Atrial Fibrillation

A Study of Substrate and Triggers

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Chapter 1

Introduction

1.1 The Nature of the Clinical Problem

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. It is diagnosed electrocardiographically by the absence of 'P' waves and the presence of irregular coarse fibrillation or 'f' waves and irregular QRS complexes (Figure 1.1). The loss of sinus rhythm and the development of AF is characterised by random incoordinate movement of the atria resulting in impairment of atrial function. Data from the UK general practice database suggest that AF affects approximately 1.2% of the UK adult population, or an estimated 650,000 adults in England and Wales.[1] A recent study from Birmingham[2] found a prevalence of 2.4% in patients older than 50 years, and workers in Sheffield[3] noted an incidence of 5.4% in patients over 65 years of age. Wheeldon et al[3] also highlighted the increase in prevalence with age from 2.3% in those aged 65-69 years up to 8.1% in those over 85 years of age. Data from the USA shows a similar prevalence of AF (5.5%) in patients over the age of 65 years.[4] AF has been described as the epidemic of the future as its prevalence will increase with the aging of the population in developed countries. The age standardized prevalence of AF has also increased through the 1990s[1] suggesting that in addition to an increase in AF due to the aging of the population more patients are likely to develop AF at younger ages in the future.

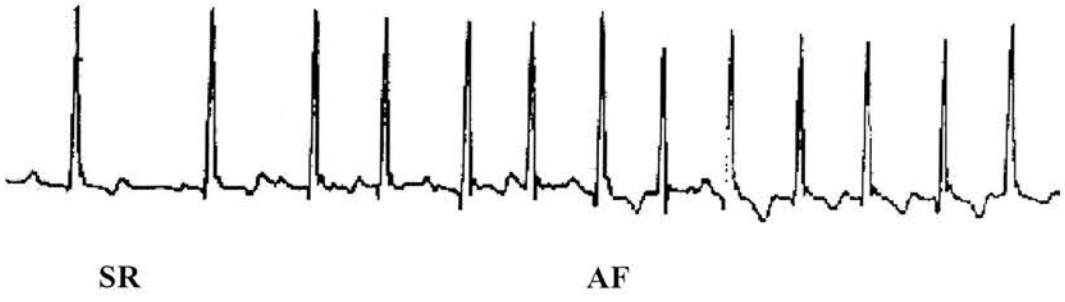

Figure 1.1 Onset of atrial fibrillation (AF). SR – sinus rhythm

Epidemiological data from The Framingham Study has shown a clear link between AF and cardiovascular disease.[5] Hypertension, especially in association with left ventricular hypertrophy, was the most common risk factor identified, although a history of rheumatic heart disease or cardiac failure were stronger risk factors. AF in the absence of cardiovascular disease (lone AF) represented 11% of AF patients in the Framingham study.[6] A more recent population analysis of AF in France[7] has shown some change in the epidemiology of AF in the last two decades. Rheumatic valvular disease remains a common cause in women, but not in men. More commonly nowadays AF is being identified in patients without heart disease, with approximately 30% of the population in this study having 'lone AF', especially those with paroxysmal AF.

The association between AF and cardiovascular disease initially made the study of AF related complications difficult. It became clear though, from age and risk factor controlled studies, that AF itself carried a risk independent of the underlying cardiovascular condition. The initial Framingham data[5] showed a doubling of overall mortality (Table 1.1) in patients with AF compared to age and sex matched controls, and further studies of AF in association with coronary artery disease[8] and heart failure[9] have since confirmed this estimated doubling of mortality in patients with AF.

Mortality	Men			Women		
	AF Cases	Controls	RR	AF Cases	Controls	RR
Total Deaths	59.2%*	34.3%	1.7	44.9%*	25.3%	1.8
Cardiovascular deaths	42.9%*	21.2%	2.0	40.8%*	15.1%	2.7
Average time to death	5.9 years*	7.7 years		4.6 years	6.7 years	

* Significant difference between values for AF cases and controls among all subjects 38 to 78 years old at death ($p < 0.05$). RR - relative risk. Adapted from Kannel et al, NEJM 1982;306:P1021.

Table 1.1 Mortality data from the Framingham Study showing the increased risk of AF.

The increased mortality with AF is at least in part due to an excess risk of thrombo-embolic episodes. The association of AF with thrombo-embolism was clearly defined in the early 1980s.[10] This led to several studies of the effectiveness of oral anticoagulants and aspirin as prophylactic agents to prevent thrombo-embolism in the late 1980s.[11-16] Pooled analysis from these studies shows that aspirin at a dose of 300-325mg/day reduces the risk of thrombo-embolism by approximately 20% and that warfarin at an INR of 2.0-3.0 reduces the risk by 68%.[17] The risk of stroke with placebo was 4.5% per annum and with warfarin 1.4% per annum. The calculated number needed to treat (NNT) with warfarin therapy over 1-year in order to prevent 1 stroke is 32.

1.2 The Progressive Nature of Atrial Fibrillation

In clinical practice the presentation of AF is variable. Some patients present with short-lived episodes of AF that resolve spontaneously. Others develop AF that can only be converted to sinus rhythm by chemical or electrical cardioversion, and in some patients sinus rhythm cannot be restored. This led to the 3 'P' classification[18] of **P**aroxysmal, **P**ersistent and **P**ermanent forms of AF.

An important aspect of the 3 'P' classification is that it bears a strong relationship to the observed natural history of AF. Clinical observation has suggested that AF is a progressive condition. As early as 1930[19] the transition from paroxysmal to persistent AF was identified, with progression to persistent AF in ~25% of patients with paroxysmal AF over several years of follow-up. A survey of the natural history of AF in 1212 patients found the transition rate from paroxysmal to persistent AF to be 33% over a three-year period.[20] Although this might be explained by a deterioration of the underlying heart disease the progression from paroxysmal to persistent forms of AF has also been noted in patients with lone AF,[7,21,22] suggesting that AF itself is progressive regardless of any underlying cardiac condition. In addition to the recognition that AF is a

progressive condition, the transition rate from paroxysmal to persistent AF appears to be increasing over the last decade. The study from Olmsted County, Minnesota published in 1987[21] found the rate of transition was 12% over 13.4 years. Two studies published in 1999 showed higher rates of progression of AF with a transition rate of 23% over a mean of 7-years in a study from Trieste, Italy,[22] and recent data from France[7] has shown a transition rate of 8% in 6-months. This suggests that recent advances in therapy have done little to alter the natural history of AF.

Despite medical treatment many patients will progress from paroxysmal to persistent AF. At this point most physicians will attempt restoration of sinus rhythm by pharmacological or electrical cardioversion. Akin to the progressive nature of paroxysmal AF over time, the success of cardioversion in restoring long-term sinus rhythm is related to the prior duration of AF. This is particularly true for chemical cardioversion. Flecainide results in successful restoration of sinus rhythm in around 90% of patients with recent onset AF (<24 hours), whereas the success rate of cardioversion of chronic AF (>24 hours) is only around 40%.[23-25] The same pattern is seen for other drugs such as propafenone.[26] Increased difficulty in restoring long-term sinus rhythm with lengthy durations of AF is also noted in patients undergoing DC cardioversion. Longer durations of AF require higher shock energies to restore sinus rhythm at the time of DC cardioversion[27] and recurrence of AF is more common with a longer duration of AF prior to DC cardioversion.[28-32]

Atrial fibrillation is a progressive condition independent of the underlying cardiac condition. With the passage of time paroxysmal AF will often develop into persistent AF, and if not cardioverted promptly persistent AF to permanent AF. This led researchers to ask whether AF itself was important in its own maintenance. It was on this basis that Maurits Allessie asked the question *"Does AF beget AF?"* i.e. is it self-perpetuating? In combination with Maurits Wijffels he developed a chronically

instrumented goat model of AF[33] in order to study the effect of repetitive paroxysms of AF on a healthy heart. Using a left intercostal thoracotomy approach goats were fitted with silicon strips containing unipolar electrodes on the surface of both atria and across Bachmann's bundle. The wires from the electrodes were tunneled to the back of the goat's neck where they were exteriorised. A cable then connected the wires to a personal computer. The computer acted as a fibrillation pacemaker inducing AF by burst pacing. Following the onset of AF the burst pacing was inhibited and the computer simply monitored the atrial rhythm. Whenever sinus rhythm was detected further burst pacing was performed to reinduce AF. AF could thus be maintained for prolonged periods. This landmark work went on to show that repetitive reinduction of AF resulted in a gradual prolongation of the duration of the induced AF episodes and eventually the onset of stable chronic AF (Figure 1.2).

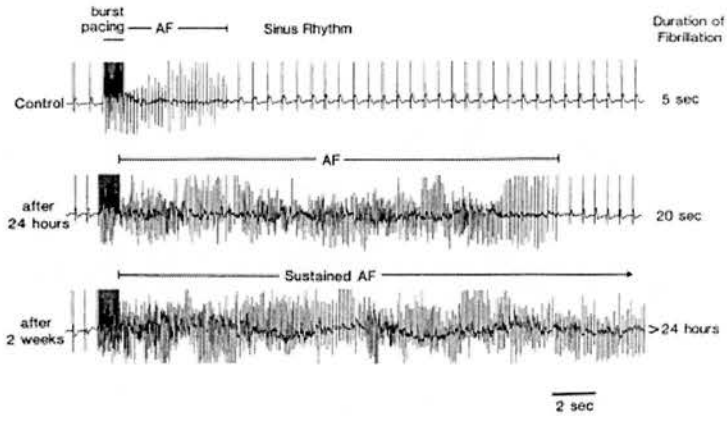

Figure 1.2 Prolongation of the duration of episodes of electrically induced AF after maintaining AF for respectively 24 hours and 2 weeks. The three tracings show a single atrial electrogram from the same goat during induction of AF by a 1-second burst of stimuli (50Hz, 4 x threshold). In the upper tracing the goat has been in sinus rhythm all the time and AF self-terminated within 5 seconds. The second tracing was recorded after the goat had been connected to the fibrillation pacemaker for 24 hours and shows a clear prolongation of the duration of AF to 20 seconds. The third tracing was recorded after 2 weeks of electrically maintained AF. After induction of this episode AF became sustained and did not terminate. *From Wijffels et al. Circulation 1995;92:1954-68.*

Associated with the prolongation of AF episodes there is a reduction in the atrial effective refractory period (AERP) and loss of its adaptation to rate, a process termed atrial electrical remodelling (Figure 1.3). The importance

of atrial electrical remodelling and the associated reduction in AERP is the resultant reduction in atrial wavelength (Atrial wavelength = atrial refractory period x conduction velocity). According to Moe's multiple wavelet hypothesis of AF[34] a shorter atrial wavelength promotes the maintenance of AF. The recognition of atrial electrical remodelling as a ***'substrate'*** for the maintenance of stable AF has directed research into the study of factors influencing the onset and recovery of atrial electrical remodelling.

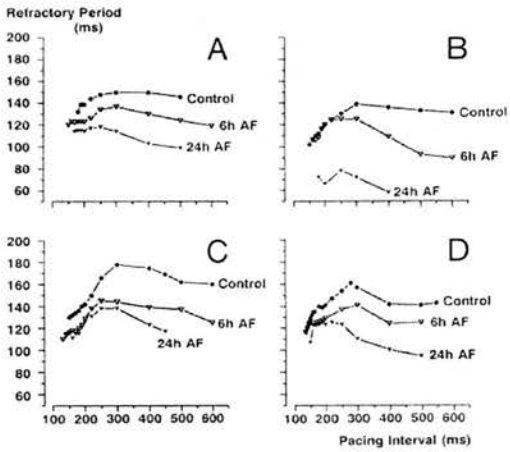

Figure 1.3 Four examples of changes in atrial refractoriness in the course of the first 24 hours of fibrillation. In all goats the refractory period shortened markedly at all pacing intervals. In general the amount of shortening was higher at slower heart rates, resulting in reversal or attenuation of the normal physiological rate adaptation of the refractory period. *From Wijffels et al. Circulation 1995;92:1954-68.*

In addition to the identification of a ***'substrate'*** for the self-perpetuation of AF there has been renewed interest in the importance of atrial ectopy as a ***'trigger'*** for AF. This surge of interest in the triggers for AF was generated following the description by Haissaguerre and coworkers of a 'focal' form of AF dependent on frequent repetitive discharges from a single source, predominately within the pulmonary veins, and amenable to treatment by radiofrequency ablation.[35,36] Figure 1.4 shows mapping of a focal source of AF. This 'focal' form of AF has generally been described in young patients with paroxysmal AF and frequent atrial ectopy.

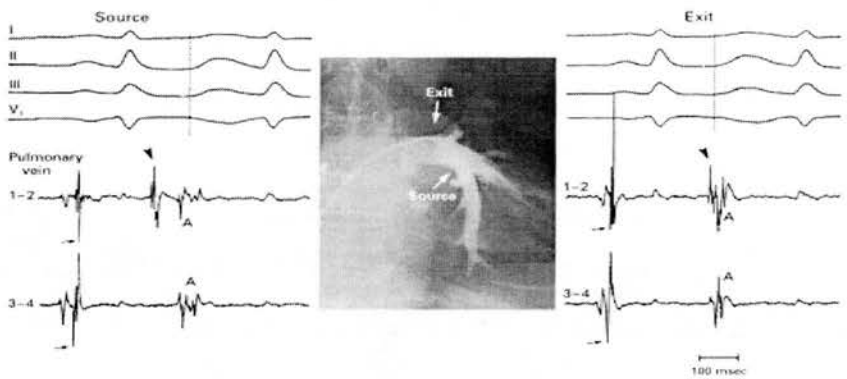

Figure 1.4 Electrograms and Angiogram of a Left Inferior Pulmonary Vein Depicting the Source and Exit of Ectopic Activity. The radiograph (centre panel) shows the position of electrographic recordings inside the pulmonary vein. There are changes in timing of the electrogram depending on the position of the recording catheter in the pulmonary vein. With an increasingly distal catheter position (toward the source), the spike was recorded progressively later during sinus rhythm (left-hand panel, arrows) and correspondingly earlier during ectopic activity (arrowhead). Conversely, in a proximal position at its exit into the left atrium (right-hand panel), the spike was not as delayed during sinus rhythm (arrows) but also not as early during ectopic activity (arrowhead). *Figure and text adapted from Haissaguerre M et al. NEJM 1998;339:659-66*

1.3 Aims of the thesis

Substrate

The aim of the first part of the study was to study atrial electrical remodelling in two situations:

(1) In an animal model.

(2) In patients with clinical AF undergoing cardioversion for persistent AF.

1. Animal model

In order to study the process of atrial electrical remodelling we developed an animal model based on the original Allessie goat model. Using adult female goats implanted with pacemakers, we developed and validated a new fully implantable goat model of AF. Having confirmed the reproducibility of data from the new model we were able to study the effects of drugs on the process of atrial electrical remodelling. Data from animals[37] and humans[38] had shown that the L-type calcium channel blocker verapamil attenuated atrial electrical remodelling induced by short

durations of AF or rapid atrial pacing. It was not clear, however, whether this effect on atrial electrical remodelling had any meaningful antifibrillatory effect on the atria. Our initial studies confirmed that verapamil attenuated atrial electrical remodelling, but despite this action verapamil had a profibrillatory action on the atria (Dr W. J. C. Hobbs, MD Thesis). Despite the profibrillatory action of verapamil in the experimental setting clinical data suggested a beneficial effect of verapamil combined with propafenone in preventing recurrent AF following DC cardioversion of persistent AF.[39] In view of this the first part of the thesis was to study the effects of propafenone on the profibrillatory action of verapamil.

The second part of the thesis required longer durations of AF. A particular advantage of the fully implantable version of the Allessie goat model was the ability to study the effects of longer durations of AF on the atria without the risk of infection. In his initial work Wijffels noted a discrepancy between the time course of atrial electrical remodelling and the onset of stable AF. Despite the onset of maximal changes in atrial refractoriness in a relatively short time following activation of the fibrillation pacemaker, stable AF often did not occur till several days later. Gaspo and colleagues[40] made the same observation in their canine model of AF and this led Zipes to question whether factors other than atrial refractoriness may be important in the self-perpetuation of AF.[41] The discrepancy in the effects of verapamil with attenuation of atrial electrical remodelling but promotion of AF stability also led us to question whether a 'second factor' independent of atrial refractoriness might be involved in the onset of stable AF.

A previous study[42] using sequential 5-day episodes of maintained AF found no evidence of a 'second factor'. In this study, using the original Allessie chronically instrumented goat model, Garratt and coworkers[42] studied repetitive 5-day periods of AF reinduction to examine the hypothesis that an AF-induced increase in AF stability might be due to a

mechanism (a so-called second factor) with a longer time course than that of changes in atrial refractoriness. No progressive increase in AF inducibility, vulnerability or stability was demonstrable in this study, indicating either that a second factor did not exist or had a longer onset than the 5 days selected in the protocol.[43] Our aim was to retest the above hypotheses using 4-week periods of AF. This duration of AF was chosen because it has been shown that AF of this duration in addition to causing atrial electrical remodelling leads to ultrastructural changes in atrial myocardium,[44] a possible candidate for the 'second factor'.

2. Clinical Study

The study of atrial electrical remodelling in patients with persistent AF focused on the question of whether atrial electrical remodelling reversed following cardioversion of persistent AF. Atrial electrical remodelling[33,40,45] and its reversal following conversion to sinus rhythm had already been demonstrated in animal models of AF.[33] Atrial electrical remodelling had also been shown in man,[46] but only in the setting of short-lived, pacing-induced episodes of AF in patients without a prior history of AF. We sought to determine first, whether atrial electrical remodelling was present in patients with persistent AF, and second whether periods in sinus rhythm resulted in reversal of atrial electrical remodelling. In order to do this atrial fibrillation cycle length and atrial refractoriness were determined in patients undergoing internal DC cardioversion for persistent AF. If a patient required repeat cardioversion for recurrent AF the measurements were repeated at this time. In patients with recurrent AF requiring repeat internal DC cardioversion we demonstrated reversal of atrial electrical remodelling as indicated by an increase in atrial fibrillation cycle length and a prolongation of atrial refractoriness.[47](Dr W. J. C. Hobbs, MD Thesis) As part of this study I measured the coupling intervals of atrial premature beats in the first 2-minutes following cardioversion at the time of the initial cardioversion and again after repeat cardioversion(s). In addition, using the coupling intervals of atrial premature beats detected on

Holter monitoring as an index of atrial refractoriness, I also assessed reversal of atrial electrical remodelling in the initial 72-hours following cardioversion in patients without AF recurrence.

Triggers

In addition to studying the ***'substrate'*** of atrial electrical remodelling the internal DC cardioversion procedure allowed us to closely analyse atrial ectopy following cardioversion to sinus rhythm. Recurrence of AF following DC cardioversion is due not only to the persistence of a suitable atrial substrate (atrial electrical remodelling) but also the triggering effect of premature atrial ectopic beats.[48] It is believed that critically timed premature atrial beats (***'triggers'***) result in AF due to division of the atrial wavefront as it meets areas of atrial refractoriness. If repeated division of the wavefront occurs the result is the formation of multiple wavelets of atrial activation i.e. multiple wavelet reentry. Intracardiac electrogram recordings from the distal poles of catheters placed in the right atrium and coronary sinus allow accurate recording of all atrial ectopy following cardioversion. The coupling intervals of all atrial premature beats were measured for the first 2-minutes following cardioversion. The coupling interval of atrial premature beats in the first 2-minutes following the patients first cardioversion was also assessed as a predictor of the timing and likelihood of AF recurrence.

Further analysis of the intracardiac electrograms recorded following cardioversion found evidence of frequent short-lived episodes of atrial arrhythmia following cardioversion and that some patients were prone to repeated episodes of immediate reinitiation of AF (IRAF). Focal atrial tachycardias have been recognised for many years as a trigger for AF and recently reproducible episodes of IRAF have also been shown to have a focal origin amenable to treatment by radiofrequency ablation.[49] We sought to determine whether there was evidence of focal atrial

arrhythmias, and the significance of such findings, in patients undergoing DC cardioversion of persistent AF.

The final part of the study was to determine whether prolonged periods of AF resulted in changes in heart rate variability following DC cardioversion of persistent AF either by influencing sinus node function or the autonomic nervous system input to the atria. It was postulated that a long period of persistent AF might result in changes in sinus node function secondary to atrial electrical remodelling or that changes in atrial autonomic innervation might occur during AF that could be important in recurrent AF or in the recovery of atrial electrical remodelling following cardioversion. Holter tapes were analysed to determine measures of heart rate variability at various time periods following cardioversion.

1.4 Summary of the thesis

1. Introduction

2. History and Overview of Atrial Fibrillation

3. A New Fully Implantable Goat Model of Atrial Fibrillation

4. The Profibrillatory Action of Verapamil is Not Prevented by Propafenone

5. Repetitive Four-Week Periods of Atrial Electrical Remodelling Promote Stability of Atrial Fibrillation – Evidence for a Second Factor Independent of Atrial Refractoriness in the Self-Perpetuation of Atrial Fibrillation

6. Atrial Ectopy - The Coupling Interval of Atrial Premature Beats Following DC Cardioversion of Persistent AF Predicts Subsequent Recurrence of AF

7. Atrial Ectopy – Evidence for Reversal of Atrial Electrical Remodelling

8. Prevalence and Significance of Focal Sources of Atrial Arrhythmia in Patients Undergoing Cardioversion of Persistent Atrial Fibrillation

9. Changes in Heart Rate Variability Following Cardioversion of Persistent Atrial Fibrillation in Man

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Chapter 2

An Overview of Atrial Fibrillation

2.1 The History of Atrial Fibrillation

2.2 The Mechanism of Atrial Fibrillation

2.3 Factors Important in Promoting Atrial Fibrillation

2.1 The History of Atrial Fibrillation – from Delirium Cordis to DC Cardioversion

Delirium Cordis

The initial description of atrial fibrillation (AF) was probably given by William Harvey in 1628.[1] In his animal work Harvey noted fibrillatory movement of the right atrium at the time of death. The recognition of an irregularly irregular pulse in humans was first made in 1827 when Adams, using the recently developed stethoscope of Laénnec, described it as a sign of mitral stenosis. At this time AF was termed 'delirium cordis'. Further observations of the clinical characteristics of AF were made by Hope in 1839 when he noted that on exercise the irregularity of the pulse was increased. The first recording of AF was a pulse tracing by Marey published in 1863 from a patient with mitral stenosis and AF. In the late 19th century James McKenzie, a Scottish general practitioner working in Burnley, using an ink-writing polygraph to record jugular venous pulses made important observations in patients with AF.[2] He noted the loss of the 'a' wave in patients who changed from a regular to an irregular pulse, but initially attributed this to a change from sinus rhythm to an atrioventricular nodal rhythm.[3] He was later to recognize that the underlying aetiology for the loss of the 'a' wave was the onset of auricular fibrillation when shown electrocardiographic tracings by Thomas Lewis. The initial link between the clinical finding of AF in humans (delirium cordis) and experimental AF in animals was made by Arthur Cushny[4] when he noted the similarity of pulse tracings from a dog with auricular fibrillation and a lady with 'delirium cordis' and suggested that the two conditions may be the same.

The single most important breakthrough in recording AF came with the development of the string galvanometer and the recording of the first electrocardiograms (ECG) by Einthoven in 1900. Thomas Lewis then went on to record an ECG of AF in 1909[5] and did initial work on the mechanism of the arrhythmia. His conclusion that the irregular pulse

observed in patients with mitral stenosis was due to AF was based on a mixture of clinical and experimental evidence.[6] He noted that the irregular pulse was reproduced by experimentally induced AF, that electrocardiograms from patients with AF showed fibrillation waves between QRS complexes and that if a regular pulse returned these disappeared (probable paroxysmal AF), and finally that the 'a' wave of venous flow was lost in patients with AF. At around the same time in Vienna, Rothberger and Winterberg published electrocardiograms from patients with 'pulsus irregularis perpetuus' observing the irregular nature of the QRS complexes, absence of 'P' waves and the presence of fibrillatory waves.[7]

Pharmacological Therapy

The recognition of atrial fibrillation then led to interest in its treatment. It is likely that the first description of successful therapy for AF was the description in 1785 by William Withering of the therapeutic properties of the foxglove plant (Digitalis pupurea). The improvement in cardiac failure likely represented improved rate control of the ventricular response in AF, although this was not appreciated at the time. Wenkebach made the first description of pharmacological cardioversion of AF to sinus rhythm with quinine in 1914.[8] Frey extended this work and found that quinidine, an isomer of quinine, was the most effective of the cinchona alkaloids in converting AF.[9] Drury, a pupil of Lewis, reported results from a series of patients undergoing pharmacological cardioversion at University College Hospital, London in 1921.[10] In this paper cardioversion of AF to sinus rhythm using oral quinidine was achieved in 6 of 13 cases. The authors showed slowing of the fibrillatory rate by carefully recording serial ECGs. The risk of conversion to flutter with 1:1 ventricular conduction, due to the associated anticholinergic actions of quinidine, was also appreciated. In an accompanying editorial[11] Thomas Lewis goes on to explain that the action of quinidine is dependent on its prolongation of the atrial refractory period. He also notes the slowing of conduction velocity by quinidine and

comments that this will favour reentry. Although at this time Lewis believed AF to be due to a single wandering wavelet with a random path (thus distinguishing it from flutter where the path of the wavelet is constant, see Figure 2.3) his understanding of the underlying electrophysiological mechanisms for persistence of re-entry was remarkable. Following the early descriptions of efficacy the use of quinidine entered into clinical practice. Initial enthusiasm was followed relatively quickly by disappointment when the risk of serious adverse effects and the frequency of relapse in unselected cases was realised. With further experience the choice of patients where the danger is least and the potential for benefit greatest established a clinical role for quinidine in chemical cardioversion of AF,[12] a similar scenario to the adoption of focal AF ablation in the 21st century.

DC Cardioversion

The most important advance in the management of AF came when Lown described DC cardioversion in the 1962.[13] Interest in the use of DC cardioversion for AF followed the refinement of cardioversion for life threatening ventricular arrhythmias. The first description of electrical cardioversion of ventricular fibrillation (VF) was a successful AC cardioversion in 1956.[14] AC cardioversion was then used for drug resistant ventricular tachycardia but was associated with a high risk of proarrhythmia and the development of VF. The advent of DC cardioversion allowing synchronization of the shock to the R-wave so reducing the risk of provoking ventricular fibrillation extended the use of DC cardioversion to non-life threatening cardiac arrhythmias such as AF. The first experience of DC cardioversion in AF was in 10 patients undergoing mitral valvotomy and 2 patients with mitral regurgitation and AF resistant to cardioversion with quinidine.[13]

Reports from the UK of the successful use of DC cardioversion of AF soon followed. In 1964 McDonald and coworkers[15] reported successful

DC cardioversion of 43 of 50 patients resistant to quinidine, illustrating the superior efficacy of electrical cardioversion to chemical cardioversion. An appreciation that, as with pharmacological cardioversion, recurrence of AF following DC cardioversion was also a problem was highlighted by Oram et al[16] who reported successfully cardioverting 84 of 100 patients, but with recurrence in 44 cases. They noted that younger patients tended to have a better outcome. Other authors found evidence for reduced risk of recurrence in patients with a short duration of AF[17] and in patients with 'lone' AF.[18] Patients with significant left atrial enlargement were also shown to have a higher risk of recurrent AF.[19] With the appreciation of the significant chance of recurrent AF following cardioversion studies on the role of drug therapy in maintaining sinus rhythm soon followed. Quinidine was shown to result in a longer duration of sinus rhythm than placebo[20] but recurrence was still common in both groups. Since the 1970's there have been many studies on DC cardioversion of AF, but to this day we have still not found a reliable way to maintain sinus rhythm following cardioversion.

2.2 History of Theories on the Mechanism of Atrial Fibrillation

Throughout the latter part of the 20th century the *'multiple wavelet'* hypothesis developed by Moe in 1962[21] and confirmed experimentally by Allessie in 1985[22] was the generally accepted hypothesis to explain the underlying mechanism of AF. Prior to Moe's landmark work, however, there had been two schools of thought on the underlying mechanism of AF: the *circus movement theory* and the *ectopic focus theory*. Following the description of focal AF by Haissaguerre and coworkers[23] the debate as to the underlying dominant mechanism in AF has again arisen.

Circus Movement Theory

Workers in the UK primarily supported the circus movement theory. In 1906 Mayer demonstrated circus movement in a ring of paralysed jellyfish tissue. Once stimulated a circulating contraction could continue for days.

Inspired by this work Mines repeated the findings in ring preparations of tortoise atrium. Mines recognized that the circulating excitation was dependent on the combination of a short refractory period and slow conduction.[24] (Figure 2.1) Garrey[25] then went on to demonstrate the importance of tissue mass in the process of fibrillation. Using fibrillating turtle ventricle he noted that when the ring size was reduced from 2cm diameter to 1cm diameter the incoordinate fibrillatory contractions organized into a single circus wave of contraction. Garrey realized that multiple circus movements (multiple wavelets) could exist in the larger tissue masses thereby giving the appearance of fibrillation and correlated this with an observation that large hearts were more likely to fibrillate. (Figure 2.2) Extending the findings of Mines and Garrey, Sir Thomas Lewis[26] went on to induce experimental atrial flutter in dogs and demonstrate that the arrhythmia was due to a single re-entrant circuit around the caval veins. Following this he determined that the atrial activation pattern in human atrial flutter was similar to that observed in dogs by studying the electrical axis of the atria.[27] Lewis believed that fibrillation was also due to a circus movement but one where the circulating wave does not run a constant course. (Figure 2.3)

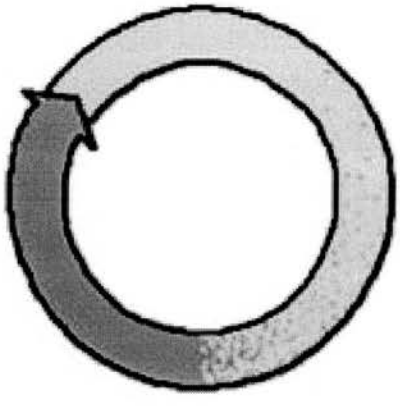


Figure 2.1 Illustration of anatomical re-entry. The light grey area indicates excitable myocardium and the dark grey area indicates the atrial wavefront with its non-excitable tail. If the conduction velocity is fast the wavefront will catch its own tail and be extinguished. If the refractory period is long the myocardium will not have recovered excitability by the time the wavefront next arrives, excitation will not occur and the wavefront will die out. Therefore re-entry in a ring of tissue of a certain size is dependent on a slow conduction velocity and/or a short refractory period.

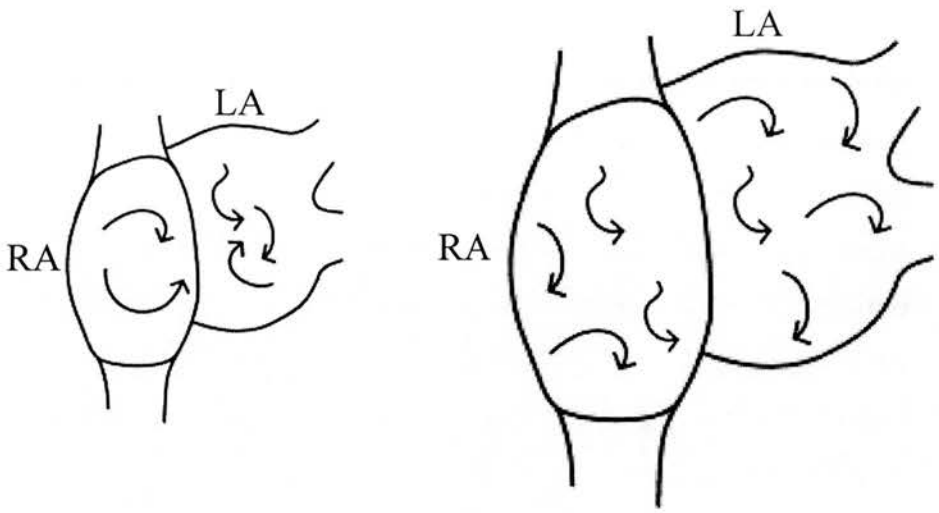


Figure 2.2 Illustration of the importance of atrial size. For a given atrial wavelength (as indicated by the length of the arrows) more wavelets of excitation can exist in the larger atria on the right. RA – right atrium, LA – left atrium.

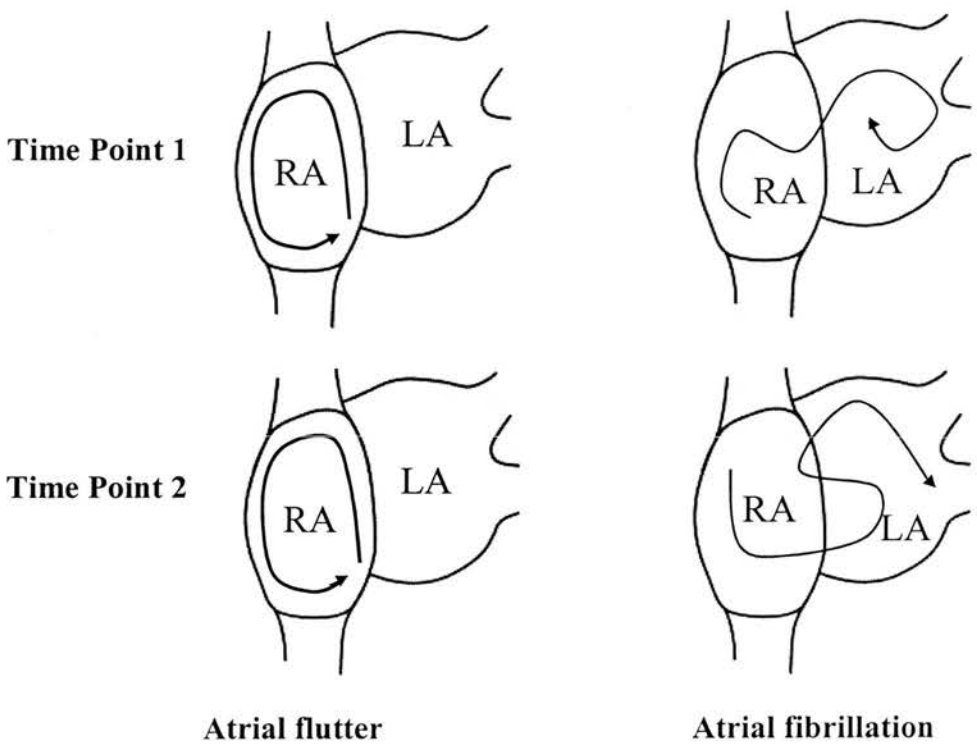


Figure 2.3 The mechanism of atrial fibrillation as proposed by Thomas Lewis. The pathway of electrical activation of the atria is constant in atrial flutter, indicated by identical diagrams at time points 1 and 2. In atrial fibrillation Lewis proposed that the single wave of atrial excitation had a random coarse resulting in the fibrillatory waves on the ECG. This is illustrated by the difference between time points 1 and 2 in the diagrams on the right.

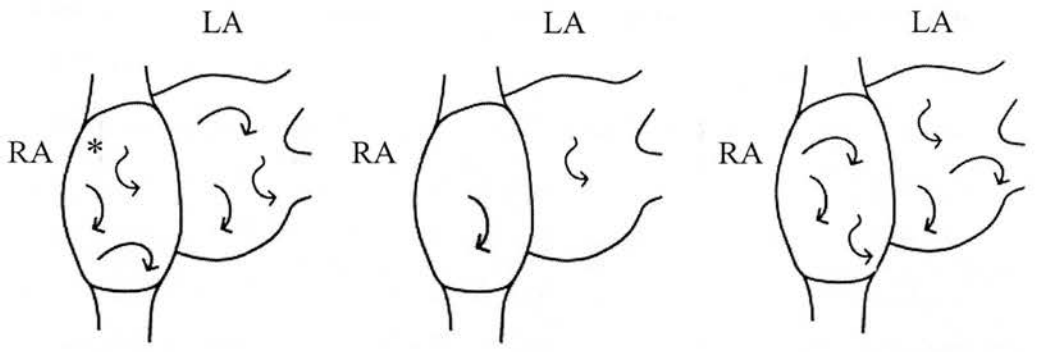
Ectopic Focus Theory

The ectopic focus theory had its origins in Germany. Engelmann first proposed the theory in 1896 and further work by Scherf in 1947[28] led him to support the ectopic focus theory and strongly oppose the circus movement theory. Scherf found that after he injected aconitine into the atrial wall rapid irregular activation of the atria occurred that disappeared when the area injected with aconitine was cooled and reappeared when cooling was interrupted. He concluded that fibrillation was initiated by rapid impulse formation in a single centre.[29] The work of Gordon Moe[30] in the late 1950's and his formulation of the 'multiple wavelet hypothesis' in the early 1960s[21] resulted in the ectopic focus theory being disregarded. However, it has returned to prominence in the last few years following the work of Haissaguerre[23] and others on the pulmonary vein initiation of AF.

Multiple Wavelet Hypothesis

Moe was the first to link the ectopic focus and circus movement theories into one experimental model. Although both theories had a sound experimental basis, Moe believed that neither could result in the sustained arrhythmia of AF. His experimental work on dogs[30] led to an understanding of the importance of factors for both 'triggering' and 'perpetuating' AF. Using an open chest dog model he induced AF by either rapid atrial pacing or aconitine injection in the right atrial appendage. AF persisted as long as rapid atrial pacing was continued. Following aconitine injection AF persisted until the base of the right atrial appendage was clamped off. If vagal stimulation was applied AF persisted when atrial pacing was discontinued or a clamp applied to the base of the right atrial appendage. In the absence of vagal stimulation the induced fibrillation was non-sustained (Figure 2.4). Moe had demonstrated that AF could be a self-sustaining arrhythmia independent of focal discharge, and he emphasised the importance of dispersion of atrial refractoriness induced by vagal stimulation for the maintenance of AF. Based on this experimental work Moe and colleagues developed a computer model of

AF which showed that self-sustained atrial electrical activity could be induced.[31]



A. Rapid right atrial pacing / aconitine injection. * site of pacing / injection

B. Cessation of rapid right atrial pacing / clamping of site of aconitine injection in the absence of vagal stimulation

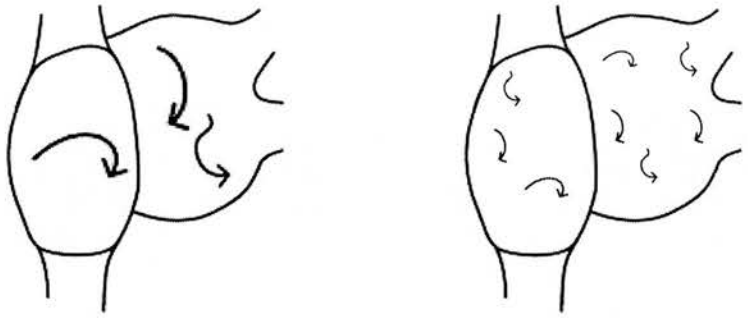
C. Cessation of rapid right atrial pacing / clamping of site of aconitine injection with continued vagal stimulation

Figure 2.4 Illustration of Moe's experimental work.[30] In panel **A** rapid right atrial pacing or aconitine injection (*) results in focal activation of the atria with fibrillatory conduction. Panel **B** illustrates the situation following cessation of pacing or clamping of the aconitine injected area. In the absence of vagal stimulation the wavelets die out. Sinus rhythm will soon resume. Panel **C** shows the situation following cessation of pacing or clamping of the aconitine injected area in the presence of vagal stimulation. AF persists as long as vagal stimulation continues.

It took a further 25 years to confirm Moe's computer model experimentally. Allessie and coworkers studying AF induced by acetylcholine in isolated Langendorff perfused canine hearts were able to record the atrial activation pattern during AF.[22] By recording simultaneously from 192 electrodes they were able to reconstruct the atrial activation pattern during sustained AF. Allessie showed that the atria were activated by multiple wavelets which behaved in a random fashion, occasionally meeting another wavelet and extinguishing themselves and at other times dividing into daughter wavelets. He concluded that between three and six wavelets were required over the atria to result in stable AF and also noted that the stability of the induced AF was inversely related to the number of wavelets. Subsequently experimental work in dogs[32] and

intra-operative mapping studies in patients[33] have also supported Moe's hypothesis.

The importance of a short atrial wavelength for the maintenance of AF has been understood since the observations of Thomas Lewis in the early 1920s. With a shorter wavelength more wavelets may co-exist in atria of any size and the more likely AF is to be sustained[34] (Figure 2.5). Atrial wavelength is the product of the conduction velocity and the refractory period. Thus either slowing of atrial conduction or shortening of atrial refractoriness will result in a reduction in atrial wavelength and an increase in AF stability. It is on this basis that the process of atrial electrical remodelling[35] with its associated shortening of atrial refractoriness has such a strong theoretical basis for being important in the self-perpetuation of AF.



A. Longer wavelength **B. Shorter wavelength**

Figure 2.5 Illustration of the importance of atrial wavelength on the perpetuation of AF. It can be seen that with a shorter wavelength (B) many more wavelets of excitation may coexist in atria of a given size, compared to the longer wavelength (A), thus promoting the maintenance of AF. The atrial wavelength may be reduced by slowing conduction velocity or shortening atrial refractoriness.

Reentry

The onset and maintenance of AF depends on the production of stable multiple wavelet reentry in atrial tissue. This in turn is determined by a combination of the atrial wavelength and the available size of the atrial

tissue. Until recently it was considered that two forms of reentry predominated in AF.

(1) Anatomical reentry occurs following unidirectional block of an extrastimulus, and is sustained around an anatomical barrier, such as the orifice of a pulmonary vein or an atrioventricular valve ring (Figure 2.1). It persists as long as the length of the excitation wave is shorter than the anatomical path around which it runs. The difference in this length makes up the excitable gap.

