The Remodeled Atrium: Causes, and
Implications for Curative Ablation

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ABSTRACT

Atrial fibrillation has been described as an evolving epidemic in the setting of an aging population. Ongoing research into the atrial substrate responsible for maintaining atrial fibrillation is fundamental to therapeutic advances. There have been considerable advances in ablation techniques aimed at treating and potentially curing atrial fibrillation. To date success has been achieved predominantly in patients with paroxysmal atrial fibrillation with structurally normal hearts where presumably the triggers are more important than the substrate. The developments of technology and ablation techniques are currently evolving more rapidly than an understanding of their impact on the remodeled atria. It remains unclear whether “sinus rhythm begets sinus rhythm” a key premise in AF ablation strategies.

The aims of this thesis were to provide important original insights into both the electrical and structural remodeling responsible for atrial arrhythmias; and to the therapeutic implications for a procedure targeting this arrhythmia that is becoming increasingly performed in an expanding patient population.

Hypertension is the most prevalent, independent and potentially modifiable risk factor for atrial fibrillation. In Chapter 2 conventional electrophysiologic studies were performed in patients with hypertension and no prior history of atrial fibrillation. The aim of this study was to gain insight into the underlying substrate before it is modified by the arrhythmia itself. This has been recognized as “atrial remodeling of a different sort”.

In Chapter 3 we studied a population of patients with idiopathic pulmonary hypertension to study the atrial effects of pulmonary hypertension in the absence of the confounding effects of other disease states, such as obstructive sleep apnoea and chronic obstructive pulmonary disease. A better understanding of the atrial effects of pulmonary hypertension may help dissect out the relevant pathophysiologic factors responsible for the vulnerability to AF in these varied clinical conditions.

In Chapter 4 the comparison of atrial substrate changes between patients with atrial fibrillation and atrial flutter are presented. Atrial fibrillation and atrial flutter are the most common sustained arrhythmias seen in clinical practice. Whilst there may be
alternate expression of both AF and AFL in an individual patient, clinically one of these arrhythmias often predominates. Although it has been well recognized that both arrhythmias are associated with atrial substrate remodeling, to date there has been no direct comparison of atrial substrate changes in patients with AFL vs. AF.

It has recently been recognized that atrial fibrillation is a risk factor for dementia in an aging population. However, the prevalence of neurocognitive abnormalities in a young low-risk population of AF patients is unknown. Chapter 5 describes the prevalence of neurocognitive abnormalities in patients with atrial fibrillation (paroxysmal and persistent atrial fibrillation); and an age-matched population of patients with supraventricular tachycardia, compared to normative controls.

Our understanding of the efficacy and safety of catheter ablation is continuing to evolve as the procedure becomes more widespread and with longer follow up. Chapter 6 describes the change in neurocognitive outcomes after ablation for AF in patients with PAF and PeAF and in patients with ablation for supraventricular tachycardia, in comparison to patients with AF without ablation. The aetiology of neurocognitive abnormalities post AF ablation is likely to include cerebral microembolism. Chapter 7 describes the prevalence of cerebral microembolism occurring during AF ablation. Importantly, and a highly original finding, we report the composition of cerebral emboli (gaseous vs. solid) using a multi-frequency transcranial Doppler ultrasound.

A significant part of this thesis details the formation of the atrial substrate that supports atrial fibrillation yet triggers from rapidly firing foci in the right and left atrium may be responsible for the initiation of focal atrial tachycardia. In Chapter 8, the incidence of tachycardia-induced cardiomyopathy among patients with focal atrial tachycardia is presented, with the electrophysiologic characteristics and the long-term clinical outcomes after successful catheter ablation.

In summary this thesis provides insights into the atrial substrate responsible for arrhythmias that is critical in the development of further therapeutic advances. However, advances in therapy must include a comprehensive understanding of the safety profile. Further insights into these will lead to better clinical management and improvement in treatment strategies.
DECLARATION

The work described in this thesis was carried out at the Royal Melbourne Hospital, Melbourne and the Alfred Hospital, Melbourne, under the supervision of Professor Jonathan M Kalman and A/Professor Peter M Kistler.

This is to certify that:

i. The thesis comprises only my original work towards the PhD except where indicated in the Preface,

ii. Due acknowledgement has been made in the text to all other material used,

iii. The thesis is fewer than 100 000 words in length, exclusive of tables, maps, bibliographies and appendices

Caroline Medi

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Atrial Electrical and Structural Changes Associated with Longstanding Hypertension in Humans: Implications for the Substrate for Atrial Fibrillation.

Pulmonary Vein Antral Isolation for Paroxysmal Atrial Fibrillation: Results from Long-term Follow-up.

Tachycardia-mediated cardiomyopathy secondary to focal atrial tachycardia: long-term outcome after catheter ablation.

Supraventricular tachycardia.

Prediction of the Atrial Flutter Circuit from the Surface Electrocardiogram.
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Medi C, Sparks PB, Morton JB, Vohra JK, Kistler PM, Kalman JM. Long-Term Outcome Following Ablation of Atrial Flutter late after Surgical Atrial Septal Defect Repair: High Cure Rate for "Flutter" and High Incidence of Late Atrial Fibrillation. Heart Rhythm Society Boston MA, May 14 2009.


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Winner of Eric N. Prystowsky Clinical Research Award
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Atrial electrical and structural changes associated with long standing hypertension in humans: implications for the substrate for atrial fibrillation. Medi C, Kalman JM, Teh A, Kistler PM.
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CHAPTER 1

Literature Review
1.1 Introduction

Atrial fibrillation (AF) is the most common sustained heart rhythm disturbance, and accounts for significant morbidity and mortality in the adult population (1). In what has been described as a burgeoning “epidemic”, the prevalence of AF is anticipated to rise 2.5-fold by 2050 (2). This carries significant implications for public health, with a substantial anticipated increase in chronic disease and disability, hospital admissions, and reduction in quality of life in affected individuals. The recent era has also seen profound changes to the management of this disease with the advent of radiofrequency catheter ablation (3). After pulmonary vein isolation for the treatment of AF, the majority of patients with paroxysmal AF have a significant reduction or elimination of symptoms (4, 5). However catheter ablation will only service a minority of the patient population with AF. To further advances in pharmacologic and interventional strategies a better understand of the epidemiology and pathophysiologic mechanisms responsible for AF is fundamental.

1.1.1 Atrial Fibrillation Prevalence and Risk Factors

The prevalence of AF in the general population is estimated to be approximately 0.4-1%, however this significantly increases with age (6, 7). In adults under 60 years, the prevalence of AF is low; the prevalence doubles with each subsequent decade, and affects approximately 10% of the population by 80 years (6). The median age of AF patients is around 75 years, with about one-third of affected individuals aged 80 years or older (6). The lifetime risk of developing AF is approximately 25% for men and women over 40 years, and approximately 16% in the absence of predisposing factors such as ischaemic heart disease and heart failure (8). In addition, the true prevalence
of AF may be significantly underestimated. Thirty percent of patients in the Cardiovascular Health Study (9) and approximately 45% of patients in the Stroke Prevention in Atrial Fibrillation study (10) were diagnosed with AF incidentally. It is anticipated that the prevalence of AF will increase substantially over the next few decades, partly due to the expanding aging population (6). However, large population studies have found an increase in the age- and sex- adjusted prevalence of atrial fibrillation (11) and the factors driving this increase are not fully understood.

Additional risk factors important in the development of AF include: male sex; hypertension; diabetes mellitus; obesity; ischaemic heart disease; valvular heart disease; and heart failure (12). Due to the high prevalence in the community, hypertension is responsible for more AF in the population than any other risk factor responsible for AF (13). Echocardiographic predictors of AF include left atrial enlargement, left ventricular wall thickness and fractional shortening (14). More recently, additional novel risk factors for AF have been recognized, including inflammation (15), the obesity-induced metabolic syndrome (16), and sleep apnoea (17). There is emerging evidence that genetic variation also modulates the risk of developing AF (18). The Framingham Study found that individuals whose parents have AF have a two-three fold increased risk of developing the condition (18).

Atrial fibrillation results in significant morbidity including: palpitations; lightheadedness; fatigue; dyspnoea; thromboembolic complications, as well as precipitating angina in the presence of underlying coronary artery disease, and of aggravating heart failure. These AF-related symptoms are responsible for a significantly reduced quality of life in AF patients compared to healthy controls and the general population (19). AF independently predicts excess mortality, with a mortality rate approximately double that of patients in sinus rhythm (20).
proportion of the excess deaths associated with AF are due to cardiovascular complications, particularly heart failure and thromboembolism (21). Approximately 10-35% patients with congestive heart failure have concurrent AF, and this is associated with a greater symptom severity (22, 23). In the large heart failure trial, Studies of Left Ventricular Dysfunction (SOLVD), the presence of AF in patients with symptomatic and asymptomatic left ventricular dysfunction was a powerful independent predictor of death and hospital readmission due to heart failure (24).

1.1.2 Atrial Fibrillation and Thromboembolic Risk

Atrial fibrillation is an independent risk factor for stroke, associated with a four-five fold increased risk compared to patients in sinus rhythm (25). Patients with paroxysmal AF have an annual stroke rate (3.2%) similar to patients with persistent AF (3.3%) (26). In patients with nonvalvular AF, the strongest independent predictor of stroke is prior stroke or transient ischaemic attack, (relative risk 1.9-3.7) (27), increasing the annual stroke risk to 12%/year on no antithrombotic therapy, and 10%/year on aspirin (28). Increasing age increases the relative risk of stroke/systemic embolism by 1.4 with each decade (29). Hypertension is a powerful independent predictor of stroke in nonvalvular AF (29), and is associated with left atrial stasis and thrombus formation on transoesophageal echocardiography, which confers a high risk of thromboembolism (30). Other independent risk factors include diabetes mellitus (relative risk 1.7) and recent heart failure or moderate-severely impaired left ventricular ejection fraction (relative risk 1.4) (29).

Embolic strokes caused by AF are typically larger, more commonly disabling and fatal, and occur at a more advanced age compared with strokes occurring in sinus
rhythm (31). The assessment of thromboembolic and bleeding risk in individual patients is critical in selecting the most appropriate treatment for optimal stroke risk reduction.

1.1.3 Atrial Fibrillation and Antithrombotic Treatments

Anticoagulation with warfarin has consistently been shown to be superior to placebo and antiplatelet agents in secondary prevention, and in primary prevention in patients at moderate-high risk of stroke (32). A meta-analysis of antiplatelet therapy compared with placebo showed that antiplatelet therapy with aspirin was associated with a modest reduction in the incidence of stroke (relative risk reduction 22%) by reducing non-disabling non-cardioembolic strokes. When antiplatelet therapy was compared with warfarin, a significantly greater reduction was observed with warfarin (relative risk reduction 39%) (33).

The use of anticoagulation with warfarin has several limitations, notably the requirement for regular monitoring and dose-adjustment; the many drug and dietary interactions; and the risk of major bleeding, including intracranial haemorrhage. In clinical studies with careful monitoring of INR, treatment with warfarin increases the risk of major bleeding by 0.3-0.5%/year, and increases the risk of intracranial hemorrhage by 0.2%/year compared with patients without warfarin (34, 35). However, higher bleeding rates are seen in patients on warfarin in the community, with an average annual rate of major hemorrhage of 1% to 5%, varying with the degree of anticoagulation and age (36). These problems have led to a significant under treatment of a large proportion of patients with AF; patients with known AF not on appropriate warfarin therapy who have presented with ischaemic stroke account
for a significant burden of disability and mortality. In 1 study, one-third of patients were on no antithrombotic therapy, one-third were on antiplatelet treatment, and one-fourth were on warfarin with a subtherapeutic INR (37). The reasons for undertreatment are complex but include lack of knowledge about clinical trials and guidelines, perceived “potential contraindications,” fear of bleeding, and inconvenience of monitoring. A perceived lower risk in patients with paroxysmal AF compared to persistent/chronic AF and in patients with CHADS2 ≥2 leads to a systematic undertreatment in high-risk patients (38).

The practical difficulties with warfarin administration with dose fluctuation, INR monitoring and bleeding risk have stimulated interest in the development of alternative antithrombotic agents that do not require monitoring and dose adjustment. Dabigatran, a direct thrombin inhibitor, was one of the first agents to be reported (39), and has now been approved for use in AF by the Therapeutic Goods Administration (TGA) in Australia. Results from large trials evaluating the orally effective anti-Xa agents rivaroxaban and apixiban have recently been reported (40, 41). In patients with CHADS2 score≥1, these agents appear superior to warfarin in net clinical benefit (risk of ischaemic stroke vs. risk of intracranial haemorrhage). When risk of bleeding and stroke are both high, dabigatran, rivaroxaban and apixaban all appear to have a greater net clinical benefit than warfarin (42).

Other alternative strategies to minimize thromboembolic complications in AF include left atrial appendage closure devices. In PROTECTion in Patients With Atrial Fibrillation (PROTECT-AF), a percutaneous closure device occluding the LAA (WATCHMAN) was compared with conventional treatment with warfarin in patients with AF and CHADS2 ≥1 (43). The device was non-inferior to warfarin in the primary efficacy outcome (stroke, systemic emboli, cardiovascular, or other death)
with fewer hemorrhagic strokes and 90% of patients able to stop warfarin. However, adverse events (combining major bleeding, pericardial effusion, and device embolization) were higher in the device group, largely driven by the increased incidence of pericardial effusion. Although this device may have a role in thromboprophylaxis in those at high stroke risk with contraindications to warfarin, it will not prevent embolism originating outside the atrial appendage, and its long-term efficacy is uncertain.

1.1.4 Natural History of Atrial Fibrillation

The natural history of AF may vary between individuals. In many patients, there is a natural progression from paroxysmal to persistent and permanent AF in response to atrial remodeling caused by the arrhythmia itself elegantly described by Allessie as “AF begets AF” (44), or secondary to progression of underlying heart disease (45). AF-related electrical remodeling, resulting from altered expression and/or function of cardiac ion channels, favors the development of functional reentry, which ultimately progress to irreversible structural changes, and the development of persistent AF (46, 47). Lone atrial fibrillation is defined as AF in the absence of structural heart disease or hypertension, and has a lower risk of progression to permanent atrial fibrillation. Lone AF is associated with an equivalent long-term mortality to an age- and sex-matched population without AF (48). However the risk of thromboembolism in patients with lone AF increase substantially with aging and the development of systemic hypertension (48).

The description of pulmonary vein foci triggering atrial fibrillation has revolutionized our understanding of AF pathogenesis (3) and led to the development of successful
ablation strategies. The procedure evolved from a focal approach to an ostial segmental technique and then to a wider pulmonary vein (PV) antral isolation (PVAI) procedure, with increasing success rates (49-51) and less frequent PV stenosis. In patients with paroxysmal AF, this procedure has been associated with success rates frequently in excess of 80% at follow-up of approximately 1 year. In patients with heart failure, catheter ablation is effective in restoring sinus rhythm in up to 69% patients, accompanied by improvements in left ventricular function and heart failure class (52). The technology used in the ablation procedure continues to evolve, and the optimal strategy to achieve permanent long-term success after catheter ablation has yet to be defined, particularly in patients with persistent AF. Although the indications are widening, and the procedure is being performed in a more diverse group of patients (such as those with long-lasting persistent AF, and in elderly patients), the procedure is most successful in younger patients with structurally normal hearts with symptoms refractory to medical management. To date there have been no multicentre studies to support stroke reduction or improvements in survival despite substantial reductions in AF burden. Preliminary results from the Catheter Ablation vs. Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) were presented at the American College of Cardiology 2010 Scientific Sessions, Atlanta GA. These results indicate that patients treated with catheter ablation had a 58% reduction in relative risk of symptomatic AF compared to patients treated with antiarrhythmic drugs. The assessment of long-term mortality and stroke in this study is ongoing.

1.2 Electrophysiologic Mechanisms of Atrial Fibrillation

The concepts attempting to define the mechanisms of atrial fibrillation have developed from theories first posed in the early twentieth century. In 1907,
Winterberg proposed that AF was due to multiple rapidly firing foci within the atria (53). In 1914 Mines advanced the circus movement theory of reentry, and that AF requires a critical mass of tissue to sustain, after observing that the atrial appendage ceased to fibrillate after separation from the remainder of the fibrillating atrium (54). In both the rapid focal firing theory, and the single reentrant circuit theory, fibrillatory activity may result due to inability of all or part of the atrium to follow 1:1 conduction (55). It is now appreciated that these foci may play a role not only in the maintenance of AF, but are initiators of AF where the foci classically arise from the myocardial sleeves of the pulmonary veins (3). These theories and variations upon them were considered the dominant concepts of AF mechanism until Moe and Abildskov proposed the multiple wavelet hypothesis (56). Over time, the concept of multiple circuit reentry has come to be accepted as the principle conceptual model of AF.

1.2.1 Multiple Wavelet Hypothesis

Moe and Abildskov proposed an alternate theory for the mechanism of AF, arguing that the rapidly firing focus and circus movement theories were insufficient to explain the long persistence and stability of AF episodes (56). The “multiple wavelet hypothesis” considered AF in a conceptual sense to be fundamentally chaotic and self-sustaining, and occurring in an environment of electrical heterogeneity; that is, where there is variation in electrical refractoriness as a result of preceding activation, such that some areas of the tissue may be activated by propagating wavelets whereas others are unable to be activated. In this theory, the wavelets were wandering as distinct from earlier concepts of reentrant circuits returning to a consistent starting point. Whether fibrillation becomes sustained is dependent on the number of wavelets that can be supported by the tissue. This critical number is determined by the tissue
mass, refractory period and conduction velocity. Atrial fibrillation becomes more stable with increased wavelets due to a lower likelihood of simultaneous fusion and subsequent termination. Following the advancement of this hypothesis, Moe et al published their seminal computer model study on AF, providing additional support for their theory (57).

The later development of high-resolution simultaneous electrode mapping systems permitted the recording of electrograms from hundreds of sites within the atrium simultaneously, and demonstrated the chaotic activity during AF. Allessie et al mapped the spread of excitation within canine atria in the presence of acetylcholine in a rapid pacing-induced model of AF (58). These experiments provided the first in vivo proof of multiple wavelets resulting in fibrillation. Allessie and co-workers also described a threshold number of 4-6 wavelets required to maintain fibrillation, consistent with the experiments of Wang where the termination of AF by class 1C drugs was preceded by a decrease in the mean number of wavelets (59, 60). Allessie further characterized the behaviour of the wavelets, and described the random nature of wavelet re-entry with each wavelet having a short lifespan. New “daughter” wavelets form as existing wavelets divide around areas of conduction block or as a result of new impulse formation. A continual mechanism for new wavelet formation was recognized as an important mechanism of avoiding spontaneous termination. The combined effect of re-entry and spontaneous discharge was thought to result in the highest likelihood of sustaining AF, consistent with the earlier observations of Moe. These mechanisms are supported in more recent research in both animal and intra-operative human mapping studies (61, 62).
1.2.2 The Concept of Rotors

Schuessler et al isolated right atrial canine specimens and examined them in the presence of increasing acetylcholine concentrations (63). As the levels of acetylcholine increased, atrial refractoriness shortened and multiple reentrant circuits were associated with brief episodes of induced AF. Further increase in acetylcholine concentrations converted the multiple reentrant circuits to a single high frequency reentrant circuit that resulted in fibrillatory conduction when the surrounding atrial tissue was unable to sustain 1:1 conduction. Rotors may be associated with underlying anatomic anchor points such as pectinate muscles, vein orifices and valve rings, or alternately may be underpinned by the functional (electrical) properties of the tissue (64).

More recent observations have challenged the notion that all AF is caused by multiple-circuit re-entry. Jalife et al advanced the theory that the presence of a single small re-entry circuit (“rotor”) is the primary driver of AF in an ovine vagotonic model. Rotors are thought to maintain AF by emanating a continuous supply of spiral wavefronts (65). Power spectral analysis in an isolated, Langendorff-perfused sheep heart was performed in an attempt to localize the AF source (i.e., the site of periodic activity with the highest frequency) (65). Fast Fourier transformation was used to determine the local dominant frequency of activation to identify the rotors (66). In this model, the areas with the highest dominant frequency included the posterior left atrial wall in the region of the pulmonary vein orifices; in the groove between the PV ostium and left atrial appendage; and at the base of the left atrial appendage itself. The predominant location of rotors within the left atrium is consistent with the recognized role of the pulmonary veins as the predominant source of AF triggers (3). Within the right atrium, the number and magnitude of dominant frequencies declined. These
frequency gradients occurred at sites of wavefront conduction block as wavelets propagate from left atrial sources meeting anatomic obstacles such as the crista terminalis and pectinate muscles (67).

Lazar et al demonstrated a similar left-right atrial dominant frequency gradient in patients with paroxysmal AF undergoing ablation, with the highest dominant frequencies seen at the pulmonary vein/left atrial junction (68). Sahadevan et al found a rapid regular rhythm located in the region of the left-sided pulmonary veins and left atrial appendage by epicardial mapping of patients in chronic atrial fibrillation during open-heart surgery (69). In 6 of 9 patients a frequency gradient was evident with fibrillatory conduction. Therefore there is increasing clinical evidence supporting the role of a dominant “driver” causing fibrillatory conduction as a mechanism of AF.

