and flecainide have been shown to be effective in the prevention of atrial fibrillation (Berns et al. 1987; Antman et al. 1988; Hammill et al. 1988; Kerr et al. 1988; Connolly and Hoffert 1989; Kyles et al. 1991). We followed up 81 patients treated for atrial fibrillation with propafenone over a 3-year period. The majority of these patients had failed on multiple antiarrhythmic drugs and had had frequent recurrent episodes requiring therapy. After 3 years, approximately one third of patients remained on propafenone. Twenty patients had complete symptomatic control of their arrhythmias and another ten had marked improvement such that they stated that propafenone was the best drug they had been on and they wished to stay on this drug. Propafenone in these patients was well tolerated, with only 11 patients stopping the drug due to side effects. This long-term follow-up demonstrated several late drug failures. This underscores the fact that many patients with atrial fibrillation have progression of their disease and become more refractory to drug treatment (Kyles et al. 1991).

Class Ic drugs slow conduction with little effect on atrial muscle refractoriness. This may lead to change of atrial fibrillation to atrial flutter. Of 81 patients taking propafenone for atrial fibrillation, we observed 14 who developed atrial flutter, often at a slow atrial rate of 200–250 beats per minute (Murdock et al. 1990). Because of the relatively smaller effect on AV nodal refractoriness, this can lead to more rapid AV conduction and we observed two patients with 1 : 1 AV conduction. Thus, concomitant use of drugs to slow AV conduction, such as once-a-day beta-blocking drugs or calcium channel blockers, should be considered in patients treated with class Ic drugs.

Similar efficacy and similar risk of developments of atrial flutter have been observed with flecainide (Crijns et al. 1988).

Class III Drugs

Amiodarone has long been known to be effective for the prevention of atrial fibrillation (Gold et al. 1986). However, because of its toxicity, there appears to be reluctance to utilize this medication, even though it may be effective in low doses which are well tolerated.

Sotalol, a class III drug with beta-blocking activities, appears to be effective and is being used more frequently for the treatment of atrial fibrillation. By prolonging atrial refractoriness the atrial re-entry circuit may be blocked. Furthermore, the beta-blocker effect and class III effects will prolong AV nodal refractoriness, preventing the risk of rapid ventricular response that may occur with class I antiarrhythmic drugs. Several studies have shown that sotalol may be effective in preventing atrial fibrillation (Antman et al. 1990; Juul-Moller et al. 1990).

Thus, antiarrhythmic drug therapy is often required to improve symptoms in patients with atrial fibrillation. There is a gradual tendency away from the class Ia antiarrhythmic drugs to class 1c and class III antiarrhythmic drugs. In patients with frequent symptomatic recurrence, nonpharmacological treatment may be considered.

Pacing Therapy

Unlike paroxysmal supraventricular tachycardia, atrial fibrillation cannot be terminated by atrial pacing. Thus, antitachycardia pacing is not useful in the treatment of atrial fibrillation.

However, there are some individuals in whom the atrial fibrillation appears to be dependent on sinus bradycardia. A particular subset of patients, originally described by Coumel, comprises young males with little or no underlying heart disease who appear to have atrial fibrillation as a result of high vagal activity (Coumel et al. 1978). These patients develop atrial fibrillation at rest and the atrial fibrillation is usually preceded by prolongation of the cycle length. They are particularly refractory to drug treatment and, in some circumstances, have been shown to be well controlled by pacing the atrium.

Other patients develop sick sinus syndrome in conjunction with atrial fibrillation, the tachycardia-bradycardia syndrome. This is probably due to the same pathological process involving the atrium and sinus node, leading to alternation between atrial fibrillation and marked sinus bradycardia, often symptomatic. These patients require pacing in order to permit antiarrhythmic treatment, and pacing in the atrium often reduces the frequency

of the atrial fibrillation and occasionally prevents it entirely. Certainly it permits the administration of antiarrhythmic drugs without exacerbation of underlying bradycardia.

Several retrospective studies have suggested the possibility that pacing in the atrium will reduce the risk of subsequent atrial fibrillation compared with ventricular pacing (Rosenqvist et al. 1988; Feuer et al. 1989; Santini et al. 1990). These studies have utilized retrospective analyses of different patient populations treated with either AAI, VVI, or DDD pacing. AAI pacing appears to be superior to VVI pacing, with a marked reduction of subsequent development of atrial fibrillation and a possible improvement of long-term survival. Studies also suggest that DDD pacing may be superior to VVI pacing in preventing subsequent development of atrial fibrillation. In these patient populations, the primary indication for pacing was bradycardia, atrial fibrillation. A prospective study evaluating the efficacy of atrial or dual-chamber pacing in preventing atrial fibrillation in patients with this arrhythmia has not been performed. Furthermore, the above studies have been retrospective, and prospective studies are required to confirm the protective effect of atrial pacing.