(2) Functional reentry occurs in the absence of an anatomical barrier. This was demonstrated by Allessie in a preparation of rabbit atrium[36,37] where excitation waves were seen to circulate around areas of functional conduction block. The induction of functional reentry is dependent on heterogeneities of the electrophysiological properties of cardiac muscle resulting in unidirectional conduction block. In functional reentry there is no excitable gap and the size of the circuit is equal to the length of the excitation wave. In the context of persistent AF both types of reentry are likely to be important.

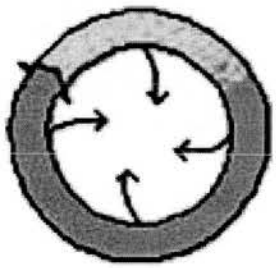


Figure 2.6 Illustration of functional reentry. The circuit passes around an area which remains refractory at all times, due to the collision of centripetal wavefronts from the circuit. The excitation wavelength (dark grey) is approximately equal to the length of the circuit.

More recently another form of reentry, called spiral waves, has been described. Spiral waves represent a form of functional reentry, but without centripetal activation of the central area. They have been demonstrated in experiments in isolated hearts[38,39] to exist as self-sustaining rotors that cause high-frequency activation of the atria. These rotors predominately exist in the posterior left atrium, are stable and can have a very short wavelength (~70ms). The remainder of the atria are activated by

fibrillatory conduction with some degree of organisation. It has been proposed that spiral waves are important in the maintenance of AF and that the left atrium, as the source of these waves, acts as the predominant driver of AF.

2.3 Factors Important in Promoting Atrial Fibrillation

In accordance with Moe's multiple wavelet hypothesis[21,31] of AF the inducibility and stability of AF are dependent on at least 3 factors:

(1) atrial wavelength (refractory period x conduction velocity)

(2) atrial size (atrial surface area),

(3) dispersion of atrial refractoriness

Clinical and experimental work has shown that in addition to these important determinants of AF the autonomic nervous system, localised abnormalities of atrial conduction and atrial ischaemia may also play a role in the onset and maintenance of AF.

Reduced Atrial Wavelength

As discussed above, during AF the atria are activated by multiple reentrant circuits (the multiple wavelet hypothesis).[22,31] The stability of AF is related to the number of wavelets of activation that can exist simultaneously in the atria. The shorter the atrial wavelength the more wavelets will be able to coexist in a defined area of atrium. Therefore a shorter wavelength will result in a larger number of wavelets so reducing the chances of all the wavelets simultaneously dying out, and increasing the stability of AF. Based on the experimental work of Allessie,[22] the number of wavelets required to maintain stable AF is felt to be somewhere between three and six.

The atrial wavelength (WL) is the product of the conduction velocity (CV) and the refractory period (RP). (WL = CV x RP) Factors, which reduce either of these, will also reduce wavelength and hence promote AF (Figure 2.5). It is reasonable to suppose that a reduction in atrial wavelength might be the 'final common pathway' for factors that promote AF.

(i) Atrial Refractory Period

The link between short atrial refractory periods and clinical AF is well established. As early as 1971 Olsson et al[40] demonstrated short

monophasic action potentials in patients immediately after cardioversion of AF. These results were confirmed by Cotoi et al[41] who also noted a correlation between the duration of the monophasic action potential and the risk of AF recurrence. These results were not expanded upon till about 20 years later when Kumagai showed atrial refractory periods to be shorter following cardioversion of persistent AF.[42] Abnormalities of atrial refractoriness were also found in patients with a history of paroxysmal AF, with some authors finding shorter atrial refractory periods[43] and others a shorter atrial fibrillation cycle length during AF.[44]

Experimental work has shown that with rapid atrial pacing rates there is shortening of atrial refractoriness[34,45,46] and an increase in atrial vulnerability to AF. Vagal stimulation,[45,47,48] acetylcholine[49,50] and adenosine[51,52] are all known to have profibrillatory effects on the atria, which are thought to be mediated via shortening of atrial refractoriness.

The most important study linking changes in atrial refractoriness with AF was that published by Wijffels in 1995.[35] Using a conscious goat model implanted with epicardial electrodes these authors continually reinduced AF using a personal computer capable of detecting sinus rhythm and delivering a 1-second 50Hz burst of atrial pacing. Over the first few days of AF reinduction they noted shortening of atrial refractoriness and loss of its normal adaptation to rate followed by an increase in the stability of induced AF episodes. They described this domestication of AF as 'AF begets AF'. The shortening of atrial refractoriness leading to a shortening of the atrial wavelength made good theoretical sense as a process whereby AF could promote its own sustenance. The process was termed atrial electrical remodelling. This introduced the concept that AF itself could alter atrial electrophysiology to promote its own maintenance.

Abnormalities in atrial refractoriness that predispose to AF are not confined to shortening of the atrial refractory period. Nearly 20 years ago

Attuel and coworkers[53] measured the atrial refractory period in patients at cycle lengths of 280-1500ms. They showed that loss of the normal physiological rate adaptation of atrial refractoriness was associated with an increased vulnerability to AF. Boutjdir[54] also found impaired rate adaptation of atrial refractoriness in his microelectrode studies of isolated strips of human atrium from patients with AF. The finding that loss of rate adaptation of atrial refractory periods is an integral part of atrial electrical remodelling supports the importance of these early findings.

(ii) Atrial Conduction Velocity

(a) Interatrial conduction velocity – a link between reduced atrial conduction velocity and AF is well established. Atrial conduction velocity is reduced in patients following DC cardioversion of persistent AF.[42,55,56] These patients also show a prolonged P-wave duration.[42,56] Patients with paroxysmal AF appear to show conduction abnormalities intermediate between control patients and patients with persistent AF suggesting some progression of conduction velocity abnormalities in the transition from paroxysmal to persistent AF.[55] The recovery of changes in atrial conduction velocity following cardioversion of persistent AF is significantly longer than the time course for recovery of atrial refractoriness.[56,57]

Canine models of AF using sustained rapid atrial pacing have shown slowing of atrial conduction velocity, suggesting an AF-induced reduction in conduction velocity may contribute to the self-perpetuating process.[58-60] The underlying mechanism for the slowing of conduction velocity may be a reduction in the fast Na current.[61] Goats studies, however, using the fibrillation pacemaker have not shown significant changes in conduction velocity in association with the onset of AF.[35,62]

Studies of patients in sinus rhythm have demonstrated reduced atrial conduction velocity at rapid pacing rates,[63] which in combination with the

shorter atrial refractoriness induced by rapid pacing, results in a significantly shorter atrial wavelength and an increased vulnerability to AF. Reduced conduction velocity at rapid atrial pacing rates has also been shown in isolated rabbit atria[45] and in conscious dogs.[34] The introduction of premature atrial extrastimuli results in conduction velocity delay which is more pronounced in patients with a history of atrial arrhythmias compared to controls and may create an electrophysiological substrate for the onset of AF.[43,64]

(b) Local conduction abnormalities - Local conduction disturbances in the atria also appear to be important in AF. A recognised manifestation of local conduction delay is fragmentation of local electrograms.[65] Delayed atrial conduction[66] and fragmented electrograms[67] have been demonstrated in patients with atrial flutter. In addition fractionation of ventricular electrograms has been linked to an increased risk of primary ventricular fibrillation[68] and ventricular fibrillation in association with hypertrophic cardiomyopathy.[69] Increased fragmentation of local atrial electrograms has been demonstrated following cardioversion of persistent AF [42] and in patients with paroxysmal AF.[70-72] More recently fragmentation of atrial electrograms has been shown in several areas of the right atrium in patients with AF and atrial flutter.[73] There is also some evidence that local conduction delays, as shown by marked broadening of the posterior triangle of Koch electrogram, are dependent on the site of stimulation and are more prominent in pacing from the high right atrium than the coronary sinus.[74] The mechanism by which biatrial pacing prevents AF may be by reducing such local conduction delays.[75]

Local conduction disturbances can also be produced by vagal stimulation,[76] rapid atrial pacing[77] and hypoxia[78] all of which have been shown experimentally to promote AF. In addition to primary electrophysiological changes in the atria, it has been postulated that progressive atrial fibrosis with increasing age is associated with

inhomogeneity of atrial conduction and may be responsible for the observed increase in the incidence of AF in the elderly.[79,80]

Increased Atrial Size

The recognition that fibrillation was more stable in larger masses of tissue was first made by Garrey in 1914.[25] He recognised that reducing the size of the tissue mass (turtle ventricle) eventually led to abolition of fibrillation. It took many years for any advances to this piece of work. In the early 1960's West et al[81] repeatedly divided segments of rabbit atria to determine the minimum tissue mass required to maintain AF. In vivo the induction of experimental AF is easier in larger dogs,[82] and spontaneous chronic AF is more common in the larger breeds than smaller ones.[83] Experimentally induced AF is significantly more stable in animals with larger atria,[84] with AF durations in some adult cattle persisting for up to 8 weeks whereas in calves and goats AF durations were generally less than a minute.

We understand from Moe's multiple wavelet hypothesis[21] that the stability of AF is related to the number of wavelets that can be present simultaneously in the atrial wall. A short wavelength, as already discussed, will allow more wavelets in a defined area, but an increase in atrial size will also result in an increase in the number of wavelets (Figure 2.2). The increase in atrial refractory period and conduction velocity in larger animals is relatively small compared to the increase in atrial area thus explaining their increased propensity to AF. Rensma[34,85] calculated the number of wavelets that might coexist in different species according to atrial wavelength and the atrial surface area. The shortest atrial wavelength obtained by extrastimuli in rabbits is about 3.5cm, 8cm in dog, 12cm in man, 30cm in horse and 45cm in whale. The comparable atrial surface areas show a much larger increase from $3cm^2$ in the rabbit increasing to $35cm^2$ in dogs, $60cm^2$ in man, $300cm^2$ in horses and $3000cm^2$ in whales. This means that in rabbit atria a maximum of 3 wavelets may coexist, not

enough to sustain AF. In dog and in man this increases to 5-6, to 10 in horses and 19 in whales. Allessie[22] suggested that a minimum of 4-6 wavelets are required for sustained AF. These findings relate closely to observed practice where AF is short and non-sustained in rabbit atria[86] but can occur spontaneously and persist in both dog[83] and man.[80] AF is also seen frequently in larger animals such as cattle[87,88] and horses.[89]

There is a clear relationship between atrial dilatation and AF, but there has been debate about whether the observed atrial dilatation in patients with AF is a cause or a consequence of the AF.[19,90-94] Data from the Framingham study showing a strong association between left atrial dilatation and the subsequent onset of AF (with a risk factor of 8.3 in men and of 15.3 in women).[79] Patients with mitral valve disease can remain in sinus rhythm despite left atrial dilatation but most eventually develop AF strongly suggesting that left atrial dilatation is a significant risk factor for development of AF.[92] Cardioversion of persistent AF in patients with atrial dilatation is less successful and relapse into AF more common.[19,95,96] The induction of AF in the experimental setting is enhanced by atrial dilatation (induced by volume expansion or mitral insufficiency) in otherwise normal hearts.[33,97-99]

There is also evidence that atrial fibrillation itself causes atrial dilatation. Induction of experimental AF by rapid atrial pacing leads to atrial dilatation in dogs.[100] Patients with 'lone' AF when followed by echocardiography have been shown to develop progressive atrial dilatation.[101] Further evidence for AF itself as a cause of atrial dilatation is the reduction in left atrial size observed following cardioversion of persistent AF,[102] and also in the reduction in left atrial size noted in patients using the implantable atrial defibrillator.[103] The relationship between AF and atrial dilatation appears to be reciprocal – both promote each other.

It has been proposed that atrial dilatation may promote AF by mechanisms other than simply providing a larger atrial surface area for the multiple wavelets. Although there is some discrepancy in the literature most studies have suggested that atrial dilatation alters atrial electrophysiology. Acute atrial stretch induced by an intra-atrial balloon,[97] simultaneous atrial and ventricular pacing[104] or by increased afterload[105] have all been shown to shorten atrial refractoriness. Experimental work using atrial muscle specimens obtained at the time of cardiac surgery[106] has found the action potential duration in chronically dilated atria to be shorter than in non-dilated atria. Voltage clamp studies showed the likely mechanism to be a reduction in L-type calcium current density. Other work has suggested that atrial dilatation may promote AF through an increase in dispersion of atrial refractoriness.[98] Thus atrial dilatation may not act solely as a physical promoter of AF but may also have an electrophysiological action.

Increased Dispersion of Atrial Refractoriness

Inhomogeneity of atrial electrical properties is important both to the induction and maintenance of AF. Conduction block, as occurs when excitation reaches an area of the atrium with a longer refractory period, is important in the division of wavelets of excitation into daughter wavelets,[36] the formation of which are essential in the induction and stability of AF.

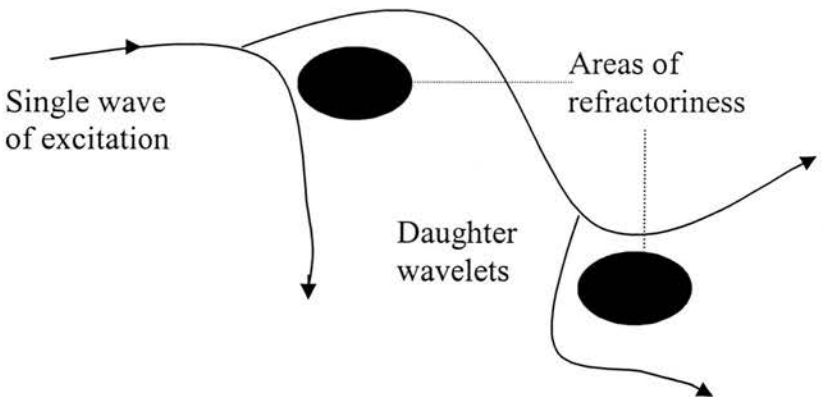


Figure 2.8 Schematic diagram of the formation of daughter wavelets when a single wave of excitation encounters islands of refractory tissue (black ovals).

The importance of areas of conduction block in the initiation of atrial arrhythmias has been shown experimentally. Using isolated canine atria perfused with acetylcholine Schuessler et al[107] showed that initiation of reentry was dependent on the block of premature impulses at areas of functional block that occurred as a result of the cholinergically induced dispersion of atrial refractoriness. Dispersion of atrial refractoriness is also increased at higher heart rates,[108,109] by high vagal tone,[48,110,111] by atrial stretch[98] and by atrial ischaemia.[78] These are all factors recognised as being important risk factors for AF in patients.

Experimental data on changes in dispersion of atrial refractoriness associated with AF have been variable. Studies in the goat model[35,112] found no change in dispersion of atrial ERP. Short durations of rapid pacing in anaesthetised dogs do not alter dispersion of atrial ERP,[113] but longer durations of atrial pacing associated with persistent AF in the canine model result in an increase in dispersion of AF cycle length[58] and an increase in dispersion of atrial ERP.[59,114] There does appear to be a genuine inter-species difference between the goat and dog.

An increase in dispersion of atrial ERP in patients with paroxysmal AF has been recognized for a number of years.[44,115] Increased dispersion of atrial ERP has also been noted in patients with sinoatrial node disease[116] and to be associated with increasing age[117] both of which are strong risk factors for AF. Ramanna et al[118] have shown that patients with paroxysmal AF have an increase in dispersion of AF cycle length during AF compared to control patients and have suggested that this may be the substrate for the enhanced inducibility and vulnerability to AF observed in these patients.

Patients with persistent AF have been shown to have an altered spatial distribution of atrial refractoriness[55,119] compared to controls, but there have not been any studies showing an increase in dispersion of atrial refractoriness. In fact, dispersion of atrial refractoriness has been found to

be lower in patients with chronic AF compared to both patients with paroxysmal AF[120] and patients in sinus rhythm.[119] It may be that loss of the 'normal' spatial dispersion of atrial refractoriness (where atrial refractoriness is longer in the high right atrium near to the sinus node and shorter further away[121,122]) is important in the maintenance of AF.

Our group has found dispersion of atrial fibrillation cycle length to be increased at the time of DC cardioversion in patients who subsequently have recurrence of AF compared to non-recurrers (Dr SP Fynn, MD Thesis). Following a period in sinus rhythm dispersion of atrial fibrillation cycle length has been shown to fall suggesting dispersion of atrial fibrillation cycle length may be linked to atrial electrical remodelling.[123]

The Autonomic Nervous System

There are strong links between the autonomic nervous system and AF. Clinical forms of both vagal and adrenergic paroxysmal AF have been described, the first often occurring at rest or after meals and the latter more often associated with stress or exercise.[124,125] Vagal activity has been used to induce and maintain AF experimentally for many years[22,30,126-128] and is known to shorten atrial refractoriness[34,45,129,130] and thus the atrial wavelength due to a increase in the outward potassium current by activation of the I_{KAch} channel. Vagal stimulation may also promote AF by increasing dispersion of atrial refractoriness.[48,131]

The effects of the sympathetic nervous system are less clear. Although several studies have reported shortening of atrial refractoriness/action potential duration, [49,50,131,132] with sympathetic stimulation or administration of adrenaline/ noradrenaline, others have reported no change,[48,133] or even a prolongation of atrial refractoriness.[45,134] The differing effects seen in these studies may relate to the concentrations of adrenaline/noradrenaline used and/or the differential effects of alpha and beta-adrenergic receptors.[135] There is evidence from studies on ventricular

muscle preparations that the effect of adrenergic stimulation on refractoriness is dependent on the concentration of noradrenaline.[136,137]

More recently interest in the role of the sympathetic nervous system in sustained AF has increased. Olgin and co-workers[138] have shown that heterogeneous atrial sympathetic denervation, resulting in an increase in dispersion of atrial refractoriness, increases the stability of induced episodes of AF in dogs. Further work by the same authors[139] has shown that induction of sustained AF by 6-weeks of rapid atrial pacing in dogs results in a heterogeneous increase in atrial sympathetic innervation, as measured by positon emission tomography (PET) scanning and tissue concentrations of norepinephrine. Other authors have also found significant nerve sprouting and sympathetic hyperinnervation in a canine model of sustained AF produced by prolonged right atrial pacing.[140] Bilateral stellectomy, with resultant homogeneous atrial sympathetic denervation, prevents the induction of sustained AF by rapid atrial pacing suggesting a key role for the sympathetic nervous system in promoting the onset of persistent AF.[141] So despite the lack of a consistent effect of the sympathetic nervous system on atrial electrophysiology the sympathetic nervous system may well have an important role in persistent AF.

Atrial Ischaemia

Ischaemic heart disease (IHD) is known to be associated with AF. In the Framingham study IHD was present in 25% of men and 14% of women who developed AF.[79] AF is observed frequently (~ 10%)[142,143] in the setting of acute myocardial infarction. However, in this setting ischaemia may not be the only factor promoting AF with other factors such as changes in autonomic tone, atrial dilatation due to pump failure or pericarditis also being important. The most compelling evidence for atrial ischaemia / infarction in the onset of AF is suggested by the increased risk of AF associated with myocardial infarction due to occlusion of the proximal circumflex artery compared to more distal circumflex artery

occlusion or occlusion of other arteries at the time of myocardial infarction.[144] In addition, there is an increased risk of perioperative AF at the time of CABG in patients with disease of the sinoatrial or atrioventricular nodal arteries.[145] The exact mechanism whereby atrial ischaemia promotes AF is not understood but ischaemia can cause a shortening of the action potential duration by promoting movement of potassium out of cells,[146] local adenosine release[147] or by increasing local atrial conduction abnormalities.[78] Experimental AF also results in an increase of 2-3 fold in atrial blood flow and oxygen consumption[148] raising the possibility that AF itself may cause atrial ischaemia and so promote its own maintenance.

Conclusions

The induction and maintenance of AF is the result of interplay between a number of factors. Some such as atrial dilatation are likely to have an independent role, whereas others such as the autonomic nervous system and atrial ischaemia are likely to promote AF by altering atrial electrophysiology. The final common pathway for the maintenance of stable AF is likely to be a reduction in atrial wavelength achieved by shortening of atrial refractoriness or a reduction in atrial conduction velocity. The relative importance of each varies from patient to patient illustrating the heterogeneous nature of AF. Therapeutic approaches can vary according to the predominant factors in each patient.

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Chapter 3

Atrial Electrical Remodelling and A New Fully Implantable Goat Model of Atrial Fibrillation

3.1 Atrial Electrical Remodelling
- **Experimental Work**
- **Evidence in Humans**

3.2 Other AF Induced Changes in Atrial Electrophysiology

3.3 Cellular Aspects of Atrial Electrical Remodelling

3.4 A New Fully Implantable Goat Model Of Atrial Fibrillation
Presented at The British Cardiac Society May 2000 Heart 2000:83;Supp 1,22

3.1 Atrial Electrical Remodelling

The Experimental Work

In a landmark experiment Wijffels et al[1] showed that repeated induction of AF in a conscious goat model resulted in the development of persistent AF with time, demonstrating the self-perpetuating nature of AF, and coining the phrase 'AF begets AF'. The induction of AF was accompanied by changes in atrial electrophysiology: a shortening of the atrial effective refractory period (AERP), loss of its normal adaptation to rate and an increased vulnerability of the atria to induction of AF, the combination of which was termed 'atrial electrical remodelling'.

In their study Wijffels et al secured multielectrode patches to the atrial epicardial surface (see Figure 3.1) and tunnelled the wires from these patches to the skin surface. Following a recovery period of 2-3 weeks, the wires were connected to an external pacemaker and AF induction was commenced. The fibrillation pacemaker monitors atrial electrograms and during sinus rhythm detects a period of atrial electrical quiescence. On detection of atrial electrical quiescence (sinus rhythm) a 1-second burst of 50Hz pacing is delivered to the atrium inducing AF (Figure 3.2). During AF the pacemaker detects constant atrial electrical activity and is inhibited. Thus AF can be induced and maintained continuously.

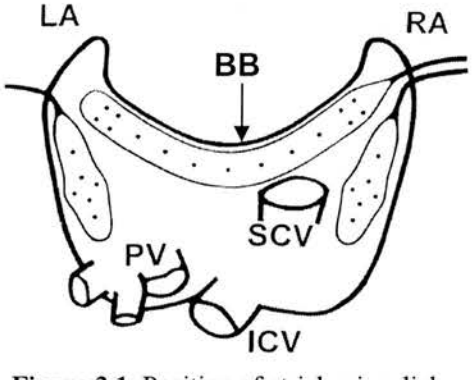

Figure 3.1 Position of atrial epicardial electrodes. LA-left atrium, RA-right atrium, PV-pulmonary veins, SCV-superior vena cava, ICV-inferior vena cava, BB-Bachmann's bundle. *From Wijffels et al, Circulation 1995; 92; 1954-1968*

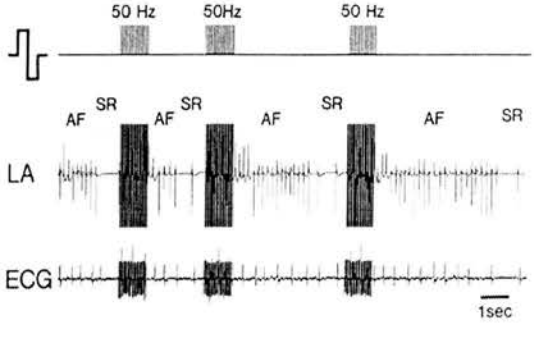

Figure 3.2 Illustration of the fibrillation pacemaker. LA-left atrium, SR-sinus rhythm, AF-atrial fibrillation. *From Wijffels et al, Circulation 1995; 92; 1954-1968*

Using the fibrillation pacemaker Wijffels demonstrated changes in atrial behaviour with repeated episodes of burst pacing. With increasing durations of burst pacing episodes of induced AF lasted for longer periods, finally resulting in the induction of persistent AF (Figure 1.2, P9). Atrial electrophysiology also changed over this time with a reduction in atrial ERP and loss or reversal of its normal rate adaptation (Figure 1.3, P10).

The key features of atrial electrical remodelling:

- Reduction in the atrial effective refractory period.
- Loss/reversal of the normal rate adaptation of the refractory period.
- Increased vulnerability to induction of AF.

The Underlying Mechanism of Atrial Electrical Remodelling

Wijffels et al then proceeded to attempt to define the underlying mechanism(s)[2] of atrial electrical remodelling. Using the same goat model they examined the effects of the autonomic nervous system, atrial ischaemia, atrial stretch and the high rate of atrial electrical activation per se that occurs in AF.

In order to determine whether the autonomic nervous system was responsible for the observed changes in atrial electrophysiology propranolol and atropine were used to block the sympathetic and parasympathetic arms of the autonomic nervous system respectively. No difference in atrial electrical remodelling was found with full autonomic blockade implying that the changes observed were not due to the autonomic nervous system.

Previous work had shown that induction of AF in anaesthetised dogs resulted in a 2-3 fold increase in atrial perfusion and an increase in oxygen consumption of the atrial myocardium.[3] It was postulated that during AF the atria could become ischaemic resulting in opening of ATP-regulated potassium channels, which might lead to a reduction in the action potential duration and so a shortening of the atrial refractory period. In order to test

this hypothesis the ATP-regulated potassium channels were blocked by intravenous administration of glibenclamide. Glibenclamide resulted in an increase in the R-R interval during AF and slightly prolonged the atrial fibrillation cycle length (AFCL), but the mean AFCL was still markedly reduced compared to the non-remodelled goat. It should be noted that the glibenclamide infusion was only commenced following induction of AF and in the presence of established atrial electrical remodelling. Glibenclamide was also administered to 3 goats following DC cardioversion of persistent AF. It had no significant effect on AERP.

In order to simulate the effect of atrial dilatation and/or the increase in atrial pressure that occurs in AF, 0.5-1 litre of colloid was infused into goats under general anaesthesia. The fluid load did not result in change in the atrial refractory period.

To model the high rate of atrial electrical activation that the atria experience in AF the atria were paced at a cycle length of 180ms. This rapid atrial pacing resulted in almost identical changes to the fibrillation pacemaker with shortening of the atrial refractory period and increased inducibility of AF. Wijffels also found that the cycle length of the atrial pacing was important. Pacing the atrium at a cycle length of 360ms did not result in significant changes in atrial refractory period compared to pacing at a cycle length of 180ms. It was therefore concluded that the observed changes in atrial refractoriness are a consequence of the high rate of atrial electrical activation that occurs in AF.

Wijffels also observed changes in the nature of the electrogram during AF with increasing durations of atrial electrical remodelling. Initially the atrial electrograms in AF were organised, but later they became more fragmented and disorganised (Figure 3.3). This coincided with a shortening of the AF cycle length and the atrial refractory period. The greater fragmentation of the atrial electrograms may be due to activation at a single point coming from

more than one direction, which might occur if there is an increased number of wavelets (as could occur with shortening of the atrial refractory period and therefore the atrial wavelength). The persistence of AF was also linked to a reduction in the atrial fibrillation cycle length, especially when this fell below a value of 120ms.

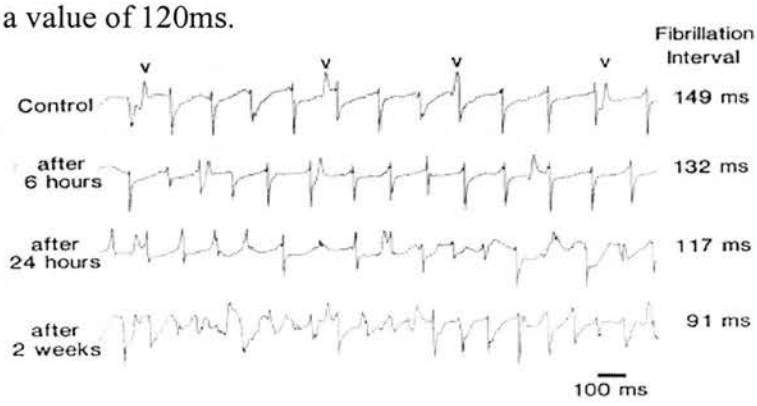

Figure 3.3 Changes in atrial fibrillation cycle length and the organisation of the atrial electrograms over increasing durations of AF. *From Wijffels et al, Circulation 1995; 92; 1954-1968*

Wijffels noted in his initial work that there was a discrepancy between the time course of the onset of stable AF and atrial electrical remodelling. Atrial electrical remodelling occurred quickly following the activation of the fibrillation pacemaker but stable AF often took a further 2-3 days to become established. This observation coupled with the observation that animals with a similar degree of atrial electrical remodelling (as measured by changes in atrial refractory period and the AF interval, Figure 3.4), showed considerable variation in the time to onset of persistent AF (Figure 3.5), suggested the presence of other factors in the onset of stable AF.

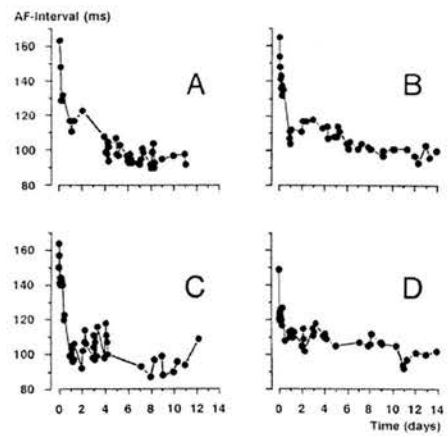

Figure 3.4 Changes in AF cycle length over time. Most reduction occurs in the first 2 days. Note the similarity of all 4 curves. *From Wijffels et al, Circulation 1995; 92; 1954-1968*

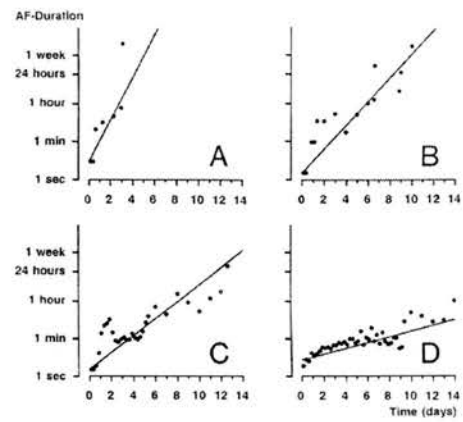

Figure 3.5 Data from the same 4 goats in Figure 3.6. Note the variation in durations of induced episodes of AF, despite the similar changes in AF interval seen in Figure 3.6. Also note the delay in onset of sustained AF. *From Wijffels et al, Circulation 1995; 92; 1954-1968*

Subscquent to the work undertaken in Allessie's laboratory by Wijffels and colleagues there was interest elsewhere in developing an animal model of AF. Morillo et al[4] developed a dog model of AF using rapid atrial pacing (400 beats/min). Using this model persistent AF could be induced in 82% of animals over a period of 6 weeks. In association with the ability to induce persistent AF there was a reduction in atrial refractory period, an increase in atrial vulnerability and enlargement of both atria (Figure 3.6). Nattel's group [5] also developed a rapid pacing dog model of atrial fibrillation. They were interested in assessing the underlying mechanisms that lead to the induction of sustained AF using rapid atrial pacing. They noted that the majority of the change in atrial ERP occurs before AF becomes sustained[5] and that changes in atrial conduction velocity, which occur more gradually, were also important in AF stability with longer periods of rapid atrial pacing.

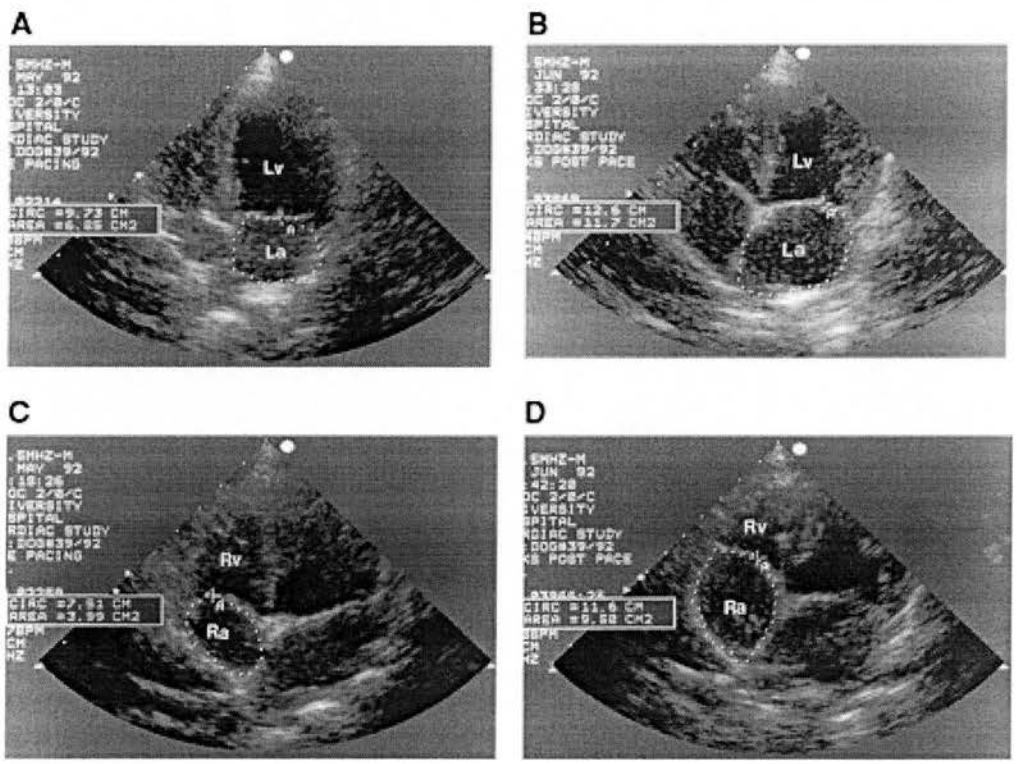

Figure 3.6 Two-dimensional echocardiogram of the dog heart. There is an increase in left (**A** – 6.85cm^2) and right (**C** – 3.99cm^2) atrial areas from baseline to after 6 weeks pacing (**B**-LA 11.7cm^2 and **D**-RA 9.5cm^2). LV – left ventricle, RV – right ventricle. *From Morillo et al, Circulation 1995; 91; 1588-1595*

Morillo and coworkers went on to analyse the structural changes occurring in the atria using electron microscopy. They found changes compatible with a significant perturbation of metabolic activity, with enlarged and disarrayed myocardial fibres and giant mitochondria. Work in Allessie's lab also confirmed these changes in cellular substructure in association with atrial electrical remodelling.[6] Following longer durations of induced AF in the goat model[6] (>9 weeks) the majority of atrial myocytes have marked changes in their cellular substructures, such as loss of myofibrils, accumulation of glycogen, changes in mitochondrial shape and size, fragmentation of sarcoplasmic reticulum, and dispersion of nuclear chromatin. These changes were accompanied by an increase in size of the myocytes (up to 195%). There were virtually no signs of cellular degeneration, and the interstitial space remained unaltered. Many of the changes observed are similar to the changes that occur in the ventricle due to chronic ischaemia causing 'hibernating myocardium'.[7,8] These cellular and structural changes were felt to be important in the atrial contractile dysfunction observed during and soon after atrial fibrillation.

The Role of Calcium

The cellular changes seen to occur with atrial electrical remodelling implied a major disruption to cellular processes was occurring. The importance of calcium influx into atrial myocardial cells as a mechanism for these changes was proposed and several further important studies took place. The role of calcium in atrial electrical remodelling is reviewed in detail at the start of Chapter 4.

Atrial Electrical Remodelling – Evidence in Humans

As early as 1971 Olsson et al[9] demonstrated short monophasic action potentials in patients immediately after cardioversion of AF. These results were confirmed by Cotoi et al[10] who also noted a correlation between the duration of the monophasic action potential and the risk of recurrence of AF. Attuel et al[11] demonstrated that in addition to a shortened duration of the atrial refractory period there was loss of the normal rate adaptation of atrial refractory periods in patients following cardioversion of AF. These early findings illustrated that changes in atrial electrophysiology compatible with atrial electrical remodelling occur in humans. Franz et al[12] measured monophasic action potential durations ($MAPd_{90}$) in patients following cardioversion of chronic AF and chronic atrial flutter and found shortening of $MAPd_{90}$ at longer pacing cycle lengths (>350ms). The finding that $MAPd_{90}$ was reduced in both AF and atrial flutter again suggested that the rapid rate of atrial electrical activation was the underlying cause for atrial electrical remodelling.

Daoud and colleagues[13] first demonstrated the onset and recovery of atrial electrical remodelling in humans. Subjects with no history of AF and without structural heart disease undergoing electrophysiology testing or radiofrequency ablation were studied. Baseline atrial refractory period measurements were made at a drive cycle length of 350ms and 500ms. AF was then induced and maintained for 5 minutes by burst pacing. After 5 minutes AF was allowed to revert spontaneously to sinus rhythm, and measurements of atrial ERP were repeated at the same two cycle lengths. The results showed that even this short duration of AF resulted in a reduction in atrial ERP (Figure 3.7), with an increase in inducibility of AF evident during measurement of the atrial ERP post-AF (Figure 3.8).

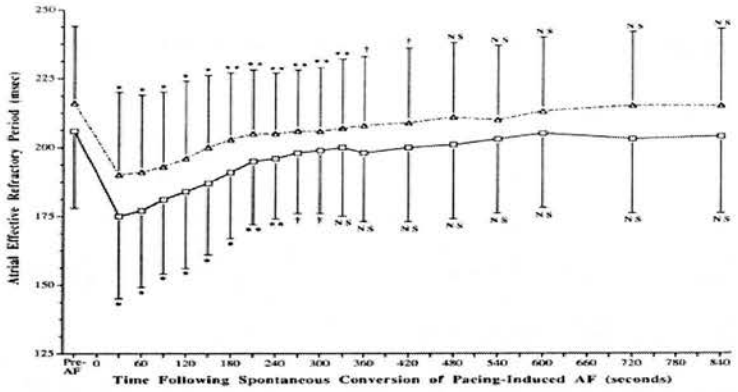

Figure 3.7 Temporal recovery of atrial ERP shortening following 5 minutes of AF. Drive cycle 500ms (Δ) and 350ms (□). Mean values with error bars ± 1 SD. *p<0.001, **p<0.01 v pre-AF ERP. *From Daoud et al, Circulation 1996; 94; 1600-1606*

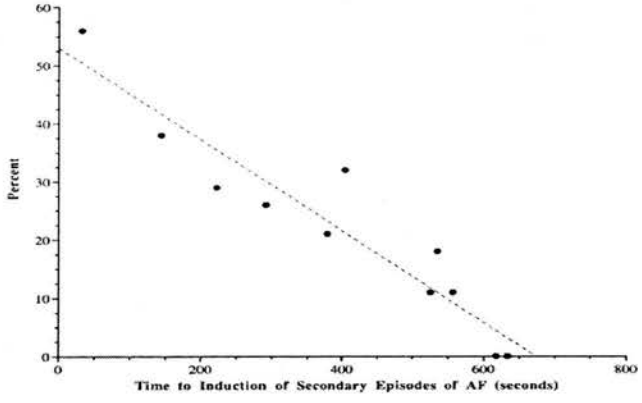

Figure 3.8 Inverse relationship between time to induction of secondary episodes of AF during ERP testing and the percentage of such measurements inducing AF (r = 0.94, p<0.0001). The results from the 350ms and 500ms drive trains are combined. *From Daoud et al, Circulation 1996; 94; 1600-1606*

Daoud and co-workers extended their findings by using the same protocol to study the effects of verapamil and procainamide on atrial electrical remodelling.[14] Pretreatment with verapamil, but not procainamide, resulted in attenuation of acute AF induced changes in atrial electrophysiology. Of note these workers found that verapamil in addition to reducing the shortening of atrial ERP also reduced the inducibility of AF during extrastimulus testing.

Daoud's studies on patients without a history of AF showed that the process of atrial electrical remodelling could occur in humans and that it caused the

same spectrum of changes in atrial electrophysiology as in animals. The time course involved (minutes) however, was quite different to the initial goat studies (hours) suggesting that different mechanisms may be involved.

Studies on patients with AF were the next priority. Two important questions required an answer:

1) Did the changes in atrial electrophysiology observed after cardioversion[9,10,12] represents a cause or a consequence of the AF?
2) and if the changes were a consequence of AF, were they reversible?

These questions were the basis for the serial cardioversion protocol used in our patient study.[15] The protocol is described in detail in Chapter 6. In summary unselected patients with persistent AF were internally cardioverted. Electrophysiological parameters including AF cycle length, atrial refractoriness and the coupling interval of atrial premature beats occurring immediately following cardioversion were measured. Patients with recurrent AF were admitted as quickly as possible following detection of AF recurrence for repeat internal cardioversion. The aforementioned electrophysiological parameters were again measured. Comparison was made between the electrophysiological parameters at the time of initial cardioversion and at the time of the second cardioversion following a period of sinus rhythm or 'reverse remodelling'.

3.2 Other AF induced changes in atrial electrophysiology

Dispersion of Atrial Refractoriness

In his initial studies, Wijffels[1] found that changes in atrial refractoriness and atrial fibrillation intervals were similar in both atria with no evidence of an increase in dispersion of atrial refractoriness. This has been verified in subsequent work on atrial electrical remodelling in the goat model.[16,17] Results from canine models of AF have shown an increase in dispersion of atrial refractoriness in association with atrial electrical remodelling.[18,19] Following 24 hours of rapid atrial pacing (400/min), epicardial mapping

using multiple electrodes (mean of 66 per dog) was used to determine the regional variability in atrial ERP.[19] Rapid pacing for 24 hours resulted in a reduction of atrial ERP and an increased dispersion. In addition to the major regional differences observed variability of atrial ERP within each area was also increased. In this dog model of AF rapid atrial pacing causes a nonuniform shortening of the atrial ERP both between and within different atrial regions. Fareh and colleagues[19] also assessed atrial vulnerability to AF in their model. They found that atrial vulnerability was most strongly linked to ERP heterogeneity, rather than the shortening of atrial ERP or atrial wavelength.