1.3. Triggers and Initiators of Atrial Fibrillation

1.3.1 Pulmonary Vein Foci as the Trigger of Atrial Fibrillation

Atrial fibrillation requires triggers to initiate the arrhythmia and substrate to maintain the arrhythmia. Triggers include atrial ectopy or tachycardia, autonomic stimulation, supraventricular tachycardia and acute atrial stretch. In 1998, Haissaguerre and co-workers described pulmonary vein foci as an important source of initiating AF (3). In a landmark paper, Haissaguerre et al studied 45 patients with very frequent episodes of paroxysmal AF, and mapped the origin of atrial triggers (ectopic beats) that were responsible in initiating an episode of AF. In 41/45 (94%) patients, triggering ectopic beats were found to originate from within the pulmonary veins, most frequently the left superior and right superior pulmonary veins. Multiple foci were found in approximately one-third of patients. A focal approach resulted in success off
antiarrhythmic drugs in 62% of patients at a mean follow up of 8 months. As such, isolation of the pulmonary veins has become the cornerstone for catheter ablation for AF (3).

1.3.2 Non-Pulmonary Vein Foci as the Trigger of Atrial Fibrillation

Extra-PV structures may also be the source of initiation of AF. In the original paper by Haissaguerre, 4/45 patients were found to have ectopics originating from the right atrium (3 patients) and the posterior left atrium (1 patient). Larger studies have subsequently described common extra-PV sites at the superior vena cava, the ligament of Marshall, coronary sinus, crista terminalis, left atrial posterior wall, and left atrial appendage (70-74). The reported incidence of extra-PV initiators varies from 3.2% to 47% (70-74). Non-pulmonary vein triggers and right atrial foci may play an important role in the incidence of very late recurrence of AF after an ablation procedure (recurrence occurring ≥12 months after the initial ablation procedure). Mainigi et al reported that in 8 of 10 patients with very late recurrence, 25% of inducible triggers originated from non-PV sites, and 75% of triggers arose from the pulmonary veins, with pulmonary vein reconnection seen in 93% of previously isolated veins (75). Hsieh et al reported a 50% incidence of right atrial foci and lower incidence of pulmonary vein foci in patients who presented at a mean of 26 months post-ablation, compared to patients who represented at a mean of 3 months post ablation (76). These authors also reported a relatively high incidence (67%) of PV foci in patients who developed very late recurrence.
1.3.3 Arrhythmogenic Properties of the Pulmonary Veins

In addition to their role as an initiator of AF, the pulmonary veins have been implicated in the maintenance of AF. In some patients with paroxysmal AF, PV isolation performed during AF has resulted in progressive prolongation of AF cycle length culminating in the termination of AF in up to 75% of patients (77). In 57% of these patients, AF was rendered non-inducible after PV isolation, suggesting the PVs alone are responsible for AF in this patient population recognising the limitations of AF inducibility as an endpoint for AF ablation procedures (78).

The principal anatomic culprits in rendering the PVs arrhythmogenic are the muscular sleeves, which are variable myocardial extensions from the left atrium into the pulmonary veins (79). Anatomic studies have indicated that the muscle sleeves are longer in the superior veins extending for up to 25mm from the pulmonary vein-left atrial junction (79). The electrophysiologic mechanisms by which the PVs become arrhythmogenic have yet to be defined, but may include automaticity and re-entry. Abnormal automaticity has been demonstrated within the PVs in experimental studies, where either early or delayed after depolarization generate electrical impulses (80, 81). The structural characteristics of this region may also give rise to re-entrant conduction. A complex muscle fibre arrangement with interwoven fibrous tissue creates areas of non-uniform anisotropic conduction that may support AF (82).

Pathologic studies have found no change (83) or an increase (84) in the length of myocardial sleeve extensions in patients with AF compared to those in sinus rhythm. Studies have suggested that larger diameter PVs may have an increased arrhythmogenic potential (85); however others have demonstrated no difference when PV diameter was indexed for left atrial size (86). The mechanisms through which PV’s assume arrhythmogenicity remain an area of intense research.
1.4 Left Atrial Substrate and Maintenance of Atrial Fibrillation: The Posterior Left Atrium

The role of pulmonary vein ectopic beats in triggering AF is well understood, however it appears that the interaction between the pulmonary veins and posterior left atrium is a critical component in the propensity for initiation and maintenance of atrial fibrillation (87). Anatomical and functional characteristics of the posterior left atrium are unique in comparison to other structural components, and it is hypothesized that these differences underlie arrhythmogenicity. The posterior wall has been shown to demonstrate more complex and rapid activity than other structural components of the left atrium (88, 89). In a canine study of persistent AF, small areas of very short cycle length were located in the posterior LA wall (90). In a study of patients with mitral valve disease and chronic AF undergoing mitral valve surgery, the atrial regions with shortest cycle length were mapped to the base of the left atrial appendage, and to the posterior wall lateral to the left-sided pulmonary veins (91). Ndrepepa et al mapped the posterior left atrium with a 64-electrode basket catheter during sustained atrial fibrillation in patients with paroxysmal and persistent atrial fibrillation, and compared AF cycle lengths to those recorded within the pulmonary veins. They found that AF cycle length was shorter at the posterior wall in comparison to the pulmonary veins, and that pulmonary vein activation was directed in a proximal to distal orientation, suggesting that the posterior left atrium acted as a driver for AF, and that during sustained AF, the pulmonary veins are activated passively from the posterior wall during sustained AF (92).

Histologic studies have demonstrated a complex interweaving of myocardial fibres inserting into the left atrial myocardium and may provide the basis for anisotropic conduction and reentry at this site. Atrial myocardial sleeves extend into the posterior
wall at differing depths and distances, creating a complex anatomy suitable for conditions of reentry to occur and sustain (93). In addition, crisscrossing strands have been observed connecting the superior and inferior veins on both the epicardial and endocardial surfaces (93).

Todd et al performed postoperative electrophysiologic studies in patients undergoing surgical isolation of the pulmonary veins and posterior left atrium. 5/14 patients in the post-operative study developed sustained AF in the isolated posterior LA region, however AF could not be induced in any other atrial region despite provocation with an aggressive pacing protocol (87). Markides et al described the electrophysiologic properties of the posterior left atrium in patients with paroxysmal AF using non-contact mapping (94). Left atrial activation was found to propagate around a line of functional conduction block between the superior and inferior pulmonary veins, of which the anatomic correlate was a change in subendocardial fibre orientation at this region. During the initiation of AF, this functional line of block formed the substrate for reentry, whereby pulmonary vein wavefronts exiting pulmonary veins resulted in LA macroreentry or formation of daughter wavefronts.

A further mechanism for the arrhythmogenicity of the posterior left atrium includes the unique activation and repolarization response to autonomic inputs. Using high-resolution optical mapping, Arora demonstrated the substrate for reentry at the PV-LA junction in the presence of isoproterenol or acetylcholine in Langendorff-perfused pulmonary veins (95). In a subsequent experiment, these authors demonstrated the effect of vagal stimulation to create the substrate for functional reentry by shortening refractoriness preferentially and heterogeneously within the posterior left atrium (96). They performed epicardial mapping in dogs and measured the response to autonomic manipulation with vagal stimulation. A greater decrease in refractoriness of the
pulmonary veins and posterior left atrium was defined compared to the left atrial appendage, and the heterogeneity of vagal effects was most pronounced in the posterior left atrium (96). Differences in refactoriness are thought to be underpinned by the variability in distribution of IK_Ach channels, an ion channel primarily responsible for mediating vagal effects on atrial electrophysiology.

Roberts-Thomson et al highlighted the arrhythmogenic role of the posterior left atrium particularly in patients with structural heart disease (97). These authors performed detailed epicardial mapping studies on 4 groups of patients at the time of cardiac surgery; (1) normal left ventricular function undergoing coronary artery bypass grafting; (2) severe left ventricular dysfunction undergoing coronary artery bypass grafting; (3) severe mitral regurgitation; and (4) aortic stenosis. A line of functional conduction delay and block traversing the posterior wall vertically between the pulmonary veins was found in all patient groups, particularly marked in patients with more advanced left atrial enlargement. This correlated with a greater extent of conduction slowing, block and conduction heterogeneity in patients with more advanced structural disease. Conduction in the region of the line of block showed significant anisotropy with marked conduction slowing when wave fronts propagated perpendicular to the line, resulting in a circuitous wavefront course around the region of block and the formation of reentry. These authors also demonstrated that fractionated electrograms and double potentials are almost universally recorded along the line of slow conduction.
1.5 Atrial Anatomy and Intra-Atrial Conduction

1.5.1 Atrial Dilation and the Propensity to Atrial Fibrillation

Increased left atrial size is also known to be an independent predictor of major cardiovascular events, including non-fatal stroke, coronary artery disease, congestive heart failure, and cardiovascular mortality (98). In addition, left atrial enlargement is well established as an independent risk factor for atrial fibrillation, with a HR of 1.4 for every 5mm increase in left atrial diameter (14, 99). Atrial dilation may promote the development of atrial fibrillation through a number of mechanisms:

1. An increase in the number of wavelets, as the number of wavelets increases proportionate to the square of the atrial diameter (44).
2. Acute atrial dilation and wall stress results in slowing of conduction, an increase in intra-atrial conduction block, and conduction heterogeneity (100).
3. An increase in intra-atrial pressure increases the number and organization of waves emanating from the PV’s (101).

Allessie and co-workers in 2 complementary studies described the electrophysiological changes during progressive atrial dilation in chronically instrumented goats. Progressive atrial dilation resulted in conduction slowing and an increase in the duration of inducible AF (102). A follow up study demonstrated a wider excitable gap during AF in dilated atria due to intra-atrial conduction defects and a higher contribution of anatomically defined re-entrant circuits (103). The spatial excitable period refers to the difference between pathlength and wavelength. The existence of an excitable gap during AF allows regional entrainment of the atria (61, 104). Widening of the excitable period reduces the chance of wavelets encountering regions of partially refractory tissue thereby preserving conduction and decreasing
wavefront fragmentation. Increasing the excitable gap also favours fusion of wavelets shifting the balance toward extinction rather than generation of wavelets.

1.5.2 Atrial Anatomy

Atrial endocardial structures may act as barriers to the propagating wavefront thereby resulting in conduction slowing or block and the foundation for reentry. The pectinate muscles have been identified as atrial structures that serve as a site for reentrant circuits to anchor, leading to sustained and stable reentry. Gray et al described epicardial breakthrough patterns from reentrant excitation through the pectinate muscles (105). Chen et al performed detailed mapping and computer simulation studies on acetylcholine-perfused isolated right atrial canine tissue. 20/28 episodes of reentry were initiated by conduction block along large ridges of pectinate muscle. The reentrant vortices rotated around these sites, providing a natural anchor to the reentrant wave front (106). On computer simulation modeling, a critical thickness of the pectinate muscles is required for reentry to “anchor”, leading to the preferential expression of atrial macroreentry (“atrial flutter”) compared to disorganized atrial fibrillation.

The crista terminalis also acts as an anatomic barrier that has an important role in the pathogenesis of atrial arrhythmias. The crista terminalis extends from the junction of the superior vena cava to course anteriorly to form the Eustachian ridge beyond the inferior vena cava, and separates the anterior trabeculated right atrium from the smooth walled posterior right atrium. Waldo et al described the role of the crista terminalis as a site of both anatomical and functional block in patients with atrial flutter. Transitional atrial fibrillation usually precedes atrial flutter, forming a
functional extension of the anatomic line of block at the crista terminalis to form the posterior barrier to the reentrant circuit (107). In patients with atrial flutter, the coupling interval which results in functional conductional block along the crista terminalis is significantly longer in patients with atrial flutter compared to patients with atrial fibrillation (108). During initiation of atrial fibrillation, there is anisotropic, decremental conduction across the crista terminalis, similar to that observed during pacing from the pulmonary veins, and providing the substrate for typical flutter in these patients (109).

1.5.3 Autonomic Ganglia and the Genesis of Atrial Fibrillation

Parasympathetic and sympathetic activation have been shown to modulate atrial conduction velocity and refractoriness. Epicardial mapping studies have demonstrated that the posterior left atrium is the most richly innervated with parasympathetic nerve receptors compared to other atrial sites (110).

Vagally triggered atrial fibrillation is a well-described clinical entity, with a proportion of patients exhibiting a pattern of clinical arrhythmia where the majority of episodes are triggered by vagal stimuli. Coumel classified vagal atrial fibrillation as episodes that are triggered by food intake or occur nocturnally (111). Adrenergic atrial fibrillation episodes occur during waking hours and are precipitated by emotional or physical stress (111). The prevalence of vagal atrial fibrillation has been estimated at 6-12%, and that of adrenergic atrial fibrillation 15-16% (112, 113). Rosso et al reported in a young population of patients in the absence of significant structural heart disease, antral circumferential pulmonary vein isolation is equally effective in
patients with vagal atrial fibrillation, adrenergic atrial fibrillation, and non-autonomic atrial fibrillation (114).

Vagal stimulation has been shown to accelerate rapid pulmonary vein activity and the initiation of atrial fibrillation. In canine pulmonary veins, modulation of cholinergic influences resulted in a shortening of pulmonary vein action potential duration and rapid pulmonary vein initiated tachycardia (115). In a canine model, both sympathetic and parasympathetic autonomic influences have been shown to underlie the initiation of atrial fibrillation in the ligament of Marshall (116).

Clinical studies have reported that ablation modifying vagal inputs into the left atrium may reduce the recurrence of post-operative atrial fibrillation. In a study of patients with evoked vagal reflexes abolished by radiofrequency ablation, adjunctive vagal denervation during pulmonary vein isolation reduced the frequency of recurrence of atrial fibrillation (117). Other investigators have also reported additional benefit after atrial fibrillation ablation when ablation of ganglionated plexi was used as an adjunct (118). Nakagawa et al targeted autonomic ganglia in close proximity to the PV’s with radiofrequency energy eliminating the vagal response and significantly reducing AF inducibility (119). Therapeutic strategies targeting the parasympathetic supply around the PV ostia may improve the success of future ablation procedures.

1.6 Atrial Substrate in Atrial Fibrillation

Alllessie et al first proposed the landmark observation that “atrial fibrillation begets atrial fibrillation” after changes were observed in the electrical properties of the atria in response to atrial pacing (44). Nattel and coworkers studied the effects of experimental congestive heart failure by rapid atrial pacing compared to controlled
ventricular pacing in a canine model of atrial fibrillation. The duration of induced atrial fibrillation and heterogeneity of conduction increased in the rapid atrial pacing model, due to the emergence of discrete regions of slowed conduction (120). Examination of histologic specimens revealed extensive interstitial fibrosis, providing the substrate for the “second factor” in the maintenance of atrial fibrillation. The perpetuation of atrial fibrillation has therefore been attributed to both electrical and structural remodeling.

1.6.1 Electrical Remodeling in Atrial Fibrillation

Atrial Refractoriness

Electrical remodeling as a consequence of tachycardia is manifested by a generalized shortening of atrial refractoriness, loss of the physiologic rate dependent shortening of refractory periods to decreasing cycle lengths, and a progressive increase in the inducibility and duration of AF (44, 90). In a seminal study, Wijffels described a progressive increase in the duration of atrial fibrillation episodes in response to progressive increases in atrial tachypacing (44). Episodes of atrial fibrillation were associated with shortening of refractoriness and the concept that atrial fibrillation is self-perpetuating was born as “AF begets AF”. These authors suggested that the shortening of atrial refractoriness would stabilize episodes of AF by decreasing atrial wavelength, thereby increasing the potential number of electrical reentrant wavelets in the atria and increasing AF stability as predicted by the multiple wavelet hypothesis. These investigators also demonstrated that electrical remodelling is reversible after restoration of sinus rhythm, where the recovery of atrial refractoriness follows a rapid then more gradual trajectory (44).
Electrical remodeling may occur after brief episodes of atrial fibrillation, and appears to be related to the duration of atrial fibrillation. After 7 minutes of induced AF, Daoud et al found significant shortening of atrial refractory periods in conjunction with recurrent paroxysms of AF, with complete recovery of refractoriness after a mean of 8 minutes (121). There is a correlation between the shortest coupling interval of atrial extrastimuli after cardioversion of persistent atrial fibrillation and the risk of recurrence of AF (122). Hobbs et al measured AF cycle length in the left and right atrium before cardioversion in patients with persistent AF, and repeated these measurements in patients who re-presented for a subsequent cardioversion for recurrent AF (123). These authors demonstrated reversal of electrical remodeling, by demonstrating an increase in AF cycle length from the initial cardioversion to that measured at the subsequent cardioversion for AF recurrence, with the magnitude of increase positively correlated with duration of sinus rhythm before AF recurrence.

Teh et al evaluated 31 patients with either paroxysmal or persistent atrial fibrillation and compared electrophysiologic studies to age-matched control patients with supraventricular tachycardia (124). Patients with paroxysmal AF showed variable results in assessment of refractoriness compared to control patients, with either no change or an increase in ERP depending on the site tested. Patients with persistent AF showed overall significantly reduced atrial refractory periods compared to patients with paroxysmal AF and to controls.

*Atrial Refractoriness and Cycle Length in Atrial Fibrillation*

The major determinant of the maximum rate at which the myocardium can depolarize is the refractory period, however the measurement of atrial refractoriness in human
atrial fibrillation is difficult to evaluate. An approximation of refractoriness can be made by assessment of the AF cycle length. Animal studies have demonstrated the minimum local AF cycle length measured from at least 10 seconds of AF approximates the local ERP (125). In human paroxysmal AF, there is a strong correlation between mean AF cycle length and the atrial effective or functional effective refractory period at the same atrial site (126). The evaluation of AF cycle length from multiple sites with high-density plaques provides a means of estimating regional variability in refractoriness.

Rapid atrial activation results in a decrease in AF cycle length over time, with an increase in regional heterogeneity of refractoriness (127). Along with changes of conduction slowing and wavelength, these changes contribute to the increase in stability and duration of atrial fibrillation.

**Atrial Conduction**

Conduction abnormalities predispose to atrial fibrillation by reducing the wavelength for re-entry (128). P wave duration is largely determined by interatrial conduction and atrial size. Patients with paroxysmal AF in sinus rhythm demonstrate a prolongation in P wave duration (129). Atrial conduction velocity decreases in response to atrial fibrillation, classically with a slower time-course than the changes in atrial refractoriness (130). Nattel and co-workers measured refractory periods and conduction velocities at 1, 7, and 42 days in an atrial tachypacing model (127). Maximal changes in conduction velocity occurred at 42 days, with maximal changes in refractory periods at 7 days. The duration of sustained atrial fibrillation increased further between day 7 and 42 after a plateau in atrial refractoriness, paralleling the
time course of conduction slowing. Activation studies revealed regional variability in local AF cycle length, resulting in an increase in the number of functional re-entry zones during AF of progressively increasing duration.

In an ovine right atrial Y-Lesion model of atrial flutter, Morton et al investigated the electrophysiologic consequences of sustained atrial flutter (131). Episodes of flutter produced a significant reduction in left and right atrial refractoriness, with the majority (74%) of the reduction occurring within the first 3 days of sustained arrhythmia. Conduction velocity significantly slowed, however over a comparatively longer time course. The combination of these changes produced the substrate for development of sustained atrial fibrillation.

1.7 Atrial Structural Remodeling: The “Second Factor”

Despite normalization of electrical remodeling after an episode of AF, a persistent vulnerability to AF remains. Allessie proposed the existence of a “second factor” that maintains the predisposition to recurrent AF (132). It has been proposed that this “second factor” includes structural and gap junction remodeling that develop in parallel with the development of persistent AF (132). Structural remodeling characterized by tissue fibrosis and the resultant changes in fibre orientation result in generalized conduction slowing and an increase in conduction heterogeneity with an increase in the propensity to AF.

Teh et al describe structural abnormalities in their cohort of patients with paroxysmal and persistent AF (124). Compared to control patients, AF patients had lower mean voltages and a higher proportion of low voltage areas, slower conduction, and more complex signals. Many of these structural abnormalities were more pronounced in
patients with persistent compared to paroxysmal AF, suggesting a longer duration of arrhythmia may be associated with more advanced remodeling.

Structural remodeling at the ultrastructural level has shown regional variations in distribution, with a predilection for the left atrial posterior wall (133). Ultrastructural changes include loss of myofibrils; glycogen accumulation; alterations in mitochondrial size and shape; fragmentation of sarcoplasmic reticulum; dispersion of nuclear chromatin; and an increase in myocyte size (133). At the macroscopic level, atrial interstitial fibrosis is seen representing the morphologic substrate for AF, seen in the form of an excess in the extracellular matrix consisting mainly of fibroblasts and collagen fibres (134). Animal studies have provided insights into the mechanisms of structural remodeling in AF: collagen fibril accumulation and disarray leads to conduction heterogeneity by impairing inter-myocyte coupling, which ultimately results in alterations of connexins located within gap junctions. An increase in atrial myocardial connexin expression has been shown to significantly increase the likelihood of atrial fibrillation (135).

A combination of necrosis and apoptosis has been observed in AF models. Caspases are important proteins in regulating apoptosis, the pathologic hallmark of which includes cell shrinkage, loss of cell shape, membrane blebbing, protein fragmentation, chromatin degradation, and nuclear fragmentation (136). Apoptotic changes have been observed in rapid atrial pacing models with induction of heart failure, but not when ventricular rate was controlled (120, 137).
1.7.1 Mediators of Structural Remodeling

Pro-Fibrotic Proteins

Fibrosis results when the balance of pro and anti-fibrotic proteins is disrupted and favours proteins promoting the development of fibrosis. Transforming Growth Factor \( \beta \) (TGF-\( \beta \)) is a pro-fibrotic cytokine that interacts with TGF-\( \beta \) receptors on myofibroblasts leading to increased extracellular matrix formation (138). In patients with persistent AF increased levels of TGF-\( \beta \) and its signal transduction proteins have been found compared to patients in sinus rhythm. Connective tissue growth factor (CTGF) modulates extracellular matrix deposition, is regulated by TGF-\( \beta \), and promotes the proliferation of fibroblasts (139). Patients with AF have been shown to have a marked up-regulation in the CTGF expression in left atrial myocardium compared to patients in sinus rhythm (140). Platelet-derived growth factor appears to be involved in the increased responsiveness of atrial fibroblasts, and results in an overall increased fibrotic response in the atria as compared to the ventricles (141). Other molecules, including proteoglycans, are directly involved in the pathogenesis of cardiac fibrosis by modulating the angiotensin II signaling system (142). The precise pathways involved in fibrogenesis are complex, however any factors that upregulate TGF-\( \beta \) and its related molecules results in an increased formation of fibrosis.