Finally, pacing plays an integral role when combined with ablation therapy. Ablation of the AV node in patients with frequent paroxysmal atrial fibrillation and chronic atrial fibrillation is discussed below, and placement of a VVIR and DDDR pacemaker often restores completely normal rate responsiveness in such cases.

Ablation Therapy

Atrial fibrillation appears to involve a diffuse process in the atria. Thus, ablation of the site of arrhythmia is not possible. Radical surgical procedures have isolated the majority of the atrium and restored sinus node rate response, but these interventions do not appear to be widely applicable. Similarly, catheter ablation techniques are not applicable to cure atrial fibrillation.

However, ablation of the AV node plays a pivotal role in the prevention of symptoms from atrial fibrillation. Patients with symptomatic chronic atrial fibrillation or frequent paroxysmal atrial fibrillation are candidates for AV nodal ablation. Trends are towards utilizing this technique at an earlier stage in the course of the patient's arrhythmia, eliminating the need for antiarrhythmic drug treatment. However, because ablation does not prevent the atrial fibrillation, anticoagulant therapy must be considered.

AV nodal ablation was originally performed utilizing direct current shock to the region of the AV node and His bundle (Gallagher et al. 1982;

Scheinman et al. 1982). This was highly effective but required general anaesthetic and was associated with complications such as arrhythmia and myocardial damage. More recently, more localized therapy by the delivery of radiofrequency current has become highly successful (Yeung-Lai-Wah et al. 1991). With the patient awake, pulses of radiofrequency current can successfully interrupt AV nodal conduction. By careful placement of the ablation catheter proximally in the region of the AV node, we have achieved successful ablation in nearly 100% of patients. Furthermore, the delivery of this current in the proximal location leads to a stable junctional rhythm. Recent data from our centre would indicate that the junction rhythm remains stable for the period of follow-up to 2–3 years.

Following ablation patients, undergo implantation of rate-responsive pacemakers. Patients with chronic atrial fibrillation receive VVIR pacemakers to restore a smooth and appropriate rate response. Patients with paroxysmal atrial fibrillation receive DDDR pacemakers. Recently, devices have become available that recognize the onset of atrial fibrillation and revert to VVIR pacing, preventing the sensing of the atrial fibrillation and inappropriately rapid tracking of the ventricular response, resulting in recurrent symptomatic palpitations.

In appropriately selected patients, ablation of the AV node can lead to complete symptomatic improvement without the need of antiarhythmic drugs.

Summary

There appear to be trends in the treatment of atrial fibrillation away from the conventional use of quinidine and digoxin. Newer antiarrhythmic drugs may be associated with a better side effect profile and higher efficacy. Appropriate use of pacing in selected patients with bradycardias may help to prevent atrial fibrillation. In patients who are highly symptomatic, the use of catheter ablation with appropriate pacemaker implantation may completely restore them to a functionally normal state without the cost, side effects, and inconvenience of antiarrhythmic drugs.

References

Antman EA, Beamer AD, Cantillon C, McGowan N, Goldman L, Friedman PL (1988) Long-term oral propafenone therapy for suppression of refractory symptomatic atrial fibrillation and atrial flutter. J Am Coll Cardiol 12:1005–1011

Antman EA, Beamer AD, Cantillon C, McGowan N, Friedman PL (1990) Therapy of refractory symptomatic atrial fibrillation and atrial flutter: a staged care approach with new antiarrhythmic drugs. J Am Coll Cardiol 15:698–707

Berns E, Rinkenberger RL, Jeang MK, Dougherty AH, Jenkins M, Naccarelli GV (1987) Efficacy and safety of flecainide acetate for atrial tachycardia and fibrillation. Am J Cardiol 59:1337–1341

Connolly SJ, Hoffert DL (1989) Usefulness of propafenone for recurrent paroxysmal atrial fibrillation. Am J Cardiol 63:817–819

Coplen SE, Antman EM, Berlin JA, Hewitt P, Chalmers TC (1990) Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: a meta-analysis of randomized controlled trials. Circulation 82:1106–1116