An increase in dispersion of atrial ERP in patients with paroxysmal AF was first recognized a number of years ago.[20] Dispersion of atrial refractoriness was also found to be increased in atrial tissue obtained at the time of cardiac surgery from patients with AF.[21] Increased dispersion of atrial ERP has also been noted in patients with sinoatrial node disease[22] and to be associated with increasing age,[23] a possible mechanism for the increasing incidence of AF with age. More recently Ramanna et al[24] have shown that patients with paroxysmal AF have an increase in dispersion of AF cycle length compared to controls and have suggested that this represents a mechanism of increased atrial vulnerability in these patients. Paradoxically recent studies of dispersion of atrial ERP in patients with chronic AF have given different results to those above, with either no increase in dispersion[25] or lower dispersion in AF patients than controls.[26] Although Pandozi[27] noted a significant dispersion of right atrial ERP following cardioversion of persistent AF he did not compare these findings to control patients. Our own group has found that dispersion of AF cycle length is higher in patients with recurrent AF following DC cardioversion, and that following a period of sinus rhythm dispersion of atrial refractoriness is reduced.[28]

Conduction Velocity

Having found significant changes in atrial refractoriness associated with maintained AF Wijffels[1] went on to study the effects of maintained AF on atrial conduction velocity. Conduction velocity was measured along Bachmann's bundle (the epicardial area of the atrium between the left and right atria – see Figure 3.1). No significant change in conduction velocity was found during the first 4-days of maintained AF although the authors did find that following cardioversion of chronic AF there was a slight slowing of conduction velocity along Bachmann's bundle. Although conduction velocity does not appear to change during maintained AF subsequent preliminary data has reported a link between baseline intra-atrial conduction velocity and the onset of stable AF.[29] Changes in connexin40 distribution have been found in goats with persistent AF,[30] but these do not result in significant changes in conduction velocity. The time course of change in connexin40 distribution has been shown to run in parallel with the development of persistent AF, but the exact electrophysiological mechanism of this effect has not been elucidated.[31]

Unlike the goat model, most studies using the rapid atrial pacing canine model of AF[18,32,33] have shown a significant decrease in conduction velocity, although one group[19] found conduction velocity to increase. The time course of changes in conduction velocity in the dog model of AF is also of interest. Changes in conduction velocity are not apparent during the first week[18,32] of rapid pacing in the canine model but following 6-weeks of rapid atrial pacing conduction velocity is significantly slowed.[18,32] This slower time course of onset of changes in conduction velocity is mirrored by a slower recovery following return to sinus rhythm.[32]

Reduced atrial conduction velocity[25,34,35] and an increased P-wave duration[34,35] have been demonstrated in patients with chronic AF immediately post-cardioversion. The time course of onset of changes in conduction velocity is unknown in man but the recovery of the slow atrial

conduction velocity and prolonged p-wave duration associated with chronic AF is known to take longer than recovery of atrial refractoriness with no change noted in the initial 4-days following cardioversion.[35] Full recovery of p-wave duration to equal that of control patients does occur by 1-month post-cardioversion.[36]

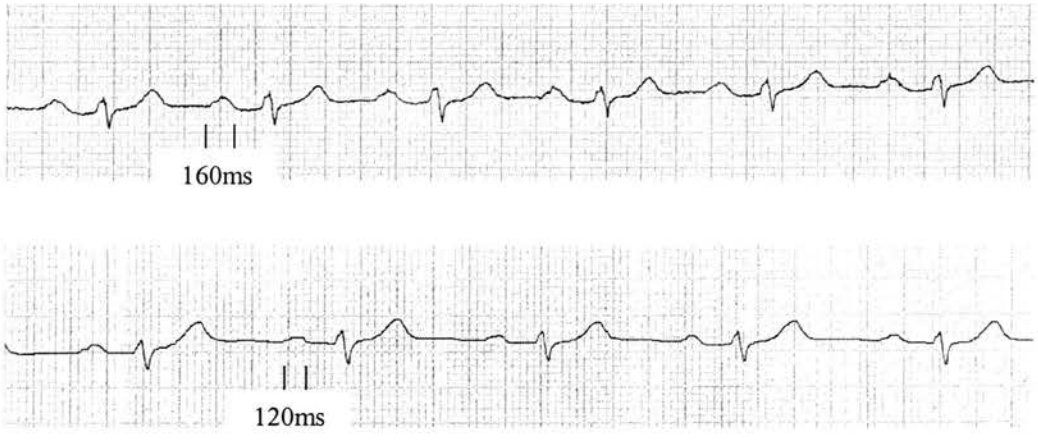

Figure 3.9 Rhythm strips (lead II) from immediately post-cardioversion (top) and following a 6-week period of sinus rhythm (bottom) from a single patient. The mean P-wave duration has decreased from approximately 160ms to 120ms during the 6-weeks.

Conclusions

Atrial fibrillation results in a number of electrophysiological changes that might promote its own maintenance. Atrial electrical remodelling occurs in both animal and human models of AF. There is also evidence that atrial electrical remodelling occurs in patients with AF but it is not clear whether it is a cause or consequence of AF. Changes in atrial conduction velocity occur in the rapid atrial pacing dog model of AF and slowing of the atrial conduction velocity has been demonstrated in humans following cardioversion of persistent AF. The role of changes in dispersion of atrial refractoriness in humans is not clear and further work in this area will be of interest.

3.3 Cellular Aspects of Atrial Electrical Remodelling

The most prominent electrical change associated with atrial electrical remodelling is a reduction in action potential duration. A schematic diagram of the cardiac action potential is shown below. The reduced action potential duration (APD) is due to an imbalance between the inward Ca^{2+} current and the outward K^+ currents. A reduced inward Ca^{2+} current, an increase in the outward rectifier K^+ current or a combination of the two will result in a shortened APD.

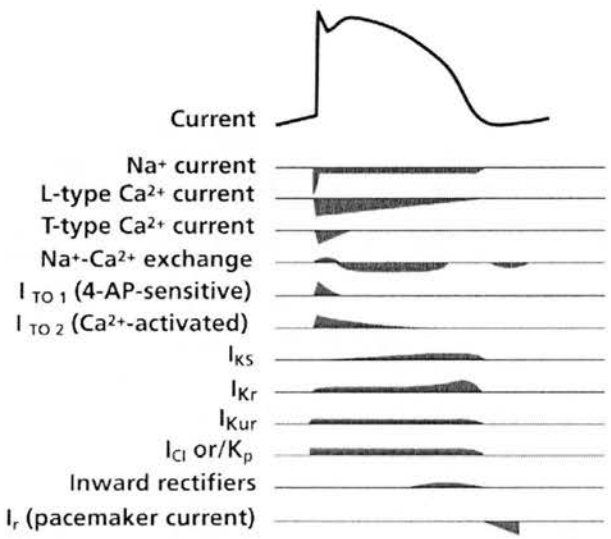

Figure 3.10 Schematic diagram showing pattern of ionic currents in the atrial action potential. *Adapted from Priori SG et al. Eur Heart J 1999;20:P174-95*

Abnormalities of membrane currents in diseased human atrial fibres were first reported in 1976 by Hordof et al.[37] Cells from dilated atria were compared to cells from non-dilated atria and found to have differences in action potential responses. Verapamil was noted to blunt APD only in the cells from non-dilated atria raising the possibility that the cells from the dilated atria already had down-regulation of Ca^{2+} currents. Abnormalities of the Ca^{2+} current in dilated atria were later confirmed by Le Grand and coworkers[38] who found the APD to be reduced and the Ca^{2+} current lower in myocytes from dilated compared to non-dilated atria. These findings

predated the description of atrial electrical remodelling. Following the description of AF-induced atrial electrical remodelling by Wijffels[1] interest intensified in the alterations of ion channel function responsible for the observed changes in atrial electrophysiology.

Animal Data

Various animal models of AF have been used to study the changes in cellular electrophysiology associated with AF. There are important differences in the results of the studies, which probably relate to the different species used and the mechanism by which atrial electrical remodelling is induced (AF v rapid atrial pacing). Nattel's group[39] published the first study of the changes in ionic channels associated with atrial electrical remodelling in 1997. This group uses a rapid atrial pacing (400bpm) dog model of AF to induce atrial electrical remodelling, and have gone on to publish widely on the ionic and molecular changes involved in atrial electrical remodelling. The study protocol involved pacing dogs for 1-day, 7-days or 42-days and comparing them to sham dogs, which have a pacemaker inserted but no rapid atrial pacing. In the study of Yue et al[39] each dog underwent electrophysiological study prior to sacrifice, during which atrial effective refractory period (AERP) and AF inducibility (by 10 Hz burst pacing) were measured. Following the study the animals were sacrificed and single cells were isolated for voltage clamp studies. The electrophysiological study prior to sacrifice showed typical features of atrial electrical remodelling. The inducibility of AF increased with longer durations of rapid atrial pacing. AERP was reduced in all the rapidly paced dogs and also showed reduced rate adaptation. The cellular studies showed the resting membrane potential to be unchanged in the paced dogs. Action potential duration (APD) was reduced for both APD_{50} and APD_{95} in the paced dogs. The associated changes in ion channel function were a progressive decrease in the Ca^{2+}-independent transient outward current (I_{to}) and the L-type Ca^{2+} current ($I_{Ca.L}$) density by about 70%.[39] In the same study the authors noted a number of other currents were unaffected by the 6-weeks of atrial tachycardia including: the inward

rectifier current (I_{K1}), the ultrarapid ($I_{kur.d}$), rapid (I_{kr}) and slow (I_{ks}) delayed rectifiers, T-type Ca^{2+} current ($I_{ca.T}$) and the Ca^{2+}-dependent chloride current.

Having demonstrated a reduction in the Ca^{2+}-independent transient outward current (I_{to}) and L-type Ca^{2+} current ($I_{Ca.L}$) the authors went on to study the effects of drugs on these currents. In order to determine the role of $I_{Ca.L}$ the authors looked at the effects of nifedipine and Bay K 8644 on action potential duration. Nifedipine, a calcium channel blocker, significantly reduced APD in sham dogs, but had little effect on the APD in dogs paced for 6-weeks. The use of Bay K 8644, a calcium agonist, restored a plateau phase to the action potential in cells from paced dogs. These results suggest that changes in the L-type Ca^{2+} current are responsible for the shortening of the APD. To study the effects of I_{to} the authors studied the effect of 4-aminopyridine (4-AP) on the APD of non-remodelled atrial myocytes. Low doses of 4-AP result in inhibition of the $I_{kur.d}$ current but not the I_{to} current. At low doses 4-AP (inhibition of $I_{kur.d}$ only) raised the plateau of the action potential but did not alter APD. Higher concentrations of 4-AP (inhibition of $I_{kur.d}$ and I_{to}) resulted in a reduction in APD, due to an accelerated phase-3 repolarisation. A reduction in APD with reduced I_{to} was not expected and therefore the effect of 4-AP on APD in the presence of nifedipine (to mimic the effect of the combined reduction in ion currents as occurs in remodelled atria) was tested. In this setting 4-AP caused only a mild prolongation of APD, suggesting that the reduction in I_{to} is much less important than the reduction in $I_{Ca.L}$ as the mechanism underlying the reduced APD in AF. In addition to the experimental evidence above, mathematical models[40] of the action potential suggest that changes in $I_{Ca.L}$ are important in the reduction of APD and AERP observed in the setting of atrial electrical remodelling.

The rapid atrial pacing dog model of AF has consistently been shown to result in a reduction of atrial conduction velocity.[18] This would support the maintenance of AF by reducing the atrial wavelength that would favour multiple circuit reentry. To study the underlying cellular and ionic

mechanisms of the reduction in atrial conduction velocity Gaspo et al used whole-cell patch-clamp techniques to study atrial myocytes isolated from control dogs and dogs subjected to rapid atrial pacing for 7 or 42 days.[41] They specifically studied the rapid inward (phase 0 of the action potential) Na current (I_{Na}), which is an important determinant of conduction velocity in atrial tissue. The protocol they used was similar to previous work by the same group. Dogs were rapid atrially paced (400 bpm) for periods between 7 and 42 days. An electrophysiological study was performed prior to sacrifice. Conduction velocity was measured using a silicon sheet with an array of 40 bipolar electrodes sutured onto the right atrial epicardial surface. Following the study single atrial myocytes were prepared for voltage-clamp studies. The results showed that AF durations and AF inducibility increased with longer durations of rapid atrial pacing. Conduction velocity was significantly reduced in the dogs subjected to rapid atrial pacing for 7 or 42 days. The voltage-clamp study showed that I_{Na} was also significantly reduced in the paced dogs. There was a strong correlation between the changes in I_{Na}, the logarithm of AF duration and conduction velocity. The underlying mechanism of the reduction in I_{Na} was not determined but a rise in intracellular Ca^{2+} $[Ca^{2+}]_i$ can lead to down regulation of Na channel expression.[42] It is also possible that other factors such as connexin expression may be important in changes of conduction velocity.

Following their work showing decreases in the ionic current density of the L-type Ca^{2+} current ($I_{Ca,L}$), the transient outward current (I_{to}) and the Na current (I_{Na}), Nattel's group went on to look at the molecular mechanisms underlying these changes.[43] Using a competitive reverse transcriptase-polymerase chain reaction, mRNA concentrations were quantified in control dogs and in dogs subjected to 7 days (P7) and 42 days (P42) of rapid atrial pacing. Changes in mRNA levels for the $alpha_{1c}$ subunit of the L-type Ca^{2+} channel, for Kv 4.3 (the putative gene for I_{to}) and for the alpha subunit of the cardiac Na channel were all significantly reduced in both P7 and P42 dogs. The level of reduction was similar to the observed changes in atrial ionic current densities

and the reductions were more marked in P42 than P7 dogs. The authors then studied the levels of protein expression for Kv 4.3 and the alpha subunit of the Na channel using western blot analysis and found these to be similarly reduced. The levels of mRNA and protein expression for other currents previously identified as not being involved in atrial electrical remodelling were not altered. The same group had already shown that rapid atrial pacing reduces the number of dihydropyridine receptors (L-type Ca^{2+} channels) as assessed by radioligand binding and that longer durations of rapid atrial pacing resulted in greater reductions.[44] On the basis of these findings the authors concluded that there is an underlying molecular basis for the self-perpetuating nature of AF.

The ionic and molecular changes in dogs have been well illustrated by Nattel's group, however important differences between the manifestations of atrial electrical remodelling in the goat and dog model have previously been noted. For instance in the dog model various groups have noted changes in conduction velocity associated with atrial electrical remodelling,[18,32] but previous work on the Allessie goat model has failed to show any significant changes in conduction velocity[1] despite changes in connexin distribution.[30] Van der Velden and co-workers[45] explored the molecular changes underlying atrial electrical remodelling in the original Allessie goat model of AF. They measured monophasic action potential (MAP) durations at the time of the initial surgery to implant the epicardial patches and again following a mean of 135 days of maintained AF. AERP was also determined at baseline and again following a mean of 11 days of AF. Following sacrifice mRNA levels were determined using the reverse transcriptase-polymerase chain reaction. The results showed that following cardioversion of AF the MAP was significantly reduced compared to control measurements and showed a marked reversal of rate adaptation. AERP was also markedly reduced when measured. The mRNA analysis showed a significant reduction in expression of the $alpha_{1c}$ subunit of the L-type Ca^{2+} channel and the Kv 1.5 potassium channel gene that underlies I_{Kur}. No significant changes were found in the

mRNA levels encoding for the rapid Na channel, the Na / Ca^{2+} exchanger or the Kv 4.2/4.3 channels responsible for I_{to}. The results correspond with the findings of Yue et al[43] for the $alpha_{1c}$ subunit of the L-type Ca^{2+} channel but differ significantly for the potassium channels Kv 1.5 and Kv 4.3, and for the fast Na channel. These differences, especially the lack of a change in Na current mRNA in the goat model, may explain the different findings in terms of conduction velocity changes in association with atrial electrical remodelling.

Following this work using models of persistent AF, other workers have studied the changes in ion channel function and mRNA expression that occur with short durations (<8 hours) of rapid atrial pacing in an anaesthetised rat model.[46] A total of 9 genes encoding for voltage-dependent K^+ channels were studied, but the authors did not study the L-type Ca^{2+} channel. No change in the expression and function was found for 6 of the genes studied. An increase in Kv 1.5 mRNA and protein and a progressive decrease of the mRNA levels of the Kv 4.2 and Kv 4.3 and their proteins was found. To determine whether the changes in Kv 1.5 mRNA and channel expression were significant the authors recorded monophasic action potentials (MAP) from the atrium after 4 hours of rapid pacing (when changes in Kv 1.5 were maximal). The rapidly paced atria showed a significant shortening of the MAP_{d90} compared to sham operated atria. This change in MAP_{d90} was almost abolished by a low concentration of 4-aminopyridine (a relatively specific Kv 1.5 blocker). The Kv 1.5 gene is thought to encode the ultrarapid delayed rectifier current ($I_{kur,d}$). This finding is different to that of previous workers.[39,45] The changes in Kv 4.2 and Kv 4.3 mRNA (which encodes for I_{to} in rats) would be compatible with previous findings of a reduction in I_{to} with longer durations of rapid atrial pacing in dogs.[39]

The ionic mechanisms underlying regional action potential heterogeneity have also been investigated. Feng and co-workers[47] studied action potential heterogeneity in non-remodelled atria from dogs. There was a tendency to a

longer action potential duration in cells from the crista terminalis compared to other regions in the right atrium confirming previous data gathered using standard microelectrode techniques.[48] The longer action potential durations were associated with a larger L-type Ca^{2+} current in the crista cells. Cells from the right atrial appendage showed a reduced I_{to} current. Li and coworkers found left atrial ERP to be shorter than right atrial ERP in isolated canine atrial myocytes. Whole cell patch clamping showed an increased I_{Kr} in the left atrial myocytes.[59]

Human Data

Although animal work is crucial in developing an understanding of the likely mechanisms underlying atrial cellular and ionic physiology, complementary human data to back up the animal work is important. Studies on human atrial tissue, however, have a number of methodological problems. The contributions of the underlying heart disease, drugs and varying durations of AF should all be considered. In addition the harvesting of human atrial tissue is limited to the time of cardiac surgery and handling conditions can often be suboptimal. These factors may explain the considerable variation of the findings in the literature.

Abnormalities of trans-membrane currents in dilated human atria were recognized several years ago.[38] Using standard microelectrodes Le Grand et al found that in trabeculae taken from dilated atria (at the time of cardiac surgery) the action potential was shortened and the plateau was markedly depressed compared to trabeculae taken from non-dilated atria. The most significant change in ionic current to explain this shortening of the action potential duration was a marked reduction in the calcium current density in the cells from dilated atria.

The first study of the ionic changes in human AF using isolated atrial myocytes and patch clamp techniques focused on changes in K^+ currents and the K^+ channel alpha-subunit proteins (Kv 1.5 and Kv 2.1).[49] Van Wagoner

et al used atrial tissue samples taken at the time of cardiac surgery from patients in chronic AF (undergoing mitral valve repair and/or the Maze procedure) and compared them to control patients in sinus rhythm at the time of bypass surgery or cardiac transplantation. The results showed that outward K^+ sup currents are reduced in patients with AF. The most significant reductions (~ 60%) were noted in the I_{to} and the I_{ksus} currents. Western blot analysis was performed to determine whether there was a corresponding reduction in voltage-gated K^+ sup channel alpha-subunit proteins. The Western blots showed a reduction in Kv1.5 but not Kv2.1 expression in the membranes of myocytes from patients in AF. A reduction in K^+ currents results in prolongation of the APD and was the opposite of the expected result.

In view of the findings of his first study Van Wagoner et al then went on to study the atrial L-type Ca^{2+} currents in patients with AF.[50] Again they used atrial tissue from patients undergoing cardiac surgery to isolate atrial myocytes for patch clamp and voltage clamp recordings. Patients with AF were found to have a significant reduction (~ 60%) in L-type Ca^{2+} current (I_{Ca}).

Other authors have also found changes in gene expression and proteins involved in calcium transport.[51] Using right atrial appendage tissue collected at the time of cardiac surgery from patients with paroxysmal and persistent AF and control patients in sinus rhythm mRNA levels were assessed using a semi-quantitative reverse transcription polymerase chain reaction. Protein expression was analysed using slot-blot analysis. The results showed a significant reduction in both the mRNA and protein expression of the L-type Ca^{2+} channel α_1-subunit and sarcoplasmic reticulum Ca^{2+}-ATPase in patients with persistent AF (>8 months) compared to controls and patients with paroxysmal AF. It is also of note that no changes were found in patients with paroxysmal AF, despite this group representing the severe end of the spectrum with daily long-lasting bouts of AF. In similar previous work[52] this

group had noted changes in the L-type Ca^{2+} channel α_1-subunit mRNA were related to the duration of AF, with the most significant changes in patients with AF of >6 months duration.

Other authors have also found similar changes in mRNA levels.[53] In a study using atrial tissue collected from right and left atrial appendages and free walls of both atria at the time of cardiac surgery, patients with persistent AF were noted to have reduced levels of mRNA for the α-subunit of the L-type Ca^{2+} channel and the sarcoplasmic reticulum Ca^{2+}-ATPase. There was no spatial dispersion of gene expression from the 4 sites studied. The same group then went on to study changes in potassium channel mRNA expression using the same atrial tissues.[54] They found a reduction in the mRNA encoding Kv 1.5, HERG and KVLQT1 in patients with persistent atrial fibrillation for more than 3 months. In contrast, the mRNA level of minK was significantly increased in patients with persistent atrial fibrillation for more than 3 months. These changes, however, would not account for the shortening of action potential duration.

Bosch and co-workers studied the relationship between action potentials and ionic currents in human AF.[55] Using right atrial appendage tissue obtained at the time of cardiac surgery single atrial myocytes were studied by patch clamping. The action potential duration was reduced in cells from patients with chronic AF compared to control patients (sinus rhythm). Associated with the change in APD there was a reduction of about 70% in the inward Ca^{2+} current (I_{CaL}). There was also a marked reduction in I_{to} currents but no change in the I_{ksus} current (different from Van Wagoner). No change was found for the rapid Na^+ current.

Other workers have also assessed the effects of persistent AF on potassium currents. Grammer and colleagues[56] studied the effects of remodelling on the gene expression of Kv 4.3 and Kv 1.4 (pore-forming subunits for I_{to}), and Kv 1.5 (pore-forming subunit for I_{ksus}, I_{Kur}) Changes in function of the Kv 4.3 potassium channel, which putatively encodes for I_{to} have previously been

described by Yue et al[39] in their dog model of AF. Atrial tissue obtained at the time of cardiac surgery from patients in chronic AF was compared to atrial tissue from patients in sinus rhythm. Ion currents were studied in single atrial myocytes using the patch-clamp technique and mRNA expression was assessed using a semi-quantitative reverse transcription-polymerase chain reaction. The atrial myocytes from patients in AF showed a marked reduction in I_{to} but little change in I_{ksus}. Associated with the reduction in I_{to} there was a reduction of 61% in mRNA encoding for Kv 4.3. There was no significant change in the second subunit involved with I_{to}, Kv 1.4, or in the level of Kv 1.5. The results for I_{to} are similar to those of Yue et al[39] in the dog model, but the lack of change in I_{ksus} and Kv 1.5 is different to the findings of van Wagoner et al[49] who found a reduction in Kv 1.5 protein expression in patients with AF. The parallel changes in I_{to} and Kv 4.3 suggest transcriptional regulation as the underlying mechanism for changes in current densities.

Further work incorporating measurement of atrial effective refractory period (AERP) with quantitative analysis of mRNA and protein expression of ion channels has more recently been published.[57] Patients undergoing cardiac surgery with paroxysmal or persistent AF and controls in sinus rhythm were studied. The AERP was determined at both the left and right atrial appendages during surgery. Following this the atrial appendages were removed, RNA was isolated and using this cDNA synthesized. This was then amplified using a single polymerase chain reaction. Protein analysis was performed by quantitative slot-blotting. The results showed that patients with paroxysmal and persistent AF had significantly lower AERPs than patients in sinus rhythm. The mRNA analysis showed a reduction in mRNA content for L-type Ca^{2+} channels and for 5 potassium channels (Kv 4.3, Kv 1.5, HERG, mink, and Kir3.1) in patients with persistent but not paroxysmal AF. The protein analysis showed a correlation between the protein levels of all the ion channels studied with both the AERP and the rate adaptation of the AERP. The changes in protein level were noted in both paroxysmal and

persistent AF, unlike the mRNA changes that were noted only in persistent AF. This is the first study to show a discrepancy between mRNA changes and protein expression. It suggests that short paroxysms of AF may result in changes in protein expression independent of changes in mRNA. The authors suggest a possible proteolytic control system (the calpain system).

Most recently the issue of whether down-regulation of ion channels is expressed exclusively through modulation of the pore-forming α-subunit has been raised. Grammer and colleagues[58] have found that the reduction of certain isoforms of the α-subunit of the L-type Ca channel is greater than the β-subunit.

Conclusions

Both human and animal data show a downregulation in L-type Ca^{2+} channel function is the principal ionic abnormality underlying the shortening of the atrial action potential duration seen in AF.[39,43-45,50-53,55,57] There is downregulation of L-type Ca^{2+} channel mRNA and channel protein synthesis, suggesting a strong role for transcriptional down-regulation. Decreases in I_{to} are also consistently found although the importance of this abnormality for action potential changes and arrhythmia promotion is less clear.[39,43,46,55-57] Again this seems to be principally controlled by transcriptional down-regulation. No clear patterns of change have been observed for other currents with some authors finding a reduction in Kv 1.5 mRNA levels[45,49,54,57] others finding no change,[55,56] and one group even an increase.[46] Changes in Na channel activity in association with slowing of conduction velocity have been described in dogs[41] but despite the recognition of changes in conduction velocity in human AF no changes in Na channel mRNA or ionic activity have yet been described. The interpretation of the data is clouded by the various species of animal model used and the variety of clinical backgrounds from which human AF samples are taken.

Experimental Model	Authors	Duration of Pacing/AF	*Changes* Ionic	mRNA	Protein
Dog RAP	Yue et al (39)	up to 6-weeks	↓ I_{to} (~70%) ↓ $I_{Ca.L}$ (~70%)		
Dog RAP	Gaspo et al (41)	up to 6-weeks	↓ I_{Na}		
Dog RAP	Yue et al (43)	up to 6-weeks		↓ $I_{Ca.L}$ ↓ I_{to} ↓ I_{Na}	 ↓ Kv 4.3 ↓ I_{Na} α-subunit
Dog RAP	Gaspo et al (44)				↓ L-type Ca
Goat AF	Van der Velden et al (45)	mean of 135 days		↓ $I_{Ca.L}$ ↓ Kv 1.5 no change I_{Na} or Kv 4.3	
Rat RAP	Yamashita et al (46)	up to 8-hours		↓ Kv 4.2 / 4.3 and ↓ proteins ↑ Kv 1.5	

Table 3.1 Summary of the changes in ionic currents, mRNA and proteins reported in the literature in animal studies. The numbers in parentheses indicate reference numbers. RAP – rapid atrial pacing.

Authors	Type of AF	Changes		
		Ionic	mRNA	Protein
Van Wagoner (49)	Persistent	↓ I_{to} (~60%) ↓ I_{Ksus}		↓ Kv 1.5(I_{Ksus})
Van Wagoner (50)	Persistent	↓ $I_{Ca.L}$ (~60%)		
Brundel (51)	Persistent		↓ $I_{Ca.L}$ ↓ SR Ca-ATPase and	↓ α-subunit ↓ protein
Van Gelder (52)	Persistent		↓ $I_{Ca.L}$	
Lai (53)	Persistent		↓ $I_{Ca.L}$ ↓ SR Ca-ATPase	
Lai (54)	Persistent		↓ Kv 1.5 ↓ HERG ↓ KVLQT1	
Bosch (55)	Persistent		↓ $I_{Ca.L}$ (~70%) ↓ I_{to} no change in I_{ksus} or I_{Na}	
Grammer (56)	Persistent		↓ I_{to} no change in I_{ksus}	
Brundel (57)	Paroxysmal / Persistent (note - mRNA changes only in persistent AF, protein in both)		↓ $I_{Ca.L}$ ↓ Kv 4.3 ↓ Kv 1.5 ↓ HERG ↓ min K ↓ Kv 3.1	↓ $I_{Ca.L}$ ↓ Kv 4.3 ↓ Kv 1.5 ↓ HERG ↓ min K ↓ Kv 3.1
Workman (60)	Persistent	↓ $I_{Ca.L}$ (~60%) ↓ I_{to} (~60%) ↑ I_{K1} no change I_{Ksus}		

Table 3.2 Summary of the changes in ionic currents, mRNA and proteins reported in the literature in human studies. The numbers in parentheses indicate reference numbers.

3.4 A New Fully Implantable Goat Model Of Atrial Fibrillation

Background

Currently available fully implantable animal models of atrial fibrillation (AF) use rapid atrial pacing (Figure 3.11) rather than AF to induce atrial electrical remodelling. As a consequence the effect of the remodelling process on AF stability (duration of individual episodes of AF) and AF inducibility cannot be determined. In contrast, the original Allessie goat model (Figure 3.2) allowed measurements of these two variables continuously, but until now has not been incorporated into a fully implantable system.

The key components of the fully implantable goat model of AF are the ability to induce AF, to record durations of induced AF episodes and to be able to measure atrial refractory periods by extrastimulus pacing. The new model used two pacemakers, two right atrial leads and one right ventricular lead. The first pacemaker was dual chamber and incorporated specially designed software for the induction of AF. The atrial electrogram was continually analysed and when atrial electrical quiescence was detected (as occurs in the periods between P-waves in sinus rhythm) a 2-second burst of 64 Hz pacing was delivered at four times diastolic threshold (Figure 3.15). During AF when continuous atrial activity was sensed the burst-pacing algorithm in the pacemaker was inhibited. The pacemaker stored a log of all burst pacing allowing assessment of AF durations. The ventricular lead was required to ensure that appropriate atrial sensing was occurring (at least 100ms separate from sensed ventricular activity), as atrial lead dislodgement and inappropriate burst pacing in the ventricle would be catastrophic. The second pacemaker was a single chamber device used for extrastimulus pacing to determine atrial refractory periods. During measurement of atrial refractory periods the burst–pacing algorithm was inhibited by programming the dual chamber pacemaker to single chamber mode. The atrial lead in the dual chamber pacemaker was used to record atrial capture (by telemetry

from the pacemaker interrogation wand) during extrastimulus pacing thus allowing accurate assessment of atrial capture (Figure 3.12).

Methods

Using 14 goats we developed a fully implantable pacemaker-based model of AF. The experiments were conducted in accordance with the project license issued by the United Kingdom Home Office under the Animals (Scientific Procedures) Act 1986. The animals were allowed free access to food and water and were unrestrained in their pens throughout the experiments. The new model is a modified pacemaker-based model of AF in which the original Allessie burst pacing protocol is incorporated, thereby allowing continuous monitoring /recording of the self perpetuating process in addition to measurements of atrial refractoriness and AF inducibility.

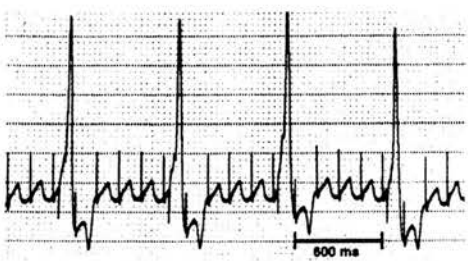

Figure 3.11 Surface ECG illustrating rapid atrial pacing. Atrioventricular node ablation has been performed and the ventricles are paced at 75/min.

Pacemaker implant

Anaesthesia was induced and maintained using 3% Isoflurane and a 2:1 mixture of O_2 and N_2O. The animals were placed in the left lateral position and 1 gram of flucloxacillin was given intravenously. Using aseptic surgical technique an incision was made in the lateral aspect of the neck exposing the right internal jugular vein. The vein was mobilised and ligated and three active-fixation bipolar steroid eluting leads introduced via a small venotomy and positioned on the septal portion of the right atrium (2 leads) and right ventricular apex (1 lead). Sensing and threshold characteristics were determined before connecting one atrial lead to an Intermedics pacemaker and the remaining leads to the atrial and ventricular channels of a Medtronic

Thera® pacemaker. The leads were secured and pacemakers buried subcutaneously prior to wound closure. An ECG telemetry unit (Data Sciences Inc) was buried subcutaneously in the right flank through a further small incision.

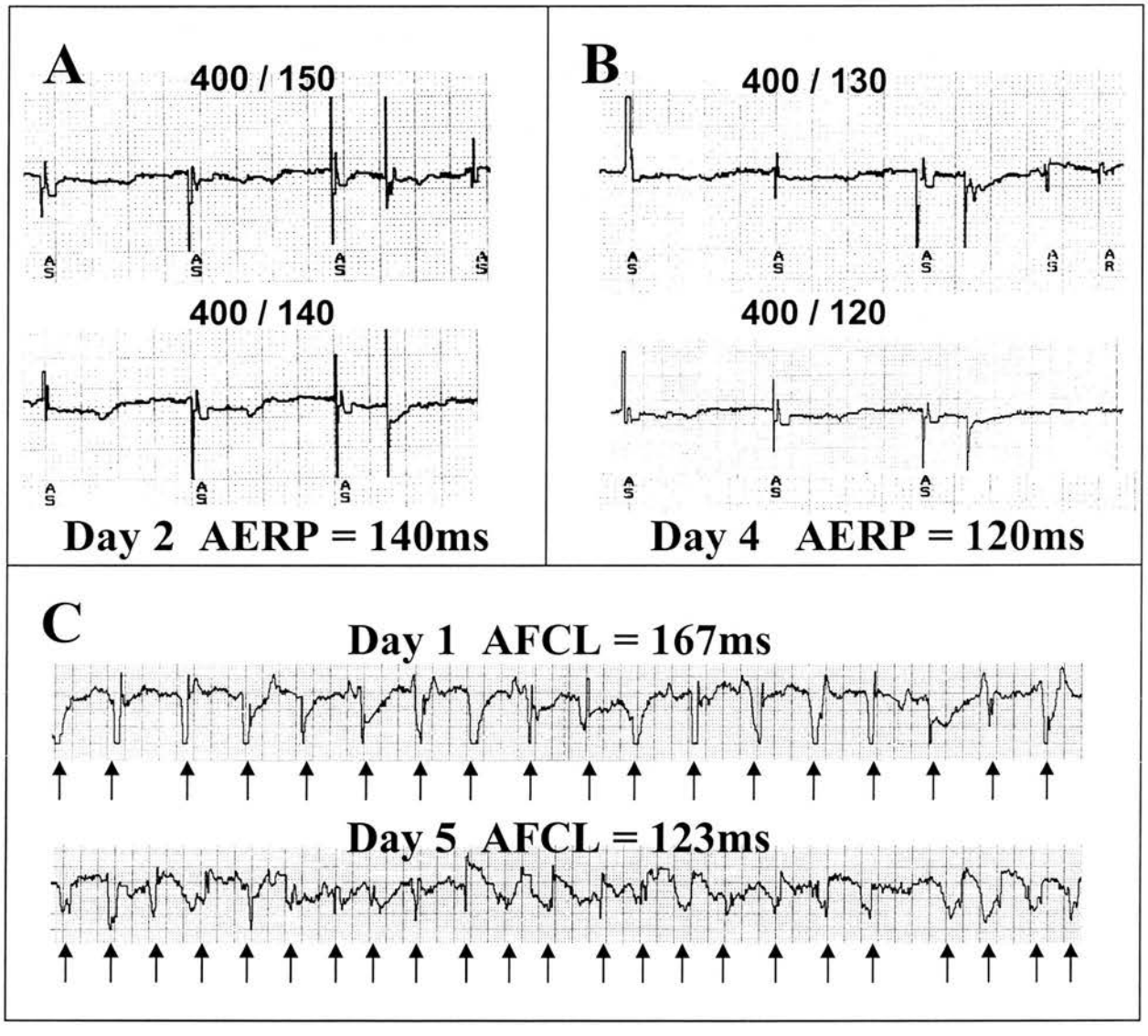

Figure 3.12 The upper part of the figure illustrates measurement of refractory periods. The left panel (A) is taken from Day-2. Following a drive train of 8 cycles at 400ms an extrastimulus with a coupling interval of 150ms results in atrial capture. The lower trace shows that the extrastimulus at 140ms does not result in capture. The right hand panel (B) shows refractory period measurement from the same goat on day-4. The upper trace shows atrial capture with an extrastimulus at 130ms associated with 2 repetitive atrial responses. The lower trace shows that an extrastimulus at 120ms does not result in atrial capture. The lower part of the figure (C) shows atrial fibrillation cycle length (AFCL) measurements from day-1 and day-5. Each cycle is marked with an arrow. The AFCL shortens from 167ms on day-1 to 123ms on day-5.

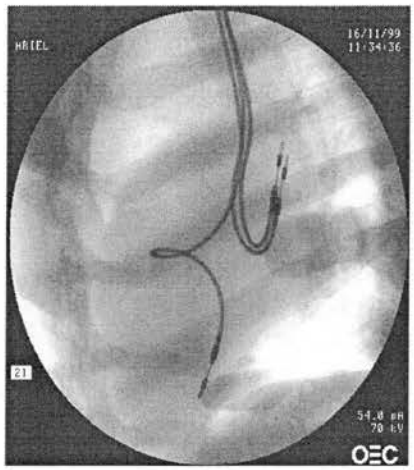

Figure 3.13 Lateral radiograph of positions of pacemaker leads. Two leads can be seen in the right atrium and one in the right ventricle. The cardiac silhouette can also be seen. The ventricular lead and one atrial lead were connected to a Medtronic Thera pacemaker responsible for burst pacing. The second atrial lead was connected to an Intermedics pacemaker and was used to determine atrial effective refractory periods using non-invasive programmed stimulation (NIPS).

Methodological Problems

The initial validation protocol was hampered by several problems.

1. Atrial lead displacement – following pacemaker implant atrial lead displacement occurred in several goats. This was more of a problem initially. Particular issues that contributed to lead displacement included how active the goat was on recovery from general anaesthesia and good stability of the leads during robust testing at the time of implant. In one goat atrial lead displacement was not detected during post-implant testing. Burst pacing through this lead resulted in a fatal ventricular arrhythmia.
2. Ability to programme pacemakers independently – in creating the pacemaker pocket for the two pacemakers, care had to be taken to separate the pacemakers in the pocket in order to allow effective individual programming and telemetry from each pacemaker.
3. Left atrial measurements – we also implanted coronary sinus leads in a number of goats in order to measure left atrial refractory periods. Although good positions were found in a number of animals long term stability was not adequate and therefore we abandoned this part of the protocol.
4. DC cardioversion – cardioversion of the goats was greatly facilitated by the use of adhesive electrodes. Conventional DC cardioversion using 'paddles' was unsuccessful in most cases.
5. Spare equipment was essential as the goats frequently chewed the cables involved in pacemaker programming.

Validation protocol

Previous work by Garratt et al[17] using the original Allessie goat model had shown that changes in atrial refractoriness and the onset of AF stability were reproducible over two consecutive 5-day periods. The validation protocol was designed to assess the reproducibility of these variables over two consecutive 5-day periods in the new fully implantable model. A schematic diagram of the validation protocol is shown in Figure 3.14. If changes in atrial refractoriness and AF stability were reproducible in the new model we would be able to test the effect of drugs on atrial electrical remodelling and AF stability using 5-day protocols. The important elements of reproducibility were considered to be changes in atrial refractoriness and the onset of AF stability, as our first prospective drug study was to assess the relationship between these factors in the presence of verapamil.

After pacemaker implant the animals were allowed to recover for at least 5-days. The animals then commenced repetitive reinduction of AF for the first 5-day period (remodelling 1). Specifically designed software in the Medtronic pacemaker was used to deliver burst pacing during sinus rhythm via the right atrial lead in a manner similar to that in the originally described Allessie goat model. Whenever sinus rhythm was detected the pacemaker delivered a 2-second burst of pacing at 64 Hz. Burst pacing was inhibited whenever AF was detected. During the 5-day period measurements were made of AERP, inducibility of AF by extrastimulus pacing, AF stability, AF cycle length and ventricular cycle length at t = 0, 4, 8, 12, and 24 hours, then twice daily until the 5th day. At the end of the 5-days the goats were DC cardioverted under general anaesthesia. Thereafter AERP was measured daily until it recovered to baseline. Following a mean period of 10-days repetitive reinduction of AF was commenced for the second 5-day period (remodelling 2). At the end of the second 5-day period the goat was again DC cardioverted and AERP measured daily until recovery.

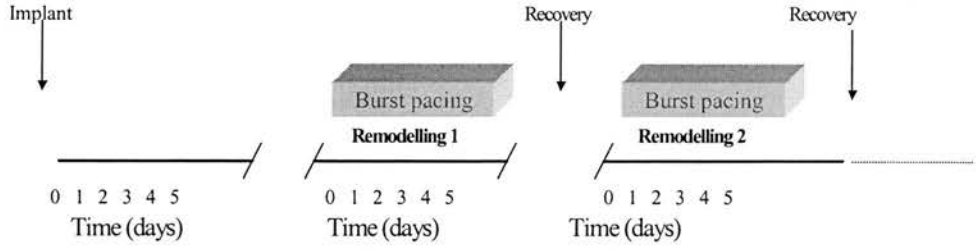

Figure 3.14 Illustration of the validation protocol

Measurement of refractory periods and AF cycle length

The Intermedics pacemaker was used to deliver extra stimulus pacing via the external programmer to determine atrial effective refractory periods (AERP) during a basic pacing drive of 400ms. A standard drive train of 8 extrastimuli (S_1) was followed by a single S_2, all at four times diastolic threshold. The initial S_1-S_2 coupling interval was commenced at a shorter interval than the expected AERP and increased incrementally until atrial capture was achieved. The AERP was recorded as the mean of the two longest S_1-S_2 that failed to capture the atrium (Figure 3.12). To determine AFCL we recorded 10-second segments of bipolar atrial electrogram at 100 mm/s via telemetry from the atrial lead in the Thera pacemaker (Figure 3.12). Two independent observers then calculated mean AFCL and these two values were averaged.