Inflammation and Oxidative Stress

Frustaci et al analysed atrial biopsy specimens of patients with paroxysmal AF and found inflammatory infiltrates, and areas of necrosis and fibrosis (143). The role of inflammation in AF is complex; inflammation may promote the development of AF, and may also be a consequence of the arrhythmia, further promoting AF (144).
Myeloperoxidase is a marker of atrial inflammation, and acts as a key profibrotic mediator involved in structural remodeling (145). C-Reactive Protein (CRP) is a marker of systemic inflammation, and increased CRP levels are associated with an increase in the risk for future development of AF (15). In addition, CRP has been found to be preferentially distributed within the left atrium during AF, although it is as yet unclear whether higher CRP levels are a cause or consequence of AF (146).

Oxidative injury, mediated through the reactive oxidative metabolites, has been implicated in AF-related remodeling (147). NADPH oxidase generates reactive oxygen species in cardiomyocytes, and demonstrates an increased activity in the atrium in the presence of AF (148). Nattel and co-workers studied the effects of simvastatin in dogs subject to 7 days of atrial tachypacing. Simvastatin was shown to largely prevent shortening of atrial refractoriness and AF promotion and attenuated downregulation of L-type calcium channels (149).

Cai et al studied a porcine model of rapid atrial pacing and demonstrated that one week of AF resulted in downregulation of nitric oxide synthase and nitric oxide production and an increase in the prothrombotic plasminogen activator inhibitor-1 (PAI-1) (150). These changes were confined to the left atrium and may contribute to the increased risk of thromboembolism in AF.

*Activation of the Renin-Angiotensin-Aldosterone System*

Patients with AF demonstrate an increase in expression of angiotensin converting enzyme mRNA and changes in the expression angiotensin receptors (151, 152). Atrial stretch results in activation of the angiotensin I receptor in the absence of angiotensin II (153). In rat atrial cardiomyocytes, the angiotensin II receptor blocker losartan
reduced all stretch-mediated changes in ion currents including shortened action potential duration, reduction in hypertrophy, and changes in the regulation of pro and anti-fibrotic mediators (154, 155). In heart failure models inhibition of the renin-angiotensin-aldosterone system by ACE-inhibitors and angiotensin II receptor blockers demonstrated a reduction in atrial structural remodeling and less inducible AF (156).

*Calcium Overload*

Patients with AF have been shown to demonstrate changes in calcium handling proteins, leading to calcium overload and to altered signal transduction (138). Activation of calcium dependent proteins including calcineurin and calpanin is increased, resulting in altered gene expression and hypertrophy, and degradation of muscle proteins (138).

1.8 *Atrial Reverse Remodeling*

Tops et al evaluated changes in left atrial volume and the recurrence of AF after catheter ablation. A >15% decrease in LA volume was associated with a lower recurrence rate of AF (12%) compared to a recurrence rate of 69% in patients where LA size did not change (157). Choi et al compared LA size after catheter ablation and cardioversion (158). Both procedures resulted in a significant reduction in left atrial size at 3 months, however improvement in LA ejection fraction was only seen after cardioversion.
Reversal of structural remodeling following prolonged episodes of sustained AF occurs slowly and incompletely (159). Four months following restoration of sinus rhythm in an animal model of AF, there was: incomplete recovery of myolysis; expansion of the extracellular matrix per myocyte; and alterations in structural proteins and the organization of the sarcoplasmic reticulum and mitochondria. These persisting structural changes were associated with significantly longer episodes of induced AF.

John et al found significant reversal in atrial electrical remodeling in patients with mitral stenosis after mitral commissurotomy (160). Immediately after mitral commissurotomy a decrease in LA volume, mean LA pressure, shortening of P-wave duration, and increase in atrial conduction velocity and voltage was observed. At long-term follow-up, there was progression in the reversal of these early changes, in addition to significantly reduced atrial refractory periods. These changes were associated with a trend to a decreased vulnerability to AF in the long-term, suggesting that the substrate predisposing to atrial arrhythmias due to chronic atrial stretch may be reversible with elimination of the condition leading to atrial stretch.

Teh et al showed mixed results in an evaluation of reverse remodeling in patients with paroxysmal AF who were studied remotely (>6 months) following an initial ablation procedure for AF (161). At long-term follow-up, patients with AF demonstrated significantly lower voltage; either no change or progressive conduction slowing; further prolongation of regional refractoriness; and reversal of left atrial dilation. These findings were seen even after successful catheter ablation with clinical and electrocardiographic evidence of maintenance of sinus rhythm.

In a study of patients with paroxysmal and persistent atrial flutter, Sparks et al demonstrated disparate time courses of recovery of electrical remodeling dependent
on the duration of arrhythmia, with atrial refractory periods approaching normalization at 30 minutes in the paroxysmal arrhythmia group, and at 3 weeks in the persistent arrhythmia group (162).

1.9 Atrial Stretch

Many disease states associated with an increased risk of atrial fibrillation are accompanied by increased atrial stretch, including hypertension, heart failure and mitral valve disease. (163). Nazir et al described mechanoelectric feedback in acute atrial stretch model in isolated guinea pig hearts. Acutely, transient stretch resulted in changes in epicardial action potentials with a decrease in amplitude, and an increase in duration due to the presence of early afterdepolarisations (163). In vivo animal models of stretch including mitral valve disease and volume overload are associated with an increased vulnerability to AF (164-166). Cellular studies demonstrate that atrial stretch leads to cellular hypertrophy, de-differentiation, extracellular matrix remodeling and electrical remodeling (154).

1.9.1 Human Studies of Atrial Stretch

Ravelli et al studied the role of stretch-induced conduction changes in the creation of a proarrhythmic substrate by quantifying the spatial distribution of local conduction velocities (CVs) in the human atrium during acute atrial dilatation induced by simultaneous atrioventricular pacing (167). An acute increase in atrial volume resulted in a significant decrease in atrial conduction velocity and an increased incidence of slow conduction sites and areas of local conduction block (167). Acute
atrial dilatation concurrently increased AF vulnerability, with 6 of 10 patients developing AF episodes under acute stretch conditions.

In a chronic study of atrial stretch secondary to asynchronous VVI pacing, Sparks et al demonstrated an increase in refractoriness, P wave duration, corrected sinus node recovery times and biatrial size following long term VVI pacing (168). Atrial mechanical function was also impaired in the VVI group with a reduction in left atrial appendage emptying velocities and the appearance of spontaneous echocardiogram contrast. All parameters recovered to baseline values with the reestablishment of AV synchrony (169).

**Atrial Remodeling in Atrial Septal Defect**

Morton et al performed detailed electrophysiologic studies on 13 patients with atrial stretch due to uncorrected atrial septal defects (ASD) in the absence of atrial arrhythmia (130). Electrical remodeling was demonstrated with an increase in refractory periods, an increased in sinus node recovery time, and in conduction delay across the crista terminalis as reflected by an increased number of crista catheter bipoles recording discrete double potentials. In a follow up study after ASD closure, there was persistence of conduction abnormalities at the crista terminalis, with extensive widely split double potentials, providing the substrate for the long-term predisposition to the development of atrial flutter and fibrillation.
**Atrial Remodeling In Heart Failure**

Approximately 30-40% of patients with congestive cardiac failure develop atrial fibrillation (170), and it is associated with an increased morbidity and mortality (22). In dogs with pacing induced heart failure, Li et al found an increase in atrial refractoriness at shorter cycle lengths, with no change at longer cycle lengths. There was no change in conduction velocity, however there was a significant increase in heterogeneity of conduction due to discrete regions of slow conduction associated with interstitial fibrosis (120). These structural changes were associated with a high prevalence of sustained AF.

Shinagawa et al studied the consequences of rapid atrial pacing in a similar canine pacing-induced heart failure model (171). The addition of rapid atrial pacing during the 5th week of rapid ventricular pacing resulted in an attenuation of the usual shortening of refractoriness seen with atrial tachypacing in the normal heart, along with maintenance of rate adaptation and a reduction in conduction velocity. The addition of atrial pacing on a heart with established heart failure did not increase the vulnerability to AF, but was associated with an increase in the prevalence of prolonged episodes of AF. Heart failure significantly increased atrial fibrosis, which was not seen in atrial tachypacing alone. The effects of hemodynamic and echocardiographic resolution of heart failure were then investigated. Recovery led to a reduction in AF inducibility, however conduction heterogeneity and fibrosis remained unchanged during recovery, indicating that structural remodeling had not resolved. Electrical remodeling reversed to baseline levels after a 5 week recovery period after cessation of atrial tachypacing (172).

Sanders et al performed detailed electrophysiologic and electroanatomic evaluation of the human atria in patients with symptomatic congestive heart failure (173). Patients
with heart failure demonstrated an increase in atrial refractoriness, an increase in atrial conduction times, prolongation of the P-wave duration and corrected sinus node recovery times, and greater number and duration of double potentials along the crista terminalis. Electroanatomic mapping demonstrated regional conduction slowing with a greater number of electrograms with fractionation or double potentials, associated with areas of low voltage and electrical silence. These changes were associated with an increased propensity for AF with single extrastimuli, and an increase in the duration of induced atrial fibrillation.

*Atrial Remodeling in Mitral Regurgitation*

In canine studies of atrial dilation secondary to mitral regurgitation, histopathologic changes including disruption of sarcomeres, loss of myofibrils, aggregates of irregular mitochondria and glycogen granule deposition have been observed (174). In patients with mitral regurgitation and co-existent atrial fibrillation there is evidence of myocyte hypertrophy and death (133). These changes are considered to represent de-differentiation due to the rapid atrial rate and subsequent loss of normal contractility with atrial stretch (175).

Verheule et al studied the chronic electrophysiologic changes as a consequence of partial avulsion of the mitral valve (166). A significant increase in left atrial dimensions was associated with an increase in atrial refractoriness and no change in conduction velocity. Despite the increase in atrial wavelength the mitral regurgitation group were more susceptible to sustained AF. Using high resolution optical mapping an increase in conduction heterogeneity and anisotropy was demonstrated in the LA of the mitral regurgitation group, which was not seen in the RA, controls or rapid
atrial pacing group (176). The changes in conduction were shown to occur in regions of increased fibrosis and fibre separation with associated chronic inflammation.

1.10 Atrial Remodeling in Systemic Hypertension

The prevalence of systemic hypertension in the adult population is currently 30%, with an increase in incidence of approximately 30% from 1988 to 1999-2000 (177). The prevalence rises to 60% in those aged >65 years, and in patients with AF, up to 60% have a history of hypertension (178-181). Systemic hypertension is an independent and potentially modifiable risk factor for AF, (12, 99) with the risk of AF increasing with each incremental elevation in systolic blood pressure (182). Once AF develops, hypertension significantly increases stroke and systemic embolic events. In combination, AF and hypertension are associated with an 8-fold increased risk of stroke (183), and in a high-risk hypertensive population, preexisting or new-onset AF is associated with increased mortality (181).

Kistler et al studied the effects of chronic hypertension in an ovine model of hypertension after prenatal corticosteroid exposure (184). In this model, pregnant ewes were exposed to corticosteroid for 48 hours in the first trimester of pregnancy, in order to produce offspring with hypertension from the first few months of life, which is more marked in males and progresses with age (185). Twelve sheep with chronically elevated blood pressure were studied with open chest electrophysiologic and pathologic studies. Hypertension was associated with widespread conduction abnormalities, shortening of atrial wavelength, and an increase in AF in the absence of changes in refractoriness. Pathologic examination revealed atrial myocyte hypertrophy and myolysis in all 12 hypertensive sheep and focal scarring in 6 of 12
sheep. Histopathologic examination demonstrated mitochondrial and nuclear enlargement and increased collagen fibrils in hypertensive sheep, findings that were absent in control sheep. Increased numbers of intercellular collagen fibrils, and an increase in apoptotic markers were also apparent in the atria of hypertensive sheep.

In an alternate ovine model of hypertension, Lau and co-workers performed open-chest electrophysiologic study with biatrial epicardial plagues, and cardiac magnetic resonance imaging to assess functional changes (186). Hypertension of mean duration 7 weeks was associated with atrial remodeling characterized by significantly enlarged left atrial size; reduced left atrial ejection fraction; increased refractory periods; slower conduction velocity; an increase in conduction heterogeneity; an increase in inflammatory cell infiltrates and interstitial fibrosis on microscopy; and an increase in the inducibility and duration of atrial fibrillation.

In a “one-kidney, one-clip” model of chronic hypertension, these authors studied the effects of chronic hypertension (mean 15 weeks) in an ovine model (187). Progressive biatrial hypertrophy, left atrial dysfunction and greater inducibility of AF was seen early with increased inflammatory changes. Delayed changes included significant conduction slowing, increased conduction heterogeneity, and increased interstitial fibrosis resulting in longer and more fractionated episodes of AF.

To date, there are no studies evaluating the effect of chronic hypertension in humans. This is particularly relevant, as hypertension is the most common modifiable risk factor for stroke, and there is an upward trend in the incidence of hypertension over the past 2 decades (188). In addition, patients with hypertension are more likely to experience a recurrence of arrhythmia after pulmonary vein isolation (189). To address this significant gap, we performed detailed electrophysiologic and
electroanatomic studies in patients with chronically treated hypertension. The results from this study are presented in Chapter 2.

1.11 Pulmonary Hypertension and Atrial Fibrillation

Pulmonary hypertension as assessed by echocardiography is a frequent finding in patients with atrial fibrillation, occurring in approximately 58% of patients hospitalized for AF, compared to 31% hospitalized patients in sinus rhythm (190). However, little is known of the direct electrophysiologic effects of pulmonary hypertension in humans.

In a study of >500 000 inpatient hospital discharges, Deshmukh and colleagues evaluated the prevalence and outcomes of patients with a diagnosis of pulmonary hypertension and atrial arrhythmias (191). Patients with pulmonary hypertension had significantly higher prevalence of atrial arrhythmias after adjustment, with a two-fold increased frequency of AF (95% CI 1.92-2.03); 1.7 times increased risk of atrial flutter (95% CI 1.68-1.76) and 1.4 times increased risk of supraventricular tachycardia (CI 1.30-1.43). AF was also found to be an independent predictor for mortality in patients with pulmonary hypertension (OR 1.13; 95%CI 1.06-1.23).

Assessment of atrial electrophysiologic changes in pulmonary hypertension have been confounded by the presence of other disease states shown to result in atrial remodeling, including heart failure, chronic obstructive pulmonary disease, ischaemic heart disease, and obstructive sleep apnoea. Pulmonary hypertension occurs in obstructive sleep apnoea as a result of hypoxic pulmonary vasoconstriction. The atrial electrophysiologic changes in obstructive sleep apnoea (OSA) were recently described by Dimitri et al in a comparative study of patients with AF with and without
a diagnosis of obstructive sleep apnoea (192). Patients with OSA demonstrated prolonged biatrial conduction times; an increased number and duration of fractionated signals along the crista terminalis; longer P-wave duration; longer sinus node recovery time; lower atrial voltage; slower conduction velocity; and more diffuse complex electrograms in the left and right atria. However the high prevalence of heart failure (193) and hypertension (194) in patients with OSA makes the relative contribution of pulmonary hypertension to the increased risk of AF in these patients difficult to estimate.

In order to address the question of the independent role of pulmonary hypertension in the development of AF, we performed detailed electrophysiologic and electroanatomic studies in patients with idiopathic pulmonary hypertension. The results from this study are presented in Chapter 3.

1.12 Electrophysiologic Mechanisms of Typical Atrial Flutter

Atrial flutter (AFL) is the second most frequently occurring arrhythmia seen in clinical practice, after atrial fibrillation (179). The first investigations into the mechanisms of this arrhythmia were performed by Lewis et al in 1913, who were the first to advance the proposition that AFL was due to reentry (195). In a canine model of AFL induced by rapid atrial pacing, Lewis and colleagues mapped right atrial activation patterns using epicardial recordings, and demonstrated the presence of cranial-caudal or caudal-cranial direction of activation. Lewis and colleagues mistakenly concluded that activation occurred around the vena cava, however the fundamental understanding of AFL as reentrant was born. In a later study, Rosenbleuth and Garcia-Ramos applied a crush lesion to the intercaval region and
were reliably able to induce AFL (196). These authors concluded that reentry occurred around the crush lesion based on epicardial mapping studies. However, when the crush lesion was extended from the inferior vena cava to the tricuspid valve, AF was non-inducible, suggesting that the observed AFL was isthmus-dependent. Frame et al further developed these observations by studying the activation patterns of AFL in the presence of a lesion between the vena cava with a Y extension to the right atrial appendage. High-density epicardial mapping demonstrated reentry occurring in a clockwise or counterclockwise direction around the tricuspid annulus. It was concluded that the Y lesion provided the necessary lateral boundary to limit reentry to the tricuspid valve annulus and to prevent the flutter wavefront from extinguishing through short-circuiting (197). In this model, the 2 barriers to conduction (the Y lesion and the tricuspid annulus) represented fixed barriers of conduction.

An experimental model by Boyden et al demonstrated the importance of areas of functional block as providing potential barriers to the flutter circuit. Boyden induced right atrial dilatation by severing the chordae tendinae of canine tricuspid valve leaflets, and went on to perform endocardial mapping studies. With the introduction of progressive extrastimuli, Boyden and colleagues showed conduction slowing and heterogeneity, with eventual fixed conduction block occurring and maintaining with continual introduction of extrastimulus. Once the extrastimulus was ceased, the wavefront from the last paced beat propagated across the right atrial free wall and produced reentry by circulating around the line of functional block. In this way, either counterclockwise or clockwise reentry may be induced, supported by both fixed and functional barriers (198).

Other canine models have been developed where the reentrant wavefront also propagates around a functional line of block. In the canine sterile pericarditis model,
the atrial surfaces are covered with sterile talcum powder, and an electrode array positioned on the epicardial surface of both atria to create epicardial activation maps of pacing-induced atrial flutter (199). In this model, Waldo and colleagues found transitional atrial fibrillation resulted in wave fronts that produced a localized zone of slow conduction. In the area of slowed conduction, unidirectional block occurred resulting from an area of functional block. The propagating wave front then turns around this area of block thereby initiating reentry. The area of functional block was represented by double potentials representing activation on either side. Zones of slowed conduction were represented by fractionated potentials, in particular the turnaround points of the reentrant wave front (199).

1.12.1 Mapping of Human Atrial Flutter

*Activation Mapping*

Puech at al used multisite endocardial mapping in patients with AF, and demonstrated that septal activation occurs inferiorly to superiorly, and the anterolateral wall is activated superiorly to inferiorly (200). Klein et al performed both endocardial and epicardial mapping of typical atrial flutter in affected patients (201). This early study demonstrated macroreentry as the underlying basis of typical AFL in humans. In these patients, atrial endocardial mapping showed earliest activation at the orifice of the coronary sinus, with low septal activation, high lateral activation, and low right atrial activation following, respectively. Intraoperative epicardial mapping during AFL demonstrated a wavefront propagating from the posteroseptal region to the superior and lateral right atrium, respectively, before returning to the coronary sinus to complete the reentrant circuit. Left atrial activation appeared to be passive and arising
from both the anteroseptal and posteroseptal regions. Importantly, a zone of slow conduction was observed in the cavo-tricuspid isthmus, in a narrow obligate area of the circuit. Cryoablation of the isthmus prevented short-term recurrence of AFL in these patients.

**Entrainment Mapping**

Waldo et al. first elegantly described entrainment to demonstrate that AFL was a reentrant arrhythmia (202). Utilizing both activation and entrainment mapping from sites adjacent to the tricuspid valve annulus during AFL, Kalman et al. described counterclockwise rotation of the flutter wave around the tricuspid annulus (203). Entrainment mapping of all sites around the tricuspid annulus established that these sites were all within the flutter circuit (203). This study was a landmark in establishing the tricuspid annulus as the fixed anterior barrier in human atrial flutter.

Using intracardiac echocardiography to position endocardial catheters along the crista terminalis and Eustachian ridge, Olgin et al. demonstrated that entrainment along the radius from the tricuspid annulus anteriorly to the crista terminalis or Eustachian ridge posteriorly results in a postpacing interval equal to the flutter cycle length, indicating that the entire trabeculated right atrium is within the reentrant circuit of flutter, and that the crista terminalis and Eustachian ridge comprise the posterior barriers to conduction (204). In many patients with atrial flutter, this line of block is likely to be partially fixed, with functional extension (107). Saffitz et al. demonstrated preferential longitudinal conduction and poor transverse conduction along the crista terminalis, consistent with a fixed line of block (205). Olgin cites the demonstration of bidirectional block by pacing immediately lateral and septal to the ablation line after
cavo-tricuspid ablation as further suggestive proof of the fixed nature of block: post-ablation, when pacing from the low lateral right atrium, activation proceeds superiorly and then inferiorly down the septum, with the coronary sinus os activated latest. If there was no fixed line of block, Olgin argued that the septum and lateral regions would be activated simultaneously, even in the presence of complete isthmus block (206). Waldo considers that this posterior line of block is predominantly functional (107), based on observations from canine (207) and human mapping studies (208). Whether this line of block is fixed or functional, it is clear that the presence of a second barrier is critical in the maintenance and stabilization of the flutter circuit.