Coumel P, Attuel P, Lavellee J, Flammang D, Leclercq JF, Slama R (1978) Syndrome d'arrhythmie auricularie d'origine vagale. Arch Mal Coeur 6:645–656

Crijns HJ, van Gelder IC, Lie KI (1988) Supraventricular tachycardia mimicking ventricular tachycardia during flecainide treatment. Am J Cardiol 62:1303–1306

Feuer JM, Shandling AH, Messenger JC (1989) Influence of cardiac pacing node on long-term development of atrial fibrillation. Am J Cardiol 64:1376–1379

Gajewski J, Singer RB (1981) Mortality in an insured population with atrial fibrillation. JAMA 245:1540

Gallagher JJ, Swenson RH, Kasell JH (1982) Catheter technique for closed chest ablation of the atrioventricular conduction system: a therapeutic alternative for the treatment of refractory supraventricular tachycardia. N Engl J Med 306:194–200

Gold RL, Haffajie CI, Charos K, Sloan K, Baker K, Baker S, Alpert JS (1986) Amiodarone for refractory atrial fibrillation. Am J Cardiol 57:125–127

Hammill S, Wood DL, Gersch BJ, Osborn MJ, Holmes DR (1988) Propafenone for paroxysmal atrial fibrillation. Am J Cardiol 61:473–474

Juul-Moller S, Edvardsson N, Rehnqvist-Ahlberg N (1990) Sotalol versus quinidine for the maintenance of sinus rhythm after direct current cardioversion of atrial fibrillation. Circulation 82:1932–1939

Kerr CR, Chung DC (1985) Atrial fibrillation: fact, controversy and future. Clin Prog Electrophysiol Pacing 3:319–337

Kerr CR, Klein GJ, Axelson JE, Cooper JC (1988) Propafenone for prevention of recurrent atrial fibrillation. Am J Cardiol 61:914–916

Kyles AE, Murdock CJ, Yeung-Lai-Wah JA, Vorderbrugge S, Kerr CR (1991) Long-term efficacy of propafenone for prevention of atrial fibrillation. Can J Cardiol

Lewis T (1925) Clinical disorders of the heart beat. Shaw, London

Murdock CJ, Kyles AE, Yeung-Lai-Wah JA, Vorderbrugge S, Kerr CR (1990) Atrial flutter in patients treated for atrial fibrillation with propafenone. Am J Cardiol 66:755–757

Peterson P, Godtfredson J (1984) Atrial fibrillation: a review of course and prognosis. Acta Med Scand 215:5–9

Peterson P, Godtfredsen J, Boysen G, Anderson ED, Andersen B (1989) Placebo-controlled, randomized trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. Lancet 1:175–179

Rosenqvist M, Brandt J, Schuller H (1988) Long-term pacing in sinus node disease: effects of stimulation mode on cardiovascular morbidity and mortality. Am Heart J 116: 16–22

Santini M, Alexidou G, Ansalone G, Cacciatore G, Cini R, Turitto G (1990) Relation of prognosis in sick sinus syndrome to age, conduction defects and nodes of permanent pacing. Am J Cardiol 65:729–735

Scheinman HM, Morady F, Hess DS, Gonzalez R (1982) Catheter-induced ablation of atrioventricular junction to control refractory supraventricular arrhythmias. JAMA 248:861–855

Stroke Prevention in Atrial Fibrillation Study Group (1990) Preliminary report of the stroke prevention in atrial fibrillation study. N Engl J Med 322:863–868

Wolf PA, Dawber TR, Thomas HE, Kannel WB (1978) Epidemiologic assessment of chronic atrial fibrillation and risk of stroke; the Framingham Study. Neurology 28:973–977

Yeung-Lai-Wah JA, Alison JF, Lonergan L, Mohama R, Leather R, Kerr CR (1991) High success rate of atrioventricular nodal ablation with radiofrequency energy. J Am Coll Cardiol

An Organized Approach to a Disorganized Atrial Arrhythmia

R. W. F. Campbell *

Introduction

Atrial fibrillation has long been recognised. It probably is the commonest important cardiac arrhythmia to afflict man. It jeopardises cardiac output, produces sensations of palpitations and general malaise, and carries an important risk of thromboembolism. It is surprising, then, that not more attention has been paid to its management.