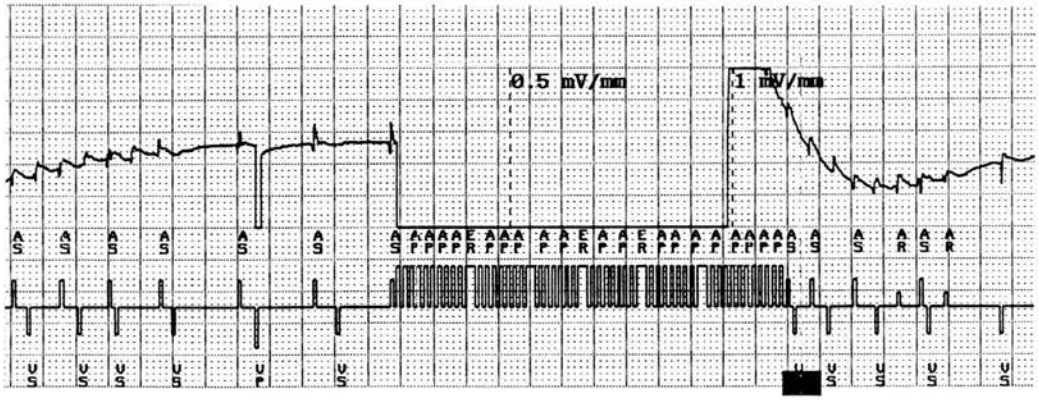

Figure 3.15 Illustration of an intracardiac recording of the burst pacing algorithm in action. The ECG is telemetered from the Thera pacemaker and shows atrial fibrillation (AF) on the left, reverting to sinus rhythm, and upon detection of sinus rhythm (2 beat detection programmed) a 2-second 64Hz burst of atrial pacing that successfully reinduces AF. The episodes of AF are short lived typical of the findings in the early stages of remodelling.

Duration of induced AF

The duration of induced episodes of AF was determined using 1) direct telemetry of the endocardial atrial signal via the pacemaker programmer and from 2) the surface ECG telemetered via the Datasciences implant (Figure 3.16) which was continuously displayed and recorded on a computer. In addition the Thera software recorded a log of time and cumulative number of bursts delivered.

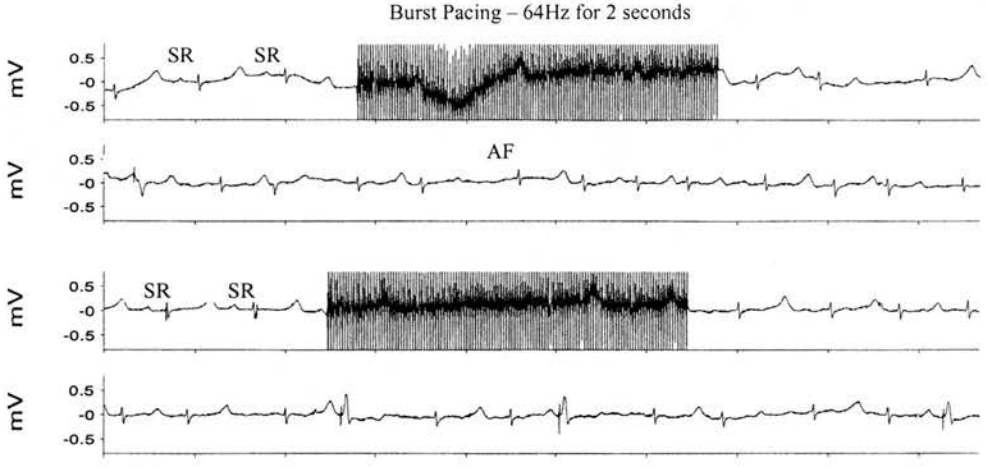

Figure 3.16 Surface ECG transmitted from the Datasciences implant. SR indicate the sinus beats prior to a 2-second burst at 64Hz of atrial pacing that reinduces AF. (mV – millivolts)

The time course of changes in atrial refractory periods (AERP) were reproducible with a mean AERP at baseline of 165±15ms for remodelling 1 and 165±20ms for remodelling 2, 141±19ms v 136±20ms after 24-hours of repeated reinduction of AF, 135±23ms v 123±21ms at 48-hours, 122±19ms v 116±9ms at 72-hours and 118±21ms v 118±17ms at 120-hours (all P=NS). The inducibility and stability of AF were also reproducible. The time periods of repeated induction of AF required to induce AF of duration 1-hour, 6-hours and 24-hours were 84±31hrs v 62±28hrs, 95±27hrs v 92±31hrs, 104±28hrs v 104±28hrs respectively (all P=NS). The time course of changes in atrial refractoriness and onset of AF stability in individual goats was also reproducible.

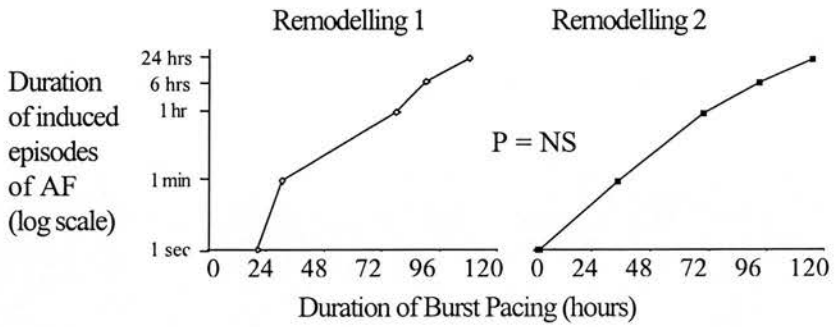

Figure 3.17 The stability of induced AF. The graphs show similar durations of burst pacing required to induce each of the prespecified durations of AF in remodelling 1 and 2.

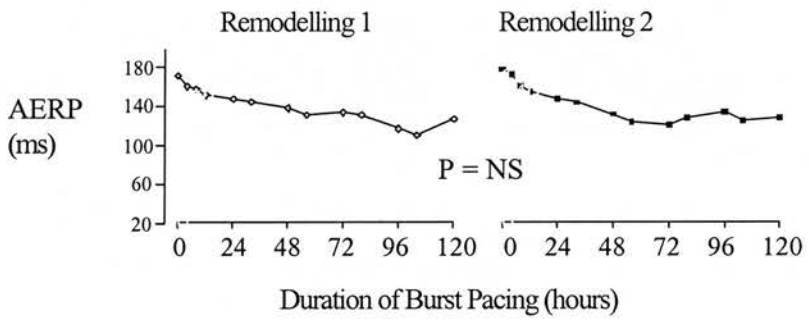

Figure 3.18 Changes in atrial effective refractory period (AERP). The graphs show that changes in AERP were similar in remodelling 1 and 2.

Conclusions

A new fully implantable equivalent of the original Allessie goat model of AF has been developed. Changes in atrial refractoriness and the onset of AF stability are reproducible over consecutive 5-day periods of maintained AF similar to the original Allessie model.[17] The new model has the advantage of being fully implantable and allows assessment of the stability of AF in addition to atrial refractoriness.

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Chapter 4

The Profibrillatory Effect of Verapamil is not Prevented by Propafenone

4.1 Verapamil – and the role of calcium in atrial electrical remodelling

4.2 The Verapamil / Propafenone Combination

4.3 The Profibrillatory Effect of Verapamil is not Prevented by Propafenone

Presented as an abstract at The British Cardiac Society 2001. Heart 2001: 85 (Supp 1); pg 9 & European Society of Cardiology 2001. Eur Heart J 2001: 22 (Abst Supp); P2960

4.1 Verapamil

The description of atrial electrical remodelling[1] and the understanding that 'AF begets AF' led immediately to interest in how this process might be prevented or attenuated. The goal of being able to modify the natural history of AF seemed to be in sight. Wijffels then went on to show that the stimulus for atrial electrical remodelling was the rapid rate of atrial electrical activation that occurs in AF[2] and this was confirmed by the description of models of AF based on rapid atrial pacing.[3,4] Morillo et al[3] showed that in conjunction with atrial electrical remodelling rapid atrial pacing resulted in biatrial enlargement and cellular structural changes which might result in a reduction in contractile function. There was an obvious parallel between the experimental model and the changes found in patients with AF such as atrial enlargement and loss of contractile function,[5,6] which are thought to be important in promoting left atrial thrombus and the risk of cerebrovascular accidents.

The coexistence of atrial electrical remodelling and atrial contractile dysfunction in the rapid atrial pacing model of AF suggested the possibility of a common underlying aetiology and mechanism. Previous work had shown that rapid pacing increases cell cytosolic calcium levels[7,8] and that intracellular calcium overload causes cardiac contractile dysfunction.[9,10] This led to the suggestion that an increase in intracellular calcium could be the mechanism for the observed electrical and structural changes in AF.

The potential role of intracellular calcium overload as the underlying mechanism of atrial electrical remodelling and atrial contractile dysfunction in AF led to interest in the use of calcium-channel blocking drugs to prevent these deleterious effects of AF. Interest focused on the L-type calcium-channel blocker verapamil, which has been used to control the ventricular rate in AF for many years.[11,12] Although there had been reports of verapamil being of some use in converting AF of short duration

to sinus rhythm either alone[12] or in combination with quinidine[13] most of the data on the use of verapamil in AF did not suggest a useful potential antiarrhythmic action of verapamil in AF. For instance, verapamil exerts unfavourable effects in patients with WPW and pre-excited AF by shortening the refractory period of the accessory pathway so promoting conduction to the ventricle[14] which can result in ventricular fibrillation.[15] In the controlled setting of the electrophysiology laboratory verapamil and diltiazem were found to increase durations of AF induced by programmed electrical stimulation in patients with paroxysmal AF.[16] The effects of verapamil on atrial electrophysiology in patients with paroxysmal AF are also not favourable.[17] Verapamil slows atrial conduction velocity and results in an increase in fragmented atrial electrical activity[17,18] both of which have the potential to promote AF.

Verapamil, however, was shown to exert favourable effects on AF-induced atrial contractile dysfunction. Using an open-chest pig model Leistad and coworkers[19] induced AF for short periods in the presence of both verapamil and Bay K8644 (which increases calcium entry via L-type calcium channels). Following conversion from AF to sinus rhythm the authors assessed the degree and duration of atrial contractile dysfunction using echo. They found that while verapamil attenuated atrial contractile dysfunction Bay K8644 increased the dysfunction strongly suggesting that intracellular calcium overload was responsible.

Studies of the effects of verapamil on atrial electrical remodelling followed shortly after. Using an anaethetised rapid atrial pacing dog model Goette[20] showed that electrical remodelling could be induced despite autonomic blockade and without any changes in right atrial pressure. Verapamil blocked atrial electrical remodelling and calcium overload accentuated it. This beneficial effect of verapamil on atrial electrical remodelling was confirmed in experiments on humans. Daoud and colleagues induced AF for 5-10 minutes using rapid atrial pacing. This

short period of AF was shown to be adequate to develop changes in atrial refractoriness.[21] Pretreatment with verapamil, but not procainamide, resulted in attenuation of the acute AF-induced changes in atrial refractoriness and a reduction in the number of secondary episodes of AF induced during determination of the atrial refractory period.[22] Similar results for verapamil were found by others using 10-minute periods of pacing induced AF in humans.[23] In the same study conventional antiarrhythmic drugs such as procainamide, propafenone, sotalol and amiodarone had no effect on atrial electrical remodelling.[23]

In addition to preventing short-term atrial electrical remodelling (minutes) verapamil was shown to reduce atrial electrical remodelling induced by 24-hours of rapid atrial pacing in the goat model.[24] Lee et al[25] also found verapamil to prevent atrial electrical remodelling at 24-hours in their rapid atrial pacing dog model but that this effect did not persist for longer durations of atrial electrical remodelling (1-week and 6-weeks). In addition, verapamil increased the durations of episodes of AF induced at electrophysiological study (performed in full autonomic blockade) in the dogs paced for 1-week and 6-weeks. Despite the lack of effect of verapamil in preventing atrial electrical remodelling induced by longer durations of AF or rapid atrial pacing the T-type calcium channel blocker, mibefradil, has been found to be effective at preventing atrial electrical remodelling induced by rapid atrial pacing of up to one-week in duration.[26,27]

In association with evidence showing the beneficial effects of verapamil on atrial electrical remodelling clinical reports of the effects of verapamil in patients undergoing cardioversion of persistent AF were published. Tieleman and colleagues[28] evaluated the time of recurrence of AF following DC cardioversion using daily trans-telephonic monitoring. The highest incidence of recurrence was in the first 5-days following cardioversion. The authors suggested this might be due to persistence of

atrial electrical remodelling during this time. On further analysis of the data the use of calcium-lowering drugs during AF was the only independent predictor of maintaining sinus rhythm, suggesting that calcium-lowering drugs had modified the substrate (atrial electrical remodelling) for recurrence. De Simone et al[29] found that pretreatment with verapamil and propafenone for 3 days before cardioversion of persistent AF resulted in a reduced rate of recurrence compared to pretreatment with propafenone alone. Verapamil has also been shown to reduce the incidence of recurrent ERAF (early recurrence of AF) following cardioversion.[30]

The available data suggested that verapamil exerted beneficial effects on atrial electrical remodelling and also on AF recurrence following cardioversion. However, none of the studies had addressed the issue of whether verapamil's action in attenuating atrial electrical remodelling led to any reduction in the stability of AF. In order to study the relationship between the effects of verapamil on atrial electrical remodelling and AF stability an animal model based on the original Allessie goat model with continuous reinduction of AF, allowing measurement of AF durations and atrial refractoriness, rather than rapid atrial pacing alone would be required. The development of our fully implantable version of the Allessie goat model allowed us to study the inter-relationship of these effects. Following the development of our model I collaborated with Dr Julian Hobbs in studying the effects of verapamil on the stability of AF. This work is reported in his MD thesis and was presented at The British Cardiac Society in May 2000. In summary we found that verapamil promoted the stability of AF, requiring less burst pacing to induce the prespecified durations of induced AF (Figure 4.1), despite attenuation of atrial electrical remodelling. The features of attenuation of atrial electrical remodelling are a reduction in the fall of atrial refractoriness and preservation of its rate adaptation (Figure 4.2). Atrial fibrillation cycle

length was also found to be reduced by verapamil during the first 24-hours of burst pacing.

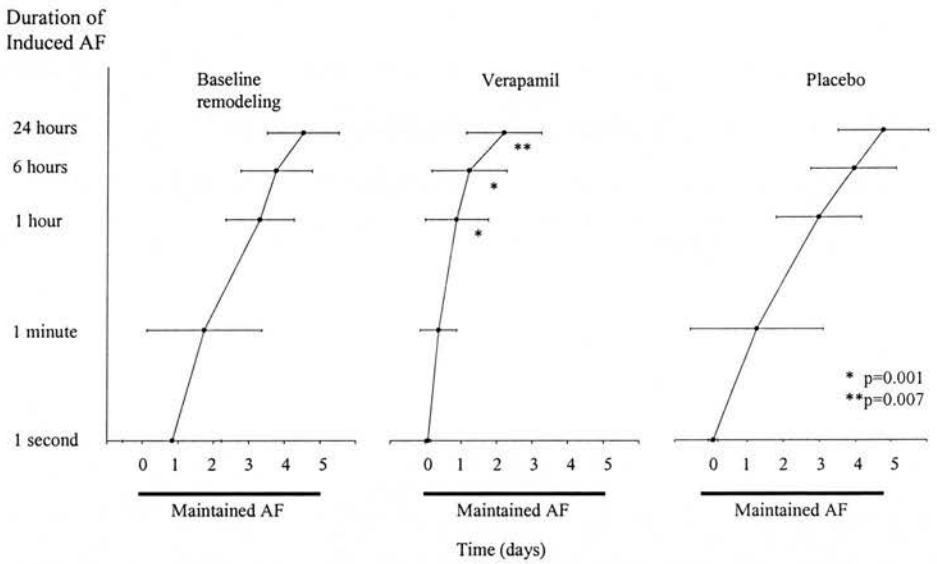

Figure 4.1 Increase in the stability of atrial fibrillation (AF) with verapamil compared to placebo and baseline remodelling. The duration of burst pacing required to induce AF durations of 1-hour, 6-hours and 24-hours is significantly reduced by verapamil. (**p=0.007, * p=0.001) *With permission Dr J Hobbs.*

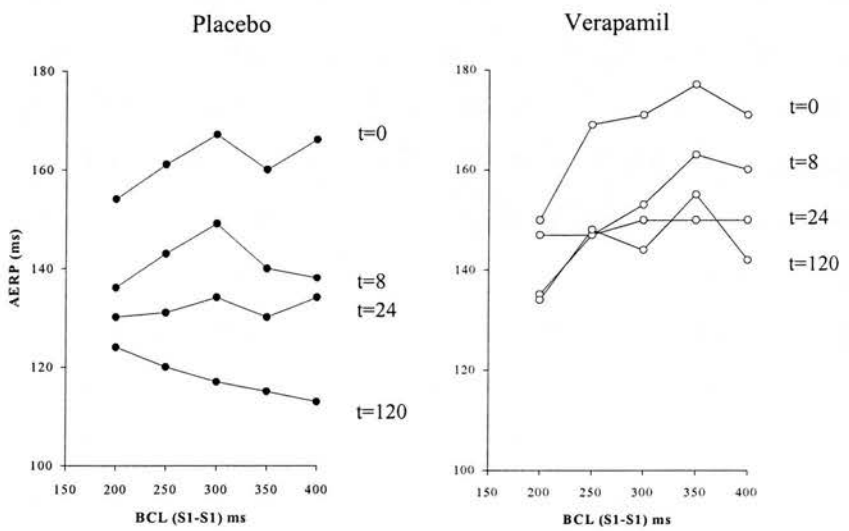

Figure 4.2 Atrial effective refractory period (AERP) at basic cycle lengths (BCL) from 200ms-400ms. Times from 0 hours (t=0) to 120 hours (t=120). Verapamil attenuates the reduction in atrial refractoriness and loss of rate adaptation. *With permission from Dr J Hobbs.*

In addition to our findings of an increase in stability of AF with verapamil other authors have found verapamil to exert a profibrillatory effect. Data

from Maastricht using the original Allessie goat model[31] showed that verapamil promotes AF stability in both the non-remodelled and remodelled atria, but that this effect was more prominent in the remodelled atrium. Verapamil had no effect on atrial refractoriness at longer (300-500ms) pacing cycle lengths but resulted in a shortening of AF cycle length and the atrial refractory period during AF (105-135ms) by approximately 15%, and caused an increase in fragmentation from type I to type II and type III AF.[32]

Friedman and coworkers also found that verapamil prolonged durations of induced AF in anaethetised dogs.[33] Using single extrastimuli to induce AF in non-remodelled atria these authors found an increase in the mean duration of induced AF from 19±6 secs in control dogs to 130±24 secs in dogs treated with verapamil. Verapamil did not significantly alter atrial refractoriness or atrial conduction velocity when measured in sinus rhythm, but induced AF tended to be faster and more disorganised in animals treated with verapamil compared to control animals. Haemodynamic monitoring showed that verapamil reduced arterial blood pressure and systemic vascular resistance but did not change cardiac output. In association with the increase in AF duration and altered haemodynamics an increase in plasma catecholamines was observed. A strong correlation between the increased duration of AF episodes and plasma catecholamine levels was noted. A small group of animals were studied with the combination of verapamil and beta-blocker (metoprolol). The pro-fibrillatory effect of verapamil was prevented by the beta-blocker, despite a more exaggerated haemodynamic effect due to the combination of drugs. The authors suggested that the profibrillatory action of verapamil is mediated by increased catecholamines. Against this hypothesis previous work has shown that sympathetic stimulation, by graded bilateral stellate ansa stimulation, does not promote sustained AF in the dog.[34]

Bernadcau and coworkers studied the effect of verapamil using multielectrode epicardial mapping in order to determine the underlying electrophysiological reasons for its profibrillatory action.[35] Using an anaethetised dog model and induction of AF by burst pacing verapamil was found to exhibit a dose-dependent promotion of AF stability. Contrary to the findings of Friedman et al[33] verapamil was found to alter atrial electrophysiology at baseline. There was a slight reduction in atrial refractoriness at a cycle length of 300ms, reduced dispersion of atrial refractoriness, and a heterogeneous increase in atrial conduction velocity. During AF the AF cycle length was reduced from 94±4ms to 84±3ms. Epicardial mapping indicated that verapamil increased the number of separate zones of reactivation per cycle suggesting an increase in the number of functional reentry circuits. This is a possible mechanism whereby verapamil might promote multiple circuit reentry. Autonomic blockade prevented the profibrillatory action of verapamil and the epicardial mapping showed that autonomic blockade reduced the number of zones of reactivation (functional reentry) to control conditions.

Data from studies on patients also show that verapamil shortens the mean fibrillatory interval during AF.[36] Atrial fibrillation cycle length was measured before and after administration of verapamil in a group of patients with chronic AF. Verapamil resulted in a reduction in the mean fibrillatory interval in the right atrial appendage, the right atrial free wall and the coronary sinus. The monophasic action potential duration (MAP_{d90}) was also reduced following verapamil suggesting that verapamil shortened atrial refractoriness in AF. There was no alteration in the relationship between fibrillation interval and MAP_{d90}, suggesting that verapamil does not influence the excitable gap during AF. The authors point out that verapamil was given slowly over 10 minutes with no significant change in blood pressure or right atrial pressure.

Conclusions

The studies suggest that despite beneficial effects on short-term atrial electrical remodelling,[20,22-24] longer term atrial electrical remodelling cannot be prevented by L-type calcium channel blockade.[25,27] The maximum duration of effective attenuation of atrial electrical remodelling by L-type calcium channel blockers is 5-days as shown in our study.(Dr WJ Hobbs, MD thesis) Despite the advantageous effect of verapamil on atrial electrical remodelling AF stability is increased,[31,33](Dr WJ Hobbs, MD thesis) probably by reducing atrial refractoriness in AF[31] and increasing functional reentry.[35] A potential role for catecholamines in the profibrillatory action of verapamil is suggested by the finding by some workers that beta-blockers prevent this effect.[33,35] It should be noted however that others have found the profibrillatory action still to be present following autonomic blockade.[25]

4.2 The Verapamil / Propafenone Combination

Verapamil has beneficial effects on atrial electrical remodelling but this does not translate into a reduced stability of AF. We postulated that the combination of verapamil with an antiarrhythmic drug might produce a beneficial effect. Propafenone was chosen to test for two reasons. First there are theoretical reasons to believe that propafenone would be effective in preventing the profibrillatory action of verapamil. Propafenone is known to cause a use-dependent prolongation of atrial refractoriness,[37] which should counteract the verapamil induced reduction in atrial refractoriness during AF.[31,35] Second recent clinical data has shown good efficacy for the combination of verapamil and propafenone in preventing recurrent AF following cardioversion.[29] In addition propafenone has no role in preventing atrial electrical remodelling[23] but is effective at preventing secondary episodes of AF during refractory period testing.

Propafenone is a Class Ic antiarrhythmic drug with electrophysiologic actions of sodium-channel blockade and beta-blocking activity.[38] The sodium channel blockade is both rate (increases at faster rates) and voltage-dependent (increases at less negative membrane potentials).[39] Although not recognised in its classification as a Class Ic agent, propafenone is known to prolong atrial refractoriness and action potential duration in atrial myocardium with marked use-dependence.[37] The beta-blocking potency is 1/20 to 1/80 than that of propranolol on a molar basis, but as plasma concentrations of propafenone may be 50x higher these effects may be relevant. [40,41] In addition to its effects on fast Na channels and its beta-blocking activity propafenone also blocks K^+ currents including I_{Kr} , I_{K1} , and I_{to} ,[42,43] but the clinical relevance of this action is not well defined.

The mechanism of action of propafenone in terminating atrial arrhythmias has been studied in some detail. Termination of reentrant atrial excitation (atrial flutter) by propafenone correlates with prolongation of the atrial

conduction velocity,[44,45] but not with wavelength prolongation. In a cholinergic dog model of AF propafenone has been shown to increase atrial refractoriness in a use-dependent manner and terminate AF by reducing the number and size of reentry circuits.[41] Although propafenone was also shown to slow conduction velocity in this model its net effect on atrial wavelength was prolongation and this was felt to mediate its anti-fibrillatory action.

Clinically, propafenone is well known to be effective in suppressing episodes of paroxysmal AF[46-48] and in cardioverting AF of recent onset.[49] Propafenone has also been shown to prevent the induction of AF,[50] and to terminate acute AF in patients with WPW[51] by prolongation of the atrial fibrillation cycle length. In view of the previous findings of a possible catecholamine mediated profibrillatory action of verapamil it is important to note that propafenone retains its ability to prolong AF cycle length and to cardiovert AF in the presence of adrenergic stimulation.[52]

Propafenone has a combination of favourable actions that suggest it may prevent the profibrillatory action of verapamil including prolongation of atrial refractoriness, an ability to prolong AF cycle length (even in the presence of adrenergic stimulation) and beta-blocking activity.

4.3 The Profibrillatory Effect of Verapamil is not Prevented by Propafenone

Methods

The study was performed using the new pacemaker based version of the Allessie goat model (see Chapter 3 for details). Eleven adult female goats (mean weight 58±7 kg) were used in the study. The experiments were conducted in accordance with a project license issued by the United Kingdom Home Office under the Animals (Scientific Procedures) Act 1986. The animals were allowed free access to food and water and were unrestrained in their pens throughout the experiments.

Pacemaker implantation, measurement of duration of induced AF, refractory periods and AF cycle length was performed as outlined in Chapter 3.

Study protocol

Following pacemaker implant the animals were allowed to recover for at least 5 days. Atrial refractoriness was measured on a daily basis to ensure its stability. When a baseline AERP had been determined the animals then underwent a 5-day protocol of repeated reinduction of AF followed by a recovery period of at least 5 days duration. During this period measurements were made of AERP, AF stability, AF cycle length, and ventricular cycle length at t = -4, 0, 4, 8, 12, 24, 32, 48, 56, 72, 80, 96, 104, 120 hours (Figure 4.3). The t= -4 hours measurement was taken as the baseline AERP. At t = 120 hours burst pacing was discontinued and the animals DC cardioverted under general anaesthetic. Anaesthesia was induced and maintained using 3% Isoflurane and a 2:1 mixture of O_2 and N_2O. The AERP was measured at time intervals of t = 4, 8, 12, 24, 32, 48, 56, 72, 80, 96, 104, 120 hours following cardioversion. In all animals AERP returned to baseline by 120-hours. Animals (n = 7) in the first part

(P1) of the study were then randomised to placebo, verapamil or verapamil/propafenone infusion in random order (Figure 4.3) and in second part (P2) of the study (n = 4) to placebo or propafenone infusions in random order. The second part of the study was cut short due to the onset of foot and mouth disease in the UK in the year 2000.

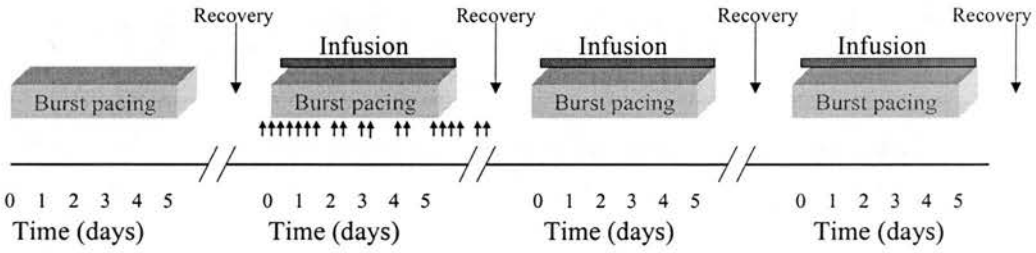

Figure 4.3 Schematic diagram of study protocol. ↑- indicates time of measurements.

Infusion protocol

We inserted 6F sheaths (Cordis®) into the left internal jugular vein under local anaesthetic and secured them with a single suture and a collar fashioned from a sphygmomanometer cuff. Each animal wore a harness to which an infusion pump (Graseby Medical MS 16A®) was secured. A Portex® infusion line with an in-line bacterial filter was used to connect the pump and central line. Loading doses followed by infusions were commenced 4 hours before burst pacing to allow a steady state to develop with electrophysiological measurements both prior to the start of the infusions (baseline) and immediately prior to the start of burst pacing (t = 0). Verapamil was given as an initial bolus of 0.1mg/kg over 10 minutes followed by a continuous infusion of 5mcg/kg/min during the rest of the experiment. Propafenone was given as an initial bolus of 1mg/kg followed by a continuous infusion of 333µg/kg/hr, up to a maximum of 480mg per day (maximum dose to goats of 60kg and above). The dose used was based on the manufacturers (Knoll Pharmaceuticals) recommended dose for intravenous use humans and was the maximum human dose in 9 of the 11 goats. A higher dose was used in 2 further animals but was discontinued due to side effects. The results for these animals are not

included. During the verapamil/ propafenone infusion the bolus doses were separated by 30 minutes to prevent side effects. During the placebo infusion the same volume of normal saline was infused. The central lines were removed immediately following each 5-day infusion and new lines re-inserted at the beginning of the next infusion.

Statistical analysis

Data analysis was performed using the statistical package SPSS version 8.0. Analysis of serial measures was performed by converting the data to a single measure using the area under the curve technique.[53] The logarithm of non-parametric data was used to transform the data to a normal distribution for statistical analysis. A two tailed p value of less than or equal to 0.05 was taken as significant.

Results

Effect of the drug infusions on baseline AERP and electrical remodelling

The protocol was successfully completed by 10 of the 11 goats. Due to problems with venous access one goat completed only two of the three infusions (placebo and verapamil/propafenone) in P1 of the study protocol. Measurements of AERP were obtained in all 11 goats. Neither placebo nor verapamil had any effect on baseline AERP prior to the onset of the pacing protocol. The verapamil/ propafenone infusion resulted in a significant increase in AERP from a baseline of 164±20ms to 179±19ms ($p < 0.01$, Figure 4.4). Propafenone alone also resulted in a significant increase in AERP from a baseline of 148±36ms to 163±45ms ($p = 0.02$, Figure 4.5). During placebo infusion and burst pacing AERP fell by a mean of 32±15ms at 24-hours, 46±18ms at 48-hours and by 48±23ms at 120-hours. The fall in atrial refractoriness was greatly attenuated by both the verapamil and the verapamil /propafenone infusions. During the verapamil infusion and burst pacing AERP fell by a mean of 13±19ms at 24-hours, 7±22ms at 48-hours and by 17±10ms at 120-hours ($p < 0.01$ *v placebo*).

During the verapamil/propafenone infusion and burst pacing AERP fell by a mean of 1±6ms at 24-hours, 8±14ms at 48-hours and by 16±17ms at 120-hours ($p < 0.01$ *v placebo,* Figure 4.4). During propafenone alone and burst pacing AERP fell by a mean of 0±37ms at 24-hours, 23±48ms at 48-hours and by 48±10ms at 120-hours ($p = 0.26$ *v placebo*). The initial increase in atrial refractoriness secondary to propafenone was abolished following 120-hours of atrial electrical remodelling (Figure 4.5). The absolute AERP values for P1 and P2 of the study are shown in Tables 1 and 2.

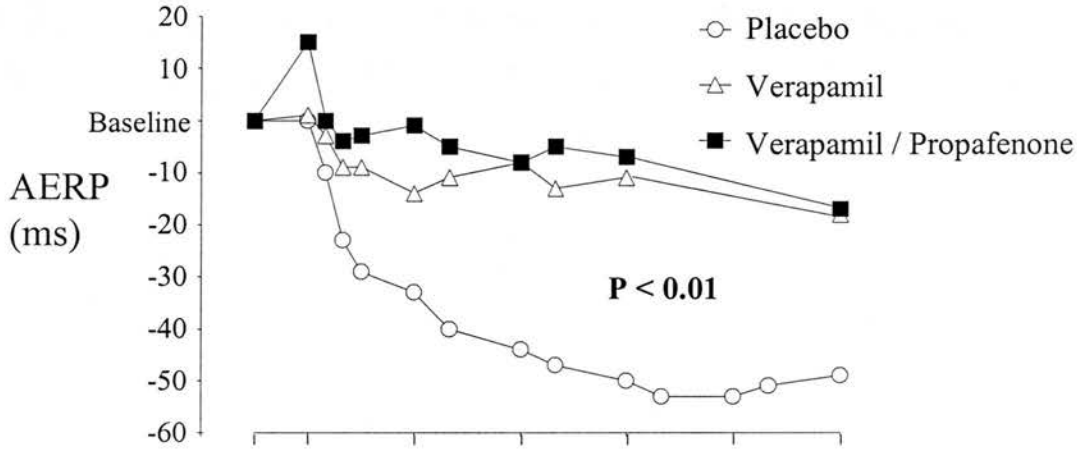

Figure 4.4 Changes in atrial refractoriness (AERP) at a drive train of 400 milliseconds (ms) for n = 7 goats, P1 of the study.

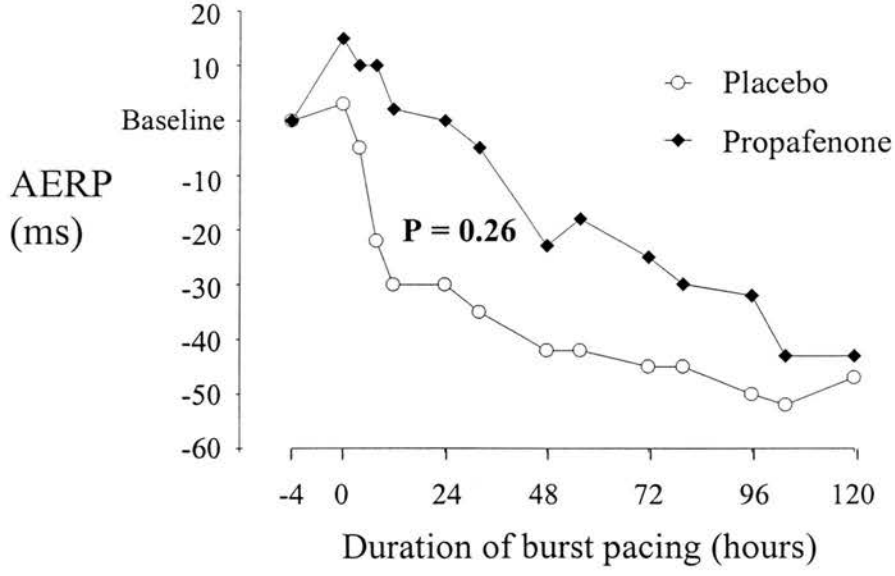

Figure 4.5 Changes in atrial refractoriness (AERP) at a drive train of 400 milliseconds (ms) for n = 4 goats, P2 of the study.

Table 1 : P1 of study. Mean atrial effective refractory periods			
Infusion	Placebo	Verapamil	Verap/Prop
-4 hrs	180±40ms	175±33ms	164±20ms
0 hrs	180±38ms	177±28ms	179±19ms
24hrs	147±36ms	162±31ms	163±21ms
72 hrs	130±42ms	165±32ms	157±28ms
120 hrs	131±42ms	158±33ms	147±32ms

Table 2 : P2 of study. Mean atrial effective refractory periods		
Infusion	Placebo	Propafenone
-4 hrs	155±33ms	148±44ms
0 hrs	158±36ms	163±55ms
24hrs	125±34ms	148±66ms
72 hrs	110±29ms	123±73ms
120 hrs	108±30ms	105±51ms

Overall effect of drug infusions on the stability of induced AF

In agreement with previous findings, despite attenuation of atrial electrical remodelling verapamil accelerated the self-perpetuation of AF in the goat model. The profibrillatory action of verapamil was not prevented by propafenone (Figure 4.6). Durations of burst pacing with the verapamil and verapamil/propafenone infusions required to induce individual durations of AF 1-second (11 hours and 7 hours), 1-minute (12 hours and 10 hours), 1-hour (39 hours and 29 hours), 6-hours (44 hours and 62 hours) and 24-hours (70 hours and 78 hours) were broadly similar. Propafenone alone resulted in a reduction in AF stability compared to placebo (Figure 4.7).

Effect of drug infusions on AF cycle length

There was a high correlation ($r = 0.96$) between measurements of mean AF cycle lengths made by the 2 observers. In agreement with previous findings AF cycle length was lower with both the verapamil and the verapamil/propafenone infusions than placebo in the first 24-hours ($p = 0.02$). In contrast to previous findings the AF cycle length remained on average lower than placebo with both the verapamil and verapamil/ propafenone infusions for the entire 120-hour period of burst pacing (Figure 4.8). Propafenone alone caused a non-significant increase in AF cycle length compared to placebo over the 120-hour period (Figure 4.9).

The effectiveness of propafenone on the non-remodelled atrium

Further analysis of the data shows that the effects of propafenone are more noticeable on the non-remodelled atria. Over the full 5-day period there are no significant differences in atrial refractoriness or AF cycle length for the infusions containing propafenone either alone or in combination with verapamil. However, atrial refractoriness shows a trend to being longer prior to commencing burst pacing with verapamil/ propafenone infusion compared with verapamil alone ($p = 0.08$). With propafenone alone compared to placebo atrial refractoriness is not only shows this trend at baseline prior to commencing burst pacing but also shows a trend to remains longer than placebo ($p = 0.068$) over the initial 48-hours of infusions. Atrial refractoriness could not be measured during AF so AF cycle length was used as a surrogate for atrial refractoriness. AF cycle length showed a similar pattern with a significant prolongation of AF cycle length in the first 72-hours of the verapamil/ propafenone infusion compared to verapamil alone ($p = 0.043$). In fact in the first 72-hours AF cycle length is not significantly different between the placebo and verapamil/ propafenone infusions ($p = 0.34$, Figure 4.8). This analysis of AF cycle length was not possible for propafenone compared to placebo as one goat had no AF and the numbers were too small. It is worth noting that despite the favourable early effects of propafenone on atrial refractoriness

and AF cycle length there was no difference in the durations of induced episodes of AF with the verapamil/propafenone infusion compared to verapamil alone during the initial 24-48 hours of burst pacing. Propafenone alone resulted in a trend to less AF than with placebo, but due to small numbers this did not reach statistical significance.

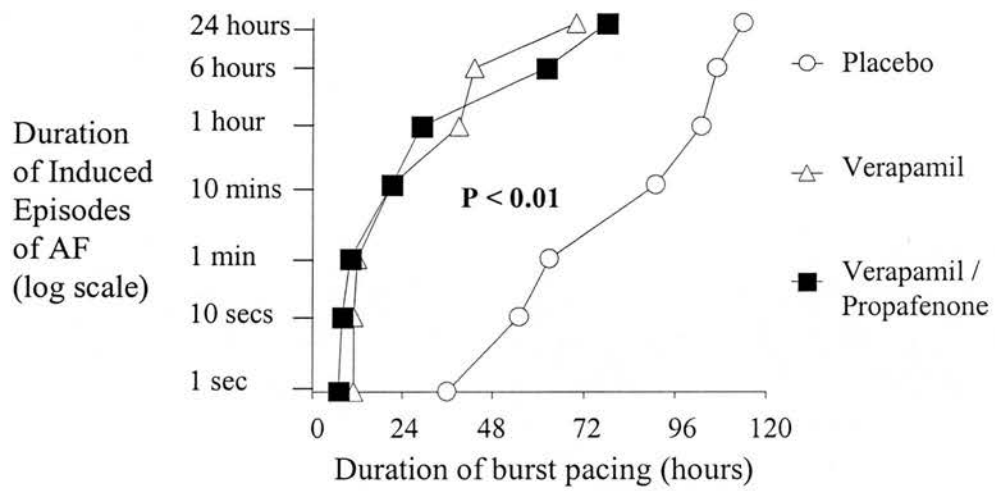

Figure 4.6 Duration of induced episodes of AF plotted against duration of burst pacing. n = 7 goats, P1 of the study.

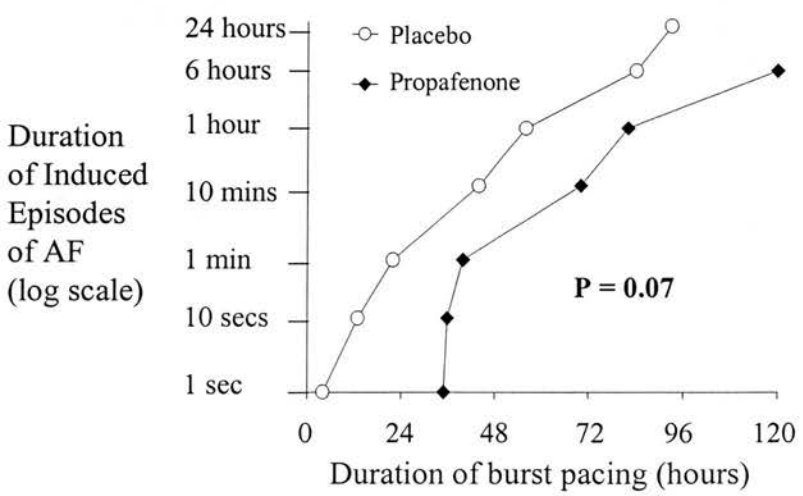

Figure 4.7 Duration of induced episodes of AF plotted against duration of burst pacing. n = 4 goats, P2 of the study.