1.12.2 Interaction Between Atrial Fibrillation and Atrial Flutter

It is well recognised in clinical practice that atrial fibrillation and atrial flutter are closely related. Atrial fibrillation may “convert” to atrial flutter after the administration of class 1C agents (209); AF may become clinically apparent after elimination of AFL by radiofrequency ablation of the cavo-tricuspid isthmus (210, 211); and there may be spontaneous conversion between AF and AFL, with transitional atrial fibrillation preceding the onset of AFL (107). Waldo et al studied epicardial recordings of patients who developed spontaneous atrial flutter during or in the immediate postoperative periods after cardiac surgery (212). In all 27 episodes of spontaneous AFL, a transitional rhythm of atrial fibrillation (mean 9.3sec) triggered by a premature beat preceded the onset of typical AFL. Other groups have also described similar observations after both induced and spontaneous atrial flutter (213-215). In the canine sterile pericarditis model, the conversion of AFL to AF was associated with a shortening of the length of the functional line of block, with the recurrence of clinical AFL seen in association with the reformation of an extensive
line of block traversing the intercaval distance and protecting the reentrant circuit (214). After making these observations, Waldo advanced further the theory that transitional atrial fibrillation is a prerequisite for atrial flutter, through the formation of a functional line of block as the necessary lateral boundary for the circuit to sustain reentry and prevent short-circuiting. This close inter-relationship has many clinical implications; long-term follow up studies of patients post successful cavo-tricuspid isthmus ablation have shown up to 70% patients subsequently manifest clinical atrial fibrillation (216). In the context of the pathogenesis of AFL, a high incidence of AF long-term in these patients is understandable, and the incidence of clinical and subclinical AF in these patients may be even higher. This has important implications for both strategies for catheter ablation in patients with co-existent AF and AFL, and long-term anticoagulation management.

1.13 **Focal Atrial Tachycardia**

1.13.1 **Electrophysiologic Mechanisms of Focal Atrial Tachycardia**

Focal atrial tachycardia (AT) is a relatively uncommon arrhythmia, accounting for up to 10% cases of supraventricular tachycardia (217). It is distinguished from atrial flutter or “macro-reentrant” AT where the underlying electrophysiologic mechanism is reentry. Focal atrial tachycardia is defined by a slower P-wave rate and an isoelectric interval between P waves, originating from an area of atrial myocardium arbitrarily defined as <2cm in diameter (218). By definition, AT does not use the atrioventricular junction or an accessory pathway as an essential portion of its circuit, and can continue indefinitely and independently of them (219).
Focal AT may have an automatic, triggered, or micro-reentrant mechanism. The most common mechanism is thought to be abnormal automaticity, caused by a positive ionic influx during phase 4 depolarization. Clinically, automatic tachycardias are characterized by a “warm up” and “cool down’ over 3-4 beats at the onset and termination of the arrhythmia episode, respectively. In the electrophysiology lab, the classical features of automatic arrhythmias include their facilitation by endogenous or exogenous catecholamine surges; and that they are not inducible with programmed stimulation. Chen et al evaluated the mechanisms of AT in detail, and found additional characteristics of automatic AT to include: transient suppression during overdrive pacing; termination with propranolol; persistence despite administration of adenosine, dipyridamole, verapamil, Valsalva maneuver, carotid sinus massage and edrophonium; and absence of after-depolarizations (220).

Triggered activity and micro-reentry are less common mechanisms of focal AT, and share similarities in the method of induction and termination with programmed stimulation. Triggered activity occurs when delayed after potentials that occur after repolarization reach the depolarization threshold, and activate inward ionic channels triggering an action potential (220). Triggered tachycardias are commonly inducible by constant rate atrial pacing, and may be both accelerated and terminated by overdrive pacing (220). AT due to micro-reentry is classified as focal if the reentrant circuit is <2cm. Due to the small circuit size, classical features of reentry may be difficult to demonstrate. Areas of atrial myocardial fibrosis (221, 222), associated with slowed conduction and anisotropy have been shown in some patients with focal AT, and may provide the substrate for micro-reentry and predisposition to AT in these patients.
1.13.2 Site of Origin of Atrial Tachycardia

It has been well described that the origin of focal atrial tachycardia, and the anatomic location of successful catheter ablation, do not occur randomly throughout the left and right atrium, but tend to cluster at pre-defined anatomic locations within the left and right atrium (223). Within the right atrium, the common sites of origin include the length of the crista terminalis (224), the tricuspid annulus (225), the ostium of the coronary sinus (226), and the perinodal region. Within the left atrium, the common sites are the pulmonary veins, with the mitral annulus, left atrial appendage and the left septal areas recognized albeit less frequent locations of origin.

Right Atrium

Approximately two-thirds of right-sided focal atrial tachycardias originate from the crista terminalis (224). Embryologically, it forms the juxtaposition of the smooth and trabeculated right atrium, within an area of tissue anisotropy, thus leading to potential micro-reentry (205). Additionally, the sinus node complex lies within the superior portion of the crista terminalis, and the combination of sinus node automatic tissue and anisotropic conduction explains the increased incidence of atrial tachycardia from this location (227).

The tricuspid annulus is the next most frequently occurring location of focal AT. Morton et al described in a large series of patients, 13% arose from the tricuspid annulus (225). In this series, the majority arose from the inferoanterior aspect of the annulus, however, the origin may arise from the entire annular surface. McGuire et al identified the presence of myocytes surrounding the tricuspid annulus that are histologically similar to atrial myocytes however contain nodal-like
electrophysiologic characteristics (228). These cells may also function as the substrate for focal AT arising from the tricuspid annulus.

The coronary sinus ostium is an unusual site of origin for focal atrial tachycardia. Kistler et al described approximately 7% patients in a large series of tertiary-referred patients with focal AT had an origin at the coronary sinus ostium (226). This anatomic location is characterized by alterations in myocardial fibre orientation, which may potentially facilitate reentry (229). Other less common sites include the atrioventricular (AV) node and surrounding transitional tissue, the right atrial appendage (230), and the superior vena cava (231).

**Left Atrium**

Within the left atrium, the most common site of origin for focal AT is the ostium of the pulmonary veins. Kistler et al described a cohort of patients with pulmonary vein atrial tachycardia, accounting for 16% of the total population of AT patients (232). In most (78%) patients with PV atrial tachycardia, the focus originates from the superior pulmonary veins. A number of important differences exist between patients with AT compared to patients with atrial fibrillation with triggers from the pulmonary veins: in AT, the foci tends to be localized, with a single focus in a single vein responsible for triggering the arrhythmia; the foci usually occurs at the ostium rather than distally within the pulmonary veins; the cycle length is slower than that of pulmonary vein foci triggering atrial fibrillation and focal ablation is associated with high long-term success rates, compared with pulmonary vein isolation for atrial fibrillation (232).

The next most frequently occurring site within the left atrium is the mitral annulus. The left fibrous trigone in the vicinity of the mitral aortic continuity may be the site of
primitive AV nodal tissue, which has persisted after embryologic development. Wit et al demonstrated that these fibres exhibit AV-nodal type characteristics with both spontaneous automaticity and anisotropic conduction properties potentially providing the substrate for abnormal automaticity or microreentry (233, 234). Less common locations include the left atrial appendage (235), the body of the coronary sinus (236) and the left atrial septum (237).

1.13.3 P Wave Morphology in Focal Atrial Tachycardia, and Relationship to Site of Origin

The P wave morphology provides a useful guide to the likely site of origin of atrial tachycardia in patients with structurally normal hearts. Leads aVL and V1 are the most useful to distinguish between left-sided and right-sided origin of tachycardia (238). Lead V1 is generally more accurate than leads aVL and I (223). A positive or biphasic P wave in lead aVL predicts right-sided AT with a sensitivity of 88% and specificity of 79% (238), although is frequently negative for tachycardias arising from the crista terminalis (223). A positive P wave in V1 has a sensitivity of 93%, a specificity of 88%, a positive predictive accuracy of 87%, and negative predictive accuracy of 94% in predicting a left-sided AT (238). A negative P wave indicates an origin from the right atrium.

Kistler et al developed an algorithm to localize focal atria tachycardia based on the P wave morphology with a positive predictive value of 93% (223). Using this algorithm, a positive–negative V1 P-wave (or positive V1 during tachycardia and sinus rhythm), positive lead I and II, and negative aVR predicted a cristal origin with 93% sensitivity, 95% specificity, 84% positive predictive value, and 98% negative
predictive value (223). The comparison of P wave morphology between tachycardia and sinus rhythm was useful in distinguishing cristal tachycardia from right superior pulmonary vein tachycardia, 2 sites that lie in close anatomic proximity. In AT originating from the right superior pulmonary vein, V1 is upright in tachycardia and biphasic in sinus rhythm. The P wave in cristal atrial tachycardia is of the same polarity to the sinus rhythm P wave (223).

A common feature of tricuspid annular tachycardia is the presence of an inverted P-wave in V1 and V2 with late precordial transition to an upright appearance. In general, the polarity of leads II and III is deeply negative for an inferoanterior location, and low amplitude, positive, or biphasic for a superior location. The right atrial appendage lies in close proximity to the superior tricuspid annulus, therefore the P-wave morphology of the 2 anatomic locations is very similar (223). At this location, leads V1-V2 are universally negative, with notching seen in the majority of patients. The inferior leads are usually low amplitude positive in the majority (9/10) patients (230).

In AT originating within the coronary sinus, the P wave morphology is highly characteristic with deeply inverted P-waves in II, III, and aVF. V1 is usually isoelectric-positive or negative– positive, with variable precordial transition. P-waves are invariably positive in aVL and aVR (226). For AT arising from the interatrial septum, an isoelectric P-wave in lead V1 was associated with a specificity and a positive predictive value of 100% and a negative predictive value of 97% for right-sided AT’s, with a sensitivity of 50%. Alternately, the P-wave in V1 has been reported to be low amplitude negative, positive–negative biphasic or, in some instances, negative– positive biphasic. Left septal and left perinodal foci may demonstrate either a positive P-wave in V1 or most commonly a biphasic appearance.
The pulmonary veins lie posteriorly within the left atrium, therefore the P-wave morphology associated with PV tachycardia is positive in lead V1 and in all the precordial leads (223). In comparison with right-sided pulmonary veins, the left-sided pulmonary veins are broader, with a notched appearance in leads V1 and in the inferior leads. Generally, a distinction could be made between the superior and inferior pulmonary veins based on the P-wave amplitude in the inferior leads: the P-wave arising from inferior pulmonary vein tachycardia was low amplitude positive or negative, compared to a positive P-wave in the inferior leads with superior pulmonary vein tachycardia.

The left atrial appendage lies in close anatomic proximity to the superior pulmonary veins, and the differences in P-wave morphology between the 2 locations may be subtle. A P-wave morphology that is broad and positive in lead V1 and the inferior leads, with a negative P-wave in lead 1 is most commonly associated with a left atrial appendage origin (223, 239).

1.14 Therapeutic Approaches: Catheter Ablation of Atrial Tachycardia, Atrial Flutter and Atrial Fibrillation

1.14.1 Catheter Ablation of Focal Atrial Tachycardia

Successful ablation of focal atrial tachycardia relies on the presence of spontaneous or induced tachycardia to enable mapping of the tachycardia focus. Activation mapping is the most commonly used technique, where the earliest local activation is compared with the onset of the tachycardia P wave. Using this technique, identification of electrograms with an activation time 30-60msec before the onset of the P wave are targeted for ablation. Multielectrode catheters, including duodecapolar catheters
placed around the tricuspid annulus, and crista catheters placed in the region of the
crista terminalis, are used to refine the target anatomic locations and guide initial
mapping (224). Three-dimensional mapping systems may be used as an adjunct to
mapping and ablation of focal AT, and have the advantage of a significant reduction
in fluoroscopic time and radiation exposure. Numerous studies evaluating this
technique have demonstrated the ability to construct a high-resolution map in the
region of earliest activation and to pinpoint the tachycardia focus, in the presence of
sufficient tachycardia or ectopy (240-242). Other systems have been developed in an
attempt to overcome the limitations of transient non-sustained tachycardias, or
tachycardias that are haemodynamically unstable. The EnSite three-dimensional
mapping system uses a 64-wire array mounted to a balloon catheter. After the
endocardial map has been created using conventional catheters and techniques, the
system superimposes simultaneous recordings of >3000 virtual electrograms obtained
by mathematical reconstruction to create an activation map from a single tachycardia
beat. This system has been used with success in patients with infrequent
tachycardia/ectopy (243, 244), however the spatial resolution is compromised in a
very large atrium.

Once the target site has been identified, application of radiofrequency energy for 60
seconds at 25-50W energy with a standard 4mm ablation catheter is usually sufficient
to terminate arrhythmia if the catheter is at the correct location. Immediate
termination of tachycardia upon application of energy, and acceleration of tachycardia
prior to termination are indicators of successful ablation. Success is confirmed by the
demonstration of non-inducibility of tachycardia with provocative agents or pacing
maneuvers that were able to induce tachycardia before ablation. Catheter ablation has
been shown to be safe and to be associated with excellent long-term success rates.
with a reported recurrence rate of approximately 7% (247), higher in older patients and in patients with multiple tachycardia foci (247). Complications are low, and largely reflect those associated with vascular access and intracardiac catheters, including perforation, pericardial effusion and tamponade (248). Specific complications include phrenic nerve injury when ablating cristal atrial tachycardias, and atrioventricular block when ablating foci in close proximity to the AV node (249). In general, the procedure is indicated in patients who are symptomatic despite medical therapy, or who are unable to tolerate medical therapy.

1.14.2 Catheter Ablation of Typical Atrial Flutter

As a result of the well-defined anatomic reentrant circuit, and the suboptimal effectiveness of medical therapy in controlling atrial flutter, catheter ablation has become a safe and effective first-line therapy. The development of the catheter ablation technique for atrial flutter arose from the understanding of the mechanism of macroreentry around the tricuspid annulus with an obligatory passage of the circuit though the cavo-tricuspid isthmus (CTI) (197, 201, 203). The cavotricuspid isthmus is a location of slow conduction in the flutter circuit, where conduction times may be up to 100msec, accounting for approximately one-third to one-half of the AF cycle length (250-252). The anatomical boundaries are the inferior vena cava and Eustachian ridge posteriorly, and the tricuspid annulus anteriorly. The slowed conduction within the CTI is thought to be due to anisotropic fibre orientation, where in the presence of progressively earlier premature stimuli, unidirectional conduction slowing and block occurs (253, 254). The zone of slow conduction within the CTI has become the target of radiofrequency ablation due to its accessible location and relatively shorter length than links fixed and/or functional barriers.
During radiofrequency ablation of typical AFL, a 20-pole mapping catheter positioned around the tricuspid annulus is frequently employed in addition to the His and coronary sinus catheters, to determine the right atrial activation sequence. Induction of AFL may be performed when AFL is paroxysmal, to confirm its mechanisms and isthmus–dependence. Burst atrial pacing typically produces unidirectional isthmus block and induces AFL, with the direction of AFL closely related to the location of the pacing site: when pacing from the coronary sinus, the “clockwise” direction of rotation blocks in the cavo-tricuspid isthmus, leaving the counterclockwise limb free to propagate and to initiate counterclockwise flutter. Conversely, when pacing from the low lateral right atrium, lateral to the flutter isthmus, unidirectional block occurs in a counterclockwise direction, leaving the clockwise limb to continue and initiate clockwise flutter (255).

Confirmation of the location of the reentry circuit and the inclusion of the cavo-tricuspid isthmus as part of this circuit, is ideally always performed prior to ablation to confirm the underlying mechanism. The criteria for demonstrating concealed entrainment from the cavo-tricuspid isthmus include: acceleration of the tachycardia to the pacing cycle length without a change in the ECG flutter wave morphology or in the atrial activation pattern and electrogram morphology; resumption of the tachycardia at the termination of pacing with a postpacing interval <50msec, at the original tachycardia cycle length; if during pacing within the isthmus the stimulus to flutter wave/reference electrogram is identical to the distance from this electrogram to the flutter wave/reference electrogram, respectively, during AF. By contrast, pacing at sites outside the flutter circuit results in overt entrainment with fusion of the flutter wave and of the endocardial atrial electrograms.
Initial reports of ablation of AFL showed high procedural success, however with up to 20-45% patients developing a recurrence of AFL (256-259). Acute and long-term success rates improved after the introduction of proving bidirectional block as the procedural endpoint of ablation, with acute success rates of 100% and long term success rates of >95% (260-263). Bidirectional conduction block is demonstrated by positioning the duodecapolar catheter around the tricuspid annulus, and by the presence of proximal to distal activation sequence during pacing from the proximal coronary sinus, and distal to proximal activation when pacing from the low lateral right atrium (264-266). Studies comparing large-tip ablation catheters with irrigated ablation catheters have found superior success rates with irrigated catheters (267, 268).

However, despite the excellent cure rate for AFL, long-term follow-up studies have shown the majority (up to 82% patients) may develop atrial fibrillation (210, 269, 270) due to the presence of common triggers for these 2 arrhythmias (107).

1.14.3 Catheter Ablation of Atrial Fibrillation

Pulmonary Vein Isolation

Catheter ablation for atrial fibrillation is now a proven technique for symptomatic relief and cure of AF, predominantly in patients with paroxysmal AF (271). There is accumulating evidence of the effectiveness of AF ablation in patients with more established AF (persistent or permanent AF), and in those with structural abnormalities such as left ventricular dysfunction (52, 272). The procedure has evolved from a focal procedure targeting an arrhythmogenic pulmonary vein (3), to
electrical isolation of all pulmonary veins, with additional adjunctive atrial substrate modification also employed in ablation of persistent and chronic AF.

The cornerstone of current catheter ablation strategies for AF is electrical isolation of the pulmonary veins. PV isolation, whereby PV potentials are eliminated or are dissociated from the left atrium on the circular mapping catheter, is now the accepted procedural endpoint, and is associated with single procedure success rates of 60-80% for patients with paroxysmal AF, with 30-40% patients requiring a second procedure to achieve long-term “cure” from AF (273). In patients with clinical recurrence of AF, in the vast majority pulmonary vein reconnection is identified at the repeat procedure, highlighting both the importance of the pulmonary veins as triggers of AF, and the limitations of the current technique in achieving durable electrical isolation (5, 274, 275). A proportion of patients with recurrence of AF after pulmonary vein isolation are found to have non-pulmonary vein triggers to AF, with preferential distribution most frequently seen in the superior vena cava, left posterior free wall, crista terminalis, coronary sinus ostium, ligament of Marshall, and interatrial septum, respectively (71).

In addition to isolation of pulmonary vein triggers, proximal ablation, including antral and circumferential lesions, may also modify the atrial substrate through ablation of areas of anisotropic conduction, thereby aborting reentry and the maintenance of AF (276). Pulmonary vein isolation may also have other substrate-modifying effects, including alterations of dominant frequency gradient, distribution of fractionated electrograms, and/or autonomic effects (68, 277, 278).
**Atrial Substrate Modification**

Ablation of complex fractionated electrograms has been advocated by some groups as an effective form of substrate-modification, that may either complement pulmonary vein isolation or be used as an alternative strategy (279, 280). Fractionated electrograms are cycle length dependent signals that are thought to reflect areas of anisotropic conduction, leading to rotors with high dominant frequency (65). In a study of patients with both paroxysmal and persistent AF, Nadeemanee et al demonstrated that targeting fractionated signals was an effective treatment strategy, resulting in termination of AF in 95% patients during ablation, and 91% long-term arrhythmia-free rates with multiple procedures (279). Fractionated electrograms were mainly located in the interatrial septum, pulmonary veins, left atrial roof, left posteroseptal mitral annulus, and coronary sinus os. However, the significance of fractionated electrograms is not completely understood; it is clear that in some instances, fractionated electrograms are activated passively and are unlikely to act as drivers of AF (281).

Other left atrial electrophysiologic targets employed in substrate modification of AF include ablation of ganglionated plexi, areas rich in autonomic innervation. Ganglionated plexi may act as a source of vagal reflexes capable of triggering atrial fibrillation by inducing areas of heterogeneity in refractoriness (282). Due to their proximity to the pulmonary vein ostia, it has been proposed that part of the efficacy of pulmonary vein antral isolation may be due to the effects of autonomic denervation (117). After pulmonary vein antral isolation, patients with vagal or adrenergically mediated AF have similar freedom from AF to non-automatically triggered AF over long-term follow-up (114).
Patients with persistent atrial fibrillation have overall lower success rates with pulmonary vein isolation alone compared to patients with paroxysmal atrial fibrillation (117, 272). Linear ablation was developed to alter atrial substrate by preventing large reentrant circuits involved in the maintenance of atrial fibrillation. Linear lesions may include a roof line between the right superior pulmonary vein and left superior pulmonary vein; a mitral line from the left inferior pulmonary vein to the mitral annulus, or from the right superior to right inferior vein then towards the mitral annulus; and from the left superior pulmonary vein, to the left atrial roof, across Bachmann’s bundle to a point between the anterior left atrium and the aortic root. Practically, the roof line and mitral isthmus lines are the most frequently performed, and have been shown to be associated with increased rates of sinus rhythm (69%) when performed in conjunction with pulmonary vein isolation in persistent AF patients, compared to pulmonary vein isolation alone (20%) (283). The benefit of linear ablation as an adjunct to pulmonary vein isolation appears greater in patients with persistent compared to paroxysmal AF (284). Post-ablation atypical flutters, which are notoriously difficult to treat medically, are a major limitation to the routine use of linear lesions, and arise from gaps in ablation lines (285). However, these iatrogenic flutters may be eliminated by catheter-based interventions.