Ventricular rate control of established atrial fibrillation is for many physicians the major and for some the only clinical challenge. Ventricular rate control, however, is but one aspect of the clinical problem. Others that must be addressed include ventricular rate control under conditions of stress and exercise; drug conversion of atrial fibrillation to sinus rhythm; DC cardioversion of atrial fibrillation to sinus rhythm; postcardioversion maintenance of sinus rhythm; measures to prevent paroxysmal atrial fibrillation; and a policy to minimise the risk of thromboembolism.

In the last few years, there have been dramatic improvements in our understanding of the basic electrical process of atrial fibrillation (Allessie and Janse, this volume; Franz and Koller, this volume) and in our appreciation of prognosis and the costs and benefits of therapy (Kerr et al., this volume). Thus, there may be sufficient information to provide a basis for a rational approach to the management of atrial fibrillation. The following integrates the basic and clinical knowledge of atrial fibrillation and its management as presented by the other contributors to this volume. Differences of opinion and variations in recommendations reflect neither right nor wrong but a lack of reliable data.

Managing the Aetiological Basis of Atrial Fibrillation

Adrenergic Tone

Adrenergically modulated atrial fibrillation may be defined by its historical associations or by examination of 24-h ECG recordings contain-

* The author's department of academic cardiology is supported by the British Heart Foundation.

ing episodes. In typical examples, prior to the onset of atrial fibrillation there are either crude heart rate increases or more subtle and short-term R-R interval decrements. Beta-adrenoreceptor blocking drugs may be of particular benefit in this important but numerically small group of patients (Coumel et al. 1984).

Vagal Tone

Vagotonic atrial fibrillation is also recognised but again is relatively rare (Coumel et al. 1978). There have been suggestions that atrial pacing may prevent the development of this type of atrial fibrillation (Rosenqvist et al. 1988; Feuer et al. 1989). Atrial pacing is also a therapeutic strategy advanced for the management of sick sinus syndrome (brady-tachy syndrome). In practice, at present, atrial pacing has only a modest management role. Its prophylactic efficacy may be limited and may be applicable to only highly selected patients. Furthermore, in the event that atrial fibrillation does occur, the implanted pacer is powerless to ameliorate the situation. Atrioversion capability would overcome this problem, but even low-energy shocks are poorly tolerated by the conscious patient.

Alcohol

Alcohol is emerging as a most important cause of paroxysmal atrial fibrillation. Although the association has been recognised for quite some time, the importance of moderating alcohol intake or indeed abstaining from alcohol in management has been under-emphasised. In a recent report Koskinen et al. (1990) showed that 98 consecutive patients with atrial fibrillation had a significantly higher alcohol intake than either sex- and age-matched control patients or 50 randomly selected normal subjects. In that study, alcohol was not the only factor linked to recurrences; serum potassium concentrations, associated disease and stress or lack of sleep were also relevant. The association of alcohol with arrhythmias, brought to attention by Ettinger et al. in 1978 as the "holiday heart", is particularly strong for atrial fibrillation, although other arrhythmias are involved. In Ettinger's original series over one third of patients admitted with "holiday heart" presented with atrial fibrillation; another 15% presented with atrial flutter. Cohen et al. (1988) showed the significantly increased risk of atrial fibrillation for individuals taking more than six alcohol drinks daily compared with matched control individuals who, on average, consumed less than one drink daily.

Thyroid Disease

Atrial fibrillation complicating thyrotoxicosis is a special circumstance. White's cardiology textbook (1947) quotes Trousseau who by error gave tincture of iodine instead of tincture of digitalis to a thyrotoxic patient with atrial fibrillation. The satisfactory outcome in terms of cardiac rhythm indicated the value of tackling the primary aetiology of atrial fibrillation. Administering iodine in thyrotoxicosis is no longer the preferred management strategy for complicating atrial fibrillation; radioiodine offers a long-term solution, while for acute purposes beta-adrenoreceptor blocking drugs offer impressive and rapid efficacy in controlling the rate response (Toft et al. 1976).

Mechanical Factors

Mechanical-electrical interactions may be important in the genesis of arrhythmias in patients with heart failure (Dean and Lab 1989). Almost certainly some atrial arrhythmias, including atrial fibrillation, arise either directly or indirectly from the abnormal wall stresses associated with elevated atrial pressures. There has been considerable interest in whether vasodilator therapy given to heart failure patients modifies complicating arrhythmias. The most dramatic results have been noted with angiotensin-converting enzyme (ACE) inhibitors in respect of ventricular ectopic beat rates (Cleland et al. 1984; McKenna and Haywood 1990; Webster et al. 1985). As yet there is no systematic evidence that vasodilator therapy might prevent the development of atrial fibrillation in susceptible patients, but there is much that is circumstantially supportive.