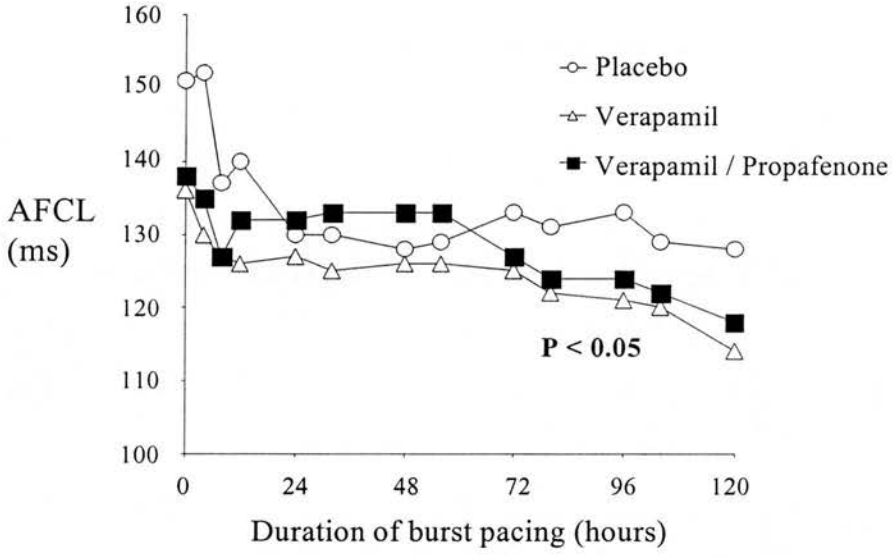

Figure 4.8 Changes in atrial fibrillation cycle length (AFCL) with burst pacing. The mean AFCL with the verapamil infusion is significantly less than with placebo ($P < 0.05$). ms- milliseconds

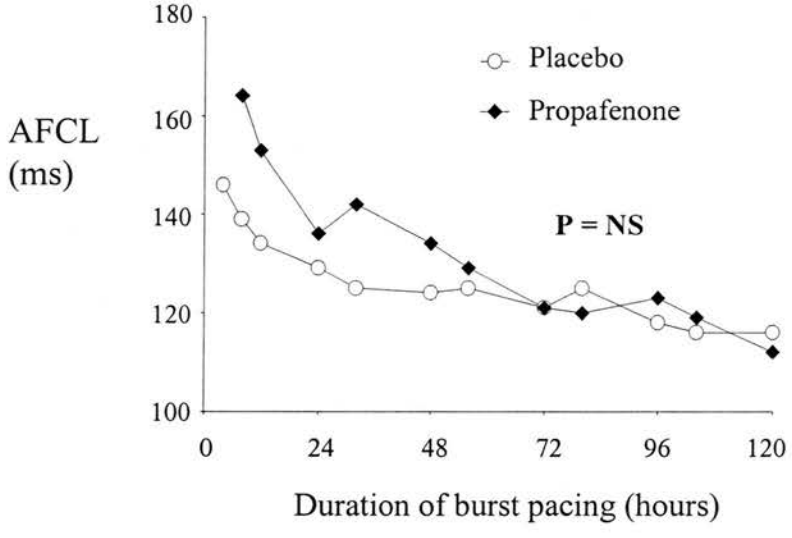

Figure 4.9 Changes in atrial fibrillation cycle length (AFCL) with burst pacing. The mean AFCL with the propafenone infusion is not significantly different from placebo over the 120-hour period (P = NS). ms- milliseconds

Effect of verapamil on ventricular cycle length during AF

Ventricular cycle length during AF was longer in the verapamil/propafenone arm (685±72ms) than in the verapamil arm (615±53ms) and both were significantly longer than the ventricular cycle length in the placebo arm (413±86ms, $p < 0.01$) throughout the 5-day pacing period, confirming the effects of the drugs on AV nodal conduction throughout the experimental period.

Discussion

Main findings of the study

The main finding of this study is that propafenone does not prevent the profibrillatory action of verapamil. Propafenone, in the absence of verapamil, reduced the durations of induced episodes of AF compared to placebo. Changes in atrial refractoriness at baseline confirm a significant electrophysiological action of propafenone at the dosage studied. The results also confirm previous findings that verapamil inhibits the reduction in atrial refractoriness (atrial electrical remodelling) associated with a 5-day period of AF, but that the effects on remodelling are outweighed by its profibrillatory actions with the net effect of an increase in the self-perpetuation of AF in the goat model. Verapamil causes a reduction in AF cycle length that is not prevented by propafenone.

Why did propafenone not prevent the profibrillatory action of verapamil?

Duytschaever and colleagues found that during episodes of induced AF in the goat verapamil caused a reduction in atrial refractoriness resulting in a reduction in the atrial wavelength.[31] Verapamil has also been shown to cause a reduction in AF cycle length and action potential duration in patients with chronic AF.[36] Propafenone might be expected to be effective in preventing or reducing this profibrillatory action of verapamil as it exerts a marked use-dependent prolongation of atrial refractoriness, and can cardiovert AF by prolongation of the atrial wavelength.[41,51] In our study there was evidence for an initial propafenone-mediated prolongation of atrial refractoriness at a pacing cycle length of 400ms. However, following a period of atrial electrical remodelling (24-48 hours) the refractory period lengthening effect of propafenone was lost (Figure 4.4 and 4.5). This was also evident for the effect of propafenone on AF cycle length, which was significantly longer with the combination of verapamil/propafenone in the first 72-hours of burst pacing than with verapamil alone. However, despite effects on atrial refractoriness, both at 400ms and during AF, propafenone did not prevent AF when used in

combination with verapamil even early in the protocol. On its own propafenone had some antifibrillatory effect, which would likely have been significant with an increased number of animals.

This raises two issues. Firstly propafenone loses its effect on atrial electrophysiology as remodelling progresses. It is possible that remodelling induced changes in ion channels occur altering the effect of propafenone. For instance, a reduction in sodium channels during atrial electrical remodelling has been described.[54] A possible explanation for the absence of a significant effect of propafenone on AF stability is the lack of a significant electrophysiological effect on the remodelled goat atrium. **** Although there is no previous data on the use of propafenone in goats, the electrophysiological effects of flecainide[55] on remodelled goat atria have been previously examined. Flecainide had no effect on the refractory period during AF and because of a reduction in conduction velocity the wavelength in AF was in fact reduced. Despite this flecainide was effective in converting AF to sinus rhythm. Propafenone also reduces atrial conduction velocity during AF and it is possible that any beneficial effects of a prolongation in atrial refractoriness during AF (if this occurs) may have been negated by a reduction in atrial conduction velocity.

Second, propafenone alone has an antifibrillatory action but not in combination with verapamil. This suggests that the profibrillatory action of verapamil is not mediated via changes in atrial electrophysiology that can be influenced by propafenone e.g. atrial refractoriness during AF. An alternative mechanism for the profibrillatory action of verapamil may be the creation of local conduction disturbances, promoting re-entry. Evidence for this hypothesis is the marked increase in fragmentation of atrial electrograms that have been noted with verapamil both in sinus rhythm[17] and in AF.[31] Changes in local conduction with increased fragmentation of wavefronts may underlie the epicardial mapping findings of AF in the presence of verapamil, which show an increase in the number

of zones of reactivation suggesting an increase in multiple wavelet reentry.[35]

The relevance of propafenone's beta-blocking action

Friedman et al[33] suggested that verapamil promoted AF stability by causing a significant sympathetic response that could be prevented by metoprolol. However, unopposed sympathetic stimulation has not previously been shown to promote AF stability in dogs.[34] Propafenone has beta-blocking activity that may have resulted in a reduction of AF stability but this was not found. The longer ventricular cycle length with verapamil and propafenone combination compared to verapamil alone (685±72ms v 615±53ms) suggests the presence of some beta-blocking effect in the study.

Possible explanations of the clinical benefit of verapamil and propafenone

The beneficial clinical effect of the verapamil and propafenone in preventing recurrence of AF following cardioversion found by De Simone et al[29] may have been secondary to an effect of verapamil on atrial ectopy (triggers) rather than atrial electrical remodelling (substrate). Increased intracellular calcium levels increase spontaneous tachyarrhythmias in cardiac muscle[56] and by blocking calcium entry into cells verapamil reduces atrial ectopy following cardioversion of persistent AF.[30] During our study protocol the trigger for AF remained constant as AF was continually reinduced by burst pacing. This would have negated any beneficial effects of verapamil on AF triggers.

Limitations of the study

The assessment of the ongoing electrophysiological processes involved in the profibrillatory action of verapamil and the lack of effect of propafenone are limited to measurement of AERP, AF cycle length and AF duration. Insights into possible mechanisms underlying the findings of this study may have been possible with measurements of conduction

velocity or of atrial refractoriness during AF itself. Mapping of atrial activation was not performed and consequently the effect of the drugs on the number and organisation of reentrant wavelets could not be determined.

Novel aspects and clinical implications.

The results indicate that the combination of verapamil and propafenone is not likely to be of any value in halting the clinical progression of paroxysmal to persistent AF and may in fact accelerate this process.

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Chapter 5

Repetitive Four-Week Periods of Atrial Electrical Remodelling Promote Stability of Atrial Fibrillation

Evidence for a second factor independent of atrial refractoriness in the self-perpetuation of atrial fibrillation

Presented as an abstract at AHA 2000 Circulation 2000:102;743 &
Judges' Choice British Cardiac Society 2001 Heart 2001:85;Supp1, P9

Circulation - *in press*

ABSTRACT

Background Episodes of atrial fibrillation (AF) are known to cause both a rapid reduction in atrial refractoriness (atrial electrical remodelling) and a more delayed increase in AF stability in the chronic goat model. The aims of this study were to examine (1) the hypothesis that an AF-induced increase in AF stability might be due to a mechanism with a longer onset and offset than changes in atrial refractoriness and (2) the possibility that repeated periods of maintained AF might cause a cumulative increase in AF stability independent of changes in atrial refractoriness.

Methods and Results AF was maintained in six goats by burst atrial pacing for three consecutive 4-week periods, each separated from each other by a mean of 6±2.1 days of sinus rhythm. Six days of sinus rhythm was just sufficient for refractoriness changes to fully reverse in all goats. Assessments of atrial effective refractory period (AERP), AF cycle length, AF inducibility and duration of individual episodes of AF were made at regular intervals. The mean duration of burst pacing required to induce individual episodes of AF of 60-seconds, 1-hour and 24-hours duration decreased progressively from month 1 to month 2 to month 3 (178 hours, 110 hours and 21 hours; 229 hours, 136 hours and 68 hours; 277 hours, 192 hours and 102 hours respectively, $p < 0.03$). The frequency with which AF was induced during extrastimulus pacing increased progressively from 16.7% in month 1, to 31.7% in month 2 and 46.9% in month 3 ($p < 0.001$).

Conclusions Sequential 4-week periods of atrial fibrillation result in an increase in AF stability independent of baseline atrial refractory period. This suggests the presence of a 'second factor' in the self-perpetuation of AF with a longer time course than changes in atrial refractoriness.

Introduction

Atrial fibrillation has a tendency to become more persistent with time and a large percentage of patients with paroxysmal AF develop persistent AF.[1,2] In an experimental study[3] Wijffels and coworkers demonstrated, in a chronically instrumented conscious goat model, that episodes of AF are self-perpetuating ("AF begets AF"). This self-perpetuating process is accompanied by a reduction in atrial refractoriness (termed atrial electrical remodelling), and there are good theoretical reasons to believe that such an electrophysiological change would lead to the stabilisation of AF.[4] The concept of atrial electrical remodelling has since become widely accepted and its presence has been confirmed in different models by a number of groups.[5-7]

Changes in atrial refractoriness, however, may not be the only factor responsible for the onset of stable AF.[8] Wijffels and others[3,9] have found that changes in atrial refractoriness do not run in parallel with the time course of onset of stable AF. Atrial refractoriness falls rapidly in the first few days of AF reinduction and maximal changes in atrial refractoriness often precede the onset of stable AF by several days. A role for factors other than atrial electrical remodelling in the recurrence of AF following cardioversion in patients has also been suggested. Some patients with previous prolonged episodes of AF continue to show persistently increased vulnerability to AF despite long periods of sinus rhythm between episodes.[10]

Using the original Allessie chronically instrumented goat model Garratt and coworkers[11] studied repetitive 5-day periods of AF reinduction to examine the hypothesis that an AF-induced increase in AF stability might be due to a mechanism (a so-called second factor) with a longer time course than that of changes in atrial refractoriness. If this were the case, then it would be expected that the increase in AF vulnerability and stability that is evident following a period of AF would remain for a longer

time than that required for atrial refractoriness to return to normal. A second aim of the study was to examine the possibility that repeated episodes of AF result in a cumulative increase in AF inducibility or stability independent of changes in atrial refractoriness. This would provide a potential means whereby recurrent paroxysms of AF might progress to persistent AF despite full reversal of refractoriness changes between successive paroxysms. No progressive increase in AF inducibility, vulnerability or stability was demonstrable in this study, indicating either that a second factor did not exist or had a longer onset than the 5 days selected in the protocol.[12] The aim of the current study was to retest the above hypotheses using 4-week periods of AF. This duration of AF was chosen because it has been shown that AF of this duration leads to ultrastructural changes in atrial myocardium.[13]

Methods

Six adult female goats (mean weight 60.5 ± 10 kg) were used in the study. The experiments were conducted in accordance with the project license issued by the United Kingdom Home Office under the Animals (Scientific Procedures) Act 1986. The animals were allowed free access to food and water and were unrestrained in their pens throughout the experiments.

A fully implantable burst pacing model of AF

Currently available implantable pacemaker-based animal models of AF use rapid atrial pacing rather than continuous reinduction of AF to induce atrial electrical remodeling. As a consequence the effect of the remodeling process on AF stability (duration of individual episodes of AF) cannot be measured continuously. We developed a modified pacemaker-based model of AF in which the original Allessie burst pacing protocol is incorporated, thereby allowing continuous monitoring/recording of the self perpetuating process in addition to measurements of atrial refractoriness and AF inducibility.

Pacemaker implant

Anaesthesia was induced and maintained using 3% Isoflurane and a 2:1 mixture of O_2 and N_2O. The animals were placed in the left lateral position and 1 gram of flucloxacillin was given intravenously. Using aseptic surgical technique an incision was made in the lateral aspect of the neck exposing the right internal jugular vein. The vein was mobilised and ligated and three active-fixation bipolar steroid eluting leads introduced via a small venotomy and positioned on the septal portion of the right atrium (2 leads) and right ventricular apex (1 lead). Sensing and threshold characteristics were determined before connecting one atrial lead to an Intermedics pacemaker and the remaining leads to the atrial and ventricular channels of a Medtronic Thera® pacemaker. The leads were secured and pacemakers buried subcutaneously prior to wound closure. An ECG telemetry unit (Data Sciences Inc) was buried subcutaneously in the right flank through a further small incision.

Study protocol

After pacemaker implant the animals were allowed to recover for at least 5 days. The animals then commenced repetitive reinduction of AF for the first 4-week period. Specifically designed software in the Medtronic pacemaker was used to deliver burst pacing during sinus rhythm via the right atrial lead in a manner similar to that in the originally described Allessie goat model. Whenever sinus rhythm was detected the pacemaker delivered a 2 second burst of pacing at 64 Hz. Burst pacing was inhibited whenever AF was detected. During this period measurements were made of AERP, inducibility of AF by extrastimulus pacing, AF stability, AF cycle length and ventricular cycle length at t = 0, 4, 8, 12, and 24 hours, then twice daily until 120 hours and then every 24 hours until the end of the 4-week protocol. At the end of the 4-weeks the goats were DC cardioverted under general anaesthesia. Thereafter AERP was measured daily until it recovered to baseline. When AERP reached baseline repetitive reinduction of AF was commenced for the second 4-week

period. At the end of the second 4-week period the goat was again DC cardioverted and AERP measured daily until recovery, prior to commencing the third period of AF reinduction. After the third 4-week period the goat was DC cardioverted and AERP measured daily until recovery (Figure 5.1).

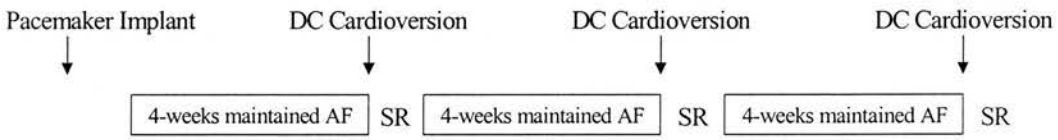

Figure 5.1 The Study Protocol. AF - atrial fibrillation, SR - sinus rhythm

Measurement of refractory periods and AF cycle length

The Intermedics pacemaker was used to deliver extra stimulus pacing via the external programmer to determine atrial effective refractory periods (AERP) during a basic pacing drive of 400ms. A standard drive train of 8 extrastimuli (S_1) was followed by a single S_2, all at four times diastolic threshold. The initial S_1-S_2 coupling interval was commenced at a shorter interval than the expected AERP and increased incrementally until atrial capture was achieved. The AERP was recorded as the mean of the two longest S_1-S_2 that failed to capture the atrium. The time course of remodelling was calculated using the logarithmic function $\tau = (AERP_t - AERP_{t=0}) / \ln(t)$, where t is time, ln is natural logarithm, and τ is the time constant of remodelling.[14] To determine AFCL we recorded 10-second segments of bipolar atrial electrogram at 100 mm/s via telemetry from the atrial lead in the Thera pacemaker. Two independent observers then calculated mean AFCL and these two values were averaged.

Inducibility of AF

At the time of measurement of AERP, the presence or absence of AF induced as a response to the earliest extrastimulus was recorded at each pacing rate. AF was considered to be induced if the single premature

response was followed by rapid irregular atrial activity lasting > 1 second on at least 2 of 3 attempts.

Duration of induced AF

The duration of induced episodes of AF was determined using 1) direct telemetry of the endocardial atrial signal via the pacemaker programmer and from 2) the surface ECG telemetered via the Datasciences implant which was continuously displayed and recorded on a personnel computer. In addition the Thera software recorded a log of time and cumulative number of bursts delivered.

Statistical analysis

Data analysis was performed using the statistical package SPSS version 8.0. Data were expressed as mean ± standard deviation. Paired data were analysed using a paired t-test for parametric data and Wilcoxon Log Rank test for non-parametric data. Analysis of serial measures was performed by converting the data to a single measure (area under the curve).[15] The logarithm of non-normally distributed data was used to transform data to a normal distribution for analysis by ANOVA. A two tailed p value of less than or equal to 0.05 was taken as significant.

Results

Stability of AF

All 6 goats successfully completed the protocol. The stability of AF increased with time over each 4-week period of burst pacing in each goat. Despite a wide variation in the onset of AF stability in individual goats there was evidence of a progressive increase in AF stability from month 1 to month 2 to month 3 in all the goats (Figure 5.2). There was a progressive reduction from month 1 to month 2 to month 3 in the mean duration of burst pacing required to induce individual episodes of AF of 1-second (65 hours, 23 hours and 1.5 hours), 10-seconds (103 hours, 83

hours and 4 hours), 60-seconds (178 hours, 110 hours and 21 hours), 1-hour (229 hours, 136 hours and 68 hours), 6-hours (258 hours, 176 hours and 87 hours) and 24-hours duration (277 hours, 192 hours and 102 hours, $p < 0.03$). There was considerable inter-goat variability in the onset of AF stability as illustrated in Figure 5.3.

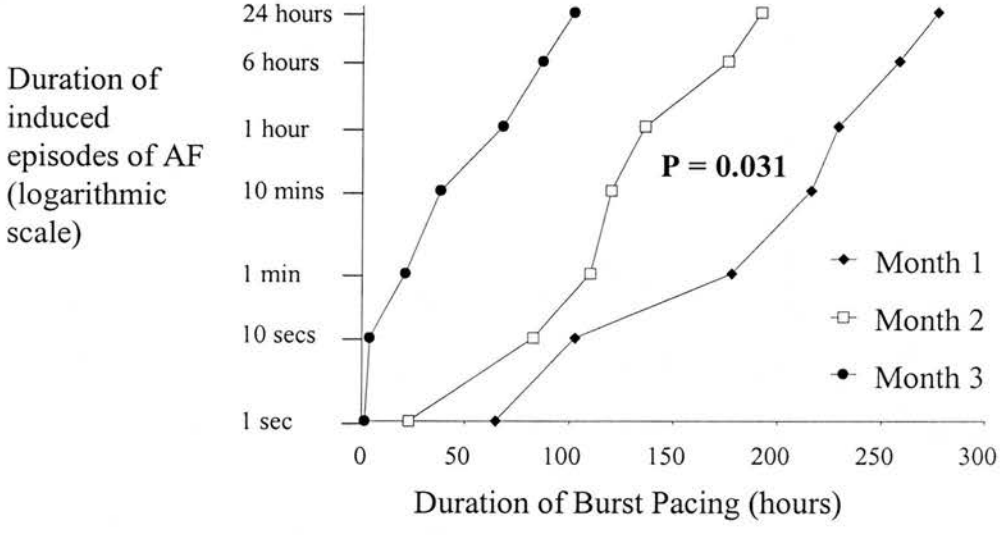

Figure 5.2 Changes in mean duration of burst pacing required to induce atrial fibrillation (AF) episodes. Results are expressed as mean of values obtained in all goats. From month-1 to month-3 there is a progressive decrease in the duration of burst pacing required to induce all of the pre-specified AF durations (indicated on the y-axis). The P value refers to ANOVA of area under each curve.[15]

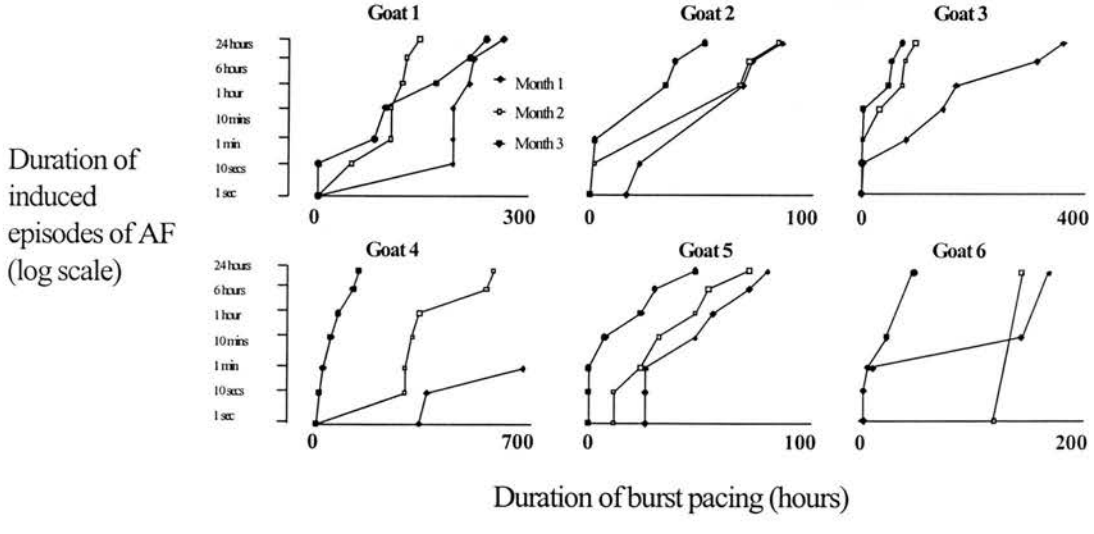

Figure 5.3 Variability in the onset of AF stability in the 6 goats. Note the different scales on the x-axis on for each goat.

Inducibility of AF

AF inducibility was assessed during extrastimulus pacing at the time of measurement of atrial effective refractory period. The frequency with which AF was induced during extrastimulus pacing increased progressively from 16.7% in month 1, to 31.7% in month 2 and 46.9% in month 3 ($p < 0.001$). Episodes of AF of greater than 1-second duration were inducible by burst pacing at baseline at the start of month 3, in contrast to months 1 and 2.

Atrial Refractoriness

Atrial electrical remodelling (defined as a reduction in atrial refractoriness measured during a 400ms drive) occurred in all 6 goats in the study. Measurement of atrial refractoriness was possible in all the goats during the first 12 hours of maintained AF. As the duration of AF episodes became more sustained over time the opportunity to measure atrial refractory periods became fewer. In month 1 this was possible in 6/6 goats at 24 hours, 6/6 goats at 32 hours, 6/6 goats at 72 hours, 4/6 at 120 hours and 2/6 at 10 days. In month 2 in 6/6 goats at 24 hours, 6/6 goats at 32 hours, 4/6 goats at 72 hours, 3/6 at 120 hours and 1/6 at 10 days. In month 3 in 5/6 goats at 24 hours, 5/6 goats at 32 hours, 2/6 goats at 72 hours, 1/6 at 120 hours and 0/6 at 10 days. Refractory period measurements during the three successive 4-week periods of maintained AF are shown in Figure 5.4. There was a trend to more rapid time course of remodelling (τ) during the first 32 hours of burst pacing from a mean of 5.3 in month-1, to 9.1 in month-2 and 14.9 in month-3 ($p = 0.07$). Following both the first and second periods of AF atrial refractoriness had returned to baseline values ($\pm$ 5%) after 6 days of sinus rhythm in all 6 goats. The mean time required for AERP to return to baseline was 144 ± 55 hours. The mean time required for AERP to return to normal did not change over the three one-month periods (month-1 144 hours, month-2 156 hours and month-3 132 hours, $p = 0.78$). The variability between goats of changes in AERP is shown in Figure 5.5.

Atrial Fibrillation Cycle Length

The shortening of atrial refractoriness was accompanied by a reduction in mean AF cycle length in all goats (Figure 5.6). There was no evidence of a cumulative effect of the episodes of maintained AF on the AF cycle length either in absolute terms or in the rate of development.

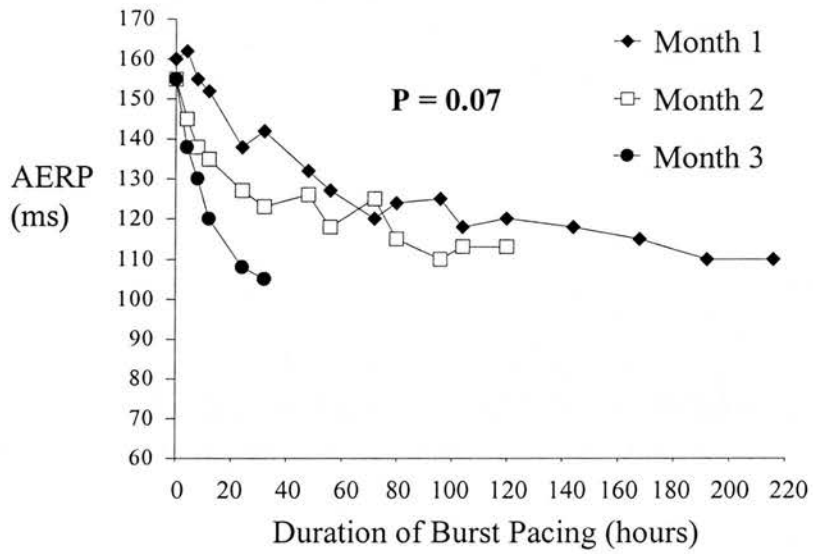

Figure 5.4 Changes in right atrial refractoriness measured during a basic pacing cycle length of 400ms at pre-specified time points throughout the protocol. Results are expressed as mean of values obtained in all goats. The P value refers to ANOVA of τ (the time constant of remodelling).[14] AERP – atrial effective refractory period, ms – milliseconds.

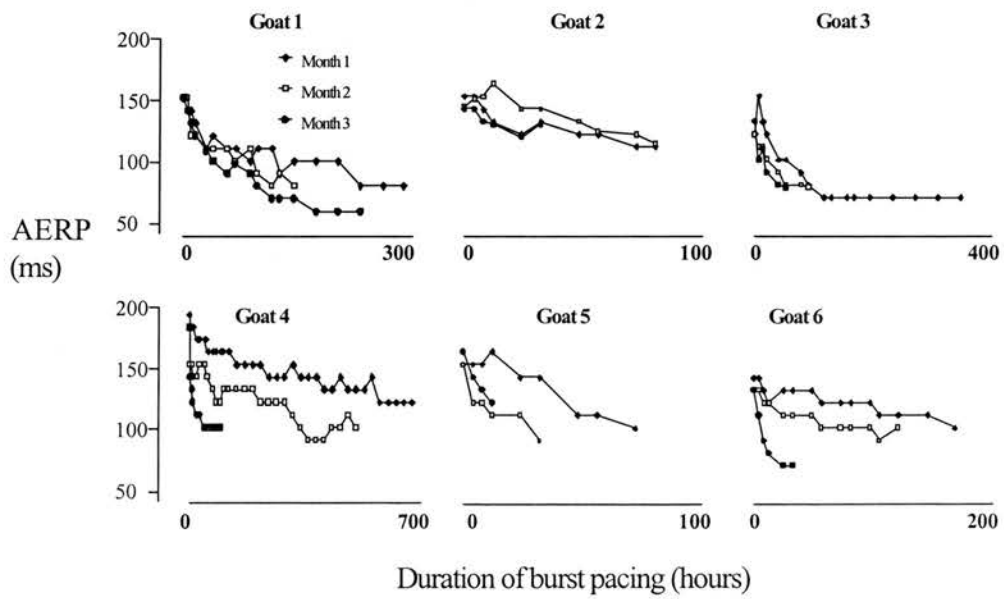

Figure 5.5 Variability in the onset of AERP changes in the 6 goats. The individual goat numbers are the same as in Figure 5.3. Note the different scales on the x-axis on for each goat.

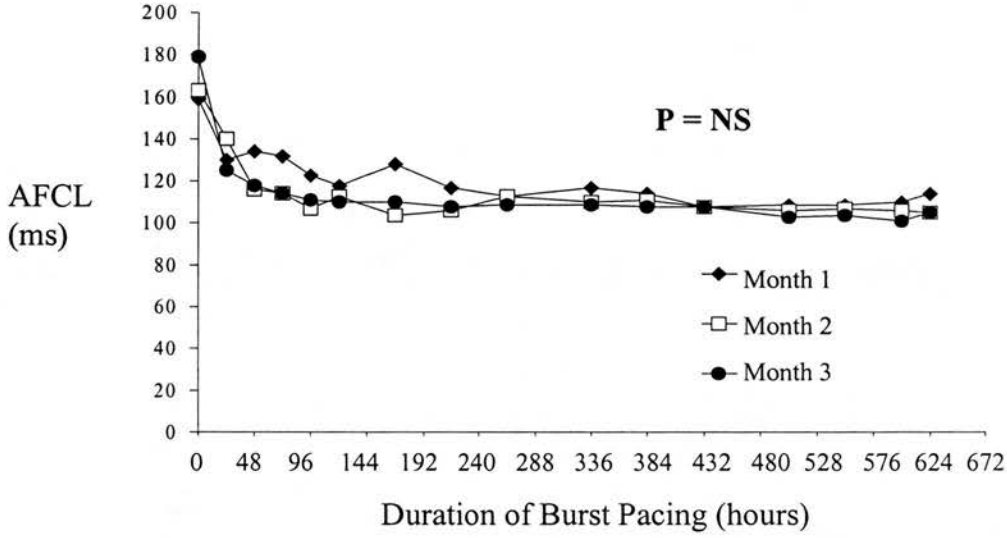

Figure 5.6 Changes in atrial fibrillation cycle length (AFCL) at pre-specified time points throughout the protocol. Results are expressed as mean of values obtained in all goats. ms – milliseconds.

Mean ventricular rate in AF

The mean ventricular rate in AF remained stable from month 1 to month 3 (393±65ms, 436±50ms, 373±23ms, p = 0.1). The mean sinus cycle length measured at 24-hours post-cardioversion also remained stable from month 1 to month 3 (504±76ms, 541±60ms, 551±47ms, p = 0.42)

Discussion

Main Findings

The principal findings of the study are that repetitive periods of maintained atrial fibrillation have a cumulative effect on AF stability and AF inducibility independent of changes in baseline atrial refractoriness i.e. there is a second factor independent of atrial refractoriness involved in the self-perpetuation of AF. The time course of the onset and offset of action of this second factor is longer than that of changes in atrial refractoriness. In this study care was taken to avoid repeated cardiac instrumentation and/or tissue biopsy, as such procedures would have complicated interpretation of the sequential measurements of AF stability. As a consequence of this study design, the question of the precise nature of this 'second factor' remains unresolved.

What is the second factor?

There are several possible candidates for a second factor including structural changes in the atria such as atrial dilatation, changes in conduction properties of the atria and changes in the spatial dispersion of atrial refractoriness.

Structural Changes

Patients with longstanding AF often have dilated atria[16] and an increase in atrial 'area' would be expected to increase AF stability in accordance with Moe's multiple wavelet hypothesis.[17] Although previous experimental work in dogs has shown biatrial enlargement following a 6-week period of rapid atrial pacing,[6] patients with brief (<2 weeks) or moderate (2-6 weeks) durations of AF do not have a measurable increase in left atrial size.[18] Several weeks of AF in the goat model causes structural changes in atrial myocytes that may predispose to atrial dilatation including loss of myofibrils and fragmentation of the sarcoplasmic reticulum.[19] These myolytic cell changes increase between weeks 1 and 8 of maintained AF[13]

and have been shown to correlate with the stabilisation of AF.[20] Following a 16-week period of AF structural changes are still present 8-weeks following return to sinus rhythm,[21] and in association with the persistence of these structural changes the atria remain vulnerable to AF. Structural changes resulting in increased atrial vulnerability to AF have also been shown in other models. Using a combined rapid atrial pacing / mitral regurgitation model of AF Everett and coworkers[22] have shown a differential time course of reversal of electrophysiological remodelling and structural remodelling in the dog.

Interstitial changes promoting vulnerability to AF have also been shown in the canine pacing-induced heart failure model of AF. In this model AF vulnerability is increased without alterations in atrial electrophysiology,[23] the likely underlying mechanism being the presence of extensive interstitial fibrosis resulting in discrete areas of slow atrial conduction. The difference between the original findings of Garratt and coworkers[11] using repetitive 5-day periods of maintained AF compared to the 4-weeks used in our study may be due to an increase in structural changes associated with the longer duration of maintained AF.

Dispersion of Atrial Refractoriness

The increased stability of AF during months 2 and 3 of maintained AF may have occurred due to a persistent increase in dispersion of atrial refractoriness. Regional variability of atrial refractoriness was demonstrated to be essential for the generation of AF in the classic computer model of Moe et al.[4] Previous studies in the goat, however, have not found any AF-induced changes in dispersion of atrial refractoriness.[3] In addition, following restoration of sinus rhythm recovery of atrial refractoriness occurs at the same rate in the left and right atria,[11] and dispersion of atrial refractoriness has even shown a trend to decrease following 24-hours of rapid atrial pacing in the goat model.[24]

The findings in dog models have been somewhat different. Chronic atrial pacing results in an increase in dispersion of AF cycle length[9] and an increase in dispersion of atrial refractoriness.[25,26] This increase in refractoriness heterogeneity increases vulnerability to AF.[25] Following restoration of sinus rhythm recovery of dispersion of atrial refractoriness is relatively rapid returning to control values within 20 hours.[27]

Significant dispersion of right atrial refractoriness is present following cardioversion of persistent AF in humans,[28] and an increased dispersion of atrial fibrillation cycle length at the time of cardioversion of persistent AF has been shown to be associated with an increased risk of recurrent AF.[29] Patients with lone paroxysmal AF have an enhanced vulnerability to AF, despite long periods of sinus rhythm, and this has been linked to an increased dispersion of atrial refractoriness, as determined by measurement of local atrial fibrillation cycle length.[30] Despite variable evidence from animal models dispersion of atrial refractoriness does appear to be an important factor in the onset of stable AF in patients with both paroxysmal and persistent AF.

Conduction Velocity

A reduction in atrial refractoriness promotes stability of AF by reducing atrial wavelength. Similarly a reduction in conduction velocity would result in a reduction in atrial wavelength so increasing AF stability.[17] Patients with chronic AF have been shown to have a reduced atrial conduction velocity[31,32] and an increased P-wave duration[31,32] immediately post-cardioversion. However, no changes in conduction velocity have been noted in the goat model of AF.[3,11] Studies in dog models of AF have shown a reduction in conduction velocity,[9,26,33] and an associated decrease in sodium current (I_{Na}) in atrial myocytes, with AF duration being related to I_{Na} density in each dog.[34] Changes in conduction velocity have been shown to have a longer time course of onset[9,26] than changes in atrial refractoriness, and a link between the onset of AF stability and changes in

conduction velocity has previously been suggested.[9] The recovery of conduction velocity to control values following conversion of AF to sinus rhythm also appears to be more prolonged than recovery of atrial refractoriness both in dogs[26] and in humans.[32]

Cellular Mechanisms

The time course of onset and offset of atrial electrical remodelling (i.e. days) suggests that processes involving altered gene expression of ion channel proteins may be involved. Several recent studies have shown changes in atrial ionic currents, protein expression and mRNA. There is good evidence from both animals and humans that the reduction in atrial refractoriness associated with atrial electrical remodelling is associated with a reduced L-type Ca^{2+} current ($I_{Ca,L}$) density of about 70% and a reduction in the Ca^{2+}-independent transient outward current (I_{to}).[35,36] Changes in mRNA levels for the $alpha_{1c}$ subunit of the L-type Ca^{2+} channel for Kv 4.3 (the putative gene for I_{to}) and in the expression of the channel proteins have also been described.[37,38] It is possible that despite recovery of atrial refractoriness to control values, mRNA and protein levels of the L-type Ca^{2+} channel remain lower than in the control situation so promoting a more rapid onset of atrial electrical remodelling when AF is again maintained. The earlier fall in atrial refractoriness during the second and third periods of maintained AF in the current study might suggest this as a possible explanation.

Connexins

Changes in intercellular conduction caused by altered expression or distribution of connexins and the resultant possible microheterogeneities in atrial conduction could promote AF stability. Expression of connexin 43 (Cx43) has variably been reported to be increased[7] or unchanged[39] in animal models of AF. Changes in connexin 40 (Cx40) distribution[39] and reduced levels of Cx40 protein expression[20] have consistently been shown in the goat model of AF. An important role for Cx40 is suggested by the

finding that Cx40 deficient mice have reduced atrial conduction velocity and are prone to atrial tachyarrhythmias.[40] A period of 2-4 weeks of maintained AF is required to generate significant inhomogeneities of Cx40 distribution in the goat model and these changes are correlated with the onset of stable AF.[20] Gap junction remodelling has a slower onset than changes in atrial refractoriness but no data are yet available on recovery of gap junction remodelling.

Clinical evidence for the efficacy of early DC cardioversion of AF

The findings from our study suggest that a longer duration of AF prior to cardioversion (4-weeks rather than 5-days as studied by Garratt et al[11]) results in changes in the atria that promote the stability of AF. There have been no clinical studies designed specifically to assess the merits of early DC cardioversion from an electrophysiological standpoint, but there have been studies looking at the safety of early cardioversion of AF using transoesophageal echocardiography (TOE). The advent of TOE to reliably exclude atrial thrombus has created interest in an alternative policy of immediate cardioversion of AF persisting for >48 hours without the need for the 3-week period of anticoagulation as currently recommended by the American College of Chest Physicians.[41] The studies performed have primarily focused on the safety of such a regime but have also provided some insight into the issue of whether earlier cardioversion using this rationale results in improved maintenance of sinus rhythm. Olsson's group found a clear benefit in the maintenance of sinus rhythm from a TOE guided early cardioversion approach.[42] In this study TOE was used to select patients for immediate cardioversion when atrial thrombus was excluded, there was no spontaneous echo contrast and the left atrial appendage outflow velocity was > $0.25ms^{-1}$. Patients with atrial thrombus, spontaneous echo contrast or a reduced left atrial appendage outflow velocity were commenced on warfarin and had cardioversion performed following 3-weeks of anticoagulation. The majority of patients (162 of 242, 66%) had immediate cardioversion. This group of patients had an

improved rate of sinus rhythm at 1-month post-cardioversion compared to the 80 patients with conventional anticoagulation for 3-weeks followed by cardioversion (75% v 45%, $p < 0.01$). However, the patients with immediate cardioversion had significant clinical differences to the delayed cardioversion group, with a lower age (62 v 67 years, $p < 0.05$) and less structural heart disease (31% v 45%, $p < 0.05$). Specifically left atrial size was lower (44 v 47mm, $p < 0.01$) and ejection fraction higher in the immediate cardioversion group. The arrhythmia pattern was also significantly different between the groups with more atrial flutter and first presentation AF in the immediate cardioversion group. Although providing encouraging results for the policy of TOE guided cardioversion in maintaining sinus rhythm the significant differences in clinical variables between the two groups does not allow any firm conclusions to be drawn.

The recently published ACUTE study (The Assessment of Cardioversion Using Transoesophageal Echocardiography)[43] has given us further insights into the role of early TOE guided cardioversion in AF. The most significant finding was that TOE guided cardioversion was as safe as cardioversion preceded by 3-weeks of oral anticoagulation in terms of the risk of thrombo-embolism and death. An important aspect of the study is that all patients had therapeutic anticoagulation with heparin at the time of the TOE guided cardioversion and this was followed by a month of oral anticoagulation. In this study the maintenance of sinus rhythm 8-weeks post-randomisation was similar in both groups (52.7% v 50.4%, $p = 0.43$) and the two groups were well matched for all clinical variables. This result suggests that the findings of Olsson's group[42] of higher rates of sinus rhythm may well have been due to the difference in clinical variables between the two groups rather than any meaningful effect of early cardioversion.

It is worth questioning why the ACUTE study[43] failed to show any benefit in maintenance of sinus rhythm from the TOE guided cardioversion

approach. In looking more closely at the results, the randomization of patients did not create a group with exclusively short durations of AF (i.e. < 3-weeks). In fact a large number of patients in the immediate TOE guided arm had relatively long durations of AF prior to cardioversion. The median duration of AF at the time of enrollment into the study was 13-days (range 4-48 days), and the mean duration of anticoagulation prior to TOE guided cardioversion was 2.3-days for in-patients and 4.3-days for outpatients. These durations of AF may well have been too long to show any clear benefit in the maintenance of sinus rhythm. Further analysis of this data would be of interest.