1.14.4 Safety of Catheter Ablation for Atrial Fibrillation

In experienced centres, the overall incidence of major complications after catheter ablation for atrial fibrillation is 4.5% (274), including a mortality rate of 0.15%. The most frequent major complication is cardiac perforation and tamponade, occurring in approximately 1.3% patients. This complication may be less frequent when routine use of transoesophageal echocardiogram is used for transeptal puncture for left atrial
access (286). Vascular complications, including femoral pseudoaneurysm (0.93%) and arteriovenous fistula (0.54%) are the next most frequently occurring complications (287). The risk of clinically apparent neurologic complication, including transient ischaemic attack and stroke, is approximately 0.9-1.2% after AF ablation (287, 288). Atrio-oesophageal fistula formation occurs rarely with a rate of 0.04%, however is associated with a >50% mortality rate (289). Other serious and infrequent complications include pneumothorax (0.09%); haemothorax (0.02%); sepsis (0.01%); significant valve damage (0.07%); and haemodynamically significant pulmonary vein stenosis (0.29%) (287).

As the procedure has become more widely performed in an increasing number of patients, an understanding of the nature and prevalence of complications has become more fully understood. The recognition of the rare but potentially fatal atrio-oesophageal fistula formation has lead to alterations in technique such as the use of oesophageal temperature monitoring, the development of real-time oesophageal location, and the use of low power when ablating on the posterior left atrium in close proximity to the oesophagus. Similarly, the recognition that pulmonary vein stenosis occurs most frequently when ablating inside the pulmonary vein has led to the practice of more proximal ablation strategies (290). Whilst the incidence of overt neurologic complications secondary to AF ablation are well understood, and strategies such as aggressive heparin anticoagulation (activated clotting time >300-350), and transeptal sheath irrigation with heparinized saline have been developed to minimize this, subtle neurocognitive abnormalities may be a plausible consequence of silent cerebral emboli occurring during ablation. A detailed evaluation of neurocognitive abnormalities that occur as a result of AF ablation has not yet been performed, and would have major implications for the safety profile of the procedure, particularly as
it is performed predominantly in young otherwise healthy patients for symptomatic relief. Therefore we evaluated the incidence of post-operative cognitive dysfunction in patients with paroxysmal and persistent AF undergoing pulmonary vein isolation, and compared them with age-matched patients with AF who had not undergone an ablation procedure. The results from this study are presented in Chapter 6.

1.15 Neurocognitive Consequence of Atrial Fibrillation

The prevalence of both atrial fibrillation and dementia increase with age, and the prevalence of both is anticipated to increase in association with the aging population (6, 291, 292). Meta-analysis of studies exploring the relationship between atrial fibrillation and the development of dementia support an increased risk of dementia in patients with AF, primarily driven by the incidence of stroke in these patients (293). In a large study of >6000 elderly patients, a positive association was found for a diagnosis of AF with both dementia and impaired cognitive function (OR for dementia 2.3 (95% CI 1.4-3.7; OR for cognitive impairment 1.7 (95% CI 1.2-2.5) (294). Interestingly, the strongest association with AF was for Alzheimer’s disease with co-existent cerebrovascular disease, rather than the vascular dementia type. These results were seen in the absence of a history of clinical stroke, although the prevalence of subclinical stroke was not evaluated in this study. Miyasaka et al evaluated the incidence of new onset dementia in patients following a diagnosis of atrial fibrillation in Olmstead County, Minnesota (11). The cumulative rate of dementia in patients with AF, excluding patients who developed intercurrent clinical stroke, was 2.7% at 1 year and 10.5% at 5 years. In addition, the occurrence of dementia in AF patients was associated with a significantly increased mortality risk compared to patients in sinus rhythm (HR 2.9, 95% CI 2.5-3.3). Atrial fibrillation is
also associated with progression to dementia in patients with baseline abnormal cognition. In a study of >500 elderly patients with normal cognition or mild cognitive impairment, atrial fibrillation was associated progressive cognitive impairment (HR 1.1, 95% CI 0.4-3.03) (295).

1.15.1 Pathogenesis of Dementia in Atrial Fibrillation

Vascular risk factors have been found to be associated with both vascular dementia and also Alzheimer’s dementia, and are likely to play a major role in the pathogenesis of dementia in patients with atrial fibrillation (296). Hypertension is the most common modifiable risk factor for atrial fibrillation, and is implicated in the pathogenesis of dementia. Longitudinal studies evaluating the effect of systemic arterial hypertension on cognitive function have found an increased incidence of development of cognitive decline 15-20 years after the onset of hypertension in midlife (297, 298). In patients with diagnosed Alzheimer's disease, hypertension is associated with increased cognitive decline over a short-term (6-month) period (299). Hypertension results in arteriosclerosis of the small vessels, and causes pathologic lesions that have been identified as white matter hyperintensities on cerebral magnetic resonance imaging (297, 298). White matter hyperintensities are associated with both an increased risk of dementia (300), and are associated with the progression of mild cognitive impairment to frank dementia over long term follow up (301). Control of blood pressure with antihypertensive therapy has been shown to reduce the progression of white matter hyperintensities and potentially cognitive decline (302). Hypertension is also thought to impact on cognitive function through effects mediated by endothelial dysfunction (303). Increased vascular permeability leads to extravasation of proteins through the blood-brain barrier, resulting in toxic beta-
amyloid accumulation within the brain tissue (304), thus resulting in an overlap between vascular dementia and Alzheimer’s disease.

Further, AF may result in cerebral damage through fluctuations in cardiac output and chronic cerebral hypoperfusion (305). Chronic cerebrovascular ischaemia leads to an increase in expression of amyloid precursor protein, which result in the formation of the hallmark amyloid plaques in Alzheimer’s disease (306, 307).

The potential association between relatively young low risk patients with atrial fibrillation and mild cognitive impairment has not been explored, and is an area in need of clarification, especially in light of the rising incidence of AF. In Chapter 5, we evaluated the incidence of mild cognitive impairment in a population of patients presenting for ablation for AF, who have a low prevalence of conventional vascular risk factors in an attempt to answer this question.

1.15.2 Atrial Fibrillation and Silent Cerebral Infarction

Silent cerebral infarcts are defined as cerebral lesions of diameter ≥3mm on T2 high intensity cerebral magnetic resonance imaging, in the absence of neurologic symptoms (308). Silent cerebral infarction, in addition to clinically apparent neurologic injury, has been shown to be associated with progressive decline in cognitive function (309, 310). Kobayashi et al (308) evaluated the prevalence of silent cerebral infarction in patients with atrial fibrillation. They reported a significantly higher number of silent cerebral embolic lesions in patients with non-valvular AF compared to age and sex-matched control patients in sinus rhythm. AF patients were found to have an increased number of infarcts encompassing a wide cerebral distribution, including the cortical, subcortical and deep white matter locations. In
patients with acute ischaemic stroke, the majority of small infarcts seen in the cortex on diffusion-weighted magnetic resonance imaging have been shown to represent small embolic phenomena (311, 312). It is therefore likely that the high rates of silent cerebral infarcts seen in the cortex and subcortex in patients with atrial fibrillation may reflect cardiogenic embolus in these at-risk patients (308).

Alternate mechanisms have been proposed for the development of cerebrovascular injury and subsequent neurocognitive effects, mediated by vascular endothelial damage and platelet activation. Endothelial dysfunction in patients with AF increases the risk for thromboembolism by inducing a hypercoagulable state (313). The effects of endothelial dysfunction are mediated by the release of prothrombotic and proinflammatory molecules, including von Willebrand factor (vWF), adhesion molecules and selectins. AF is associated with elevated plasma vWF levels (314), and correlate to a higher risk of cardiovascular events (315). In AF patients, elevated levels of vWF have been independently associated with left atrial/appendage thrombus and spontaneous echo contrast (316). Elevated levels of vWF mediate platelet aggregation and adhesion to the vascular endothelium, leading to platelet and fibrin thrombi, potentially leading to brain infarction. Other markers of endothelial cell activation have been found to be deranged in patients with atrial fibrillation.

Adhesion molecules are expressed on the endothelial cell surface and facilitate adhesion of leucocytes to endothelial cells, and are central to leucocyte chemotaxis by activating cytokines (including IL-1 and TNF-alpha). E-Selectin, an endothelial cell specific adhesion molecule, is seen under pathologic conditions, and higher levels have been reported in patients with AF compared to patients in sinus rhythm. Similarly this has been described for other prothrombotic/inflammatory markers including circulating endothelial cells (317), soluble thrombomodulin (318) and
circulating microparticles (319). These and other findings are supportive of a pathophysiologic role of endothelial dysfunction in AF to the development of intravascular thrombosis and to cerebral infarction.

1.15.3 Silent Cerebral Infarction and Neurocognitive Abnormalities

Diffusion-weighted magnetic resonance imaging (DW-MRI) is a highly sensitive technique in the detection of cerebral ischaemia. The underlying principle is based on the pathophysiological response of brain tissue to an acute ischaemic insult; oedema occurs within minutes following vascular occlusion, and results in a severe inhibition in proton-diffusion capacity, which are detected as hyper-intense (bright) lesions on DW-MRI. The sensitivity and specificity of DW-MRI in the detection of acute ischaemic stroke is 94% and 97%, respectively (320). DW-MRI is able to detect new acute ischaemic injury within a very narrow window after the onset of the insult; the signal increase becomes visible as early as 30 minutes after ischaemia, and develops within the first 24 hours, before becoming undetectable at 14 days post-ischaemia (321). Lesions that are positive on T2 weighted imaging demonstrate a delayed but persistent appearance, and reflect the development of a chronic ischaemic lesion (321).

New lesions on DW-MRI have been detected in a significant number of patients after invasive neurologic and cardiologic procedures, yet the vast majority have not been associated with clinical neurologic deficits. For example, up to 23% of patients undergoing diagnostic and interventional cerebral angiography demonstrated new silent lesions on DW-MRI in the absence of clinical neurologic deficits (322-324); a prevalence of 12-24% of new ischaemic lesions on DW-MRI after carotid
endarterectomy in the context of 5-6% incidence of overt neurologic complications has been reported (325, 326); and approximately 11-15% patients undergoing coronary angiography demonstrate new silent cerebral infarcts (327, 328), with retrograde catheterization of the aortic valve via a radial artery approach associated with an even higher (22%) incidence (329).

Despite the apparent asymptomatic nature of these silent infarcts, almost all lesions progress to form evidence of scar on T2-weighted imaging, therefore are responsible for causing established neurologic damage to the brain (328-330). On appearance, the silent lesions are indistinguishable from lesions that are responsible for causing overt neurologic deficits (331). It is thought that the location of the lesion, even if small, determines whether the consequences may be catastrophic or clinically silent (327, 329, 332, 333). It has not yet been established whether silent cerebral infarcts are truly silent, as a detailed evaluation of neurocognitive performance has not been extensively performed in patients after invasive cardiac and neurologic procedures. Impairment in global and/or specific cognitive domains, memory and psychomotor impairment in patients with new onset clinically silent cerebral infarcts requires detailed and specific testing to evaluate (331). Lund and colleagues evaluated patients undergoing coronary angiography with DW-MRI and early (day 1 post-procedure) neurocognitive evaluation (327). New cerebral lesions were found in 5/33 (15%) of the patients where coronary angiography was undertaken by radial artery approach, and in 0/9 (0%) of the patients with conventional femoral artery access. The lesions were located in the cerebellum in 4/5 affected patients, and in both the cerebellar and frontal lobes in 1 patient. Correlations with neurocognitive testing showed that 7/42 patients (17%) had evidence of post-procedure cognitive dysfunction, with a decline in z scores on post-procedure testing significantly associated with the degree of
neurologic injury seen on DW-MRI (327). In addition, it appears that the volume of lesions on DW-MRI accelerates the progression of cognitive decline in patients with established dementia. In a study in patients with vascular dementia, 70% of patients with a new onset focal deficit or neurocognitive deterioration demonstrated new regions of signal hyperintensity on DW-MRI, in comparison to patients without progression of clinical symptoms.

1.15.4 Silent Cerebral Infarction After Catheter Ablation

Lickfett and colleagues performed DW-MRI in a small cohort of 20 patients after lasso-guided ostial pulmonary vein isolation (334). 2 of 20 patients (10%) demonstrated new embolic lesions of DW-MRI, in the absence of neurologic symptoms, which were located in the right periventricular white matter and left temporal lobe in each patient, respectively. In a large study consisting of 232 patients with paroxysmal or persistent atrial fibrillation, Gaita et al performed pre- and post-procedural DW-MRI after pulmonary vein isolation with or without additional adjunctive substrate modification. A symptomatic neurologic event occurred in 1/232 (0.4%) patients, however 33/232 (14%) patients demonstrated a new area of cerebral infarction on post procedure MRI (335). In the majority of affected patients (25/33) a single new lesion was identified; and in 3/33 patients and 5/33 patients 2, and 3 new lesions were identified, respectively. In 25 cases the lesions were localized to the cortex, 7 were found in the cerebellum, and 1 lesion was localized to the basal ganglia. Both electrical and pharmacologic cardioversion to sinus rhythm during the procedure was associated with a significantly increased risk for development of new embolic lesions (OR 2.75, CI 1.29-5.89, p=0.009). Of the 62 patients who underwent cardioversion during the procedure, 16/26 (26%) had evidence of new cerebral
embolism, compared to 18/170 (11%) of patients who were not cardioverted. Embolic events occurred in 10/112 (9%) patients who presented in sinus rhythm throughout the procedure; in 8/58 patients (14%) in whom sinus rhythm was restored during ablation; and in 16/62 patients (26%) who were cardioverted back to sinus rhythm, significantly higher than the other groups (p=0.004). In addition, the intensity of anticoagulation was found to be associated with the risk of silent embolism. When ACT <250 seconds, 17% of the patients had a positive MRI, whereas for ACT value >250 seconds, 9% of the patients were positive for silent embolism. In multivariable analysis, activated clotting time level, and electrical or pharmacologic cardioversion to sinus rhythm were independently associated with a risk of periprocedural cerebral infarction (p=0.0087, p=0.0025, respectively). No clinical parameters including age, hypertension, diabetes mellitus, previous history of stroke, type of AF, and pre-ablation antithrombotic treatment were correlated with an increased risk of cerebral embolism on univariate analysis.

Subsequent to these findings, the incidence of new silent cerebral emboli has been evaluated with other techniques and devices used in pulmonary vein isolation procedures. In a study comparing patients undergoing pulmonary vein isolation with either conventional irrigated radiofrequency ablation (RF); cryoballoon ablation (CB); or ablation using a multielectrode pulmonary vein ablation catheter (PVAC) found a significantly higher number of new silent embolic lesions in patients in whom PVAC was used for ablation (37.5%) compared to patients with conventional RF (7.4%) and CB ablation (4.3%), p=0.003 (336). In patients in whom PVAC was used, there was a median of 3 acute lesions, compared to single lesions in the RF and CB groups. In the majority of patients in all groups, new embolic lesions were located in the cerebellum and within other regions in the vertebrobasilar territory. In this study, intraprocedural
anticoagulation was maintained at high intensity in all patients (target activated clotting time >300 seconds), and no difference was found between intraprocedural activated clotting time levels in patients with (ACT 316 ± 33 sec) compared to those without (ACT 322 ± 54 sec) new cerebral emboli (p=0.6). No significant difference was found between the risk of new cerebral lesions and the performance of procedural cardioversion; 18% (2/11) patients with embolic events received prior cardioversion, compared to 33% (21/63) patients who were not cardioverted, p=0.5. All embolic lesions observed in this study were clinically silent. Evaluation of neurocognitive consequences of these cerebral lesions was not performed in this study.

1.15.5 Cerebral Microembolism in Ablation for Atrial Fibrillation

Transcranial Doppler monitoring of the middle cerebral arteries is a well-established non-invasive technique used in the detection of cerebral microembolic signals (337, 338). Cerebral microembolic signals (MES) represent microembolic phenomena, and the study of cerebral MES has been evaluated in the most detail in patients with carotid disease, and during coronary and cerebrovascular surgery (327, 339-341).

During diagnostic and interventional coronary catheterization, cerebral microembolism has been detected in virtually all patients (327). The volume of microemboli appears to be related to the number of catheter flushings and injection, and to the volume of contrast used. There appears to be a higher number of microemboli during transradial compared to a transfemoral approach. When accessed from the radial artery, the guidewire passes the ostium of the right vertebral and carotid arteries, potentially dislodging atherosclerotic plaques that cluster at these locations (327).
The volume of microembolic signals detected during coronary artery bypass graft surgery (CABG) varies depending on whether an on-pump or off-pump technique is used (342). In one study performing bilateral middle cerebral artery insonation, the median MES count was 1605 (range 750-2475) for on-pump CABG compared to a median of 9 MES (range 4-28) for off-pump surgery (p<0.001). Removal of the side-clamp and aortic cross-clamp is associated with the highest rate of MES signals (339, 342).

A limited number of studies in patients undergoing ablation for atrial fibrillation have established that microembolic signals are almost universal in these patients. Kilicaslan et al studied the occurrence of MES using transcranial Doppler of the middle cerebral arteries in patients undergoing pulmonary vein isolation, where RF power was either titrated according to left atrial microbubble formation seen on intracardiac echocardiography, or where RF power was managed conventionally set to a maximum threshold and limited by temperature and impedance changes (343). They observed that in patients where RF output was titrated to avoid microbubble formation, there was a significantly lower volume of cerebral MES detected (1015 ± 438/patient) compared to 2250 ± 864/patient in the conventional RF group, p<0.05. In addition, a higher number of MES was associated with clinical events, and as a group, the patients with conventional RF titration demonstrated a higher incidence of clinically overt neurologic complications (3.1% v 0.9%, p=0.1). Subsequent studies comparing different ablation techniques suggest a variable prevalence of cerebral MES depending on the strategy employed: in one comparative study, significantly higher mean cerebral MES were associated with a conventional 4-mm radiofrequency ablation catheter (3908), compared to a mean of 1404 cerebral MES with the use of an irrigated radiofrequency catheter, and a mean count of 935 cerebral MES with the
use of a cryoballoon catheter (935 MES) (344). This study was notable for the significantly increased burden of cerebral MES associated with delivery of radiofrequency ablation compared to cryoablation. In addition, the majority of MES were detected during the RF delivery phases of the procedure, compared to the baseline, transeptal puncture, and positioning of left atrial catheter periods. This pattern of increased MES load during delivery of RF has been reflected by the findings of other investigators evaluating MES loads in AF ablation (343, 345).

There are numerous mechanisms whereby ablation for AF, in particular the delivery of radiofrequency ablation, may be associated with an increased number of cerebral MES. Gaseous emboli may result from microbubbles injected into the left atrium via contrast medium during transeptal puncture or pulmonary venography; within saline flushing of intra-atrial sheathes; as a result of catheter irrigation; or from air inadvertently entrained into the left atrium during catheter and sheath manipulation. The effect of radiofrequency ablation is highly thrombogenic, with damage to blood components, platelets and clotting factors occurring with an increased frequency as a consequence of radiofrequency compared to cryothermal ablation (346-348). Wood et al describe a step-wise increase in the stream of microbubble formation occurring in parallel with increasing tissue temperatures, relating microbubble formation to excessive thermal injury (349). In a related study Bruce et al described the relationship between catheter and tissue temperatures and microbubble formation in dogs undergoing irrigated radiofrequency ablation. They demonstrated that intermittent microbubble formation occurs over a wide range of tissue temperatures, and found that continuous microbubble formation occurred at elevated tissue temperature and is likely to reflect tissue damage and steam formation (350). An alternative mechanism for microbubble formation during ablation relates to
suboptimal catheter tip-tissue contact. Kalman et al describe the occurrence of microbubbles with poor catheter tip-endocardial contact, likely representative of blood or tissue vaporization (351). In addition, these authors also observed that embolic showers may be the precursor to coagulum formation on the catheter tip, providing a link between “gaseous” microbubbles and formation of thrombus. Kilicaslan et al found that 97% microbubbles formed during RF and seen on ICE were immediately followed by an appearance of MES on transcranial Doppler, with the number of ICE-detected microbubbles correlating positively with MES volume (343).

Detectable MES may be classified as either gaseous or solid in composition by multifrequency transcranial Doppler (TCD). The multifrequency TCD classifies microemboli depending on the difference between the embolus-to-blood ratio (EBR) at 2.5-MHz insonation frequency and the EBR at 2.0-MHz insonation (dEBR). Solid microemboli exhibit a relatively constant dEBR between 2 and 2.5-MHz compared to gaseous emboli. The dEBR limit for detection of solid is set between -0.83 and 2.05 dB, based on in vitro studies (352), and where embolic signals fall outside of this range they are classified as gaseous emboli. Solid microemboli are thought to be more pathogenic than gaseous emboli, and arise from mechanical fragmentation of atherosclerotic plaques or clot formation on catheter tips (327). The differentiation of solid and gaseous emboli from the emboli-discriminating software has led to advances in the understanding of the composition and significance of MES detected during invasive neuro-cardiac procedures. An embolus of 14dB power detected on Doppler may be due to a 4 µm gaseous MES or a 130 µm solid MES. This has important implications, as a 4 µm gas MES is likely to travel through or be dissolved in the brain microvasculature, whereas a 130 µm solid MES is likely to occlude a terminal
vessel (327). To date, there has been no study evaluating the composition of cerebral microemboli (gaseous versus solid microemboli) in patients undergoing ablation for atrial fibrillation. In Chapter 7, we describe the relative proportion of gaseous and solid microembolism during AF ablation in patients with paroxysmal and persistent atrial fibrillation to address this question.