Other Factors

Ischaemic heart disease, congenital heart disease and a variety of other forms of cardiovascular disease are complicated by atrial fibrillation. Mechanical disturbances associated with these disease processes can disrupt atrial electrophysiology, but in other cases patchy fibrotic replacement of atrial myocardium is responsible. Limitation of disease progression or even disease regression might have an antiarrhythmic effect with respect to atrial fibrillation, but very little is known of this. There are anecdotal reports of spontaneous termination of atrial fibrillation in patients with severe rheumatic mitral valve disease. Rather than reflecting amelioration of their condition, the rhythm change more likely is a consequence of

loss of electrically active atrial tissue to the extent that the critical mass necessary to support a fibrillatory process no longer exists.

Quenching Multiple Wavelets of Reentry: Restoring Sinus Rhythm

Drugs

Drug administration to convert atrial fibrillation to sinus rhythm has been popular in the past but now appears of little importance – reversion is seen as a bonus, rather than the reason for drug therapy. In 1947, White, in his textbook *Heart Disease*, noted the observations of Frey (1918), who reported that quinidine was superior to quinine in the restoration of sinus rhythm in those afflicted by atrial fibrillation. A mean success rate of 6% (range 7% – 90%) was quoted. Even at that time the toxicity of quinidine was recognised, but White suggested "that by the exercise of care, accidents and fatalities...can largely be avoided".

In the pioneering studies of Sokolow and Edgar (1950), using much larger doses of quinidine than nowadays would be considered reasonable (five doses of 0.4 or 0.6 g quinidine at 2-h intervals), conversion to sinus rhythm was observerd in 82% of patients with atrial fibrillation, with a 10% incidence of adverse reactions. Procainamide also offers a moderate conversion rate of atrial fibrillation to sinus rhythm (Halpern et al. 1980; Fenster et al. 1983).

It is only really with the advent of the Vaughan Williams class Ic drugs that the therapeutic possibility of drug conversion to sinus rhythm has received modern attention. Intravenous propaferone 2 mg/kg converted 57% of incidents of atrial fibrillation to sinus rhythm in a mean time of 29 min (Bianconi et al. 1989). An identical success rate was reported for flecainide acetate, albeit, in this instance, with a 22% incidence of unwanted effects (Donovan et al. 1991).

In a comparative study, intravenous amiodarone was more effective than digoxin in achieving sinus rhythm (Cowan et al. 1986). Quinidine and flecainide have been shown as equipotent in antifibrillatory effects, but unwanted effects were four times more frequent with quinidine (Borgeat et al. 1986). Propafenone has been shown to be more effective and faster in restoring sinus rhythm than amiodarone (Negrini et al. 1991), whilst in comparison with flecainide, propafenone was less successful (success rate 55% vs 90%) but was much better tolerated (unwanted effects 8% vs 40%) (Suttorp et al. 1990).

DC Shock

DC cardioversion offers a high success rate for restoring sinus rhythm in patients with atrial fibrillation. The effect, however, may be relatively short-lived. DC cardioversion has become less fashionable than in the past, perhaps reflecting the discouraging long-term success rate for maintaining sinus rhythm. Restoration of sinus rhythm is significantly more likely in patients with only minor degrees of underlying cardiovascular disease, who have been in atrial fibrillation for only a short time and who have little or no atrial enlargement.

There is a reasonable case to be made for attempting cardioversion in all patients with atrial fibrillation. Prior to cardioversion performed electively, patients should be formally anticoagulated as a protection against thromboembolism. Ideally, 4 weeks' anticoagulation is appropriate. Early reports of DC cardioversion provoking potentially lethal ventricular arrhythmias raised suspicions of an arrhythmogenic role for digoxin, and it is customary that this drug be stopped for some 24–48 h prior to the cardioversion attempt. It is probably only in patients who are close to or actually manifesting signs of digitalis toxicity that this complication is likely to arise.

DC cardioversion can cause myocardial damage, particularly when transthoracic energy deliveries of more than 200 Ws are used. Thus there is a need to use the lowest effective energy, but in these circumstances, the transthoracic discharge pathway becomes highly relevant. An anteroposterior delivery of energy is probably more effective in restoring sinus rhythm for any given energy than an anterolateral discharge. Sadly, the use of backplates in DC cardioversion is nowadays relatively rare.