The most compelling evidence for the efficacy of early cardioversion in maintaining sinus rhythm comes from Weigner et al.[44] In a two centre study patients with AF >48 hours or of unknown duration underwent TOE guided cardioversion over a 9-year period. Of 539 eligible patients a total of 413 were cardioverted as per protocol (70, 13.1%, were excluded due to left atrial thrombi). In those patients for whom the preceding duration of AF was <3-weeks there was a significantly higher rate of sinus rhythm at 1-year compared to patients with AF durations >3-weeks (65.8% v 44.7%, $p < 0.01$). There was also a significant reduction in recurrent AF (49.2% v 66.3%, $p = 0.01$). Patients with AF of unknown duration were excluded from this analysis. The two groups were well matched for clinical variables including age, left atrial size and left ventricular function. The mean durations of AF prior to cardioversion were significantly different at 1.1 ± 1.1 weeks v 4.7 ± 6.9 weeks, $p < 0.001$. As can be seen from the graph on the following page the majority of the advantage in maintenance of sinus rhythm was in a reduction in recurrent AF in the first 4-weeks following cardioversion. This reduction in AF recurrence is clinically meaningful as over 60% of the patients in this study had an AF duration of < 3-weeks.

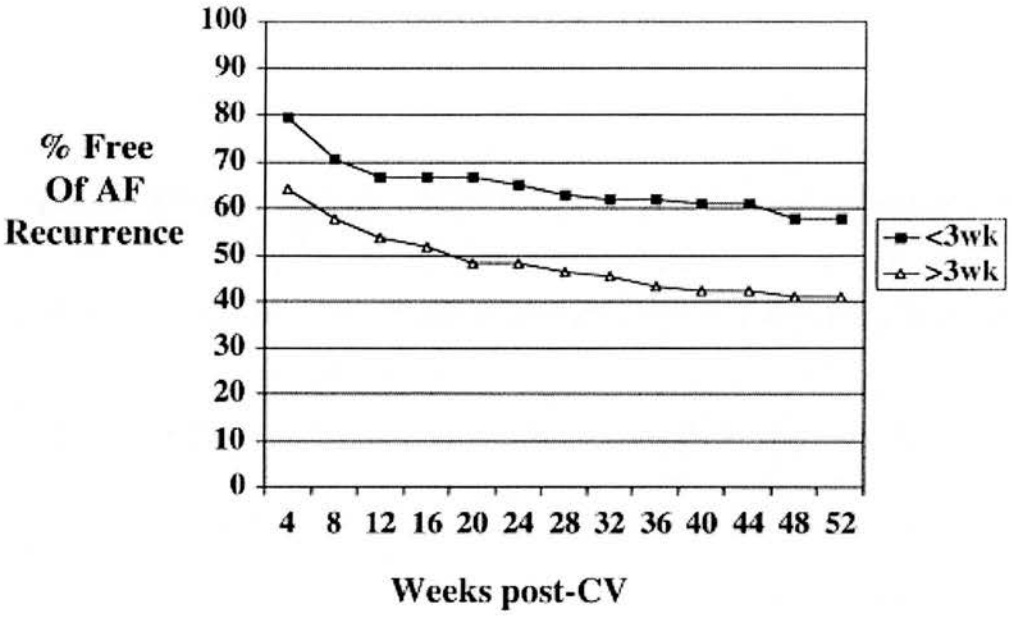

Figure 5.7 Freedom of atrial fibrillation recurrence following cardioversion was significantly ($P < 0.01$) greater among patients who were in atrial fibrillation for <3 weeks. *From Weigner et al. Am J Med 2001;110:694-702.*

Clinical Implications

The sustained increase in AF stability and vulnerability following a 4-week period of maintained AF as distinct from a 5-day period of maintained AF suggests that early DC cardioversion of persistent AF may be beneficial in suppressing AF recurrence post cardioversion. These findings support the design of prospective clinical studies to investigate this possibility.

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Chapter 6

Atrial Ectopy

6.1 Atrial Ectopy as a Trigger for Atrial Fibrillation - a review

6.2 The Coupling Interval of Atrial Premature Beats Following DC Cardioversion of Persistent AF Predicts Subsequent Recurrence of AF

Atrial Ectopy as a Trigger for Atrial Fibrillation

The first ECG recording showing an atrial premature beat (APB) triggering the onset of AF was published in 1918.[1] Widespread acceptance that episodes of AF were triggered by APBs was gained in the 1970s following the surface ECG recordings made by Killip et al[2] illustrating the mechanism of recurrence of AF following DC cardioversion and the intracardiac recordings of Bennett and Pentecost[3] from patients with atrial arrhythmias following myocardial infarction.

Holter recordings from healthy volunteers indicate that APBs occur in slightly more than 50% of people but that frequent APBs (>100/hr) occur in only a small subset of the population.[4,5] Even long distance runners have APBs, but again frequent APBs (>100/hr) were found infrequently.[6] Factors which promote atrial ectopy are little understood but of particular interest to the medical profession is that the number of APBs is increased in physicians working in the emergency department overnight,[7] suggesting that changes in autonomic tone or sleep deprivation may have a role in their genesis.

Paroxysmal AF

The frequency of APBs is quite variable between patients and even within an individual patient. Despite this large variability, an increase in the numbers of APBs does appear to be associated with AF. Analysis of Holter data from patients with paroxysmal AF has shown that APB frequency is increased in the minute prior to the onset of AF.[8] Using a 12-lead Holter system other authors have found that in addition to an increase in APB frequency in the minute prior to the onset of paroxysmal AF, the APBs resulting in AF initiation were consistently monomorphic in about 70% of patients and predominately (77%) from the left atrium.[9] Prior to coronary artery bypass grafting (CABG) an increased burden of APBs (>10/hr) on a pre-operative Holter is associated with a higher likelihood of developing AF following bypass surgery[11] and data following CABG has

shown an increase in the frequency of APBs and episodes of non-sustained AF in the hours preceding the onset of sustained AF.[10]

The frequency of APBs is clearly important in AF initiation but what particular features of one APB result in AF initiation? The more closely coupled an APB is to the previous sinus beat, the more likely it will be to encounter areas of atrial refractoriness resulting in wavefront splitting and the initiation of AF. Bennett and Pentecost[3] showed that APBs resulting in initiation of AF had a significantly shorter coupling interval than those that did not. The role of APBs with a short coupling interval in AF initiation was also highlighted by Capucci et al[12] in the initiation of paroxysmal AF and by Frost et al[13] in the initiation of AF in patients following bypass surgery. More recently the average coupling interval of APBs in the minute prior to the onset of paroxysmal AF has been shown to be shorter than at times of sinus rhythm remote from AF onset.[14] A subset of the patients in this study exhibited large numbers of APBs with similar coupling intervals in the immediate period prior to the onset of AF, suggesting a common underlying (focal) source.

Persistent AF

One of the most important clinical problems related to APBs is their role as a trigger responsible for the recurrence of persistent AF following DC cardioversion. Even with the best medical treatment and serial cardioversions only 42% of patients remain in sinus rhythm a year following cardioversion, and this falls to 17% at 4 years.[15] The timing of AF recurrence can be grouped into 3 important stages. First is the initial few minutes following cardioversion when the atria are especially vulnerable to AF. Second is the period of several days to a week during which the atria are recovering from atrial electrical remodelling when they remain vulnerable to a critically timed APB. Third is the period of late recurrence (> 1-week) and factors important in AF recurrence at this stage are less well understood.

Several studies from the electrophysiology laboratory have shown that APBs with a short coupling interval are responsible for the immediate (within 2-minutes) reinitiation of AF following cardioversion.[16-19] There is much less data, however, on the importance of short-coupled APBs occurring immediately after cardioversion in recurrences of AF after leaving the catheter laboratory. One study found the timing of AF recurrence in the month following cardioversion to be linked to the shortest coupling interval of APBs recorded by a continuous 12-lead surface ECG in the first 2-minutes following cardioversion.[20] This study showed that patients with short-coupled APBs tended to have earlier recurrence than those with longer coupled APBs, however the likelihood of AF recurrence was not predicted by either the coupling intervals of APBs or the number of APBs.[20] In general the number of APBs following cardioversion has not been found to be a strong predictor of AF recurrence, although one study did find a relationship between APB frequency and an increased risk of AF recurrence. In this study Holter monitoring in the first 24-hours following cardioversion of a broad cross-section of AF patients, similar to that found in the UK, found an APB frequency of >10/hour to be associated with an increased risk of AF recurrence over the subsequent year.[21]

Evidence from drug treatment

Although traditionally used to alter the substrate for AF recurrence, antiarrhythmic drugs in the peri-cardioversion period also reduce the frequency of APBs (triggers) and the incidence of early relapse into AF.[18,19,22-24] A range of agents have been used including procainamide,[23] propafenone,[22] sotalol,[18,24] and amiodarone.[19] The calcium channel blocker verapamil has also been shown to reduce the frequency of APBs following cardioversion of AF[25] and both it and propranolol suppress ectopic beats originating from the pulmonary veins.[23] The ability of antiarrhythmic drugs to suppress APBs or pulmonary vein ectopy does not seem to be Vaughan-Williams class dependent. It is possible that the different drugs

suppress ectopy in various ways. For instance, Class I and III agents may increase atrial refractoriness resulting in short coupled APBs being unable to capture the atrium. Beta-blockers and calcium channel blockers may reduce cellular early afterdepolarisations, by reducing inward calcium currents. Interestingly, sotalol not only reduces the frequency of APBs following cardioversion but also increases the coupling interval[18] suggesting an effect on both trigger and substrate, perhaps as a result of a combination of its beta-blocking and Class III antiarrhythmic effects.

Focal sources

In some patients a common origin for the APBs occurring early after DC cardioversion and resulting in immediate reinitiation of AF (IRAF) has been suggested. Frequent APBs with a similar P wave morphology and a consistent cycle length with less than 10ms variability have been observed in some patients with IRAF.[18] However, other authors have noted the origin of AF-inducing ectopy to be more variable.[26] The difference in findings may relate to differences in AF aetiology between the studies, the first study including a large number of patients with idiopathic AF[18] and the second study included only patients with structural heart disease, and therefore theoretically more diffuse atrial disease.[26]

The fact that the trigger for recurrent AF might have a 'focal' origin in some patients led to interest in the use of radiofrequency ablation to reduce APB frequency and prevent recurrence of AF. Natale and coworkers published the results of ablation of APBs in patients with persistent AF.[27] Patients were selected on the basis of persistent AF, left atrial size <4.5cm, ejection fraction >45%, and early recurrence of AF (<10 days) clearly precipitated by frequent APBs following electrical cardioversion. Mapping and ablation were performed in 48 patients. The origin of the APBs was the left atrium in 62.5% and the right atrium in 37.5%. After a mean follow-up of 12 months, 40 of the 48 (83%) patients were in sinus rhythm.

Targeting triggers of recurrent persistent AF for treatment by radiofrequency ablation has also been performed by analyzing the pattern of immediate reinitiation of AF (IRAF) following DC cardioversion in patients with lone AF. Lau and colleagues[28] located and ablated a focal source underlying IRAF in 4 of 32 patients (12%) with persistent AF and 5 of 12 patients (42%) with paroxysmal AF. The Bordeaux group have also reported on the use of radiofrequency ablation to target the reinitiating triggers for persistent AF.[29] Following cardioversion of persistent AF, patients with 'P on T' ectopy had mapping and ablation. A total of 32 pulmonary veins and 2 atrial foci were ablated in 15 patients. At 1-year of follow-up 60% of patients were in sinus rhythm without drugs. Other authors have found the electrogram-guided approach disappointing for patients with persistent AF with only 22% of patients free from AF following pulmonary vein ablation.[30] More recently the success of an anatomic approach involving isolation of at least 3 of the 4 pulmonary veins in preventing AF has been reported.[31] A total of 251 patients with paroxysmal (179) and persistent (72) AF were treated by circumferential radiofrequency ablation around pulmonary venous ostia. Of these, 152 (85%) patients with paroxysmal AF and 49 (68%) with persistent AF were free from AF at a mean follow-up of 10±5 months. The anatomic approach appears to be more favourable than electrical mapping of ectopy in patients with persistent AF, suggesting a more diffuse abnormality of atrial physiology in persistent AF.

Trigger / Substrate Interplay

The presence of APBs is almost universal yet AF does not occur in everyone. Insights into the reasons why some people develop AF, and the mechanism by which some APBs trigger AF is available from previous experimental work. Premature atrial extrastimuli result in delayed atrial conduction in normal hearts. The introduction of premature atrial stimuli in patients with documented previous AF results in significantly more intra-atrial conduction delay than in control patients.[32] An increase in

dispersion of atrial refractoriness may also promote AF and this has been shown to occur in association with APBs in patients with a history of AF. The introduction of extrastimuli during right atrial pacing causes an increase in dispersion of refractoriness in patients with a history of AF, but a reduction in dispersion of refractoriness in control patients.[33] Both conduction delay and an increase in dispersion of atrial refractoriness increase the chance of developing AF and these underlying electrophysiological abnormalities may be the reason for AF onset with suitable triggers in susceptible patients.

There is also evidence that atrial refractoriness has an important relationship with triggers in AF onset. Short periods of pacing-induced AF in patients with normal hearts result in a shortened atrial effective refractory period (AERP), which is associated with increased AF inducibility during AERP measurement.[34] Inducibility of AF (by atrial extrastimulus pacing) in animal models of AF is also associated with short refractory periods.[35-37] The use of verapamil to attenuate AF-induced shortening of the AERP results in a reduction in AF inducibility during AERP measurement.[38,39] The above studies provide evidence of a key interplay between atrial refractoriness and triggers in the onset of AF, but all relied on experimentally induced AF to alter substrate and atrial pacing to act as a trigger.

There is some evidence for a relationship between the timing of spontaneously occurring APBs and AF onset in patients. Tieleman et al reported the timing of AF recurrence following DC cardioversion of persistent AF. The majority of recurrences occurred in the first week following cardioversion. This was attributed to the persistence of atrial electrical remodelling at this time.[20] In addition these authors reported a relationship between the shortest coupled APB recorded in the first 2-minutes following cardioversion and the timing of AF recurrence. They hypothesised that the reason for this finding was that early following

cardioversion only short-coupled APBs meet areas of atrial refractoriness, resulting in wavefront splitting and the genesis of AF, whereas longer coupled APBs can uniformly excite the atria. Following a period of sinus rhythm, with associated reversal of atrial electrical remodelling and prolongation of atrial refractoriness, longer coupled APBs, which initially met only excitable (remodelled) atrial tissue, now encounter areas of atrial refractoriness, resulting in AF. It should be emphasised that this link is only hypothesis.

The onset of AF in clinical practice appears to rely on the presence of both APBs and a suitable substrate. The relationship between APBs and substrate has not yet been determined, but there is some evidence from clinical practice that repetitive firing of focal AF sources can, in time, result in atrial electrical remodelling and the onset of persistent AF.[40] AF in turn may also result in an increase in firing from the pulmonary veins as recently demonstrated experimentally.[41] The links between trigger and substrate continue to be defined and further elucidation of their interplay may allow greater insight into the mechanism of AF.

6.2 The Coupling Interval of Atrial Premature Beats Following DC Cardioversion of Persistent AF Predicts Subsequent Recurrence of AF

Introduction

Atrial premature beats (APBs) with a critical coupling interval are important in the recurrence of AF following DC cardioversion of persistent AF.[2,27] Internal DC cardioversion[42] affords a unique opportunity to measure the frequency and coupling intervals of APBs following cardioversion by recording intracardiac electrograms from the right atrium and coronary sinus. By discontinuing all antiarrhythmic drugs 3-days prior to cardioversion and performing internal DC cardioversion without general anaesthesia we were able to study atrial electrophysiology in the immediate post-cardioversion period without the influence of drugs. We analysed the frequency and coupling intervals of APBs in the immediate post-cardioversion period.

Patients with successful cardioversion were classified into two groups based on duration of sinus rhythm greater than or less than 7-days. The duration of 7-days was chosen because the majority of AF recurrences occur during this time period,[20] probably due to the persistence of atrial electrical remodelling,[20] which recovers within a few days following restoration of sinus rhythm.[37,43,44] Because of the persistence of atrial electrical remodelling in the initial few days following cardioversion it is more likely that a single critically timed APB, the focus of this study, would be responsible for AF recurrence. It has been suggested that AF recurrence occurring after a week or more of sinus rhythm may be due to distinct arrhythmogenic mechanisms.[45]

Methods

Study Population

Sixty-five consecutive patients (mean age 60±10 years, 41 male / 24 female) with chronic atrial fibrillation (n = 62) and atrial flutter (n = 3) were drawn from a waiting list for transthoracic cardioversion and new referrals to a tertiary referral clinic for atrial fibrillation. Assessment was by clinical history, physical examination, routine laboratory and thyroid function tests, 12 lead ECG, and transthoracic echocardiography. Patients who met any of the following criteria were excluded from the study: contraindication to anticoagulation; paroxysmal atrial fibrillation; atrial fibrillation due to a reversible cause; a history of myocardial infarction or revascularisation in the previous 6 months. All patients received at least 4 weeks of anticoagulation with warfarin to establish an INR between 2 and 3, and anticoagulation was continued through the time of the procedure. In those with an INR below 2 at any time in the 4 weeks prior to cardioversion we performed omniplane transoesophageal echocardiography under sedation to exclude left atrial thrombus before cardioversion and the patient received intravenous heparin until the INR was greater than 2. All anti-arrhythmic medication was discontinued three days prior to admission, except amiodarone, which was continued in five patients. Once anti-arrhythmic medication was discontinued it was not recommenced for the duration of the study. The study protocol was approved by the local Medical Ethics Committee, and written informed consent was obtained from all patients.

Internal Cardioversion Protocol

A TADcath model 8010 temporary transvenous defibrillation catheter (110 cm, Cournand Curve, ProCath Corp) was inserted into the coronary sinus through the right internal jugular vein. This is an 11-electrode catheter, 2 electrodes being used for bipolar pacing/sensing and 9 comprising the defibrillation electrode. A second defibrillation catheter was placed in the right atrium through the right femoral vein, with the tip in the right atrial

appendage and positioned so that the majority of the catheter electrodes had contact with the right atrial free wall. A 6-French quadripolar catheter (Daig Corp., MN, USA) was positioned at the right ventricular apex to allow synchronisation of the defibrillation shock, appropriate synchronisation being confirmed with a Defibrillation Systems Analyser (DSA, InControl). Immediately before shock delivery, 2 to 12 mg of midazolam was administered intravenously to ensure adequate sedation. Defibrillation DC shocks were delivered between the right atrial and coronary sinus electrodes at an output of 400 V with a 6/6 ms biphasic truncated exponential waveform. If the first shock was unsuccessful, the right atrial defibrillation catheter was repositioned and the procedure repeated.

Post-cardioversion Measurements

The endocardial signals were monitored continuously and stored using the Pruka CardioLab® 4.0 EPS system. Atrial premature beats (APB) were analysed for the immediate 120-seconds following internal DC cardioversion. The coupling interval of each APB was calculated as the shortest A-A interval in either the right atrial appendage or distal coronary sinus lead, and was measured with the on screen calipers at a screen speed of 100mm/sec. Only APBs occurring after sinus beats were counted. Atrial ectopic beats clearly not originating from the sinus node area, with coupling intervals greater than the previous sinus beat were not classified as APBs. If a patient had an early recurrence of atrial fibrillation (i.e. before leaving the catheterisation lab) only the APBs from the first successful cardioversion were analysed. Holter monitors were fitted to all patients in sinus rhythm within 1-hour of leaving the catheterisation lab.

Statistics

Statistical comparisons were performed by student's t-test for normally distributed data and the Mann-Whitney rank sum test when a normal distribution could not be assumed. Categorical variables were compared by

the Chi-squared test. Continuous data are expressed as mean ± SD, and a value of $P<0.05$ was considered statistically significant. Statistical analysis was performed using SPSS 9.0.

Results

Internal cardioversion was successful (sinus rhythm > 2 seconds) in 61 of the 65 patients. There were no serious complications but 2 patients developed haematomas in the neck (at the site of cannulation of the right internal jugular vein) and one patient developed a pericardial effusion, which caused discomfort but did not require drainage. A total of 34 patients (56%) experienced AF recurrence in the first week following cardioversion. The 4 patients in whom internal cardioversion was not successful had similar clinical characteristics to the 61 successfully cardioverted patients other than a larger mean left atrial size at 4.9±0.4cm *v* 4.1±0.6cm (p = 0.02). The clinical characteristics of the patients divided according to duration of sinus rhythm (> or < 7-days) are shown in Table 6.1. The most notable differences between recurrers and non-recurrers was that patients experiencing recurrent AF at < 7-days tended to have a longer previous duration of AF (P = 0.06) and were more likely to have lone AF (P = 0.04).

Atrial Premature Beats

The details of the atrial ectopy in the first 2-minutes following cardioversion are shown in Table 6.2. Patients with AF recurrence at <7-days had APBs with significantly shorter coupling intervals than non-recurrers. Multivariate logistic regression (variables – age, sex, duration of AF, diagnosis of lone AF, presence of structural heart disease, left atrial size, number of APBs and average coupling interval of APBs) showed the average coupling interval of APBs in the first 2-minutes following cardioversion to be the strongest predictor of AF recurrence before 7-days ($p < 0.01$). Immediate reinitiation of AF (IRAF) occurred in 15 patients and 12 of these patients left the lab in AF. Because IRAF is known to be

associated with short coupled APBs reanalysis of the data following exclusion of these 12 patients was performed. This showed that patients with recurrent AF still had significantly shorter mean and shortest coupling interval APBs than non-recurrers (376±77ms *v* 574±114ms, P < 0.01; 328±69ms *v* 447±137ms, P < 0.01).

In addition to an association with AF recurrence the coupling intervals of APBs were related to the timing of AF recurrence. The duration of sinus rhythm (for all patients) was significantly correlated with both the mean ($r = 0.62$, $p < 0.01$) and shortest ($r = 0.49$, $p < 0.01$) coupling interval of APBs. The correlations between the shortest and mean coupling interval of APBs and duration of sinus rhythm for patients with AF recurrence at <7-days are shown in Figure 6.1.

The relationship between shorter coupled APBs and AF recurrence can also be used to determine the likelihood of recurrent AF following cardioversion. A mean APB coupling interval of <500ms is 67% sensitive and 92% specific in predicting recurrent AF before 7-days. A shortest coupling interval of <490ms is 88% sensitive but only 71% specific for predicting 7-day recurrence. These values are illustrated on Figure 6.1.

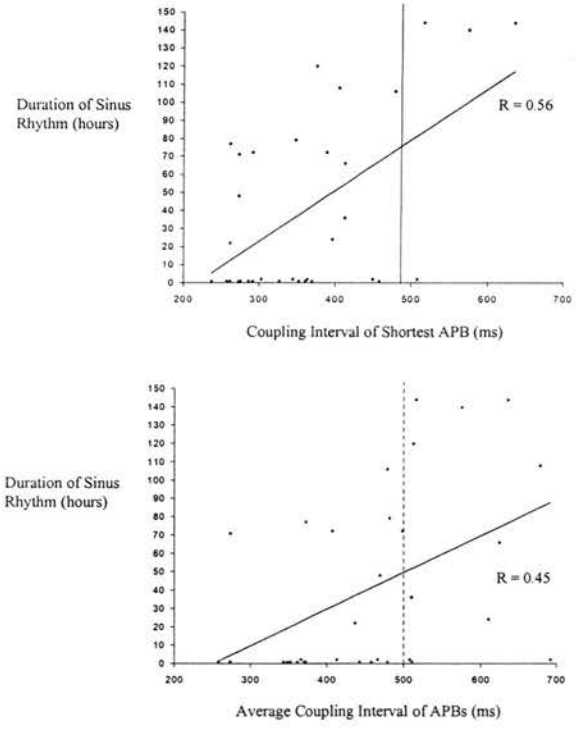

Figure 6.1 Duration of sinus rhythm compared to shortest (upper graph) and mean (lower graph) coupling interval of atrial premature beats (APBs). The correlations are both significant ($p < 0.01$). The dashed lines at 490ms (shortest coupling interval) and 500ms (average coupling interval) represent the values used for assessing the likelihood of AF recurrence before 7-days (see text).

Table 6.1

Clinical and Echocardiographic Characteristics of Patients With and Without AF Recurrence at 7-days Post Internal Cardioversion

	Recurrers (n = 34)	Non-Recurrers (n = 27)	P
Male / Female	25 / 9	20 / 7	
Age (years)			
Mean ± S.D.	60 ± 9	62 ± 10	
Range	45 –75	37 - 77	
Duration of Chronic AF (months)			
Mean ± S.D.	30 ± 35	16 ± 18	P = 0.06
Range	6 – 150	3 - 84	
Aetiology of AF			
Ischaemic	7	6	
Valvular	2	7	
Hypertensive	6	5	
Alcohol	1	2	
Lone	16	6	P = 0.04
Cardiomyopathy	2	1	
LA Diameter (cm)			
Mean ± S.D.	4.1 ± 0.6	4.0 ± 0.6	
Range	3.2 – 5.9	3.2 – 5.5	
LV Function			
EF >50%	27	21	
EF <50%	7	6	

SR – sinus rhythm; AF – atrial fibrillation; LA – left atrium; LV – left ventricular; EF – ejection fraction; S.D. – standard deviation.

Table 6.2

Atrial Premature Beats in the Initial 2-minutes Following Cardioversion

	Recurrers (n = 34)	Non-Recurrers (n = 27)	P
Number of APBs	6 ± 6	5 ± 6	P = 0.27
Average Coupling Interval (ms)	457 ± 112	615 ± 117	P < 0.01
Shortest Coupling Interval (ms)	365 ± 99	489 ± 144	P < 0.01
Average SCL pre-APB (ms)	959 ± 214	946 ± 243	P = 0.6

All values are mean ± SD. APBs – atrial premature beats;
ms – milliseconds; SCL – sinus cycle length.

The number of APBs in the first 2-minutes following cardioversion was not related to recurrence. There was a significant correlation between the number of APBs in the first 2-minutes and the total number of APBs in the first 24-hours on Holter ($r = 0.58$, $p < 0.01$). The frequency of APBs on Holter monitoring was also not associated with AF recurrence (recurrers 3375±4505 *v* non-recurrers 3761±6378, $p = 0.45$).

Discussion

Shorter coupled atrial premature beats in the initial 2-minutes following cardioversion of persistent AF are associated with an increased risk of subsequent AF recurrence. Patients with AF recurrence have shorter coupled atrial premature beats than those who maintain sinus rhythm and the patients with the shortest coupled atrial premature beats have earlier recurrences. In agreement with the previous findings of Tieleman et al[20] the frequency of APBs does not appear to be related to AF recurrence.

Several clinical variables such as longer durations of AF prior to cardioversion,[46,47] increased age[46,47] and left atrial enlargement,[46,48] are known to be associated with an increased risk of AF recurrence following cardioversion. The predictive nature of clinical variables in determining an individual patient's risk of AF recurrence has been studied,[49] but unfortunately combining clinical variables into a predictive risk score is complicated and not easily applied in clinical practice.

The coupling interval of APBs is an easily measured electrophysiological variable important in AF recurrence. Following the description of atrial electrical remodelling[37] there has been considerable interest in defining an electrophysiological variable that relates to AF recurrence. Prior to the description of atrial electrical remodelling a small early study had suggested that shorter monophasic action potential durations[50] were linked with an increased risk of recurrent AF following cardioversion. Despite the increased use of internal DC cardioversion (which allows assessment of atrial electrophysiology following DC cardioversion) there has been little further data linking atrial electrophysiology with AF recurrence. Further data from our own group did not find atrial refractoriness following DC cardioversion to be a predictor of subsequent AF recurrence,[51] although we did find an increased dispersion of AF cycle length in patients with recurrent AF. Data from a subgroup of patients with measurement of both atrial refractory period and the coupling interval of APBs (19 patients) showed a correlation between the shortest coupling interval APB in the first 2-minutes following cardioversion and the atrial refractoriness post-cardioversion ($r = 0.48$, $p = 0.038$).

The lack of association between atrial refractory period and the risk of AF recurrence following cardioversion is in agreement with the findings of other authors.[52] One group has reported an association between recurrent AF and shorter atrial refractory periods post-cardioversion.[53] The association, however, was relatively weak with an odds ratio of only 1.04

for AF recurrence in patients with lower refractory periods, which has little clinical utility.[53]

Limitations

The sensitivity and specificity calculations were performed retrospectively on the data and should be validated prospectively. As most DC cardioversions are performed externally validation of the findings using surface ECG recordings is important.

Clinical Relevance

Measurement of the coupling interval of APBs following internal DC cardioversion is a simple method for determining a patient's risk of AF recurrence and also in predicting the timing of this event. The coupling interval of APBs is more difficult to measure following external DC cardioversion, but is also possible with good quality surface ECG recordings.[20] Analysis of APBs following internal DC cardioversion can identify a group of patients at increased risk of early AF recurrence post-cardioversion who may benefit from more intensive antiarrhythmic strategies. Further studies following external DC cardioversion and in patients taking antiarrhythmic medication at the time of cardioversion would be of interest.

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Chapter 7

Atrial Ectopy – evidence for reversal of atrial electrical remodelling

7.1 Serial cardioversion evidence – Lengthening of the Coupling Interval of Atrial Premature Beats Following Repeated Early Internal Cardioversions for Persistent Atrial Fibrillation: Evidence for Reversal of Atrial Electrical Remodeling in Man. Presented as an abstract at NASPE 1999, Toronto. PACE 1999: 22:4(Part II): 661. Published as part of the paper: Reversal of Atrial Electrical Remodelling Following Cardioversion of Persistent Atrial Fibrillation In Man. Circulation 2000:101;1145-1151

7.2 Holter evidence: A Study Of 179,000 Atrial Premature Beats Indicating Reversal Of Atrial Electrical Remodeling In Man Presented as an abstract at NASPE 2000, Washington DC. PACE 2000: 23;4 (Part II): 217

7.1 Lengthening of the Coupling Interval of Atrial Premature Beats Following Repeated Early Internal Cardioversions for Persistent Atrial Fibrillation: Evidence for Reversal of Atrial Electrical Remodelling in Man

Introduction

Atrial fibrillation (AF) has a tendency to become more persistent with time. A large percentage of patients with paroxysmal AF eventually develop chronic AF.[1] Recently Wijffels and coworkers[2] have demonstrated, in a chronically instrumented conscious goat model, that episodes of AF may be self-perpetuating ("AF begets AF") and have suggested that there may be a purely electrophysiological explanation for the increased persistence of AF with time. The self-perpetuating process in this animal model is associated with a marked shortening of atrial refractoriness and loss of the normal adaptation of atrial refractoriness to heart rate (termed atrial electrical remodelling) that is reproducible in other animal models.[3-5] These authors suggested that the refractoriness changes would stabilise episodes of AF by decreasing atrial wavelength (wavelength=refractory period x conduction velocity), leading to an increase in the potential number of electrical reentrant wavelets in the atria and thereby increase AF stability as predicted by Moe's multiple wavelet hypothesis.[6]

In the animal model described above,[2] the remodelling process is reversible and atrial refractoriness returns completely to normal within 1-week of cessation of burst pacing (or DC cardioversion) and resumption of sinus rhythm. During this "remodelling reversal" phase the atria are in a state of increased vulnerability, which has been suggested as the mechanism for the markedly increased risk of AF recurrence seen in patients with chronic AF in the first week after cardioversion.[7] A logical extension of this suggestion is that if such a patient could be kept in sinus rhythm over this short period, then subsequent likelihood of recurrence

would be dramatically lowered. This possibility forms an attractive theoretical basis for the use of repeated early cardioversions in such patients. Alternatively, if atrial remodelling were found to be irreversible in humans, then it would be difficult to support such a strategy in this patient group, at least on the basis of the atrial electrical remodelling hypothesis.

The aim of this study was to examine the hypothesis that atrial electrical remodelling is reversible after DC cardioversion in patients with persistent AF. The coupling intervals of APBs (as an index of atrial refractoriness) recorded in the first 2-minutes following the time of cardioversion of persistent AF were compared with those recorded following cardioversion of subsequent spontaneous AF recurrences in the same patient group. We postulated that reversal of atrial electrical remodelling resulting in an increase in atrial refractoriness would prolong the coupling interval of atrial premature beats that occur in the immediate post-cardioversion period.

Tieleman[7] reported that short-coupled atrial premature beats (APBs) were associated with earlier AF recurrence, suggesting that short-coupled APBs are an important cause of AF recurrence in the remodelled atria. If reversal of remodelling occurs then changes in the coupling intervals of APBs would also be expected. A lengthening of the coupling interval of APBs may allow for an increase in duration of sinus rhythm.

This study was performed as part of a more detailed assessment of reversal of atrial electrical remodelling in this patient population. Atrial fibrillation cycle length was recorded in all patients prior to cardioversion and in a subset of patient's atrial refractory periods were also measured post-cardioversion.

Methods

Patient Selection

Consecutive patients with persistent AF (minimum duration of 3-months) documented by serial ECGs were considered for the study. Written informed consent was obtained through the use of an information sheet and consent form approved by the Central Manchester Research Ethics Committee, which also approved the protocol. Planned exclusion criteria for the study were a contraindication to anticoagulation, pregnancy, and a lack of willingness to undergo repeated cardioversion at short notice in the event of spontaneous AF recurrence. Only 2 patients under consideration were actually excluded from entry into the study, both because of difficulties in travelling rapidly from their homes to the hospital.

Internal Cardioversion

The methods for internal cardioversion and post-cardioversion measurements are as described previously (Chapter 6).

Patient Follow-Up and Repeat Cardioversions

Patients were discharged the day after the procedure. Antiarrhythmic therapy was not reinstituted after cardioversion (except for amiodarone, which, if present before cardioversion was continued throughout), but anticoagulation was continued for 6 weeks. We attempted to accurately define the time of recurrence of atrial fibrillation by fitting Holter monitors for the initial 72 hours following cardioversion, or if AF recurred after this period from the patient history. In addition, patients made transtelephonic recordings of their cardiac rhythm to a central monitoring station on a daily basis for 35 days after the procedure. Transtelephonic recordings were also made in the event of symptoms suggestive of return of arrhythmia during this period. In the event of a confirmed recurrence of AF, patients were readmitted as rapidly as possible for repeat internal cardioversion (CV2). Cardioversion was repeated for up to a maximum of 2 recurrences (Figure 7.1).

Statistics

Statistical comparisons were performed by student's t-test or Mann-Whitney rank sum test when a normal distribution could not be assumed. Serial measures were compared by ANOVA. Continuous data were expressed as mean ± SD, and a value of $P<0.05$ was considered statistically significant.

Results

Clinical Characteristics

Internal cardioversion was successful (sinus rhythm > 2 seconds) in 34 of the 39 patients. Five patients had repeated early recurrence of AF and left the lab in AF. Of the remaining 29 patients, 17 suffered a recurrence of AF and had a further internal DC cardioversion after a mean period of 129 hours (range 1 to 740) of sinus rhythm. The mean duration of AF from the time of AF recurrence to CV2 was 17±14 hours. Of these 17 patients, 8 patients went on to have a second recurrence of atrial fibrillation necessitating a third internal cardioversion, after a further mean period of 141 hours (range 5 to 480) of sinus rhythm. The mean duration of AF following the second AF recurrence prior to CV3 was 13±5 hours. The clinical details of the patients at each successive cardioversion are shown in Table 7.2.

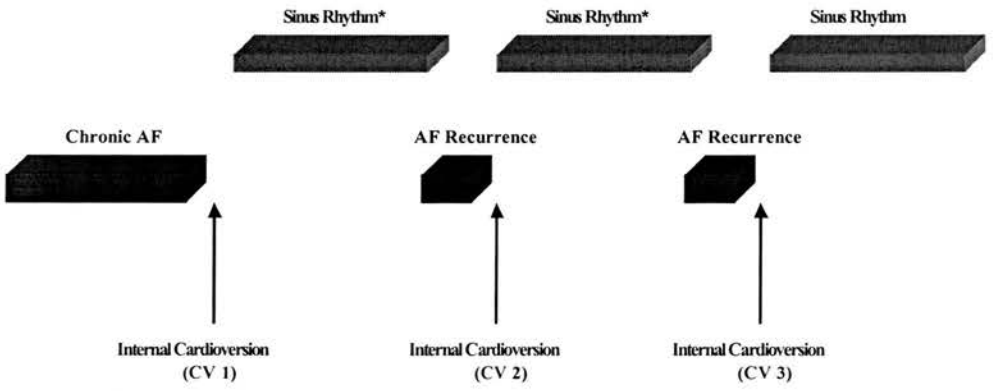

Figure 7.1 Schematic diagram of the study protocol. Following cardioversion daily transtelephonic ECG recordings are made*. In the event of AF recurrence, patients are admitted rapidly for repeat cardioversion(s) (CV 2 and CV 3).

Coupling Interval of Atrial Premature Beats

Of the 17 patients undergoing repeat internal cardioversion (CV2) for AF relapse, 16 had at least one APB in the initial 2-minutes following CV1 and 15 had at least one APB following CV2. Of the 8 patients undergoing CV3 7 had at least one APB. The results for the shortest and average coupling intervals for the atrial premature beats are shown in Table 7.1. There is a significant lengthening of the shortest coupling interval of the APBs from CV1 to CV3 (341 ± 83ms to 486 ± 137ms, $p = 0.02$). The average coupling interval is also significantly prolonged from CV1 to CV3 (481±118ms to 605±191ms, $p = 0.02$). Sinus cycle length preceding atrial premature beats does not change from CV1 to CV3 (907 ±184ms to 997 ± 209ms, $p = 0.92$). In addition to the changes in coupling interval from CV1 to CV3 there is a reduction in the number of APBs in the 2-minutes following cardioversion. The lengthening of the shortest coupling interval APB in two patients is illustrated in Figure 7.2.

Table 7.1 Coupling Intervals of Atrial Premature Beats

	ICV 1	ICV 2	ICV 3
Shortest Coupling Interval (ms)	341 ± 83	417 ± 144	486 ± 137*
Average Coupling Interval (ms)	481 ±118	506 ±156	605 ± 191*
Sinus Cycle Length pre-APB (ms)	907 ±184	924 ± 231	997 ± 209
Number of APBs in first 2 mins	8.3 ± 8.2	5.0 ± 7.3	3.2 ± 3.3*

ms – milliseconds; APB – atrial premature beat. ICV – internal cardioversion

* $p < 0.05$ compared to ICV 1

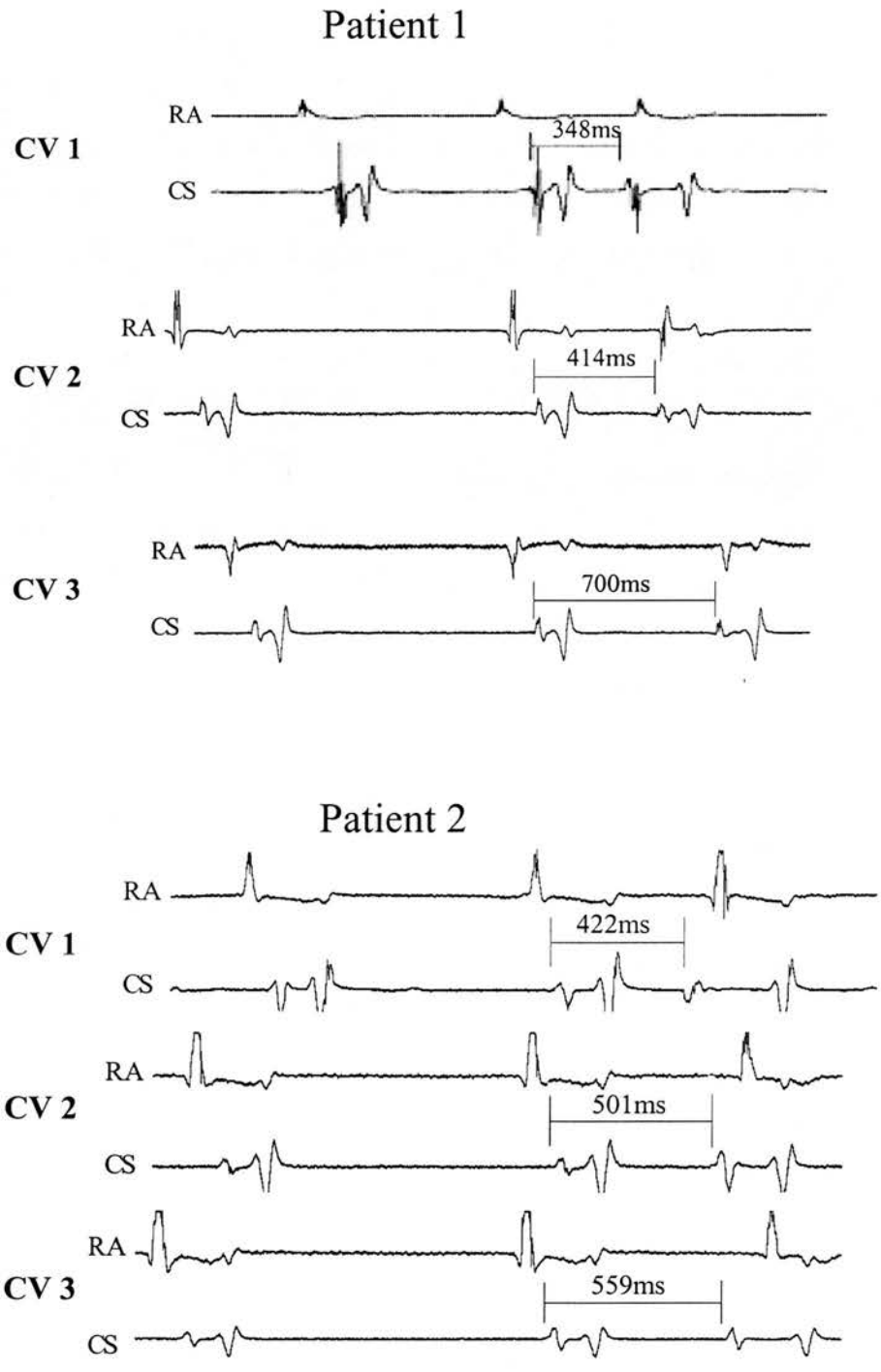

Figure 7.2 Representative examples of the shortest coupled atrial premature beats after 3 successive cardioversions from 2 patients. There is a progressive increase in shortest coupling interval with successive cardioversions. There is some variation in preceding cycle length from one cardioversion to another, but no consistent effect on sinus rate was noted. RA – right atrium; CS – coronary sinus; RV – right ventricle; ms - milliseconds

Table 7.2

Clinical and Echocardiographic Characteristics of Patients

	All patients (n = 39)	2nd Cardioversion (n = 17)	3rd Cardioversion (n = 8)
Male / Female	30 / 9	11 / 6	5 / 3
Age (years)			
Mean ± S.D.	61 ± 10	60 ± 11	54 ± 9
Range	37 – 81	37 – 77	37 - 65
Duration of Chronic AF (months)			
Mean ± S.D.	38 ± 66	25 ± 36	27 ± 24
Range	3 - 384	6 – 150	7 - 78
Aetiology of AF			
Ischaemic	7	3	1
Valvular	4	2	1
Hypertensive	8	3	1
Alcohol	3	2	3
Lone	17	7	2
Amiodarone Therapy	4	3	2
LA Diameter (cm)			
Mean ± S.D.	4.1 ± 0.7	4.4 ± 0.6	4.2 ± 0.6
Range	3.2 – 5.9	3.2 – 5.4	3.5 – 5.4
LV Function			
EF >50%	27	12	6
EF <50%	12	5	2

SR – sinus rhythm; AF – atrial fibrillation; LA – left atrium; LV – left ventricular; EF – ejection fraction

Discussion

A policy of repeated early cardioversion for recurrent AF results in a prolongation of the shortest and average coupling intervals of APBs in the first 2-minutes following cardioversion. There is also a reduction in the number of APBs in the 2-minutes following cardioversion. The changes in APB coupling interval are likely to represent a manifestation of reversal of atrial electrical remodelling.