1.15.6 Cerebral Microembolic Signals and Neuropathologic Consequences

Microembolic signals have been studied by transcranial Doppler ultrasound most frequently during cardiac and vascular surgery. In patients with asymptomatic carotid stenosis, detection of baseline microemboli has been shown to be frequent (16.5% patients), and predicts the risk of conversion to symptomatic carotid stenosis (353). In this context, microemboli are thought to be representative of highly unstable plaques or plaque ulceration. During cardiac surgery, large volumes of microemboli have been observed, and arise from numerous sources including atherosclerotic plaque, thrombogenesis from the foreign surfaces of cardiopulmonary bypass, air introduced via the bypass circuit, and from pericardial fat globules (354). It has been hypothesized that cerebral microemboli are the mediators of the neurocognitive decline that is frequently observed in these patient groups after surgical intervention. Cognitive decline has been reported in approximately 50% of patients after discharge from cardiac surgery; 36% at 6 weeks; 26-33% at 1 year; and 42% at 5 years post-operative (355, 356). Pathologic studies have identified thousands of microemboli within the brains of patients who died soon after cardiopulmonary bypass, where emboli are represented as swellings in arterioles and capillaries (357). Pathophysiologically, microemboli may result in cognitive decline by occlusion of small arterioles resulting in cerebral microinfarction. Approximately 30% of patients
after coronary artery bypass surgery exhibit new diffusion defects on cerebral magnetic resonance imaging consistent with microinfarction (358). Studies evaluating the presence of high volumes of microembolic signals, however, have yielded inconsistent results about the role of microemboli and neurocognitive decline. Meta-analysis of studies examining intraoperative MES and post-operative cognitive testing after cardiac surgery reported a positive association in 4 of 14 studies (359). Marrouche et al found an elevated number of MES were correlated with neurologic sequelae including transient ischaemia attack, stroke and cognitive decline after cardiac bypass surgery (237). Pugsley et al investigated the relationship between cerebral microembolic signals and postoperative neurocognitive deficits in 100 patients after cardiac bypass. They found a correlation with the number of microembolic signals, with patients with <200 MES had an 8.6% incidence of neurocognitive decline, compared to patients with >1000 MES had a 43% incidence of neurocognitive decline (360). Other studies have failed to show a causal link between number of cerebral MES and neurocognitive decline, although there is considerable variability in the methodology of the cognitive test battery used, in the definition of cognitive decline, and the administration times of the test postoperatively. As a result, the significance of the presence and volume of intraprocedural MES remains to be fully understood.

1.15.7 Neurocognitive Change After Atrial Fibrillation Ablation

Very limited data have been published examining the neurocognitive effects of ablation for atrial fibrillation, however available results suggest cognitive decline is a potential consequence of the procedure. Schwartz et al performed pre and post procedure neuropsychologic testing in 21 patients undergoing either radiofrequency
or cryoablation of atrial fibrillation, and compared the results to a matched community-based population sample (361). Patients undergoing ablation declined significantly in the verbal memory domain, compared to the control group. Overall 56.5% of patients post ablation deteriorated from baseline values in tests of verbal memory, compared to 17.4% of controls. No significant deterioration was seen in AF patients in the remainder of the cognitive domains including attention/concentration; word fluency; executive functioning; and visual memory. Patients also underwent pre- and post procedural diffusion-weighted magnetic resonance imaging. In 3/21 patients, new ischaemic lesions were detected, in 1 patient this was clinically evident, presenting as a catastrophic hemispheric infarct, and in 2 patients the lesions were clinically silent. Neither patients performed significantly worse than baseline testing on follow up neurocognitive assessment.

A large registry study evaluated the prevalence of mortality, heart failure, stroke and dementia in >37 000 patients who either underwent ablation for AF; who were treated medically for AF; or who were in sinus rhythm (362). It is difficult to gauge the effect of AF ablation on the long-term risk of dementia in patients with AF, as there are inherent biases in a study of this nature in patient selection for the procedure. Nevertheless, compared to patients who were medically managed, patients with AF who underwent ablation had lower rates of stroke, dementia and mortality. The results are consistent with available evidence that suggests patients with sinus rhythm have lower prevalence of cognitive impairment compared to patients with atrial fibrillation (294).
CHAPTER 2

Atrial Electrical and Structural Changes
Associated with Longstanding Hypertension in Humans: Implications for the Substrate for Atrial Fibrillation
2.1 INTRODUCTION

Hypertension is the most common modifiable risk factor associated with atrial fibrillation (AF). Systemic hypertension has a prevalence in the adult population of 20-30% rising to 60% in those aged over 65 years (178, 179). In patients with AF, up to 60% have a history of hypertension (180). In combination, AF and hypertension are associated with an 8-fold increased risk of stroke (183), and in a high-risk hypertensive population, pre-existing or new-onset AF is associated with increased mortality (181). Left ventricular hypertrophy secondary to hypertension is associated with an increase in AF occurrence. Pulmonary vein isolation has revolutionized the therapeutic approach to AF however hypertension is associated with an increase in recurrent AF following catheter ablation (363). Despite the strong association between AF and hypertension little is known of the responsible pathophysiologic mechanisms.

Prior studies using hypertensive animal models have demonstrated significant biatrial remodeling characterised by global and regional conduction slowing associated with structural changes of interstitial fibrosis (184, 186, 187). However caution must be exercised in extrapolating these findings in experimental animal models to humans. To date there is a lack of detailed electrophysiologic data in human hypertension. Therefore the aims of the present study were to determine the atrial electrophysiologic and electroanatomic changes associated with long-standing, chronically treated hypertension in humans.
2.2 METHODS

2.2.1 Study Population

The study population included 20 patients: 10 with long-standing systemic hypertension with evidence of left ventricular hypertrophy on echocardiogram; and 10 normotensive control patients with structurally normal hearts. Patients were defined as hypertensive according to the World Health Organisation criteria (364). Mild hypertension was defined as a systolic blood pressure of 140-180mmHg, and/or diastolic blood pressure of 90-105mmHg; moderate/severe hypertension was defined as a systolic blood pressure >180mmHg and/or diastolic blood pressure >105mmHg. Patients were recruited at the time of presenting for an electrophysiology procedure for supraventricular tachycardia (16 patients) or when undergoing echocardiogram for the management of hypertension (4 patients). These 4 patients were consented for an additional electrophysiology and mapping study in the absence of a clinical indication for an electrophysiology procedure. Exclusion criteria included amiodarone, LV systolic dysfunction (defined as LVEF<50%), ischaemic or valvular heart disease, diabetes mellitus, obesity (BMI >30), renal impairment or current/previous smoking. To avoid the confounding effects of AF on atrial remodeling, a detailed history of symptoms was undertaken, previous electrocardiograms were sourced, and any patients with a history suggestive of AF were excluded. The Research Development and Human Ethics Committee at the Alfred Hospital approved the study. All patients gave written informed consent prior to the study.

Transthoracic echocardiogram was performed in all patients to determine left atrial size, diastolic parameters, and left ventricular wall thickness. 24-hour ambulatory blood pressure monitoring was performed for an assessment of mean blood pressure while on stable anti-hypertensive medication. Given AF continues to occur despite
anti-hypertensive management and the aims of the study were to investigate the long-term effects of chronically treated hypertension, anti-hypertensive medication was not discontinued prior to EP study.

2.2.2 Electrophysiological Mapping

All antiarrhythmic medications including beta-blockers and calcium channel blockers were ceased 5 days prior to EP study. Electrophysiological study was performed in the fasted state with conscious sedation. The research study was undertaken following successful catheter ablation of the supraventricular tachycardia in the 30-minute waiting period. The following catheters were positioned via the femoral venous approach (Figure 1): 1) 10-pole catheter (2-5-2 mm inter-electrode spacing, Daig Electrophysiology, St. Jude Medical, St. Paul, Minnesota) within the coronary sinus (CS) with the proximal bipole at the CS ostium; 2) 20-pole “crista” catheter with 1-3-1 mm interelectrode spacing (Biosense-Webster, Diamond Bar, California) positioned with the aid of a long sheath along the crista terminalis and standardized such that the second bipole lay at the junction of the superior vena cava with RA as determined by fluoroscopy; and; 3) 3.5-mm tip electroanatomic mapping catheter (Navistar, Biosense Webster, Diamond Bar, California).

Surface electrocardiograms (ECGs) and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system for offline analysis (EP MedSystems, St Jude Medical, St. Paul, Minnesota). Intracardiac electrograms were filtered from 30 to 500 Hz and measured with computer-assisted calipers at a sweep speed of 200 mm/s.
Atrial ERP

Atrial ERP was measured from two sites: at the high septal right atrium and proximal coronary sinus. Atrial ERP was measured at twice diastolic threshold (for a pacing threshold of <2 mA) at cycle lengths (CL) of 600 and 450 ms, with an 8-beat drive followed by an extra-stimulus, starting with an extra-stimulus coupling interval of 150 ms increasing in 10-ms increments. The ERP was defined as the longest coupling interval failing to propagate to the atrium. At each site, the ERP was measured three times during each CL, and if the maximum and minimum amounts differed by >10 ms, two additional measurements were taken and the total averaged.

Atrial conduction

Atrial conduction was assessed during conventional and electroanatomic mapping as previously described (365). In brief, conduction delay at the crista terminalis was measured during pacing at cycle lengths of 600 and 450 ms and during the earliest extrastimulus that conducted to the atrium from the proximal coronary sinus and high septal RA. Conduction delay at the CT was analysed by the presence of discrete double potentials and fractionated electrograms as previously defined (365).

AF inducibility

Inducibility of AF was assessed during ERP testing as previously described. Sustained AF was defined as AF>30 seconds in duration occurring during electrophysiology testing. The maximum duration of AF was calculated as the longest episode of AF during the induction protocol. Electrical cardioversion was performed if AF persisted beyond 30 minutes.
2.2.3 Electroanatomic Mapping

Electroanatomic maps were created of the RA during pacing from the proximal coronary sinus at 600 and 300 msec. Endocardial contact during mapping was ensured by: electrogram characteristics, fluoroscopic visualization of catheter mobility in relation to cardiac motion and the catheter icon on the three-dimensional navigation system. Atrial points were then acquired if the stability criteria in space (≤6 mm) and in local activation time (≤5 ms) were met. Mapping density was uniform across the RA endocardium and the point density determined at a fill threshold of 15 mm. Editing of points was performed offline. Local activation time was manually annotated to the beginning of the first deflection from the isoelectric line on bipolar electrograms. Points not conforming to the 12-lead ECG P-wave morphology or <75% of the maximum voltage of the preceding electrogram were excluded.

Electrogram and Voltage Analysis

In the analysis of the electroanatomic map, the following definitions were used: (1) fractionated signals; complex electrograms ≥50 ms; (2) DPs; separated by an isoelectric interval, with activation time annotated at the largest potential; (3) electrically silent areas (scar), absence of recordable activity or a bipolar voltage amplitude ≤0.05 mV; and (4) low-voltage areas, contiguous areas ≤0.5 mV on bipolar voltage maps (173). Regional voltage was determined by averaging the bipolar voltage from the posterior, lateral, septal and anterior regions of the right atrium.
Conduction velocity

Isochronal activation maps of the atria were created and regional conduction velocity (CV) was determined in the direction of the wave-front propagation as previously described (366). The electroanatomic mapping system calculates the CV by expressing the linear distance between two points as a function of the difference in the local activation times (LAT). Points are selected perpendicular to isochrones created at 3ms intervals in LAT to determine regional conduction velocity. Conduction was determined as the mean of 5 pairs of points along the activation front through regions of least isochronal crowding. An index of heterogeneity for CV was obtained by calculating the coefficient (standard deviation/mean x 100%) of the entire RA.

2.2.4 Right Heart Catheterization

Right Heart Catheterization was performed with a balloon-tipped, flow-directed pulmonary artery catheter introduced via the femoral vein. We measured right atrial pressures (amplitude of the a and v waves and the mean pressure), right ventricular systolic and diastolic pressures, pulmonary artery (systolic, diastolic and mean) pressures, and pulmonary capillary wedge pressures (a and v waves and the mean pressure).

2.2.5 Statistical Analysis

All continuous variables are reported as mean ± standard deviation and assessed for normality utilizing the Shapiro-Wilk test. Comparisons between groups were performed by an unpaired students T-test. Proportions were compared by Fisher’s exact test. Statistical significance was established at p<0.05.
2.3 RESULTS

2.3.1 Baseline Characteristics (Table 1)

Twenty patients completed the study. One additional patient with systemic hypertension was excluded due to a prolonged episode of AF at the commencement of the study protocol induced during ERP testing.

The mean duration of systemic hypertension from the commencement of antihypertensive treatment was 5±2 years. A total of 4/10 (40%) patients had a history of moderate/severe hypertension, and 6/10 (60%) had a history of mild hypertension, based on WHO classification (364). Of the patients with hypertension, 8/10 (80%) were taking angiotensin-converting enzyme inhibitors or angiotensin II receptor blocking drugs, compared to no control patients. There were no significant differences between other baseline medications between the 2 groups (Table 1). As expected there was a significant difference in systolic and diastolic blood pressure between the two groups (Table 1). Systemic hypertension was associated with a significant increase in LV septal and posterior wall thickness, and left ventricular mass.

2.3.2 Diastolic and Haemodynamic Parameters

No patient with hypertension had a history of diastolic heart failure. The mean pulmonary capillary wedge pressures were within the normal range, and not significantly different between patients with systemic HT and controls (Table 2). There were no significant differences between the groups in diastolic parameters or pulmonary pressures as assessed by echocardiography (Table 2).
2.3.3 Atrial Refractoriness

The results for atrial refractoriness are presented in Figure 2. There was a trend to an increase in atrial refractoriness at all sites and all pacing cycles lengths achieving statistical significance at the high septal right atrium in patients with hypertension compared with controls.

2.3.4 Anatomically Determined Conduction Delay

Conduction delay at the CT was demonstrated in hypertensive compared with control patients as evidenced by the increased number of fractionated and double potentials recorded at this site. During coronary sinus pacing at two cycle lengths (CL), patients with hypertension had a significantly greater number of fractionated and double potentials recorded at the crista terminalis (CL 600ms 68% ±15 vs. 43% ±17, p=0.03; and CL 450ms 72% ± 4 v 43% ± 23, p=0.04, respectively; Figure 3).

2.3.5 AF Inducibility

Sustained atrial fibrillation was induced in 3/10 (30%) patients with hypertension, and in 1 additional patient with hypertension who was ultimately excluded from the study due to an episode of non self-reverting AF that occurred early in the study protocol. Sustained AF was not inducible in any control patients. One patient with hypertension required cardioversion as an episode of AF continued for 30 minutes. Two control patients developed brief episodes of AF during ERP testing <30 secs duration. The mean duration of AF during ERP testing was 180±170 sec in the hypertensive group vs. 14±9 sec; p<0.01 in the controls.
2.3.6 Electroanatomic mapping

RA Voltage (Table 3)

There was no difference in right atrial volume or surface area in patients with hypertension compared to controls (Table 3).

The overall mean voltage was not significantly different between patients with systemic HT and controls, however there was a greater proportion of areas of low voltage in patients with HT compared to controls (13% in HT vs. 9% in controls, p=0.04; Table 3). Differences in regional low voltage associated with hypertension were most apparent in the anterior and posterior RA segments (Table 4).

Electroanatomic mapping demonstrated more extensive areas of double potentials and fractionated signals in hypertensive patients particularly in the region of the posterior right atrium (26 ± 14% vs. 13 ± 9%, p=0.03, table 4). Representative examples are presented in Figure 4.

Atrial Conduction

The global right atrial activation time during coronary sinus pacing was significantly longer in patients with systemic hypertension compared with controls (Figure 5). Regional activation times were significantly longer in all anatomic segments in patients with hypertension (Figure 5).

Global right atrial conduction velocities were significantly reduced in patients with systemic hypertension compared with controls (Table 5). The conduction heterogeneity index was greater in patients with systemic hypertension compared with controls at CL 600ms (23% vs. 12.5%, p=0.09) and 300ms (16% vs. 6%, p=0.04).
There were regional differences in conduction, with a significantly reduced conduction velocity in all segments (Table 5).

2.4 DISCUSSION

This study presents detailed information on the atrial electrophysiologic and electroanatomic changes associated with long-standing, chronically treated hypertension with left ventricular hypertrophy. The following changes were seen with hypertension:

1. Significant reduction in atrial conduction as assessed by electrophysiologic and electroanatomic studies. Conduction velocity was delayed globally and regionally within the right atrium.
2. Anatomically determined functional conduction delay at the crista terminalis.
3. An increase in areas of low voltage.
4. An increase in the inducibility and duration of atrial fibrillation.

Interaction between Hypertension and Atrial Fibrillation

Systemic hypertension is an independent and potentially modifiable risk factor for atrial fibrillation (12, 99), with the risk of AF increasing with each incremental elevation in systolic blood pressure (182). Once AF develops, hypertension significantly increases stroke and systemic embolic events (182). The presence and severity of left ventricular hypertrophy appears to predict the development of AF with regression of electrocardiographic LVH associated with a reduction in the incidence of AF (367). Hence hypertensive patients required LVH for inclusion in the study to
focus on patients with cardiac sequelae and avoid the population with spuriously elevated blood pressure detected at the clinical visit.

**Prior Animal Studies**

Animal models have established a pathological link between chronic systemic hypertension and atrial structural and electrical remodeling. In a chronic ovine model of elevated blood pressure, Kistler et al demonstrated the electrophysiologic changes of biatrial conduction slowing, shortening of atrial wavelength, and an increase in AF associated with the structural effects of atrial myocyte hypertrophy, increased collagen and apoptosis (184). Similarly in a hypertensive rat model a marked increase in atrial interstitial fibrosis associated with an increase in the incidence and duration of AF was demonstrated (368). Sanders and colleagues have elegantly defined the atrial effects of short and longer-term hypertension in a “one-kidney one-clip” experimental model of hypertension. Electrical remodeling occurred early with progressive conduction slowing accompanied by left atrial enlargement and interstitial fibrosis with the endpoint of increased susceptibility to AF (186, 187). Despite the important insights gained from experimental animal studies of hypertension the translation of these findings into human hypertension has yet to be defined. In the present clinical study hypertension was associated with generalised and regional conduction slowing and an increase in the inducibility and duration of AF.

**Prior Clinical Studies**

Limited data are available regarding the changes in atrial electrophysiology in human hypertension. Left atrial volume independently predicts new-onset AF in high-risk
hypertensive populations (369). Increased left atrial size, combined with impaired atrial pump function as assessed by peak late-diastolic mitral annular velocity predicts AF in hypertensive patients (370). In a retrospective study of patients with hypertension who subsequently developed AF, the independent predictors of AF were P-wave prolongation and increased P-wave dispersion (371). There are no prior studies providing a detailed description of the electrophysiologic and electroanatomic remodeling occurring as a consequence of chronic hypertension in humans.

Pathophysiologic Mechanisms Responsible for AF in Systemic Hypertension

Hypertension is now understood to be a systemic condition with cardiac effects, which extend beyond the direct effects of chronic atrial stretch secondary to elevated end diastolic pressure. The pathophysiologic state is characterized by activation of the sympathetic nervous and renin-angiotensin-aldosterone system. These neurohumoral changes result in structural and electrical changes within the atrial and ventricular myocardium. Increased sympathetic nervous system activity augments plasma renin activity increasing angiotensin and aldosterone (372), which stimulates cardiac hypertrophy and fibrosis (373). Angiotensin type 1 receptors on cardiac myocytes are activated by circulating angiotensin II that stimulates collagen synthesis and downregulates collagenase activity (373, 374). Increased atrial expression of ACE and extracellular signal-regulated kinase MAPK3/MAPK1 also contribute to atrial fibrosis (151). Activation of the renin-angiotensin-aldosterone system increase left ventricular mass and variants of the angiotensin type-1 receptor determine the magnitude of left ventricular hypertrophy (375, 376). Blockade of the renin-angiotensin-aldosterone system by ACE inhibitors or ARB’s can reverse these pathophysiologic changes (377). In a canine rapid atrial pacing model Nakashima et
al demonstrated the prevention of atrial electrical remodeling by candesartan and captopril (378). However we did not find any acute effects on atrial electrophysiology at angiotensin II doses which produced a significant hemodynamic response in an earlier study in humans. This does not exclude an important role in chronic fibrosis-related remodeling (365).

Clinical Implications

An understanding of the role of the renin-angiotensin system in arrhythmogenesis provides some insight into recent observations from clinical studies. In patients with hypertension and left ventricular hypertrophy, higher systolic blood pressure was an independent predictor of new-onset AF, and the incidence of new-onset AF was markedly reduced by angiotensin II receptor blocker treatment compared with β-blockers with similar reductions in blood pressure (379). Similarly in patients with symptomatic congestive heart failure and/or LV systolic dysfunction, RAS inhibitors result in a reduction in the incidence of AF. Retrospective analysis of the SOLVD trials demonstrated the association of AF with worsening heart failure and all-cause mortality in patients with left ventricular dysfunction (24) and that risk of AF was significantly reduced by treatment with ACEI (380). In Val-HeFT, AF occurrence worsened the outcome in patients with heart failure, and the addition of valsartan significantly reduced the incidence of AF (381).