Maintaining Sinus Rhythm

Almost all antiarrhythmic drugs have been used in efforts to maintain sinus rhythm following successful cardioversion. Quinidine and procainamide offer modest efficacy, but unwanted effects limit their long-term success. In 1974, Härtell and colleagues showed that disopyramide was significantly better than no therapy in maintaining sinus rhythm following DC cardioversion, but follow-up assessment was made only 3 months after cardioversion.

New understanding of the process of atrial fibrillation should have prompted a more scientific approach to maintaining sinus rhythm. Atrial fibrillation is caused by multiple interlacing wavelets of reentry. The number of wavelets could be reduced by drugs which prolong refractoriness or

alternatively by those that slow conduction. Numerous uncontrolled studies have suggested a role for amiodarone, but long-term toxicity of this agent may be an important limitation on its use. Several studies of class Ic antiarrhythmic drugs, principally propafenone and flecainide (Mary Rabine and Kulbertus 1990), have demonstrated their efficacy in maintaining sinus rhythm after cardioversion. These drugs are well tolerated and unwanted effects have been minimal. Class Ic compounds represent a logical extrapolation from basic experiments to clinical cardiology. Large-scale studies are lacking, however, and it remains to be seen whether these agents merely delay the relapse to atrial fibrillation or whether they can provide successful long-term prophylaxis.

Beta-blockers may also have a role in prevention of relapse to atrial fibrillation, but digoxin has little utility for this purpose (Rawles et al. 1990). Of interest are observations that ACE inhibitor therapy may, through alterations in mechanical-electrical coupling, improve atrial electrical homogeneity or decrease the risks of triggered automaticity, and so modify atrial arrhythmias. Whether in this context ACE inhibitors are truly antiarrhythmic is a matter of philosophical debate, but the observation is sufficient to indicate that arrhythmia control may be offered by a wide range of interventions, including some which do not directly affect transmembrane ionic flux.

Prevention of Paroxysms of Atrial Fibrillation

Paroxysmal atrial fibrillation is one of the most debilitating arrhythmias. Affected patients often are bitterly symptomatic. Prophylaxis of attacks is difficult, and at present no optimal strategy has been identified. Rather, each individual patient needs careful review to identify what factors, if any, may operate to initiate the arrhythmia. In a proportion of patients, a primary initiating mechanism can be identified and may be amenable to modification, as previously discussed. For most sufferers, however, empiric antiarrhythmic therapy is the best that can be offered. Beta-blockers, propafenone, flecainide and amiodarone may be of use. Digoxin is of little value. Quinidine and procainamide offer some efficacy, but the risk-benefit ratio may not be propitious in patients in whom attacks may be occurring at only infrequent intervals.

Optimal Ventricular Rate Control in a Changing Autonomic Environment

Theoretically one of the easiest parts of artial fibrillation management, ventricular rate control may pose great problems. Conduction capacity

through the AV node is dependent upon the refractory period of that structure. This is not fixed; indeed, it can vary markedly depending upon autonomic status. Studies examining digoxin's heart rate control have produced evidence of less than desirable efficacy over 24 h of ECG scrutiny (Rawles et al. 1990).

Adjunctive therapy is commonly prescribed with digoxin for ventricular rate control. Beta-blockers and calcium antagonists are the usual choices, and both have been shown to offer useful additive effects. Given that autonomic modulation might be one of the reasons for poor initial control with digoxin, there is a rationale for beta-blockers as perhaps the first choice, but there is good evidence attesting to the value of the calcium entry blockers verapamil and diltiazem.

Surprisingly little is known of the value of beta-blockers and calcium entry blockers as monotherapy for rate control of atrial fibrillation, but more investigation of this might prove rewarding, if only in better establishing what each agent may offer.

Preventing Complications of Atrial Fibrillation

The major complication of atrial fibrillation is embolism. Systemic embolism is responsible for significant morbidity and mortality. Pulmonary embolism may also occur, but relatively little is known of its frequency; right atrial clot is rarely so extensive as to cause an important pulmonary infarction.

All patients with atrial fibrillation, whether with a chronic process or paroxysmal attacks, have an increased risk of systemic embolism compared with age- and sex-matched control individuals without the arrhythmia. The increased risk, however, is very small for individuals with paroxysmal atrial fibrillation in the absence of structural heart disease. For them, the risk-benefit assessment of anticoagulant therapy may not be favourable, but for all other patients, prophylaxis of embolism is appropriate. Assessing the risks and benefits of anticoagulation is not easy: too little is known of the natural history and embolic risks of the variety of clinical situations in which atrial fibrillation occurs; optimal anticoagulant dosing has been little investigated; the bleeding risk for individual patients is difficult to determine (and probably shows great day-to-day variability); and the compliance of the patient in actually taking the mediation is all but impossible to establish.