The repeated early cardioversion protocol found a number of pieces of evidence for reversal of atrial electrical remodelling. The AF cycle length prior to CV1 and CV2 increased from a mean of 161±22ms to 167±26ms ($p = 0.05$) in the right atrial appendage, and from 162±20ms to 168±22ms ($p = 0.01$) in the distal coronary sinus.[8](Dr W J Hobbs, MD thesis) In a small group of patients atrial refractory periods at pacing cycle lengths 500-700ms also showed a significant prolongation between CV1 and CV2.[18] (Dr S P Fynn, MD thesis) These measurements indicate a reversal of AF–induced atrial electrical remodelling following a period of sinus rhythm, despite the period of recurrent AF prior to repeat cardioversion.

There is a change in atrial electrophysiology at the time of acute recurrence of AF following cardioversion of persistent AF. The pattern of change of the three measured variables indicates a prolongation of atrial refractoriness i.e. reversal of atrial electrical remodelling. It is unlikely that the changes are artefactual due to patient familiarity with the procedure or repeated sedation as there is no evidence of changes in autonomic tone, with similar ventricular rates in AF prior to each cardioversion and sinus rates following each cardioversion.

Previous Evidence for the Reversibility of Atrial Electrical Remodelling in Humans

Shortened atrial monophasic action potential durations and atrial refractory periods have been demonstrated in patients following cardioversion of AF

and atrial flutter.[9-11] In addition, Franz et al showed a "flat" response of atrial monophasic action potential duration to changes in heart rate, similar to the flattened rate adaption curve seen in the goat model.[2] These findings have been interpreted as demonstrating the presence of atrial electrical remodelling in humans as a consequence of persistent clinical AF.

Prior to our study there was only one study that examined reversibility of atrial electrical remodelling in humans.[12] In this study the atrial refractory period response to very short episodes of induced AF was measured. Short bursts of AF resulted in reduction of atrial refractory periods (measured at 350 and 500ms pacing cycle length) and which following a few minutes of sinus rhythm returned to normal. The current study extends the findings of these authors in that it demonstrates reversibility of atrial electrical remodelling in patients with spontaneously occurring, persistent clinical AF rather than in subjects with induced, short-lasting, "nonclinical" episodes. The time course of the increase in refractoriness after AF termination in these 2 studies is very different (being much slower in the current study), which suggests that 2 distinct physiological or pathophysiological processes are involved. The fact that in the current study these changes are still demonstrable several hours after onset of AF recurrence indicates that they have a time course similar to that described in the goat model (i.e. hours rather than minutes).[13] Following the completion of our study several authors have documented reversal of atrial electrical remodelling in patients who remain in sinus rhythm following cardioversion.[14-16] The body of evidence strongly suggests that atrial electrical remodelling occurs in human AF, but as yet it is not clear that reversal of atrial electrical remodelling reduces clinical AF recurrence. Indeed atrial vulnerability can persist despite long durations of sinus rhythm.[17]

The highest risk of recurrent AF is in the initial few days following cardioversion[7] and it is during this period of time that reversal of atrial

electrical remodelling occurs.[15,16] This study suggests that changes in the 'substrate' for recurrent AF may not be the only factor involved in the reduced risk of AF recurrence following a period of sinus rhythm. The 'triggers' for recurrent AF i.e. atrial premature beats, are reduced in number and prolonged in coupling interval following a period of sinus rhythm. Fewer APBs with longer coupling intervals should represent a less potent trigger for AF recurrence (Chapter 6). However, despite favourable evidence for reversal of atrial electrical remodelling and a reduction in the number of APBs early after cardioversion, the repeated early cardioversion protocol was not successful at maintaining sinus rhythm in the majority of patients.[18] It is likely that the long duration of previous AF in our patients increased the risk of subsequent AF recurrence.[19,20] The fact that AF recurred despite favourable evidence on the reversal of electrical remodelling suggests the importance of other factors, such as atrial structural changes[21,22] in rendering the atria vulnerable to recurrent AF.

Limitations of the study

It is possible that a number of electrophysiological variables other than atrial refractoriness are "remodelled" during persistent AF. Studies in dog models of atrial fibrillation have shown a decrease in atrial conduction velocity.[23] No attempts were made to assess other variables such as atrial conduction velocity. The duration of recurrent AF prior to repeat cardioversion may have attenuated the findings, but despite this all three measures (APB coupling interval, AF cycle length and atrial refractoriness) showed clear evidence of reversal of atrial electrical remodelling.

7.2 A Study Of 179,000 Atrial Premature Beats Indicating Reversal Of Atrial Electrical Remodelling In Man

Introduction

In tandem with the study of reversal of atrial electrical remodelling in the patients undergoing serial cardioversions for recurrent AF, we also sought to assess reversal of atrial electrical remodelling in patients without AF recurrence. Patients without AF recurrence had no clinical indication for a repeat invasive electrophysiological procedure limiting assessment of reverse remodelling to non-invasive measurements. The lengthening of the coupling interval of APBs in the serial cardioversion study prompted us to assess the coupling intervals of atrial premature beats (as a measure of atrial refractoriness) from Holters recorded on each of the first 3-days following cardioversion.

Methods

Patients were drawn from the elective cardioversion waiting list as in Section 7.1. The same inclusion and exclusion criteria applied. Following successful cardioversion of persistent AF the patients were fitted with Holter monitors for 72-hours. The tapes were analysed using the Reynolds Pathfinder 700 system. Following automatic identification by the analyser careful editing was performed to accurately classify all atrial premature beats (APBs). The Holter data was then analysed using specially developed software (Reynolds Medical Research Tools©) to determine the coupling interval (R-R interval) of all atrial premature beats (APBs) with a cycle length of less than 65% of the previous normal-normal interval. The data generated was a series of numbers that were imported into a spreadsheet. In order to reduce error due to artefact all coupling intervals of less than 300ms and more than 65% of the mean sinus cycle length were excluded (<10% of the data). The mean coupling interval during each

24-hour period was calculated for each patient. The coupling interval of the 10th percentile of the shortest coupled APBs for each 24-hour period was classified as p10 and used as a measure of the shortest coupling interval.

Results

A total of 45 patients commenced Holter monitoring following cardioversion and 23 patients (mean AF duration 14.5 ± 16 months, mean age 60 ± 7 years, 16 male) completed 72 hours of Holter monitoring in sinus rhythm. Analysis of the Holter tapes identified 179,814 APBs from the 23 patients over 3 days. The number of APBs identified each day was constant over the 3-day period: day-1 58,310; day-2 65,883; day-3 52,631. The range of coupling intervals of APBs described a normal distribution (Figure 7.3). There was a significant prolongation of both the mean coupling interval and the coupling interval of the shortest 10% of APBs (p 10) from day-1 to day-3 post-cardioversion. (Table 7.3) This pattern for a single patient is shown in Figure 7.4.

	Mean CI (ms)	p 10 CI (ms)	Mean no. APBs
Day 1	547 ± 73	479 ± 67	2535 ± 4042
Day 2	559 ± 84	498 ± 83	2995 ± 3779
Day 3	577 ± 84*	512 ± 76*	2288 ± 3529

Table 7.3 Mean and p10 coupling intervals (CI) and numbers of atrial premature beats from Day 1 to Day 3 post-cardioversion of AF. *$p < 0.01$ compared to day-1

Patients were then divided into 2 groups based on the presence of recurrent AF before 1-week. Recurrent AF prior to 1-week occurred in 12 of the 23 patients. Although the increase in p10 and mean coupling intervals were not statistically different between the two groups there was an interesting trend towards a greater change of the coupling interval of APBs in the patients with AF recurrence (Table 7.4). This was especially noticeable for p10 coupling intervals which increased 43±12ms for recurrers compared to 26±29ms for non-recurrers (P = 0.07).

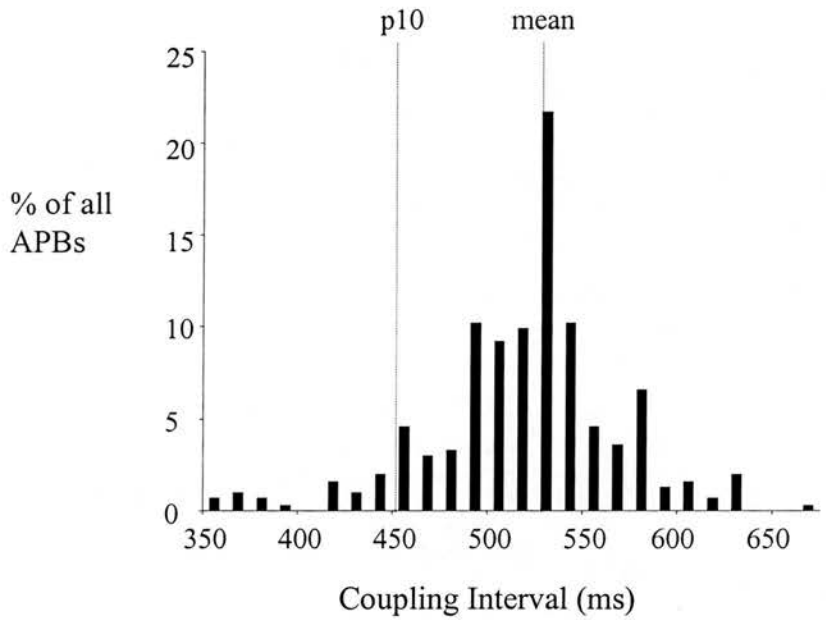

Figure 7.3 Illustration of typical normal distribution of atrial premature beat (APB) coupling intervals for a 24-hour period in a single patient

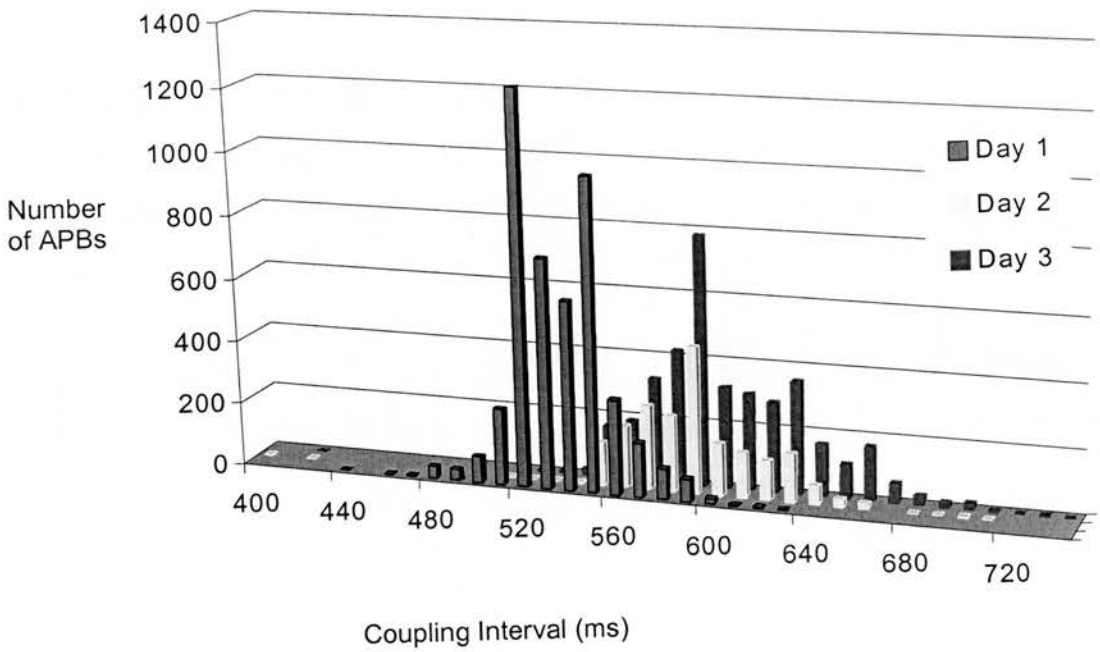

Figure 7.4 Illustration of the increase in coupling interval of atrial premature beats over a period of 3-days following cardioversion of persistent AF in a single patient.

Table 7.4 Changes in coupling intervals: recurrers v non-recurrers

	Recurrers	Non-Recurrers	P
Mean CI Day-1	544±63ms	546±85ms	0.96
Mean CI Day-3	582±66ms	572±106ms	0.87
Difference day 1 to 3	37±24ms	26±26ms	0.28
p10 CI Day-1	481±53ms	474±81ms	0.82
p10 CI Day-3	524±51ms	500±97ms	0.46
Difference day 1 to 3	43±12ms	26±29ms	0.07

CI – coupling interval; ms – milliseconds; p10 – shortest coupling interval

Further analysis of the data showed that there was no relationship between APB coupling intervals and clinical variables such as duration of AF, left atrial size, patient age or a diagnosis of lone AF. The number of APBs was also not related to these variables.

Discussion

The coupling intervals of atrial premature beats increase in duration over the first 72 hours following cardioversion of persistent AF. The level of prolongation (30ms) is compatible with changes in atrial refractoriness associated with reversal of atrial electrical remodelling over this period of time. An increase in APB coupling interval is not associated with maintenance of sinus rhythm.

Despite favourable changes in the coupling intervals of APBs on Holter monitoring for the initial 72-hours following cardioversion, the degree of prolongation of coupling interval does not relate to persistence of sinus rhythm. In fact, the opposite trend is observed with a more pronounced lengthening of the coupling interval of APBs in patients with recurrent AF. A possible explanation for the lack of an association between reversal of atrial electrical remodelling and maintenance of sinus rhythm is that reversal of atrial electrical remodelling is not related to a reduction in AF vulnerability. This would also be suggested by the data from the serial cardioversion study, where reversal of atrial electrical remodelling was demonstrated by lengthening of AF cycle length, an increase in atrial refractoriness and prolongation of the coupling interval of APBs occurring shortly after cardioversion, but recurrent AF was very common.[8,18] Other factors may be more important than remodelling such as atrial structural changes or focal initiators of AF (Chapter 8).

Another explanation is that reversal of atrial electrical remodelling in fact promotes atrial vulnerability, at least for a short period of time. A possible mechanism for increased atrial vulnerability might be an increase in

dispersion of atrial refractoriness. Dispersion of atrial refractoriness has been shown to be lower during persistent AF than sinus rhythm in man,[24] and it is possible that a non-homogeneous reversal of atrial electrical remodelling might result in an increased dispersion of refractoriness so increasing the chances of AF recurrence. Our own group has shown that an increased dispersion of atrial refractoriness, as assessed by AF cycle length at the time of cardioversion, is associated with increased AF recurrence.[25]

The numbers and coupling intervals of APBs were not related to longer durations of AF, left atrial size, increased age or the absence of structural heart disease. These results suggest that clinical variables that are important in AF recurrence are not linked to changes in the triggers for AF but exert their effect through influences on the substrate for recurrent AF.

Study limitations

A major drawback of this study was the measurement of APB coupling intervals using RR intervals. In addition to being influenced by changes in atrial coupling intervals the observed changes in APB coupling interval may have reflected changes in AV nodal conduction properties in the first few days following cardioversion. However, changes in AV nodal conduction following DC cardioversion have not previously been documented. It is possible the internal DC cardioversion itself may have influenced AV nodal conduction, but it is more likely that the shock would have prolonged AV nodal conduction so resulting in a shortening of APB coupling interval in the initial few days following cardioversion. Of particular note is that there were no changes in cardioactive medication over the time of the study.

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Chapter 8

Prevalence and Significance of Focal Sources of Atrial Arrhythmia in Patients Undergoing Cardioversion of Persistent Atrial Fibrillation

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ABSTRACT

Background: Recent reports have highlighted the importance of focal atrial arrhythmias as a curable cause for a group of patients with frequently recurrent paroxysmal atrial fibrillation (AF). The importance of this arrhythmia mechanism in the general population of patients with persistent AF is unknown.

Methods: Following successful internal cardioversion of 50 consecutive patients with persistent AF (mean age 60 years, mean duration of AF 26 months), endocardial activity in the immediate post-cardioversion period was analysed for the presence of focal atrial activity. Post-cardioversion atrial arrhythmias were considered to be focal if there was evidence of a localised source of repetitive early atrial activation, either in the form of 1) self-terminating monomorphic atrial tachycardia (at least 5 beats) or 2) recurrences of atrial fibrillation with an initial atrial activation sequence (first 5 beats) that was both monomorphic and reproducible with repeated recurrences.

Results: Evidence for a focal atrial arrhythmia was present in 20 of the total group of 50 patients (40%). Multivariate analysis of clinical characteristics revealed the diagnosis of lone AF as the only independent predictor of a focal source of AF ($p=0.028$). Thirty-nine patients were discharged from hospital in sinus rhythm. At one month follow-up 25 of these 39 (64%) had suffered AF recurrence. The only significant predictor of AF recurrence was evidence of a focal source of atrial arrhythmia immediately post-cardioversion, with a relative risk of 1.73 (1.1-2.7), $p=0.015$.

Conclusions: Focal atrial arrhythmias are common in patients presenting with "idiopathic" persistent AF, suggesting a possible causative role in the generation of this common arrhythmia.

Introduction

Atrial fibrillation (AF) is the cardiac arrhythmia most frequently encountered in clinical practice and remains a considerable clinical challenge, in part because of limitations in our understanding of the electrophysiological mechanisms underlying the condition. Conventionally, AF has been believed to result from the simultaneous existence of multiple migratory wavelets of activation in both atria[1] and a site-specific or focal mechanism has not been supported by experimental studies[2] or mapping data obtained at the time of cardiac surgery.[3,4] Recently, however, a focal form of clinical AF has been described in a number of young patients with structurally normal hearts.[5,6] These patients have a characteristic clinical presentation with unifocal atrial premature beats and frequent short runs of AF. Electrophysiological studies in this group have revealed that the atrial arrhythmias in a particular patient tend to originate from an identifiable source firing intermittently and resulting in a consistent pattern of atrial activation. This characteristic clinical presentation of very frequent shorts runs of arrhythmia is rare amongst the general patient population with AF however, most individuals having more sporadic paroxysms (weeks or months between attacks) or recurrent episodes that require electrical cardioversion for termination (persistent AF). The aim of this study was to determine the prevalence and significance of focal atrial arrhythmias in this latter group of patients as assessed in the immediate post-cardioversion period. Focal atrial arrhythmias were identified and characterised using endocardial signals from intracardiac electrodes inserted for the purpose of internal cardioversion[7-10] of persistent AF.

Methods

Patient Selection

Consecutive patients presenting to the cardiac department of a general hospital with persistent AF (minimum duration of presenting episode 3

months) documented by serial electrocardiograms were considered for the study. The study was designed to include as broad a cross section of patients with persistent AF as possible and the only exclusion criteria were a contraindication to anticoagulation or an unwillingness to enter the study. Written informed consent was obtained using an information sheet and consent form approved by the Central Manchester Research Ethics Committee, which also approved the study protocol.

Study Protocol

Initial clinical assessment included history, physical examination, 12-lead surface ECG, thyroid function tests and transthoracic echocardiography. Patients were admitted to hospital for internal cardioversion of persistent AF after at least 4-weeks of adequate anticoagulation. Blood was sampled for measurement of International Normalised Ratio (INR) weekly and also on the day prior to the planned procedure. Transoesophageal echocardiography was performed to exclude left atrial thrombus immediately prior to cardioversion in any patients with a measured INR below 2.0 at any time in the 4 weeks prior to the procedure. Anticoagulation was not stopped prior to cardioversion. Antiarrhythmic medication was stopped 3 full days prior to the procedure in all patients except those taking amiodarone, which was continued.

Internal Cardioversion

A TADcath model 8010 temporary transvenous defibrillation catheter (110cm, Cournand curve, ProCath Corp) was inserted into the coronary sinus via the right internal jugular vein. This is an 11 electrode catheter, 2 electrodes being used for bipolar pacing/sensing and 9 comprising the defibrillation electrode. A second defibrillation catheter was placed in the right atrium via the right femoral vein, with the tip in the right atrial appendage and positioned so that the majority of the catheter electrodes had contact with the right atrial free wall. A quadripolar catheter was positioned at the right ventricular apex to allow for synchronisation of the

defibrillation shock, appropriate synchronisation being confirmed using a Defibrillation Systems Analyser (DSA, InControl). Immediately before shock delivery, 2 to 12mg midazolam was administered intravenously to ensure adequate sedation. Defibrillation DC shocks were delivered between the right atrial and coronary sinus electrodes at an output of 400V with a 6/6ms biphasic truncated exponential waveform. If the first shock was unsuccessful the right atrial defibrillation catheter was repositioned and the procedure repeated up to a maximum of 4 times. Following successful cardioversion, continuous bipolar recordings were made from the distal coronary sinus and right atrial electrodes and surface electrocardiographic leads for at least 2 minutes post-cardioversion. If there was recurrence of AF in the immediate post-cardioversion period the procedure was repeated up to a maximum of 4 times.

Electrogram Analysis

Bipolar electrograms were recorded at a filter setting of 30 to 500 Hz at a gain of 5 to 10 cm/mV. The endocardial signals were acquired using a multichannel Cardiolab system (Pruka Engineering Inc.) and stored on optical disc. Individual atrial electrograms were measured with the on-screen calipers at a screen speed of 100mm/sec. Catheters were not manipulated during the recording period in order to avoid mechanically induced ectopic activity. Electrogram analysis was performed offline by 2 observers independently.

Definitions

Post-cardioversion atrial arrhythmias were considered to be focal if there was evidence of a localised source of repetitive early atrial activation, either in the form of 1) self-terminating monomorphic atrial tachycardia (at least 5 beats) or 2) recurrences of atrial fibrillation with an initial atrial activation sequence (at least first 5 beats) that was <u>both</u> monomorphic and reproducible with repeated recurrences. Reproducibility was determined in terms of electrogram morphology, activation sequence and tachycardia

cycle length. Atrial fibrillation was defined on the basis of surface electrocardiographic criteria: the absence of P waves and presence of f waves that were irregular in timing at a rate of greater than 320 beats per minute. Patients were classified as having lone or idiopathic AF in the absence of a recognised cause as determined by the patient's history, physical examination and 2-D echocardiogram.

Patient Follow-up

Patients were discharged the day following the procedure. Antiarrhythmic therapy was not reinstituted following cardioversion (except amiodarone which, if present precardioversion, was continued throughout) but anticoagulation was continued for at least 6 weeks. Patients underwent continuous Holter monitoring for 72 hours, daily transtelephonic monitoring of cardiac rhythm for 30-35 days post-procedure and clinical review with 12-lead electrocardiography at 1-month post-cardioversion. Transtelephonic assessment of cardiac rhythm was also undertaken in the event of symptoms suggestive of a recurrence of AF. Atrial fibrillation was confirmed by 12-lead electrocardiography in all cases in which recurrence was thought to have occurred.

Statistical Analysis

Patients' clinical details were compared using an independent samples t-test for continuous variables and a Chi-squared test for categorical variables. All results are expressed as mean ± standard deviation. Predictive variables of focal AF were derived from univariate logistic regression analysis. Multivariate logistic regression analysis was then undertaken with all univariate predictors and also age, sex, duration of AF prior to cardioversion and left atrial size in order to adjust for any possible baseline imbalance between the groups. Relative risks were calculated in preference to odds ratios for predictors of AF recurrence because the risk of recurrence was > 50%.[11] P values less than 0.05 were deemed

statistically significant. Statistical analysis was performed using the software package SPSS 8.0.

Results

Clinical characteristics

Internal cardioversion was successful in restoring sinus rhythm in 50 of 54 consecutive patients. Mean age of these 50 patients was 60±10 years, 37 were male, and mean duration of AF episode prior to cardioversion was 26±32 months. The baseline clinical and echocardiographic details of these patients, classified according to the presence or absence of a focal atrial arrhythmia post-cardioversion, are shown in table 8.1.

Evidence of focal arrhythmias

Evidence for at least one focal atrial arrhythmia was present in 20 of the total group of 50 patients (Table 8.2) and 18 of the 33 patients (55%) without structural heart disease based on the pre-defined criteria described above. Sixteen patients had at least one run (> 5 beats) of self-terminating monomorphic atrial tachycardia (Figure 8.1), with a mean of 16.2 ± 13.3 beats per episode. In 7 patients earliest endocardial atrial activation was recorded at the coronary sinus electrode, in 7 the right atrial electrode, and in 2 patients right and left atrial electrograms occurred simultaneously. In all but one case the onset of surface P wave activity occurred earlier than endocardial activity at these sites, indicating a site of origin distant from the catheters themselves. The mean cycle length of tachycardia in these patients was 342 ± 98ms.

Table 8.1

Baseline Clinical and Echocardiographic Details of Patients According to the Presence or Absence of a Focal Source of Atrial Fibrillation

Variables	Focal Atrial Fibrillation Present (n=20)	Focal Atrial Fibrillation Absent (n=30)	P
Demographic			
Male / Female	14 / 6	23 / 7	0.61
Age (years)	60 ± 9	60 ± 10	0.99
Clinical			
Duration of persistent AF (months)	26 ± 35	25 ± 31	0.93
Prior history of paroxysmal AF	6 / 20	7 / 23	0.6
Previous DC cardioversion	7 / 20	14 / 30	0.29
Total duration AF history (months)	42 ± 42	43 ± 50	0.93
Mean number of previous AAD	1.9 ± 1.3	1.6 ± 1.0	0.35
Continuing amiodarone therapy	2	1	
Aetiology of AF			
Lone	13	7	0.007
Other	7	23	
Ischaemic	1	7	
Valvular	1	6	
Hypertensive	5	4	
Alcohol	0	3	
Cardiomyopathy	0	1	
Pulmonary Disease	0	1	
Iatrogenic	0	1	
Echocardiographic			
LA Diameter (cm)	4.0 ± 0.4	4.2 ± 0.7	0.28
LV Function			
Normal	19	20	0.026
Reduced	1	10	

AAD – antiarrhythmic drugs: LA – left atrial; LV – left ventricular

Table 8.2

Summary of the Focal Atrial Arrhythmias Post-Cardioversion

Run (≥ 5 beats) of atrial tachycardia	16 patients
Reproducible reinitiation of AF	7 patients
Atrial tachycardia and reproducible reinitiation of AF	3 patients

	Atrial Tachycardia	**IRAF ***
Number of beats of tachycardia	16.2 ± 13.3	-
Site of first activation		
Coronary Sinus	7	1
Right Atrium	7	3
Simultaneous	2	3
Mean tachycardia cycle length	342 ± 98 ms	193 ± 15 ms

* IRAF - spontaneous reinitiation of atrial fibrillation within 2-minutes of cardioversion

Figure 8.2 shows a series of self-terminating runs of monomorphic atrial tachycardia in a patient with lone atrial fibrillation followed by spontaneous reinitiation of atrial fibrillation in the same patient. The atrial fibrillation in this case is triggered by an atrial tachycardia identical in activation sequence to the previous self-terminating episodes of atrial tachycardia. Three patients had both self-terminating atrial tachycardia and IRAF. Of the 18 patients who experienced at least one episode of spontaneous "immediate" reinitiation of AF (IRAF), 11 of these had more than one episode and 7 had evidence of a reproducible initial atrial activation pattern. These episodes of AF occurred at a mean of 29 ± 25 seconds following cardioversion. Figure 8.3 shows two episodes of reinitiation of AF following successive cardioversions in a single patient. The activation pattern, timing and electrogram morphology of the first 5 beats of atrial activation are almost identical in the 2 episodes, strongly suggestive of a common "source" of reinitiation of AF. Figure 8.4 shows

an example of non-reproducible IRAF, with marked differences in electrogram cycle length and morphology, and figure 8.5 shows three separate episodes of IRAF in a single patient with slowing of the cycle length in the third episode of IRAF following administration of flecainide. For the patients with a reproducible reinitiation of AF the mean cycle length of the first 5 beats of reinitiation of AF was 193 ± 14 ms (range 176 – 215 ms). As with the atrial tachycardias, earliest atrial activity at the onset of IRAF was evident on the surface electrocardiogram before the intracardiac electrograms, demonstrating that the catheters themselves were not the origin of the recurrence.

Relationship of focal arrhythmias to clinical characteristics

A number of clinical variables were analysed for an association with a focal source of atrial arrhythmia (Table 8.1): sex, age (>60 years), duration of persistent AF (>12 months), prior history of paroxysmal AF (present/absent), previous cardioversions (present/ absent), total duration of AF history (>12 months), left atrial size (>4cm), left ventricular function (normal/impaired), aetiology (lone AF or not lone AF), and the presence or absence of structural heart disease. Using logistic regression, univariate predictors of a focal arrhythmia were normal left ventricular function ($p=0.026$), the absence of structural heart disease ($p=0.008$) and the diagnosis of lone AF ($p=0.007$). Multivariate analysis by stepwise logistic regression of all variables revealed that the diagnosis of lone AF was the only independent predictor of a focal atrial arrhythmia ($p=0.028$) immediately post-cardioversion.

Clinical outcome

Ten of the 50 patients with initially successful shocks could not be maintained in sinus rhythm for more than a few minutes despite repeated shocks and left the electrophysiology laboratory in AF. One patient had very frequent short bursts of AF following cardioversion (Figure 8.6) and underwent successful radiofrequency ablation of a repetitively discharging

focus in the left superior pulmonary vein. The remaining 39 patients were discharged from hospital in sinus rhythm without antiarrhythmic therapy. At one month follow up 25 of these 39 (64%) had suffered recurrence of AF. A number of clinical parameters were examined as predictors of AF recurrence after discharge from hospital (Table 8.3), including the presence of structural heart disease and a diagnosis of lone AF. The only significant predictor of AF recurrence was evidence of a focal source of atrial arrhythmia immediately post-cardioversion, with a relative risk of 1.73 (1.1-2.7), p=0.015. Complications were minimal, but two patients suffered haematomas as a consequence of the internal cardioversion procedure, neither requiring an extension of hospital stay.

Table 8.3

Relative Risks of Clinical Variables for Recurrence of Atrial Fibrillation

	Relative Risk	95% CI	P
Male sex	0.69	0.45 – 1.05	0.15
Age (>60 years)	0.83	0.52 – 1.31	0.46
Duration of AF episode (>12 months)	1.19	0.75 – 1.87	0.47
Total duration of AF history (>12 months)	1.23	0.74 – 2.05	0.39
LA Diameter (>4.0cm)	1.12	0.70 – 1.79	0.63
Structural Heart Disease	0.84	0.49 – 1.43	0.49
Diagnosis of Lone AF	1.19	0.75 – 1.88	0.47
Presence of a Focal Source	1.73	1.10 – 2.72	0.015*

CI – confidence interval

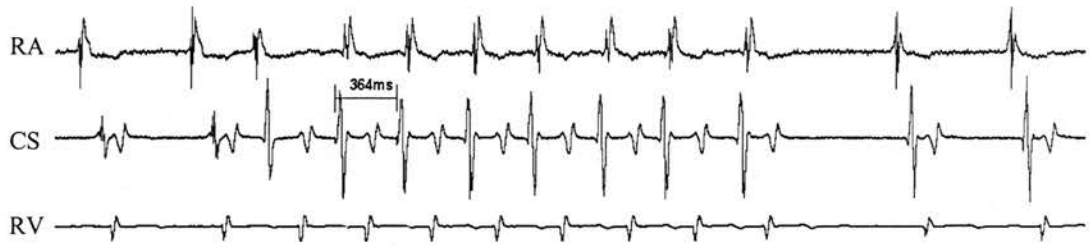

Figure 8.1 Non-sustained run of monomorphic atrial tachycardia at a cycle length of 364ms in a patient 45-seconds post-cardioversion of atrial fibrillation. (RA: right atrial electrogram, CS: distal coronary sinus electrogram, RV: right ventricular electrogram, ms: milliseconds.)

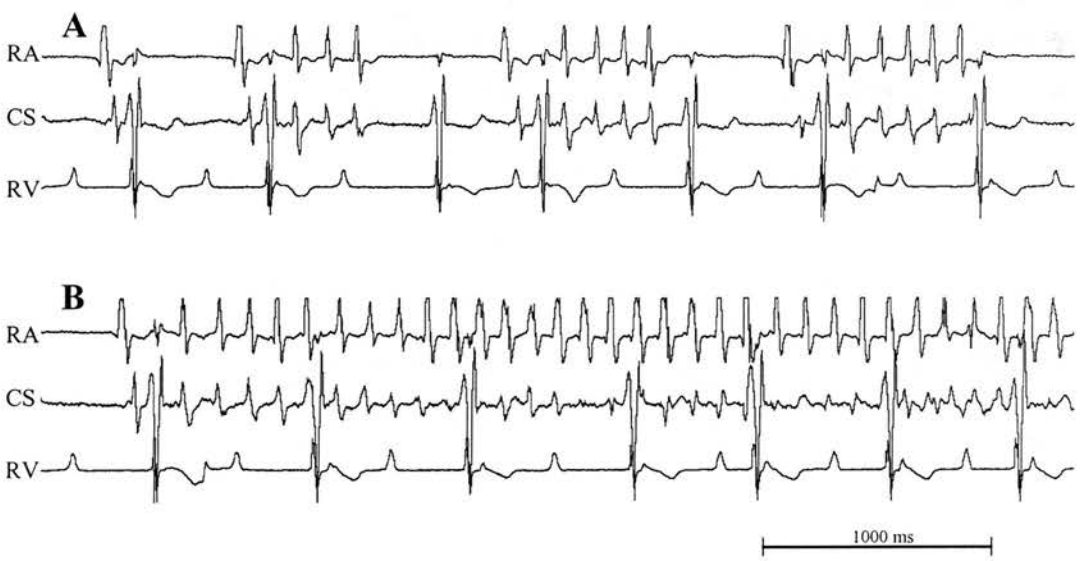

Figure 8.2 (A) Non-sustained runs of monomorphic atrial tachycardia in a patient with lone atrial fibrillation. **(B)** Initiation of atrial fibrillation by a further run of monomorphic atrial tachycardia in the same patient. (RA: right atrial electrogram, CS: distal coronary sinus electrogram, RV: right ventricular electrogram, ms: milliseconds.)

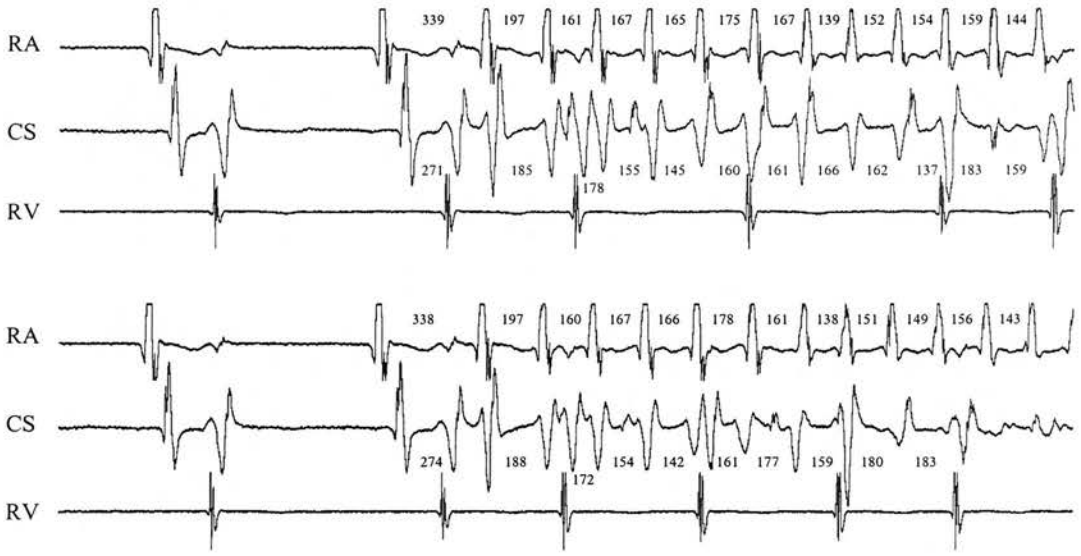

Figure 8.3 Reproducible IRAF. Two separate episodes of reinitiation of atrial fibrillation shortly after successful internal cardioversion in a patient with lone atrial fibrillation. The numbers represent the cycle length of endocardial activation in milliseconds. (IRAF: immediate recurrence of AF, RA: right atrial electrogram, CS: distal coronary sinus electrogram, RV: right ventricular electrogram.)

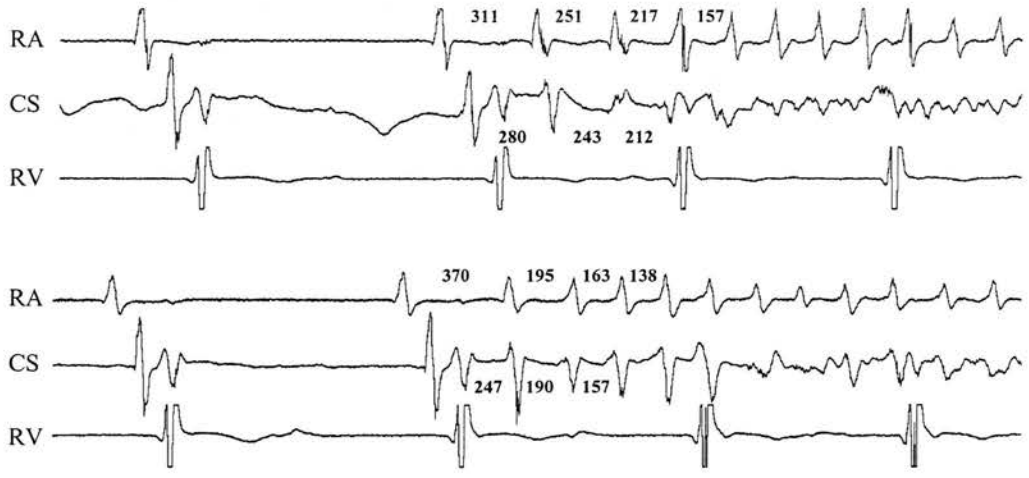

Figure 8.4 Non-reproducible IRAF. Two separate episodes of reinitiation of atrial fibrillation shortly after successful internal cardioversion in a patient with cardiomyopathy. The numbers represent the cycle length of endocardial activation in milliseconds. (IRAF: immediate recurrence of AF, RA: right atrial electrogram, CS: distal coronary sinus electrogram, RV: right ventricular electrogram.)

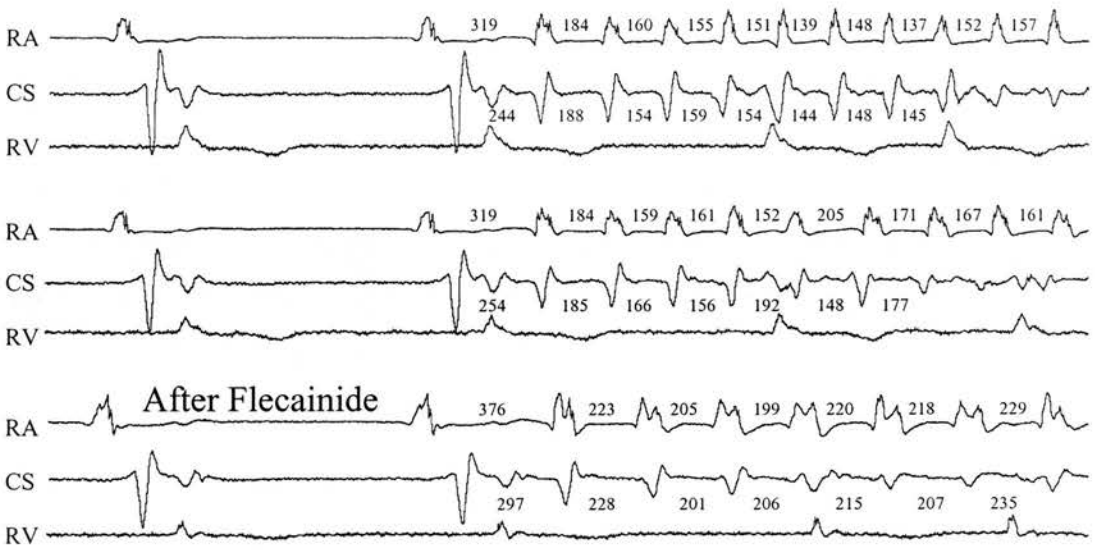

Figure 8.5 Three separate episodes of IRAF shortly after successful internal cardioversion. Following administration of flecainide the cycle length of the first 4 beats is prolonged by ~20%, with a similar degree of prolongation for each beat. The numbers represent the cycle length of endocardial activation in milliseconds. (IRAF: immediate recurrence of AF, RA: right atrial electrogram, CS: distal coronary sinus electrogram, RV: right ventricular electrogram.)