The present study demonstrates changes in atrial conduction which occurred globally and regionally particularly in the posterior right atrium in the region of the crista terminalis in a chronically treated hypertensive population. Conduction slowing was seen in the absence of significant differences in tissue voltage, although there was an
increase in areas of low voltage in the hypertensive population. This underscores the importance of early aggressive treatment of hypertension to prevent the adverse remodeling that predisposes to atrial arrhythmias.

2.5 STUDY LIMITATIONS

Whether the electrophysiological abnormalities observed in patients with hypertension in the present study are responsible for the increased incidence of clinical AF seen in patients with hypertension remains speculative, because patients with prior AF were necessarily excluded from the study. Importantly, the development of clinical AF is complex and depends not only on substrate, but also on other factors such as triggers and initiators that were not addressed by the present study. In this clinical study, detailed evaluation was confined to the RA as ethical considerations limited non-clinically indicated left atrial access. This is unlikely to have significantly impacted the results, as previous animal studies have demonstrated electrical and structural remodeling to involve both atria consistent with the notion of hypertension as a systemic disease.

2.6 CONCLUSIONS

Chronically treated systemic hypertension with LVH is accompanied by right atrial remodeling characterised by: i) global conduction slowing, ii) regional conduction delay particularly at the crista terminalis and iii) increased AF inducibility. These changes may in part be responsible for the increased propensity to AF associated with systemic arterial hypertension.
**Table 1: Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Systemic HT (n=10)</th>
<th>Controls (n=10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (y)</td>
<td>59.5 ± 11</td>
<td>53.5 ± 7</td>
<td>0.1</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>145 ± 10</td>
<td>119 ± 11</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>87 ± 6</td>
<td>69 ± 12</td>
<td>0.0004</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>41 ± 5</td>
<td>35 ± 7</td>
<td>0.1</td>
</tr>
<tr>
<td>LA Area (cm(^2))</td>
<td>22 ± 4</td>
<td>20 ± 4</td>
<td>0.5</td>
</tr>
<tr>
<td>LVDd (mm)</td>
<td>49 ± 7</td>
<td>49 ± 4</td>
<td>0.9</td>
</tr>
<tr>
<td>LVDs (mm)</td>
<td>29 ± 8</td>
<td>30 ± 6</td>
<td>0.8</td>
</tr>
<tr>
<td>LV PW thickness (mm)</td>
<td>12 ± 2</td>
<td>9 ± 1</td>
<td>0.005</td>
</tr>
<tr>
<td>LV septal thickness (mm)</td>
<td>12 ± 2</td>
<td>9 ± 1</td>
<td>0.002</td>
</tr>
<tr>
<td>LV mass index</td>
<td>103 ± 17</td>
<td>73 ± 4</td>
<td>0.005</td>
</tr>
<tr>
<td>ACEI/A2RB use (%)</td>
<td>80</td>
<td>0</td>
<td>0.0007</td>
</tr>
<tr>
<td>Calcium channel blockers (%)</td>
<td>10</td>
<td>30</td>
<td>0.6</td>
</tr>
<tr>
<td>Beta-receptor blockers (%)</td>
<td>10</td>
<td>10</td>
<td>1.0</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs (%)</td>
<td>40</td>
<td>60</td>
<td>0.7</td>
</tr>
</tbody>
</table>

ACEI: angiotensin-converting enzyme inhibitor; A2RB: angiotensin 2 receptor blocker; BP: blood pressure; HT: hypertension; LA: left atrial; LV: left ventricle; LVDd: left ventricular diameter in diastole, LVDs: left ventricular diameter in systole, PW: posterior wall
Table 2: Echocardiography Diastolic and Haemodynamic Parameters

<table>
<thead>
<tr>
<th></th>
<th>Systemic HT (n=10)</th>
<th>Controls (n=10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV E/A</td>
<td>1.1 ± 0.4</td>
<td>1.5 ± 0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Septal E/E’</td>
<td>14 ± 8</td>
<td>8 ± 4</td>
<td>0.1</td>
</tr>
<tr>
<td>MV Deceleration</td>
<td>232 ± 66</td>
<td>187 ± 32</td>
<td>0.1</td>
</tr>
<tr>
<td>Peak RVSP</td>
<td>23 ± 5</td>
<td>22 ± 6</td>
<td>0.6</td>
</tr>
<tr>
<td>PA pressure (mean)</td>
<td>13 ± 4</td>
<td>12 ± 4</td>
<td>0.5</td>
</tr>
<tr>
<td>PCW pressure</td>
<td>8 ± 6</td>
<td>7 ± 5</td>
<td>0.7</td>
</tr>
<tr>
<td>CO</td>
<td>6.3 ± 1.8</td>
<td>5.1 ± 0.8</td>
<td>0.1</td>
</tr>
</tbody>
</table>

CO: cardiac output; HT: hypertension; MV: mitral valve, PA: pulmonary artery; PCW: pulmonary capillary wedge; RVSP: right ventricular systolic pressure
Table 3: Right Atrial Electroanatomic Mapping: Global

<table>
<thead>
<tr>
<th></th>
<th>Systemic HT (n=10)</th>
<th>Controls (n=10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA volume (ml)</td>
<td>77±24</td>
<td>70±13</td>
<td>0.5</td>
</tr>
<tr>
<td>RA surface area (cm2)</td>
<td>115±19</td>
<td>102±16</td>
<td>0.1</td>
</tr>
<tr>
<td>Voltage (mV) 600ms</td>
<td>2.2±0.5</td>
<td>2.2±0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>% Low voltage</td>
<td>13%</td>
<td>9%</td>
<td>0.04</td>
</tr>
<tr>
<td>Fractionated Signals (%)</td>
<td>9±7</td>
<td>6±5</td>
<td>0.2</td>
</tr>
<tr>
<td>Double Potentials (%)</td>
<td>9±6</td>
<td>3±4</td>
<td>0.01</td>
</tr>
<tr>
<td>FS + DP (%)</td>
<td>18±9%</td>
<td>8±6%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

DP: double potentials; FS: fractionated signals; HT: hypertension; RA: right atrium
Table 4: Right Atrial Electroanatomic Mapping: Regional

<table>
<thead>
<tr>
<th></th>
<th>Systemic HT</th>
<th>Controls</th>
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<tbody>
<tr>
<td><strong>SEPTAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voltage (mV)</td>
<td>1.6±0.7</td>
<td>1.9±0.6</td>
<td>0.3</td>
</tr>
<tr>
<td>Low Voltage (%)</td>
<td>15±13</td>
<td>10±10</td>
<td>0.3</td>
</tr>
<tr>
<td>FS + DP (%)</td>
<td>18±9</td>
<td>6±7</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>LATERAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voltage (mV)</td>
<td>2.6±0.6</td>
<td>2.5±0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Low Voltage (%)</td>
<td>11±9</td>
<td>6±5</td>
<td>0.1</td>
</tr>
<tr>
<td>FS + DP (%)</td>
<td>11±13</td>
<td>7±9</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>ANTERIOR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voltage</td>
<td>2.4±1</td>
<td>2.5±0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Low Voltage (%)</td>
<td>10±7</td>
<td>4±3</td>
<td>0.01</td>
</tr>
<tr>
<td>FS + DP (%)</td>
<td>16±12</td>
<td>8±6</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>POSTERIOR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voltage</td>
<td>1.6±0.5</td>
<td>1.8±0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Low Voltage (%)</td>
<td>18±15</td>
<td>8±6</td>
<td>0.07</td>
</tr>
<tr>
<td>FS + DP (%)</td>
<td>26±14</td>
<td>13±9</td>
<td>0.03</td>
</tr>
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</table>

FS: fractionated signals; HT: hypertension; DP: double potential
Table 5: Conduction Velocity

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Systemic HT</th>
<th>Control</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conduction Velocity during proximal CS pacing at 600msec (cm/s)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>73 ± 17</td>
<td>96 ± 12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Septal</td>
<td>78 ± 24</td>
<td>101 ± 11</td>
<td>0.01</td>
</tr>
<tr>
<td>Lateral</td>
<td>70 ± 16</td>
<td>91 ± 18</td>
<td>0.01</td>
</tr>
<tr>
<td>Anterior</td>
<td>72 ± 22</td>
<td>99 ± 22</td>
<td>0.01</td>
</tr>
<tr>
<td>Posterior</td>
<td>70 ± 17</td>
<td>96 ± 12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Conduction Velocity during proximal CS pacing at 300msec (cm/s)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global</td>
<td>85 ± 13</td>
<td>95 ± 8</td>
<td>0.03</td>
</tr>
<tr>
<td>Septal</td>
<td>93 ± 10</td>
<td>104 ± 13</td>
<td>0.05</td>
</tr>
<tr>
<td>Lateral</td>
<td>76 ± 12</td>
<td>95 ± 12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Anterior</td>
<td>86 ± 15</td>
<td>94 ± 8</td>
<td>0.2</td>
</tr>
<tr>
<td>Posterior</td>
<td>78 ± 16</td>
<td>91 ± 11</td>
<td>0.05</td>
</tr>
</tbody>
</table>

CS: coronary sinus; HT: hypertension
**Catheter Fluoroscopic Images**

![Fluoroscopic images in the right anterior oblique (RAO) and left anterior oblique (LAO) projection showing catheter position of the (a) crista terminalis (CT); (b) 4mm mapping catheter at the high septal right atrial location (HSRA); and (c) coronary sinus (CS).](image)

**Figure 1**: Fluoroscopic images in the right anterior oblique (RAO) and left anterior oblique (LAO) projection showing catheter position of the (a) crista terminalis (CT); (b) 4mm mapping catheter at the high septal right atrial location (HSRA); and (c) coronary sinus (CS).
Atrial Refractoriness

Figure 2: Comparison of ERP’s with a drive train of 600msec and 450msec at 2 sites within the right atrium, proximal CS and HSRA. CS: coronary sinus; HSRA: high septal right atrium.
Conduction Delay at the Crista Terminalis

Figure 3: These figures were taken during ERP testing, and demonstrate the final beat in the drive train (S1) and the extrastimulus (S2). The left panel demonstrates an increase in fractionation and double potentials at the crista terminalis in a patient with hypertension compared with a control patient (right panel).

CS: coronary sinus; CT: crista terminalis
Electroanatomic (Bipolar Voltage) CARTO Maps

**Figure 4**: Bipolar voltage CARTO map of a patient with hypertension on the left, and a control patient on the right. Low voltage areas <0.5mV are shown in red. Fractionated signals are represented by pink dots; double potentials are represented by blue dots. Anatomic landmark points are represented in yellow. Electroanatomic mapping demonstrated more extensive areas of low voltage, and of double potentials and fractionated signals in hypertensive patients, particularly within the posterior right atrium.

IVC: inferior vena cava; LAO: left anterior oblique; PA: posteroanterior; SVC: superior vena cava
Figure 5: Atrial Activation Times. During coronary sinus pacing at CL 600msec, right atrial activation times were significantly longer in patients with systemic hypertension compared with controls.

RA: right atrial
CHAPTER 3

Atrial Electrical And Structural Remodeling
Associated With Long Standing Pulmonary
Hypertension And Right Ventricular
Hypertrophy In Humans
3.1 INTRODUCTION

Pulmonary arterial hypertension (PH) is characterized by elevated pulmonary pressures resulting in chronic pressure overload with the cardiac sequelae of right ventricular hypertrophy and right atrial dilatation. PH may be primary or secondary to a range of pulmonary and cardiac conditions (382, 383). Chronic lung disease, obesity and obstructive sleep apnoea (384) are associated with an increase in the incidence of atrial fibrillation (17, 385, 386) as well as an increase in recurrent AF following catheter ablation (387) and electrical cardioversion (388). The final common pathway for these divergent conditions includes elevated right heart pressures. The assessment of the atrial substrate is confounded further by the frequent occurrence of hypertension, ageing and coronary artery disease. Obstructive sleep apnoea (OSA) may result in pulmonary vascular remodeling and pulmonary hypertension through hypoxic vasoconstriction (389). In addition frequent nocturnal hypoxaemia and hypercapnoea, alterations in intrathoracic pressure, repetitive central nervous system arousals and autonomic imbalance may be contributory to AF susceptibility (390).

Idiopathic pulmonary hypertension provides an opportunity to study the atrial effects of pulmonary hypertension in the absence of the confounding effects of other disease states. A better understanding of the atrial effects of PH may help dissect out the relevant pathophysiologic factors responsible for the vulnerability to AF in these varied clinical conditions. Therefore we performed a detailed electrophysiologic and electroanatomic study in patients with idiopathic PH to determine the atrial effects of long standing pulmonary hypertension.
3.2 METHODS

3.2.1 Study Population.

The study population included eight patients with idiopathic PH (IPH) with evidence of right ventricular hypertrophy on echocardiogram and 16 control patients with structurally normal hearts. Control patients were age-matched and recruited in a 2:1 ratio to patients with IPH. Patients were defined as having IPH according to World Health Organization criteria (391) and defined as an increase in mean pulmonary arterial pressure (PAP) $\geq 25$mmHg at rest as assessed by right-heart catheterization (RHC) (391, 392). Patients with pulmonary hypertension were recruited at the time of presentation for a clinically indicated right-heart catheterization procedure as part of the diagnostic work-up prior to the commencement of active treatment. These patients were consented for an additional electrophysiology and mapping study in the absence of a clinical indication for an electrophysiology procedure. Control patients were recruited at the time of presenting for an electrophysiology procedure for supraventricular tachycardia. Exclusion criteria included amiodarone, LV systolic dysfunction (defined as LVEF<50%), ischaemic or valvular heart disease, systemic hypertension, diabetes mellitus, obesity (BMI >30), current/previous smoking or known lung disease or a right-left shunt. To avoid the confounding effects of AF on atrial remodeling, a detailed history of symptoms was undertaken, previous electrocardiograms were sourced, and any patients in the control or IPH group with a history suggestive of AF were excluded.

Transthoracic echocardiogram was performed in all patients to establish the presence or absence of right ventricular hypertrophy and to evaluate ventricular function.

The study was approved by the Research Development and Human Ethics Committee at the Alfred Hospital. All patients gave written informed consent prior to the study.
3.2.2 Right Heart Catheterization

Right Heart Catheterization was performed with a balloon-tipped, flow-directed pulmonary artery catheter introduced via the femoral vein. We measured right atrial pressures, right ventricular systolic and diastolic pressures, and pulmonary artery pressures. Cardiac output was measured using the pulmonary artery thermodilution technique. In brief 15mL of cold saline solution was delivered through the proximal port of the Swan-Ganz catheter into the right atrium (393) with values determined by the average of three measures.

3.2.3 Electrophysiologic Study

All antiarrhythmic medications including beta-blockers and calcium channel blockers were ceased 5 days prior to EP study. Electrophysiological study was performed in the fasted state with conscious sedation either following right-heart catheterization in PH patients or following successful catheter ablation of supraventricular tachycardia during the routine 30-minute waiting period. The following catheters were positioned via the femoral venous approach as previously described (394): 1) 10-pole catheter (2-5-2 mm inter-electrode spacing) within the coronary sinus (CS) with the proximal bipole at the CS ostium; 2) 20-pole “crista” catheter with 1-3-1 mm interelectrode spacing positioned with the aid of a long sheath along the crista terminalis and standardized such that the second bipole lay at the junction of the superior vena cava with RA as determined by fluoroscopy; and; 3) 3.5-mm tip electroanatomic mapping catheter.

Surface electrocardiograms (ECGs) and bipolar endocardial electrograms were continuously monitored and stored on a computer-based digital amplifier/recorder system for offline analysis (EP MedSystems, St Jude Medical, St. Paul, Minnesota).
Intracardiac electrograms were filtered from 30 to 500Hz and measured with computer-assisted calipers at a sweep speed of 200 mm/s.

**Sinus Node Recovery Time**

The corrected sinus node recovery time (cSNRT) was determined at a cycle length (CL) of 600 and 400 ms after a 30-second pacing train from the high septal RA and determined as the duration from the stimulus artifact to the earliest activity along the crista terminalis corrected for the baseline sinus cycle length. The cSNRT was repeated 3 times at each CL and averaged.

**Atrial ERP**

Atrial ERP was measured from two sites: at the high septal right atrium and proximal coronary sinus. Atrial ERP was measured with pulse duration of 2msec at twice diastolic threshold (for a pacing threshold of<2 mA) at cycle lengths (CL) of 600 and 450 ms, with an 8-beat drive followed by an extra-stimulus, starting at a coupling interval of 150 ms increasing in 10-ms increments. The ERP was defined as the longest coupling interval failing to propagate to the atrium. At each site, the ERP was measured three times during each CL, and if the maximum and minimum amounts differed by >10 ms, two additional measurements were taken and the total averaged.

**Conduction delay at the Crista Terminalis**

Conduction delay at the crista terminalis was measured during pacing at cycle lengths of 600 ms and during the earliest extrastimulus that conducted to the atrium from the proximal coronary sinus and high septal RA. Conduction delay at the CT was
analysed by the presence of discrete double potentials and fractionated electrograms (365)

**AF Inducibility**

Inducibility of AF was assessed during ERP testing (394). Atrial ERP was assessed from two pacing sites and 2 pacing cycle lengths, starting with an extrastimulus coupling interval of 150ms and increasing in 10ms increments, as described above. Sustained AF was defined as AF>30 seconds in duration occurring during electrophysiology testing. The maximum duration of AF was calculated as the longest episode of AF during the induction protocol. Electrical cardioversion was performed if AF persisted beyond 30 minutes.

### 3.2.4 Electroanatomic Mapping

Electroanatomic maps of the RA were created during pacing from the proximal coronary sinus at 600 and 300msec. Endocardial contact during mapping was ensured by: electrogram characteristics, fluoroscopic visualization of catheter mobility in relation to cardiac motion and the catheter icon on the three-dimensional navigation system. Atrial points were then acquired if the stability criteria in space ($\leq 6$mm) and in local activation time ($\leq 5$ ms) were met. Mapping density was uniform across the RA endocardium and the point density determined at a fill threshold of 15 mm. Editing of points was performed offline. The right atrium was divided into 4 segments for offline analysis: posterior, anterior, septal and lateral. Local activation time was manually annotated to the beginning of the first deflection from the isoelectric line on bipolar electrograms. Local voltage was defined as the amplitude of the peak positive
to the peak negative deflections. Where a >25% variance in the maximum beat-to-beat voltage occurred, poor contact was inferred and the points excluded.

**Voltage Analysis**

In the analysis of the electroanatomic map, the following definitions were used: (1) fractionated signals were complex electrograms ≥50 ms duration; (2) DPs were defined as local electrograms separated by an isoelectric interval; (3) electrically silent areas (scar) as absence of recordable activity or a bipolar voltage amplitude ≤0.05 mV; and (4) low-voltage areas, contiguous areas ≤0.5 mV on bipolar voltage maps (173). Regional voltage was calculated by averaging the bipolar voltage from the total number of signals within each of the pre-defined atrial segments.

**Conduction Analysis**

*Conduction Velocity*

Isochronal activation maps of the atria were created and regional conduction velocity (CV) was determined in the direction of the wave-front propagation as previously described (394). Conduction was determined as the mean of 5 pairs of points along the activation front through regions of least isochronal crowding.

*Atrial Activation Time*

The activation time for each of the four atrial segments was measured by subtracting the earliest from the latest activation time within each segment (124).
3.2.5 Statistical Analysis

All continuous variables are reported as mean ± standard deviation and assessed for normality utilizing the Shapiro-Wilk test. Comparisons between groups were performed by an unpaired students T-test or Wilcoxon rank sum test. Proportions were compared by Fisher’s exact test. Statistical significance was established at p<0.05. Pearson’s correlation coefficient was performed to test the relationship between pulmonary arterial pressure and atrial refractoriness. Correlation coefficient (r) is expressed on a scale from -1.0 to +1.0.

3.3 RESULTS

3.3.1 Baseline Characteristics (Table 1)

Patient characteristics are presented in Table 1. The mean age in patients with pulmonary hypertension was 50.9 ± 18.5 years vs. 46.6 ± 14.1 years (p=0.5) in controls. Mean pulmonary arterial pressure was significantly increased in the PH group (39.0 ± 15.8 mm Hg vs. 11.5 ± 4.1 mm Hg in controls, p<0.0001) as was the peak RVSP (67.3 ± 26.0mmHg in PH group vs. 20.3 ± 4.9mmHg in controls).

In the SVT group, the mean duration of symptoms was 11 ± 7 years. At electrophysiology study, AV-node reentrant tachycardia (AVNRT) was present in 12 and AV- reentrant tachycardia (AVRT) in 4, all of whom underwent successful ablation.
3.3.2 Sinus Node Recovery Times

The cSNRT at CL 600msec was 358 ± 122ms in PH group vs 330 ± 124msec in controls, p=0.5; and at CL 400msec was 394 ± 94ms in PH group vs 306 ± 121msec in controls, p=0.02.

3.3.3 Atrial Refractoriness

There was no significant difference in atrial refractoriness between the PH group and controls (Figure 1). Similarly there was no significant correlation between atrial refractoriness and mean PA or right ventricular systolic pressures (ERP at the coronary sinus compared to peak PA pressure was r=0.1 (p=0.6); and to RV systolic pressure was r=0.3 (p=0.9). For ERP at the HSRA, the correlation coefficient was r=0.1 (p=0.3) for peak PA and RV systolic pressure.