Two recent developments in anticoagulation are worthy of mention. Early reports suggest the possibility that lower doses of warfarin than are normally advised may be successful in preventing systemic thromboem-

bolism (Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators 1990). Secondly, although several studies have failed to show benefit, a recent study suggests that aspirin may offer an anticoagulant effect against systemic embolism (Stroke Prevention in Atrial Fibrillation Study Group 1991). If confirmed, this might be an important consideration for patients at relatively low risk of embolism in whom the risk-benefit ratio of full formal anticoagulation is not favourable.

The Organized Approach

There is increasing knowledge of the primary aetiological and basic electrical processes that underlie atrial fibrillation. Clearly, management must seek and address these factors, as their manipulation offers the possibility of "cure". The importance of underlying structural cardiovascular disease has long been recognised, but the effects of thyroid disease, viral illness (including HIV infection) and, more critically, of alcohol are important and should be sought in all patients.

Drug management of atrial fibrillation remains the keystone of therapy. The literature abounds with the reports of efficacy of "older" drugs investigated at a time when atrial fibrillation was the subject of great interest. After a period of dormancy, interest in atrial fibrillation is again reawakening, due in no small part to new insights on the electrophysiology of the arrhythmia. As a consequence, the pharmacological approach to atrial fibrillation has broadened, with better appreciation of the therapeutic possibilities offered by beta-blockers, amiodarone and the class Ic antiarrhythmic agents, including propafenone.

Drug management of atrial fibrillation and its complications is improving. New studies and new approaches will further extend our therapeutic armamentarium. But primary prevention must not be forgotten. Attenion must be directed to containing or curing the disease processes which destabilise atrial electrophysiology. Aggressive early management of heart failure, valvular heart disease and excessive alcohol intake will pay dividends for the future, as indeed may the damage-limiting potential of thrombolytic therapy in acute-phase myocardial infarction.

Non-pharmacological treatments also have a place in management. Atrial "corridor" surgery (Leitch et al. 1991), atrial "maze" operations (Cox et al. 1991) and AV node ablation (Jackman et al. 1991) are applicable for a minority of patients with atrial fibrillation, but could benefit more sufferers than is currently the case. As more is learned of the electrical process of fibrillation, non-pharmacological procedures may be

refined to the extent that they are incorporated as a prophylactic strategy during such surgical procedures as valve replacement and surgical correction of some congenital cardiac abnormalities.

References

Bianconi L, Boccadamo R, Pappalardo A, Gentili C, Pistolese M (1989) Effectiveness of intravenous propafenone for conversion of atrial fibrillation and flutter of recent onset. Am J Cardiol 64:335–338

Borgeat A, Goy J-J, Maendly R, Kaufmann U, Grbic M, Sigwart U (1986) Flecainide versus quinidine for conversion of atrial fibrillation to sinus rhythm. Am J Cardiol 58:496–498

Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators (1990) The effects of low-dose warfarin on the risk of stroke in patients with non-rheumatic atrial fibrillation. N Eng J Med 323:1505–1511

Cleland JGF, Dargie HT, Hodsman GP, Ball SG, Robertson JIS, Morton JJ, East BW, Robertson I, Murray GD, Gillen G (1984) Captopril in heart failure – a double blind controlled trial. Br Heart J 52:530–535

Cohen EJ, Klatsky AL, Armstrong MA (1988) Alcohol use and supraventricular arrhythmia. Am J Cardiol 62:971–973

Coumel P, Attuel P, Lavallee JP, Flammang D, Leclercq JF, Slama R (1978) Syndrome d'arythmie auriculaire d'origine vagale. Arch Mal Coeur 71:645–656

Coumel P, Escoubet B, Attuel P (1984) Beta-blocking therapy in atrial and ventricular tachyarrhythmias: experience with nadolol. Am Heart J 108:1098–1108

Cowan JC, Gardiner P, Reid DS, Newell DJ, Campbell RWF (1986) A comparison of amiodarone and digoxin in the treatment of atrial fibrillation complicating suspected acute myocardial infarction. J Cardiovasc Pharmacol 8:252–256