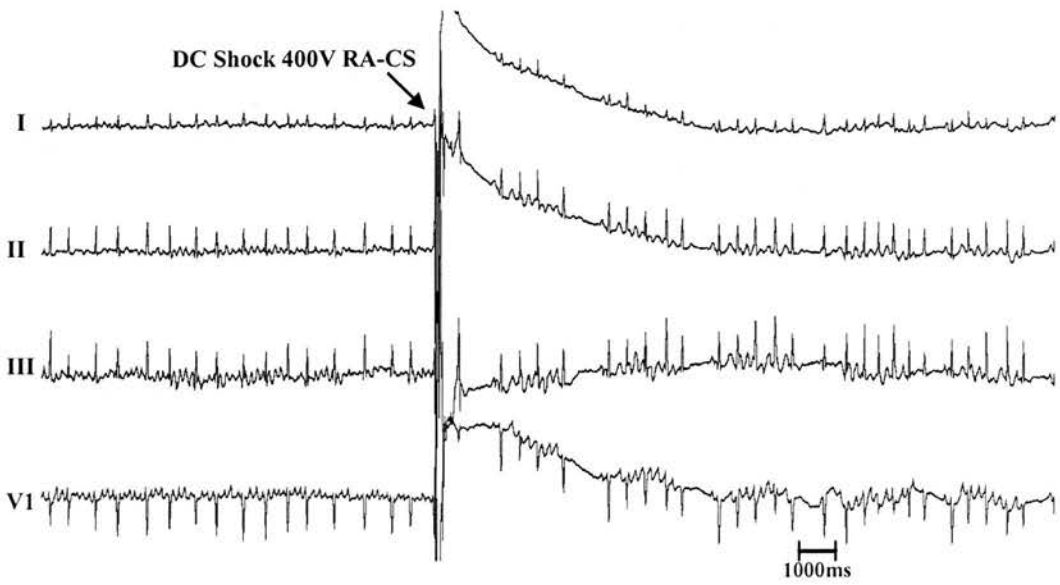

Figure 8.6 Surface electrocardiographic tracing showing successful cardioversion of persistent atrial fibrillation to sinus rhythm with frequent self-terminating runs of atrial fibrillation. (I, II, III, V1: surface ECG leads; ms: milliseconds)

Discussion

The main findings

The principal new finding of this study is that focal (monomorphic) atrial tachycardias are common following cardioversion of patients presenting with persistent atrial fibrillation. This raises the possibility that these tachycardias, recently identified as the cause of AF in a highly selected group of patients with frequently recurrent paroxysmal AF, also have a role in the aetiology of persistent AF. The fact that they are particularly common amongst those with a diagnosis of lone AF argues against their presence being consequent upon valvular or myocardial disease and supports a causative role in the generation of "idiopathic" persistent AF. Furthermore, the association of focal atrial arrhythmias with subsequent clinical recurrence of AF in this study highlights their pathophysiological significance and indicates that catheter ablation of these tachycardias may provide an important therapeutic approach to patients with the persistent form of AF.

Previous studies of internal cardioversion of persistent AF

Most previous studies of internal cardioversion of persistent AF have had an endpoint of restoration of sinus rhythm and have not reported on the characteristics of atrial activity immediately post-cardioversion. [7-10] Sra and coworkers[12] studied spontaneous reinitiation of AF in 4 patients following internal cardioversion and reported that all instances of spontaneous reinitiation were preceded by an atrial premature beat. Timmermans and coworkers[13] noted that 5 of 38 patients (13%) undergoing successful internal cardioversion of AF experienced almost immediate recurrence of AF (IRAF: defined as recurrence within one minute), always initiated by an atrial premature beat with a short coupling interval. Earliest atrial activity at the onset of IRAF was evident on the surface electrocardiogram before the intracardiac electrograms, demonstrating that the catheters themselves were not the origin of the recurrence. No clinical or echocardiographic characteristics were

predictive of immediate reinitiation and the occurrence of IRAF did not predict recurrence after discharge from hospital. Lau and coworkers[14] have recently reported the results of radiofrequency ablation of focal sources causing reinitiation of AF in a selected population of patients with paroxysmal and persistent lone AF. In their study only 4 of 32 patients (13%) with persistent AF showed evidence of a focal source, of whom two had successful radiofrequency ablation. In the current study 20 of 50 patients (40%) had evidence of a focal source of AF. This was in spite of the fact that the criteria for reproducible IRAF were stricter in the current study (five beats rather than three) than that of Lau et al and that the patient group were more representative of the general AF population. Lau et al did not report the incidence of self-terminating atrial tachycardias following cardioversion in their series and this may account for some of the difference between the two studies.

Previous work on predictors of recurrence post-cardioversion

A number of previous studies have examined risk factors for recurrence of AF following internal or external cardioversion. Previously identified risk factors include duration of AF greater than 12 months,[15-17] left atrial size greater than 6cm,[17,18] structural heart disease,[17-19] and age greater than 65 years.[18] No previous studies have identified any patterns of atrial arrhythmia recorded at the time of cardioversion that are associated with subsequent recurrence of AF. Subsequent to the publication of our study Maounis et al showed that frequent atrial ectopy (>10 / hr) and runs of non-sustained SVT (4 beats at >120/min) on post-cardioversion Holter monitoring were associated with an increased risk of recurrent AF.[20] In the current study the presence of a focal source was the strongest predictor of AF recurrence on multivariate analysis.

Significance of focal atrial arrhythmias post-cardioversion

It could be argued that "spontaneous" focal atrial activity occurring post-cardioversion may be a non-specific response of atrial myocardium or

pulmonary veins to electrode catheter movement, surges of autonomic activity or to the endocardial shock itself. It can also be postulated that they are triggered by the sudden relative bradycardia that is common post-shock.[21] The findings of this study argue against these possibilities, however. Earliest atrial activity at the onset of focal arrhythmias was evident on the surface electrocardiogram before the intracardiac electrograms, demonstrating that the catheters themselves were not the origin of the recurrence. In addition, the increased risk of subsequent clinical recurrence of AF associated with their presence is strongly supportive of an important pathophysiological role. One possibility is that the post-cardioversion period reveals focal atrial activity that is the underlying cause of the sustained arrhythmia. A series of animal studies[22-25] and clinical work[26,27] suggests that the high atrial rates associated with bursts of focal atrial activity may lead to a progressive alteration in electrophysiological properties of the atria (atrial electrical remodelling) that in turn makes perpetuation of AF more likely.

Are these arrhythmias truly focal?

In this study the term "focal" is used to indicate a site-specific activation pattern without specific knowledge of the underlying mechanism (see below). Whilst a localised source of monomorphic atrial tachycardia can be demonstrated by the presence of a consistent pattern of atrial activation throughout the arrhythmia, other criteria are required when an apparently focal arrhythmia "degenerates" into AF with completely disorganised atrial activity. One approach to this problem would be to perform detailed endocardial mapping of the initiation of AF. This was not done in this study because of the consequent requirement for additional DC cardioversion shocks for each mapping position of the catheters. Instead we restricted the definition of a focal source of IRAF to those cases in which the initial atrial activation pattern was reproducible with repeated IRAF episodes in terms of electrogram morphology, activation sequence and tachycardia cycle length. The initiation of AF in these cases had some

of the features of those of focal triggers of AF[6] described previously by Haissaguerre as originating from the pulmonary veins. In this study repetitive focal discharges had a mean cycle length of 175msec (range 110 to 270 msec), similar to the characteristics of the bursts of atrial activity reinitiating AF in the current study. Other focal sources identified in the current study originated in the right atrium, as has been described recently in patients with paroxysmal AF.[28]

Subsequent studies on persistent AF

Following completion of our study there have been further publications examining the association between focal atrial arrhythmias and persistent AF. Haissaguerre and colleagues recently reported on catheter ablation therapy for persistent AF targeting the reinitiating triggers.[29] There are more technical difficulties involved with this procedure, including the frequent recurrence of AF following cardioversion necessitating repeated DC cardioversion and the use of antiarrhythmic drugs (amiodarone and flecainide). Patients more frequently required ablation of more than one pulmonary vein (3 or 4 veins in > 50% of cases), and often the procedure required to be repeated. Like paroxysmal AF the dominant trigger areas are in the pulmonary veins but the long-term maintenance of sinus rhythm is lower in the patients with persistent AF (60%). Oral et al found the electrogram-guided approach disappointing for patients with persistent AF with only 22% of patients free from AF following pulmonary vein ablation.[30]

Natale and coworkers also published the results of ablation of APBs in patients with persistent AF.[32] Patients with persistent AF, minimal structural heart disease and early recurrence of AF following electrical cardioversion that appeared to be precipitated by frequent APBs underwent mapping and ablation. Ablation resulted in 40 of the 48 patients (83%) being in sinus rhythm at 1-year follow-up.

More recently the success of an anatomic approach involving isolation of at least 3 of the 4 pulmonary veins in preventing AF has been reported.[31]

A total of 251 patients with paroxysmal (179) and persistent (72) AF were treated by circumferential radiofrequency ablation around pulmonary venous ostia. Of these 152 (85%) of patients with paroxysmal AF and 49 (68%) with persistent AF were free from AF at a mean follow-up of 10±5 months.

Improved rates of maintenance of sinus rhythm can be achieved with the use of radiofrequency ablation of AF 'triggers', however the ideal patient and technique is yet to be defined. The studies performed so far suggest that an anatomic approach may be more favourable than electrical mapping of ectopy in patients with persistent AF. The anatomic approach also isolates a portion of the posterior left atrial wall contiguous with the pulmonary vein orifices. Isolation of this area may have additional benefits in prevention of recurrent AF or alternatively in persistent AF the origin of atrial ectopy may be more diffuse than in paroxysmal AF, possibly forming a further link between triggers and substrate.

Localisation of the source of the atrial arrhythmias

Due to the limited intracardiac electrogram recordings available it was not possible to determine the exact origin of the arrhythmias in this study. Earliest activation in the high right atrium could be due to either a right atrial source or the right superior pulmonary vein. It has recently been shown that studying the timing of endocardial atrial activation sequences in high right atrium, His bundle, proximal and distal coronary sinus allows accurate localization of the origin of atrial ectopic beats.[33] Right atrial foci (SVC and crista terminalis) can accurately be discriminated from pulmonary vein foci avoiding the requirement of trans-septal puncture in the small subgroup of patients who have only right atrial triggers. In our study we did not have either a proximal coronary sinus or a His catheter.

Limitations of the study

The identification of a focal source of atrial arrhythmias post-cardioversion does not address the underlying mechanism of lone AF on a cellular or subcellular level. Automatic or triggered mechanisms might be considered the most likely cause of repetitive electrical activity arising from a "single" source, analogous to idiopathic ventricular tachycardia arising from the outflow tract of the right ventricle.[34] Reentrant mechanisms cannot be excluded however, and Haissaguerre and coworkers have identified features of reentry (continuous electrical activity) associated with a pulmonary venous focus of AF.[6] Recent work has also suggested that stable microreentrant sources, principally located in the left atrium, may underlie AF in the isolated sheep heart.[35]

Radiofrequency catheter ablation of the presumed focal source of the arrhythmias identified in this study was not performed (except in one case). Although it might be thought that abolition of these arrhythmias by local destruction of atrial tissue would lend considerable support to the concept of a focal origin, 1) it would be impossible to be certain that disappearance of the focal atrial activity was a consequence of the ablation itself as in most cases only 2 or 3 episodes were identified (unlike the frequent paroxysmal episodes in patients selected by Haissaguerre) and 2) the absence of antiarrhythmic intervention (catheter ablation or drugs) in this study allowed us to determine the natural history of the different groups of patients with AF (focal and non-focal) relative to each other and thereby the clinical significance of focal atrial arrhythmias in this patient group.

Endocardial atrial activity was monitored for only a short period post-cardioversion and in the absence of exogenous cathecholamines, in contrast to electrophysiological studies previously performed in patients with paroxysmal AF. As a consequence it is possible that the prevalence of focal atrial arrhythmias reported in the study is an underestimate of the

true prevalence. It is also possible that some focal sources were missed as a consequence of the strict definitions used in this study, contributing further to a possible underestimation of the true prevalence.

Clinical relevance of the findings

The fact that patients with persistent "lone" AF are particularly likely to demonstrate focal atrial activity suggests that this activity may be the original cause of the arrhythmia in many of these patients. Furthermore, the association of focal atrial arrhythmias post-cardioversion with subsequent clinical recurrence of AF in this study indicates that catheter ablation of these arrhythmias may provide an important therapeutic approach to patients with the persistent form of AF. Whether such an approach is likely to be curative depends upon whether these arrhythmias are the sole cause of "idiopathic" persistent AF or rather act as important triggers in the setting of an additional abnormality.

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Chapter 9

Changes in Heart Rate Variability Following Cardioversion of Persistent Atrial Fibrillation in Man

9.1 Heart rate variability – introduction and review

9.2 Changes in Heart Rate Variability Following Cardioversion of Persistent Atrial Fibrillation in Man

Presented as an abstract at NASPE 1999. PACE 1999; 22:4 (Pt II):452

9.1 Heart Rate Variability – Introduction and Review

The beat of the healthy heart is not absolutely regular. It varies as a result of many factors, including exercise and both physical and mental stress. In addition, the intervals between normal sinus beats vary periodically because of respiration, blood pressure regulation, thermoregulation, actions of the renin-angiotensin system, circadian rhythms, and other unknown factors. Such periodic rhythms are in fact the predominant source of heart rate variability. By using Holter recordings, these rhythms can be analysed to provide a noninvasive measurement of the autonomic input to the heart.

There are two approaches to measurement of heart rate variability (HRV): analysis in the time domain or in the frequency domain. These measures are based on the analysis of interbeat intervals of normal beats determined from a 24-hour ambulatory electrocardiogram. Time domain analysis addresses the question of "How much variability is there?" Time domain values result from statistically based calculations performed on the set of interbeat intervals. Frequency domain analysis addresses the question "What are the underlying rhythms?" In the frequency domain, Fourier analysis is used to partition the total variance of the heart rate into the variance accounted for by underlying groups of frequencies, somewhat like decomposing the sound of a symphony orchestra into the underlying notes.

Time Domain

Time domain indexes are relatively easy to calculate. There are two classes of time domain variables, one based on interbeat intervals and the other based on comparisons of the lengths of adjacent cycles. Those based on interbeat intervals include SDNN (the standard deviation of all normal R-R intervals) and SDANN (standard deviation of the averages of the N-N intervals in all the 5 minute segments, averaged over a 24-hour period). A

geometric approach to quantifying interbeat interval-based HRV involves measuring the baseline width (in msec) of the main triangle (HRV triangular index) superimposed on the histogram of all N-N intervals. This method has the advantage of being less dependent on accurate classification of individual beats. Another time domain index of heart rate variability, SDNN index is the average of the standard deviations of all N-N intervals for all the 5-minute segments of the entire recording, an intermediate between long and short-term variability. These interbeat interval-based measures are broad-based and are influenced by both short-term (for example, respiratory) and long-term (for example, circadian) factors and are measured in milliseconds. The second class of time domain variables based on comparisons of lengths of adjacent cycles includes pNN5O (the proportion of adjacent cycles that are >50 msec apart, measured in percent), and RMSSD (the root mean square successive differences), which is the square root of the averaged sum of squared differences in length between all adjacent N-N cycles. These variables are virtually independent of long-term trends and predominately reflect vagal tone. Table 9.1 summarises the main time domain indices of HRV.

Frequency Domain

Analysis in the frequency domain is mathematically more complex, and requires a Holter system with an accurate timing track. Frequency domain analysis yields information about the amount of the overall variance in heart rate resulting from periodic oscillations of heart rate at various frequencies. Because heart rate is measured in milliseconds, variance, which is referred to as the "power" in a portion of the total spectrum of frequencies, is measured in milliseconds squared.

The normal approach has been to classify the power spectrum into four bands. High frequency power (HF), which is parasympathetically mediated represents primarily respiratory variation, is in the 0.15 to 0.4 Hz band. Low frequency power (LF), which is modulated by both the

sympathetic and parasympathetic nervous systems and strongly affected by the oscillatory rhythm of the baroreceptor system, is in the 0.04 to 0.15 Hz band. Very low frequency power (VLF, 0.0033 to 0.04 Hz band) and ultra low frequency power (ULF, 1.15×10^{-5} to 0.0033 Hz) may represent the influence of the thermoregulatory, peripheral vasomotor, or renin-angiotensin systems. Measurement of ULF, which contains most of the variance in the 24-hour spectrum, is based on the entire 24-hour recording and also reflects circadian rhythms, whereas VLF may be obtained from a 15-minute sequence of N-N intervals. Total power is the total variance in the signal and represents the sum of HF, LF, VLF, and ULF. Since these power frequency distributions are skewed for statistical purposes, the natural log transform of power values is used.

Indices of HRV have been shown to be stable, at least over a 3 to 65-day interval, and there is no placebo effect on HRV. This lack of intraindividual variability over time makes measurement of HRV an excellent tool for studying autonomic input to the heart.

Table 9.1 Definitions for time domain measures of heart period variability

Variable	Units	Definition
SDNN	msec	Standard deviation of all normal R-R intervals in the entire 24-hr ECG recording (also referred to as SDRR or CLV)
SDANN	msec	Standard deviation of the mean of all 5-min segments of normal R-R intervals of a 24-hr recording
pNN50	%	Percent of adjacent normal R~R intervals that are greater than 50msec apart computed over the entire 24hr ECG recording
RMSSD	msec	Root mean square of successive differences - the square root of the mean of the sum of the squares of differences between adjacent normal R-R intervals over the entire 24-hr ECG recording

Utility of Heart Rate Variability

Initial interest in HRV was in the field of obstetrics following the description of reduced HRV preceding foetal death.[1] The study of HRV in cardiology started with the description of an association between the absence of sinus arrhythmia and an increased mortality shortly after myocardial infarction.[2] Since then a reduced HRV has been shown to be associated with increased mortality following myocardial infarction (MI)[3] and in patients with heart failure.[4] Changes in HRV have also been associated with the onset of idiopathic ventricular arrhythmias[5] and in the onset of ventricular tachycardia in patients following MI.[6]

Heart rate variability has been of particular use in predicting future arrhythmic events in MI survivors. A recent review of the value of non-invasive investigations in predicting future arrhythmic events in MI survivors concluded that HRV has a potential clinical role in risk stratifying patients with one of either reduced ejection fraction (<40%) or an abnormal signal averaged ECG.[7] This review of 11 previous studies (n = 5,719 patients) found that reduced HRV had an average sensitivity of around 50% with a specificity of around 85% for predicting major arrhythmic events in the subsequent 2-year period.[7]

Heart Rate Variability and Atrial Fibrillation

Paroxysmal AF

Coumel first proposed a link between the autonomic nervous system and episodes of PAF with the description of parasympathetic and sympathetic forms based on clinical criteria.[8,9] Subsequently, studies showing changes in heart rate variability prior to the onset of paroxysmal AF have had inconsistent results with some workers finding an increase in sympathetic tone[10] and others an increase in parasympathetic tone.[11] The autonomic pattern prior to the onset of paroxysmal AF episodes appears patient dependent,[12] and may be linked to the presence or absence of structural

heart disease with a sympathetic preponderance in patients with underlying heart disease and a parasympathetic dominance in idiopathic AF.[13] A parasympathetic dominance appears to be most marked in patients with nocturnal episodes of idiopathic PAF.[11] The limited data on HRV prior to the onset of paroxysms of typical atrial flutter suggest an increase in sympathetic modulation or vagal withdrawal.[14]

Patients with paroxysmal AF do not have abnormalities of autonomic function as assessed by heart rate variability,[15,16] but rather their cardiac response to changes in autonomic tone is abnormal.[15] The use of heart rate variability to diagnose autonomically mediated AF, followed by modification of cardiac autonomic tone by medical treatment, has anecdotally been reported to be successful in alleviating episodes of vagally induced paroxysmal AF.[17]

AF post CABG

Episodes of AF occurring after CABG are generally preceded by a shift to sympathetic dominance by either increasing sympathetic tone[18] or withdrawal of vagal tone.[19] This would be no surprise to the clinician as patients developing AF following cardiac surgery tend to be older and sicker than those who remain in sinus rhythm.[20] In addition the efficacy of B-blocker therapy in reducing the incidence of post-CABG AF has been well documented.[21,22]

Heart rate variability as a remote predictor of AF onset

A reduced SDANN has been shown to be a strong predictor of the future onset of AF, requirement for mitral valve surgery and death in patients with chronic severe mitral regurgitation (over 2 years of follow-up).[23] In patients undergoing CABG a low vagal tone combined with a higher frequency of supraventricular ectopic beats as assessed by Holter monitoring pre-operatively has been shown to predict AF post-operatively.[24] The increased risk of AF associated with a reduced vagal

tone and a lower SDANN is likely to represent patients with more severe underlying heart disease, a subgroup that is already recognised to be at increased risk of perioperative AF.

The Role of the Autonomic Nervous System in AF Stability

Recent experimental work in animals has assessed changes in the autonomic nervous system in sustained AF. Olgin and co-workers[25] showed that heterogeneous atrial sympathetic denervation, resulting in an increase in dispersion of atrial refractoriness, increases the stability of induced episodes of AF in dogs. The same group then went on to show that following induction of sustained AF by 6-weeks of rapid atrial pacing in dogs, there is a heterogeneous increase in atrial sympathetic innervation, as measured by positon emission topography (PET) scanning and tissue concentrations of norepinephrine.[26] Other authors have also found an increase in the sympathetic nerve innervation associated with AF in rapidly paced dog atria.[27] An important role for the sympathetic innervation in promoting the maintenance of sustained AF is also suggested by preliminary data that shows bilateral stellectomy, and the resultant homogeneous atrial sympathetic denervation, to prevent the induction of sustained AF in dogs by rapid atrial pacing.[28] This failure to induce sustained AF occurs despite atrial electrical remodelling resulting in a similar reduction in atrial refractoriness in the stellectomised dogs as control dogs (no stellectomy) that did develop sustained AF. These results suggest that an increase in sympathetic innervation may be important in the onset of stable AF.

Importance of the sympathetic nervous system in persistent AF in man

An increase in sympathetic tone such as occurs in thyrotoxicosis and following cardiac surgery[18] is associated with the onset of sustained AF. The use of perioperative beta-blockers in cardiac surgery has been shown to reduce the incidence of AF following cardiac surgery,[21] and the use of metoprolol following cardioversion of persistent AF has been shown to

reduce the risk of subsequent AF recurrence.[22] Although the underlying action of the sympathetic nervous system in promoting AF is not clear, sympathetic nervous system stimulation by head up tilt testing results in a shortening of AF cycle length[29] and isoproterenol infusion also shortens AF cycle length.[30]

HRV after cardioversion of persistent AF

Previous studies of heart rate variability in patients with persistent AF have focused on a potential role of the autonomic nervous system in mediating recurrence of persistent AF.[31,32] Using spectral analysis of 15-minute heart rate recordings in patients following DC cardioversion of persistent AF Lombardi and colleagues[31] showed that recurrence of AF was more common in patients with a LF/HF ratio > 2, suggesting increased cardiac sympathetic modulation. Conversely other authors studying time domain parameters of heart rate variability on 24-hour Holter recordings have found that vagal influences (RMSSD) were higher in patients with recurrent AF.[32]

HRV in AF

Atrial fibrillation and the irregularity of the ventricular response have traditionally been felt to be a barrier to assessment of heart rate variability. However, by using the patient as his or her own control Van den Berg et al were able to show that HRV in AF was primarily controlled by the parasympathetic nervous system.[33] Of particular note was that there was no difference in indices of parasympathetic function in patients taking digoxin.

Changes in HRV also have prognostic implications in AF patients. A reduced SDANN (<100ms) in heart failure patients with AF was associated with a markedly increased 1-year mortality[34] and reduced high frequency variability is associated with adverse outcomes in patients with non-ischaemic mitral regurgitation.[35]

9.2 Changes in Heart Rate Variability Following Cardioversion of Persistent Atrial Fibrillation in Man

Introduction

The concept of atrial electrical remodelling (AER) is well established. The rapid rate of atrial electrical activation that occurs in atrial fibrillation (AF) and atrial flutter results in a reduction of the atrial refractory period (AERP), reversal of its normal adaptation to rate and an increase in the dispersion of atrial refractoriness.[36-39] In addition to altering the electrophysiology of atrial muscle, changes in sinus node function have also been documented in association with atrial electrical remodelling. Following a period of several weeks rapid atrial pacing in dogs[40] or chronic (mean 1-years) atrial flutter in humans[41] intrinsic heart rate is reduced[40] and sinus node recovery times prolonged.[40,41] These changes partially recover following a week of sinus rhythm in dogs[40]or 3-weeks of sinus rhythm in man.[41]

There is a considerable amount of data on the role of the autonomic nervous system in paroxysmal AF. However, the role of the autonomic nervous system in persistent AF in humans is not well documented. As discussed in section 2.3 the autonomic nervous system can influence atrial electrophysiology and promote AF. In particular the recent demonstration of an increase in atrial sympathetic innervation in association with sustained AF in dogs[26,27] raises the possibility that changes in autonomic input to the atria may be important in persistent AF.

We postulated that during a period of persistent AF changes in sinus node function and /or autonomic innervation of the atria might occur. Using Holter monitoring we measured intrinsic heart rate, as a marker of sinus node function, and heart rate variability, as a marker of atrial autonomic

activity, in a population of patients following cardioversion of persistent AF or atrial flutter.

Methods

Patients

Consecutive patients presenting to the cardiac department of a general hospital with persistent AF or atrial flutter (minimum duration of presenting episode 3 months) documented by serial electrocardiograms were considered for the study. Written informed consent was obtained using an information sheet and consent form approved by the Central Manchester Research Ethics Committee, which also approved the study protocol.

Study Protocol

Initial clinical assessment included history, physical examination, 12-lead surface ECG, thyroid function tests and trans-thoracic echocardiography. Patients were admitted to hospital for DC cardioversion of persistent AF or flutter after at least 4-weeks of adequate anticoagulation. All antiarrhythmic and cardioactive medication was stopped 3 full days prior to the procedure in all patients except those taking amiodarone (n = 5), which was continued. Patients were internally cardioverted under heavy sedation by a DC shock delivered between right atrial and coronary sinus electrodes as described in Chapter 6.

Holter Monitoring and Tape Analysis

Patients were discharged the day following the procedure. Antiarrhythmic therapy was not reinstituted following cardioversion (except amiodarone which, if present precardioversion, was continued throughout) but anticoagulation was continued for at least 6 weeks. Patients underwent Holter monitoring for measurement of HRV at day-3, 1-week, 1-month and 3-months post-cardioversion. Because of the risk of confounding factors such as patient anxiety, the recognised increase in circulating

catecholamines with cardioversion[42] and the fact that patients remained in hospital for 24-36 hours following the procedure assessment of HRV by Holter monitoring was delayed until day-3. All tapes were analysed by a single operator using the Reynolds Pathfinder 700 system. For the purpose of analysis only QRS complexes with normal morphology and within 20% of the preceding cycle length were analysed. Following editing time domain variables of heart rate variability and mean sinus cycle length were determined. The time domain variables measured were the standard deviation of all normal-normal (NN) intervals (SDNN), the standard deviation of the 5-minute averages of NN intervals (SDANN) and the square root of the mean of the sum of squares of differences between adjacent NN intervals (RMSSD). Data was excluded if the minimum number of qualified sinus beats was less than 90% over the 24-hours. Indices of spectral heart rate variability were not measured for the 24-hour period due to the difficulty in interpreting the physiological mechanisms responsible for low and high-frequency power components which cannot be considered stationary during a 24-hour period.[43]

Statistical Analysis

Patients' clinical details were compared using an independent samples t-test for continuous variables and a Chi-squared test for categorical variables. Variation in heart rate variability over time was analysed using ANOVA. All results are expressed as mean ± standard deviation. P values less than 0.05 were deemed statistically significant. Statistical analysis was performed using the software package SPSS 9.0.

Results

A total of 65 patients (49 male, mean age 60±9 years) were admitted for cardioversion. Cardioversion was successful in 61 patients, but 12 of these patients left the lab in AF due to repeated early recurrence of AF. Of the 49 patients leaving the lab in sinus rhythm 10 had recurrence of AF prior to or during the first Holter on day-3 leaving 39 patients who completed

the Day-3 Holter. AF recurred prior to the 1-week Holter in a further 12 patients. Therefore, a total of 27 patients completed the initial recording at day-3 post-cardioversion and at 1-week. From this group (27 patients) 10 patients were excluded because the number of qualified sinus beats was less than 90% over the 24 hours. This was due to frequent atrial ectopy in all cases. Results are reported for 17 patients (AF – 15, flutter – 2). A schematic of the exclusion criteria is shown in Figure 9.1. The clinical details of the 17 patients are shown in table 9.2. These patients were representative of the initial 65 patients.

The results showed a marked increase in SDNN and SDANN from day-3 to 1-week post-cardioversion and then a further small increase from 1-week to 3-months (Figure 9.2). The RMSSD increased from day-3 to 3-months but this change was not statistically significant. The mean sinus cycle length and the frequency of APBs remained constant over the series of recordings (see Table 9.3).

The day-3 Holter monitors for the 12 patients who had recurrence of AF between the day-3 Holter and 1-week were also analysed. Of these 7 were excluded because the number of qualified sinus beats was less than 90% over the 24 hours. The HRV data for the 5 remaining patients was similar to that on day-3 of the 17 patients in the study. SDNN was 99.6±18.7ms, SDANN 78.6±19.9ms and RMSSD 40.2±27.3ms (all $P > 0.2$).

Table 9.2 Clinical details of the 17 patients

Male / Female	11 / 6
Age (years)	61.7 ± 9.3
Duration AF/Fl (months)	12.3 ± 9.6
LA size (cm)	3.9 ± 0.5
LV Ejection Fraction	
>50 %	13
<50%	4
Aetiology of AF/Fl	
Lone	2
Alcohol	2
Hypertension	4
IHD	5
Valvular	4

LA – left atrium; LV – left ventricular; AF - atrial fibrillation; Fl – atrial flutter; IHD – ischaemic heart disease

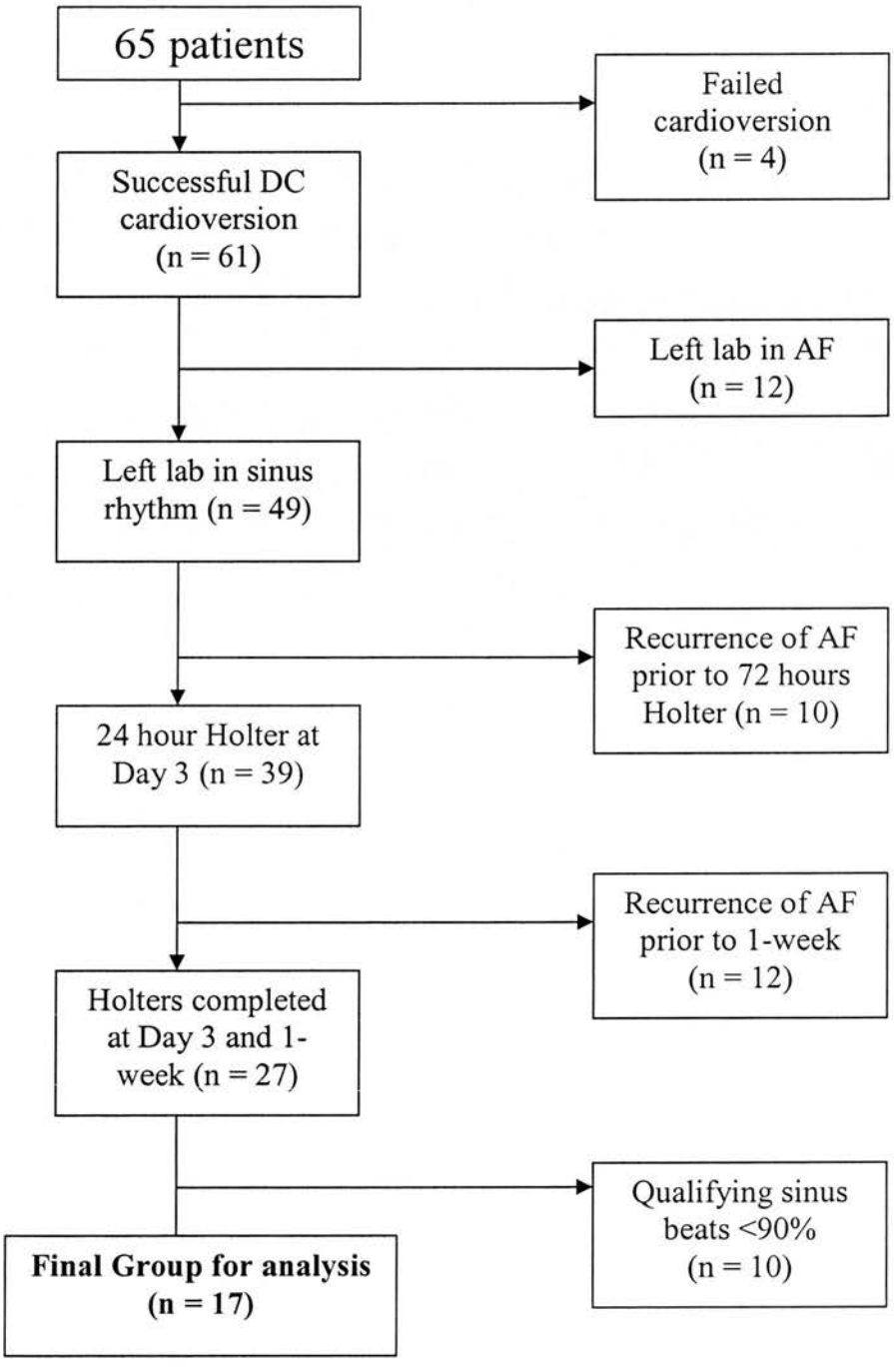

Figure 9.1 Diagram of pathway for inclusion in the study

Time	Mean RR (ms)	RMSSD (ms)	APB
Day-3	876 ± 135	29.7 ± 11.7	509 ± 459
1-week	890 ± 135	34.9 ± 17	329 ± 281
1-month	898 ± 148	37.7 ± 22.3	254 ± 245
3-months	852 ± 101	37.5 ± 15	569 ± 532
P value	0.8	0.54	0.11

Table 9.3 Results of the mean sinus cycle length (RR), RMSSD and frequency of atrial premature beats (APB). All results are mean ± S.D. P value is for ANOVA.

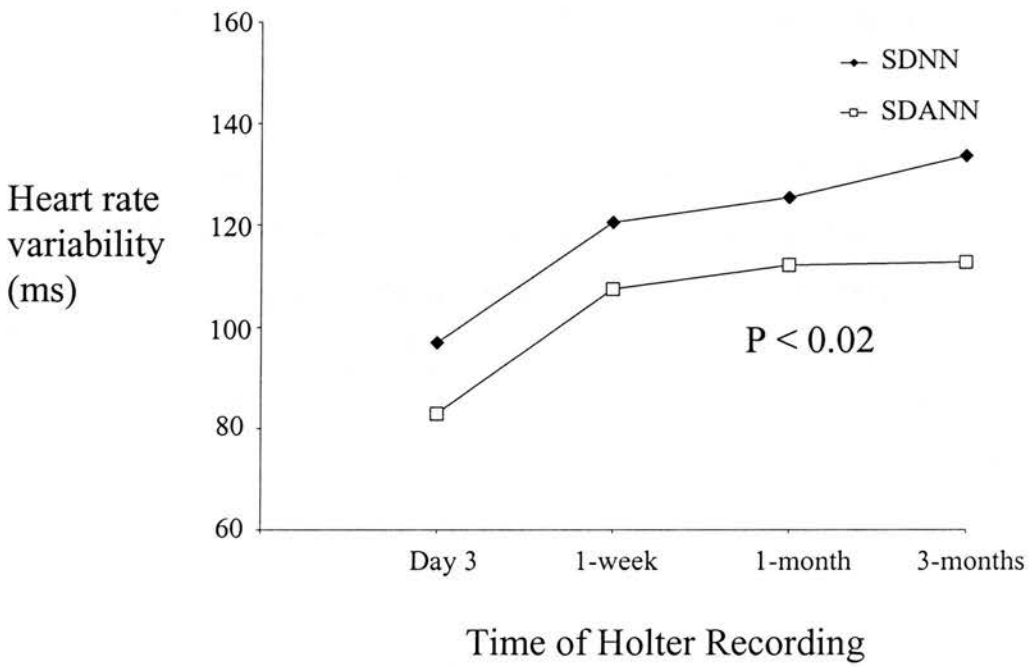

Figure 9.2 Results of SDNN and SDANN. The P-value refers to ANOVA for both SDNN and SDANN.

Discussion

Main Findings

This study demonstrates that following cardioversion of persistent AF/flutter to sinus rhythm there is a significant increase in the SDNN and SDANN measures of heart rate variability between day-3 and 3-months post cardioversion. Spontaneous sinus cycle length does not change over this period.

Changes in HRV following restoration of sinus rhythm

Changes in HRV have previously been described in man following cardioversion of persistent AF[32] and in goats during recovery of atrial electrical remodelling.[44] Kanoupakis and coworkers[32] studied patients with persistent AF, in drug washout undergoing internal DC cardioversion. The authors concentrated on the utility of HRV in predicting recurrent AF following DC cardioversion. They found a higher RMSSD and pNN50 on the first and second days post-cardioversion in patients with AF recurrence. In addition, they noted a steady increase in SDNN and SDANN indices of HRV with time following cardioversion in patients without AF recurrence. Indices of vagal modulation (RMSSD and pNN50) showed a decrease from day-1 to day-2 following cardioversion but then stabilised. These early changes may have been related to the cardioversion procedure. We did not find any difference in indices of HRV between those patients with recurrent AF and non-recurrers.

Using the rapid atrial pacing goat model of AF Blaauw and coworkers[44] found that during the recovery of atrial electrical remodelling there was an increase in the SDNN and RMSSD indices of HRV. Accompanying this increase in time domain parameters there was a significant decrease in the ratio of low frequency to high frequency power (LF/HF) in the frequency domain implying an increase in vagal input or reduction in sympathetic input. Despite the similarity to our own results it is possible that the

reduction in sympathetic input may have reflected increased familiarity of the goats with the experimental set-up.

Possible mechanisms for changes in HRV following cardioversion of AF

There is evidence from this study of changes in HRV following cardioversion of persistent AF in man. There are several possible mechanisms that could underlie these changes:

1) Sinus node remodelling – it is possible that sinus node remodelling secondary to atrial electrical remodelling is manifest as a reduced HRV rather than changes in intrinsic heart rate. Sinus node remodelling might result in a reduced sensitivity of the sinus node to autonomic input and therefore changes in HRV.
2) Improved haemodynamics – the onset of AF is associated with loss of atrial systole and an associated reduction in cardiac output. Restoration of sinus rhythm results in an improved cardiac output[45] due to the return of atrial function[46] and the return of a regular cardiac rhythm.[47] Changes in HRV following cardioversion may be due to improved haemodynamics and changes in neurohumoral hormones many of which are increased in AF.[48]
3) Mechanoelectrical feedback – the relationship between atrial stretch and changes in atrial electrophysiology is well documented.[49,50] Atrial stretch also influences sinoatrial node function by increasing heart rate.[51] Experimental work designed to explain the reduced HRV associated with heart failure[52] has shown that sinoatrial node stretch in anaesthetised pigs causes a reduction in SDNN. It is possible that AF-induced atrial dilatation[37] followed by a reduction of atrial size on returning to sinus rhythm[53] may explain the observed changes in HRV.
4) Autonomic remodelling - recent experimental work in animals has assessed changes in the autonomic nervous system in sustained AF. Induction of sustained AF by 6-weeks of rapid atrial pacing in dogs results in an increase in atrial sympathetic innervation.[26,27] Intact sympathetic innervation also appears to be essential in the maintenance

of sustained AF in dogs.[28] These results suggest that an increase in sympathetic innervation may be important in the onset of stable AF. Changes in autonomic input to the atria, such as increased sympathetic innervation, secondary to persistent AF may explain the reduced HRV following cardioversion.

Sinus node function

This study has failed to show any changes in intrinsic heart rate following cardioversion of persistent AF/flutter. The difference between these findings and the previous findings of Elvan[40] and Sparks[41] may relate to different methodologies. In both these studies sinus node function was assessed by electrophysiological testing under autonomic blockade.[40,41] However, Elvan et al[40] also noted a reduced spontaneous cycle length following cessation of rapid atrial pacing. A prolonged sinus node recovery time has been found in man following cardioversion of persistent AF[54] indicating that it is possible that sinus node dysfunction may indeed have been present in our patients but that more detailed electrophysiological testing may be required for its detection.

An important advantage of this study is that medications were not altered during the study and most patients were in drug washout. Although amiodarone has not been shown to affect indices of HRV[55,56] other antiarrhythmic drugs such as beta-blockers which increase HRV,[57,58] and Class Ic antiarrhythmic drugs which reduce HRV[56,59] were not used in the study patients.

Conclusion

During the first week of sinus rhythm following DC cardioversion of persistent AF/flutter there is a significant change in HRV. The increases in SDNN and SDANN over this period of time reflect either a change in intrinsic sinus node function or altered input to the sinus node following a period of sinus rhythm (1-week). More detailed assessment of sinus node

function and/or pharmacological manipulation will be required to determine the underlying mechanism of these changes.

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