Cox JL, Schuessler RB, D'Agostino HJ, Stone LM, Chang BC, Cain ME, Corr P, Boineau JP (1991) The surgical treatment of atrial fibrillation: III. Development of a definitive surgical procedure. J Thorac Cardiovas Surg 101:569–583

Dean JW, Lab MJ (1989) Arrhythmia in heart failure: role of mechanically induced changes in electrophysiology. Lancet 1:1309–1312

Donovan KD, Dobb GJ, Coombs LJ, Lee K-Y, Weekes JN, Murdock CJ, Clarke GM (1991) Reversion of recent onset atrial fibrillation to sinus rhythm by intravenous flecainide. Am J Cardiol 67:137–141

Ettinger PO, Wu CF, De La Cruz C, Weisse AB, Ahmed SS, Regan TJ (1978) Arrhythmias and the holiday heart: alcohol associated cardiac rhythm disorders. Am Heart J 95:555–562

Fenster PE, Comess KA, Marsh R, Katzenberg C, Hager WD (1983) Conversion of atrial fibrillation to sinus rhythm by acute intravenous procainamide infusion. Am Heart J 106:501–504

Feuer JM, Shandling AH, Messenger JC (1989) Influence of cardiac pacing mode on the long-term development of atrial fibrillation. Am J Cardiol 64:1376–1379

Frey W (1918) Ueber Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin. Berl Klin Wochenschr LV:450

Halpern SW, Ellrodt G, Singh BN, Mandel WJ (1980) Efficacy of intravenous procainamide infusion in converting atrial fibrillation to sinus rhythm. Br Heart J 44:589–595

Härtell G, Louhija A, Konttinen A (1974) Disopyramide in the prevention of recurrence of atrial fibrillation after electroconversion. Clin Pharmacol Ther 15:551–555

Jackman WM, Wang X, Friday KJ, Fitzgerald DM, Roman C, Moulton K, Margolis PD, Bowman AJ, Kuck KH, Nacarelli GV, Ptiha JV, Dyer J, Lazzara R (1991) Catheter ablation of atrioventricular junction using radiofrequency current in 17 patients. Comparison of standard and large-tip catheter electrodes. Circulation 83:1562–1576

Koskinen P, Kupari M, Leinonen H (1990) Role of alcohol in recurrences of atrial fibrillation in persons <65 years of age. Am J Cardiol 66:954–958

Leitch JW, Klein G, Yee R, Guiraudon G (1991) Sinus node-atrioventricular isolation: long-term results with the corridor operation for atrial fibrillation. J Am Coll Cardiol 17:970–975

Mary Rabine L, Kulbertus HE (1990) Clinical efficacy of flecainide acetate in atrial fibrillation. Cardiology 77/6:443–449

McKenna WJ, Haywood GA (1990) The role of ACE inhibitors in the treatment of arrhythmias. J Clin Cardiol 13 [Suppl] VII:49–52

Negrini M, Gibelli G, De Ponti C (1991) Propafenone compared with amiodarone for conversion of paroxysmal atrial fibrillation to sinus rhythm. J Am Coll Cardiol 17:131A (abstr)

Rawles JM, Metcalfe MJ, Jennings K (1990) Time of occurrence, duration, and ventricular rate of paroxysmal atrial fibrillation: the effect of digoxin. Br Heart J 63:225–227

Rosenqvist M, Brandt J, Schuller H (1988) Long-term pacing in sinus node disease: effects of stimulation mode on cardiovascular morbidity and mortality. Am Heart J 116:16–22

Sokolow M, Edgar AL (1950) Blood quinidine concentrations as a guide in the treatment of cardiac arrhythmias. Circulation 1:576–592

Stroke Prevention in Atrial Fibrillation Study Group (1991) Stoke Prevention in Atrial Fibrillation Study: final results. Circulation 84:527–539

Suttorp MJ, Kingma JH, Jessurun ER, Lie-a-Huen L, van Hemel NM, Lie KI (1990) The value of class Ic antiarrhythmic drugs for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. J Am Coll Cardiol 16:1722–1727

Toft AD, Irvine WJ, Campbell RWF (1976) Assessment by continuous cardiac monitoring of minimum duration of pre-operative propranolol treatment in thyrotoxic patients. Clin Endocrinol 5:195–198

Webster MWI, Fitzpatrick MA, Nicholls MG, Ikram H, Wells JE (1985) Effect of enalapril on ventricular arrhythmias in congestive heart failure. AM J Cardiol 56:566–569

White PD (1947) Heart disease, 3rd edn. Macmillan, New York pp 899–890

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