3.3.4 Atrial Fibrillation Inducibility

Four of 8 PH patients and 0/16 control patients developed a sustained atrial arrhythmia during ERP testing. (p=0.007). The number of AF episodes per patient was 3 ± 2.6 with a mean duration of 7.1 ± 12.8 minutes. One PH patient developed sustained atrial flutter.

3.3.5 Anatomically Determined Conduction Delay

Pulmonary hypertension was associated with a significantly higher number of fractionated signals recorded at the crista terminalis. The number of bipoles recording
fractioned signals was: 5.1 ± 1.1 in PH group vs. 3.1 ± 0.7 in controls at CL 600ms, p=0.001; and 4.9 ± 1.3 in PH group vs. 3.0 ± 0.8 in controls, p=0.005 at CL 450ms. The number of discrete double potentials at CL 600ms was 2.0 ± 2.4 in PH group vs. 0.3 ± 0.8 (p=0.09) in controls; and at CL 450ms was 2.1 ± 2.5 in PH group vs. 0.3 ± 0.8 (p=0.09) in controls. The mean duration of complex fractionated signals was prolonged in patients with pulmonary hypertension compared to controls (93± 30 ms vs. 69 ± 6 ms, p=0.02).

The proportion of signals in the region of the crista terminalis that were classified as discrete double potentials was significantly higher in PH 5.6% ± 7.3 vs. controls: 1.6% ± 3.0, p=0.03.

**3.3.6 Electroanatomic Mapping**

The mean number of points collected in the PH group was 160 ± 32 points vs. 145 ± 42 points in controls, p= NS. Right atrial volumes were significantly higher in patients with pulmonary arterial hypertension compared to control patients (103 ± 33 mL vs. 75 ± 15 mL, p=0.01).

*Right Atrial Voltage*

Pulmonary hypertension was associated with a significant reduction in mean RA tissue voltage compared with controls (PH 1.8 ±0.4mV vs. controls 2.2 ± 0.4mV, p=0.02). In addition, regions of low voltage, defined as <0.5mV were significantly increased in pulmonary hypertension (PH 13.7 ± 8.2% vs. controls; 6.2 ± 3.7%,
p=0.006). Electrically silent areas occurred in 3.2 ± 2.7% of RA area in PH patients and were not seen in controls 0 ± 0%, p=0.0001) (Figures 2A, 2B).

In all atrial segments, mean voltage was lower in patients with pulmonary hypertension compared to controls (Table 2). Differences in regional low voltage associated with PH achieved statistical significance at the posterior and septal right atrium.

**Atrial Conduction**

Right atrial conduction was significantly slower in patients with pulmonary hypertension compared to controls at CL 600ms and 300ms (Table 3). The differences in conduction velocity were statistically significant in all of the pre-defined regions: the septum, lateral, posterior and anterior right atrium (Table 3) (Figure 3).

Right atrial activation time during coronary sinus pacing was significantly longer in patients with pulmonary hypertension (Table 4). Regional activation times were also prolonged at all pre-defined regions in the PH group.

The total proportion of points demonstrating abnormal conduction was increased in the PH group. Complex fractionated activity was increased globally (PH group 10.6 ± 4.2% vs. controls 3.6 ± 4.5% as a % of points taken. p=0.002). At a regional level fractionation was increased at all predefined atrial segments in patients with PH achieving statistical significance at the septal, lateral and posterior atrial locations (Figure 4).
3.4 DISCUSSION

This study provides new insights into the atrial electrophysiologic and electroanatomic changes associated with pulmonary hypertension. In this study, patients with long standing idiopathic pulmonary hypertension were evaluated to study the atrial effects of prolonged increased atrial pressure on atrial electrophysiology. These findings provide insights into the large number of patients with a broad spectrum of common clinical conditions associated with pulmonary hypertension. The following changes were observed in the right atrium of patients with pulmonary hypertension:

1. Prolongation of sinus node recovery times;
2. A reduction in tissue voltage with an increase in areas of low tissue voltage and electrically silent areas;
3. An increase in the number of complex fractionated activity particularly in the region of the posterior RA;
4. Atrial conduction slowing with a significant reduction in conduction velocity and an increase in activation times at a global and regional level.
5. These electrophysiologic abnormalities were associated with an increased AF inducibility

Electrical Remodeling Due to Atrial Dilatation and Atrial Stretch

Pulmonary hypertension results in elevated atrial pressure and increases the propensity to atrial fibrillation by altering the electrophysiologic properties of atrial tissue. Chronic atrial stretch is fundamental to a range of clinical conditions
responsible for arrhythmogenesis including systemic hypertension (394), systolic (173, 395) and diastolic heart failure, valvular (396) and ischaemic heart disease.

Prior Animal Studies

Animal models of chronic stretch provide the opportunity to complete detailed biatrial electrophysio logic study with pathologic correlation to gain insights into the hand-in-hand relationship between electrical and structural remodeling. In the canine heart failure model, Nattel and coworkers demonstrated extensive interstitial fibrosis associated with an increase in conduction heterogeneity and an increase in AF duration (120). Importantly, a follow-up study demonstrated that with reversal of heart failure, there is complete recovery of ionic remodeling but the AF substrate and structural remodeling remained (172). In a mitral regurgitation model, Verheule et al described patchy inflammatory change, fibre separation and interstitial fibrosis within the left atrium, which was associated with an increase in AF inducibility (166). In a chronic ovine model of elevated blood pressure, structural change characterized by atrial myocyte hypertrophy, apoptosis and an increase in collagen fibrils with discrete focal scarring was observed in animals with elevated blood pressure (184). Observations from animal studies provided the platform for Allessie to describe the “second factor” to explain the persisting susceptibility to AF recurrence despite the apparent resolution of electrical remodeling. Structural remodeling characterized by tissue fibrosis and the resultant changes in fibre orientation result in generalized conduction slowing and increases in the heterogeneity of conduction with an increase in the propensity to AF (397).
Human Studies of Chronic Atrial Stretch

Studies in human conditions of chronic atrial stretch have included congestive cardiac failure (173), atrial septal defect (130) and systemic hypertension (394). In general the findings have been consistent across a range of clinical conditions with prolongation of atrial refractoriness and conduction abnormalities characterized by generalized conduction slowing with localized complex fractionated atrial activity. Electroanatomic changes included a reduction in global and regional tissue voltage, which offered an explanation for the propensity to AF in these conditions.

Sanders and coworkers recently described the biatrial changes in humans with rheumatic mitral valve disease (396). In this model of chronic atrial stretch, the most profound abnormalities observed were of atrial conduction slowing and a reduction in bipolar voltage, with evidence of reverse remodeling both acutely and long term following mitral valve commissurotomy. A reduction in AF susceptibility paralleled reverse remodeling of structural abnormalities, whilst the changes in atrial refactororiness were delayed.

In the present study idiopathic pulmonary hypertension was associated with a significant reduction in conduction velocity, tissue voltage and an increase in areas of low voltage and electrical silence. In particular, the changes of conduction slowing were profound compared to age-matched control patients. These findings are consistent with earlier studies of increased atrial pressure and support the role of chronic stretch as an important mechanism in the atrial electrophysiologic and electroanatomic remodeling observed in response to pulmonary hypertension.
Clinical Implications

Idiopathic PH is a rare condition with an estimated incidence of 2-3 per million per year (398). It is associated with an increased risk of AF with significant prognostic implications. Atrial arrhythmias occur in up to 12% of patients with IPH (399) resulting in marked clinical deterioration and right ventricular failure. Tongers et al reported a mortality of 6.3% if sinus rhythm could be restored compared to 82% in patients with persistent atrial fibrillation (399), with a follow-up period of 26 ± 23 months and 11 ± 8 months, respectively.

Although the present study is the first to describe the electrophysiologic and electroanatomic changes associated with idiopathic pulmonary hypertension, elevated right heart pressures are common to a range of more common clinical conditions known to be associated with atrial fibrillation including chronic lung disease and obstructive sleep apnoea. Here, the susceptibility to AF is likely a combination of stretch mediated effects in combination with disease-specific factors. In patients with chronic obstructive pulmonary disease, the prevalence of atrial fibrillation is higher than in patients without airways disease, and is more common in severe airflow obstruction than in mild to moderate forms (400). Sympathetic upregulation secondary to hypoxaemia (401), and the presence of chronic systemic inflammation may also contribute to the development of AF (402). Obstructive sleep apnoea has a strong association with multiple AF-related risk factors such as systemic hypertension, ageing, heart failure and obesity in addition to pulmonary hypertension (390). Prior animal studies exploring the effects of changes in blood gases in pulmonary disease and sleep apnoea demonstrated prolongation in atrial refractoriness and conduction times in response to hypercapnoea with minimal change in electrophysiologic parameters in response to hypoxemia (403).
The present study is in keeping with earlier studies of chronic atrial stretch models demonstrating widespread conduction slowing in association with a reduction in tissue voltage. A recognition of the electrophysiologic and structural change associated with long standing pulmonary hypertension is not only important in understanding the mechanisms by which a range of disease states are associated with atrial fibrillation but also why the response to pharmacologic and catheter based strategies to restore sinus rhythm are associated with lower success (404, 405). Patients with chronic lung disease have been shown to have a significantly higher prevalence of non-pulmonary vein foci arising from the right atrium (406), offering an explanation for the higher recurrence of AF after pulmonary vein isolation (406). Untreated and undiagnosed OSA is associated with a higher recurrence of AF following electrical cardioversion (388), and is also associated with a higher incidence of early and late recurrence of AF after catheter ablation (407). An understanding of the mechanisms of arrhythmogenesis in conditions of pulmonary hypertension, such as those described in the present study, may ultimately lead to more effective therapies in these challenging patients.

3.5 STUDY LIMITATIONS

The development of clinical AF is complex and depends not only on substrate, but also on other factors such as triggers and initiators that were not addressed by this study. In this clinical study, detailed evaluation was confined to the RA as ethical considerations limited non-clinically indicated left atrial access. Additionally, high density mapping with basket catheters may have yielded additional insights to
pathophysiology of induced atrial fibrillation by allowing the detailed mapping of wavefront patterns and activation that was not performed in this study.

3.6 CONCLUSIONS

Idiopathic pulmonary hypertension is associated with right atrial remodeling characterised by: generalised conduction slowing with evidence of marked regional abnormalities; reduced tissue voltage and electrical silence. These changes provide important insights into the direct effects of chronic stretch fundamental to a range of clinical conditions associated with chronically elevated pulmonary pressures, which lead to atrial fibrillation.
Table 1: Baseline and Clinical Characteristics

<table>
<thead>
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<th></th>
<th>PH</th>
<th>Controls</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>50.9 ± 18.5</td>
<td>46.6 ± 14.1</td>
<td>0.5</td>
</tr>
<tr>
<td>Male Sex</td>
<td>4 (50%)</td>
<td>8 (50%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>122.8 ± 8.8</td>
<td>121.4 ± 12.2</td>
<td>0.8</td>
</tr>
<tr>
<td>LVEF &gt;59% (%)</td>
<td>16 (100%)</td>
<td>8 (100%)</td>
<td>1.0</td>
</tr>
<tr>
<td>LA diameter (mm)</td>
<td>39 ± 5</td>
<td>36 ± 7</td>
<td>0.3</td>
</tr>
<tr>
<td>NYHA Class III/IV</td>
<td>5 (62.5%)</td>
<td>0 (0%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean PAP (mm Hg)</td>
<td>39.0 ± 15.8</td>
<td>11.5 ± 4.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak PAP (mm Hg)</td>
<td>66.4 ± 22.8</td>
<td>17.9 ± 5.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak RVSP (mm Hg)</td>
<td>67.3 ± 26.0</td>
<td>20.3 ± 4.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CO</td>
<td>4.9 ± 0.8</td>
<td>5.3 ± 0.9</td>
<td>0.3</td>
</tr>
<tr>
<td>Ca blockers (%)</td>
<td>19%</td>
<td>25%</td>
<td>1.0</td>
</tr>
<tr>
<td>B-Blockers (%)</td>
<td>13%</td>
<td>0%</td>
<td>0.5</td>
</tr>
<tr>
<td>ACEI/A2RB (%)</td>
<td>19%</td>
<td>25%</td>
<td>1.0</td>
</tr>
</tbody>
</table>

ACEI: angiotensin-converting enzyme inhibitor; A2RB: angiotensin type 2 receptor blocker; BP: blood pressure; Ca: calcium channel; CO: cardiac output; LA: left atrial; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PAP: pulmonary artery pressure; PH: pulmonary hypertension; RSVP: right ventricular systolic pressure;
Table 2: Right Atrial Bipolar Voltage

<table>
<thead>
<tr>
<th></th>
<th>PH</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA Voltage (mV)</td>
<td>1.8 ± 0.4</td>
<td>2.2 ± 0.4</td>
<td>0.02</td>
</tr>
<tr>
<td>RA Low Voltage Area (%)</td>
<td>13.7 ± 8.2</td>
<td>6.2 ± 3.7</td>
<td>0.006</td>
</tr>
<tr>
<td>RA Complex Fractionated Signals</td>
<td>14.7 ± 4.4</td>
<td>6.3 ± 4.1</td>
<td>0.0002</td>
</tr>
<tr>
<td>FS/DP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septal Voltage (mV)</td>
<td>1.5 ± 0.3</td>
<td>2.1 ± 0.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Lateral Voltage (mV)</td>
<td>2.2 ± 0.7</td>
<td>2.5 ± 0.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Anterior Voltage (mV)</td>
<td>2.2 ± 0.4</td>
<td>2.6 ± 0.8</td>
<td>0.2</td>
</tr>
<tr>
<td>Posterior Voltage (mV)</td>
<td>1.4 ± 0.5</td>
<td>1.9 ± 0.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

DP: double potential; FS: fractionated signal; PH: pulmonary hypertension; RA: right atrial
Table 3: Right Atrial Conduction Velocities

<table>
<thead>
<tr>
<th></th>
<th>PH</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CS pacing 600ms (cm/sec)</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Global RA</td>
<td>67.3 ± 5.6</td>
<td>92.8 ± 4.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septal RA</td>
<td>71.5 ± 9.1</td>
<td>96.8 ± 9.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lateral RA</td>
<td>71.3 ± 9.2</td>
<td>86.3 ± 9.4</td>
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</tr>
<tr>
<td>Anterior RA</td>
<td>67.2 ± 7.2</td>
<td>97.9 ± 9.1</td>
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</tr>
<tr>
<td>Posterior RA</td>
<td>59.4 ± 9.9</td>
<td>91.8 ± 8.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
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<tr>
<td>Global RA</td>
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<td>91.6 ± 7.3</td>
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<tr>
<td>Septal RA</td>
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<td>96.9 ± 11.9</td>
<td>&lt;0.0001</td>
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<tr>
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<td>&lt;0.0001</td>
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</tr>
<tr>
<td>Posterior RA</td>
<td>58.1 ± 7.3</td>
<td>90.6 ± 8.8</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CS: coronary sinus; PH: pulmonary hypertension; RA: right atrial
Table 4: Right Atrial Activation Times

<table>
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<th>Controls</th>
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<tbody>
<tr>
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<tr>
<td>Global RA</td>
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</tr>
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<td>0.2</td>
</tr>
<tr>
<td>Posterior RA</td>
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<td>58.7 ± 17.9</td>
<td>0.005</td>
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<tr>
<td><strong>CS pacing 300ms (msec)</strong></td>
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<tr>
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<td>131.3 ± 30.1</td>
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<td>0.001</td>
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<td>51.9 ± 26.0</td>
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</tr>
<tr>
<td>Anterior RA</td>
<td>78.8 ± 30.1</td>
<td>54.2 ± 10.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Posterior RA</td>
<td>93.8 ± 23.8</td>
<td>61.4 ± 20.4</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

CS: coronary sinus; PH: pulmonary hypertension; RA: right atrial
Figure 1: Atrial effective refractory period (ERP). There was a trend to prolongation of ERPs in patients with pulmonary hypertension compared to controls. This was significant at the proximal CS at pacing CL 600ms only.

CS= coronary sinus; ERP: effective refractory period; HSRA= high septal right atrium; PH; pulmonary hypertension
Electroanatomic Voltage Mapping

Bipolar Voltage Map: PA View

Bipolar Voltage Map: LAO View
**Figure 2:** Bipolar voltage right atrial maps in PA and LAO orientations. The left panel is a patient with pulmonary hypertension; the right panel represents a control. Areas of low voltage (<0.5mV) are represented by red. Areas of electrical silence or scar are demonstrated in grey; fractionated signals (FS) in pink; and double potentials (DP) in light blue. Compared to control patients, patients with pulmonary hypertension demonstrated a greater proportion of low voltage areas; fractionated signals and double potentials; and scar.

DP: double potential; FS: fractionated signal; IVC= inferior vena cava; LAO: left anterior oblique; PA= posteroanterior; SVC= superior vena cava; TA= tricuspid annulus.
Figure 3: Isochronal activation map. The left panel is of a patient with pulmonary hypertension; the right panel represents a control. Pulmonary hypertension is associated with isochronal crowding representing conduction slowing.

IVC: inferior vena cava; PH: pulmonary hypertension; SVC: superior vena cava
Complex Fractionation

**Figure 4:** A comparison of areas of complex fractionated signals in patients with pulmonary hypertension and controls.

PH: pulmonary hypertension
CHAPTER 4

Right Atrial Remodeling is More Advanced in Patients with Atrial Flutter than with Atrial Fibrillation
4.1 INTRODUCTION

Atrial fibrillation (AF) and atrial flutter (AFL) are the most common sustained arrhythmias seen in clinical practice. The inter-relationship between the 2 arrhythmias has long been appreciated. Atrial fibrillation may “convert” to AFL by the administration of Class 1C agents (209) or AF may become clinically apparent after elimination of AFL by curative cavo-tricuspid isthmus (CTI) ablation (210, 211). In addition, there may be spontaneous “organization” of AF into AFL or “disorganization” of AFL into AF. Indeed, atrial flutter generally initiates and terminates via transitional atrial fibrillation (107).

However, while there may be alternate expression of both AF and AFL in an individual patient over time, (408) clinically one of these arrhythmias often predominates. In particular, it is not clear why atrial flutter develops as a sustained arrhythmia in some patients, while in others the only sustained clinical arrhythmia observed is atrial fibrillation. Although it is well recognized that both arrhythmias are associated with atrial substrate remodeling (124, 162, 366, 409), there has been no direct comparison of atrial substrate changes in patients with atrial flutter vs. atrial fibrillation.

We hypothesized that the presence of sustained atrial flutter as a dominant clinical rhythm may be a marker of more advanced right atrial remodeling. We performed detailed electrophysiologic (EP) and electroanatomic (EA) studies of the right atrium (RA) in patients with AF compared with AFL to determine substrate differences that may explain differences in expression of AF/AFL in individual patients.
4.2 METHODS

4.2.1 Study Population

This study included a total of 23 patients in 2 groups: 1) 10 patients with atrial flutter undergoing cavo-tricuspid isthmus ablation; and 2) 13 patients with atrial fibrillation undergoing AF ablation. For the purposes of this study, an atrial arrhythmia was present chronically when it had been documented on at least 2 electrocardiograms separated by more than 3 months with no demonstration of sinus rhythm in the intervening period. For atrial flutter patients, atrial fibrillation had not been previously documented and in the atrial fibrillation group, atrial flutter had not been documented clinically. Patients with chronic arrhythmia were in AF/AFL at the time of presentation for electrophysiology study. Any patients with a prior history of RFA were excluded.

All patients provided written informed consent prior to the procedure. The study protocol was approved by the Alfred Hospital and Melbourne Health Research and Ethics Committees.

4.2.2 Electrophysiologic Study

All antiarrhythmic medications were withheld at least 5 half-lives before the procedure. Patients who had been taking amiodarone within the prior 6 months were excluded.

Detailed electrophysiologic evaluation was performed following the ablation procedure. Patients with AFL underwent cavotricuspid isthmus ablation with an endpoint of bidirectional isthmus block. Patients with AF underwent antral pulmonary
vein isolation (PVI) with an endpoint of entrance and exit block. Additional left atrial substrate modification was performed at the discretion of the electrophysiologist. No patients underwent right atrial substrate modification.

The following catheters were positioned via the femoral venous approach: (1) 10-pole catheter (2–5–2 mm interelectrode spacing) within the coronary sinus (CS) with the proximal bipole at the CS ostium; (2) His-bundle electrogram/right-ventricular catheter; and (3) mapping/ablation catheter.

Bipolar intracardiac electrograms and 12-lead surface electrocardiography (ECG) were recorded simultaneously on a computerized digital amplifier system (EPMed Systems, West Berlin, NJ, USA). Intracardiac electrograms were filtered between 30 and 500 Hz; offline analysis was performed with on-screen digital calipers at 200 mm/s sweep speed.

Assessment of Atrial Refractoriness

Atrial ERP was measured from 2 sites: at the high septal RA and proximal coronary sinus. Atrial ERP was measured at twice diastolic threshold (for a pacing threshold of <2 mA) at cycle lengths (CLs) of 600 and 450 ms, with an 8-beat drive followed by an extra-stimulus, starting with an extra-stimulus coupling interval of 150 ms increasing in 10-ms increments. The ERP was defined as the longest coupling interval failing to propagate to the atrium. At each site, the ERP was measured 3 times during each CL, and if the maximum and minimum amounts differed by >10 ms, 2 additional measurements were taken and the total averaged.
Sinus Node Recovery Time

The corrected sinus node recovery time (cSNRT) was determined at a cycle length (CL) of 600 ms after a 30-second pacing train from the high septal RA and determined as the duration from the stimulus artifact to the earliest activity along the crista terminalis corrected for the baseline sinus cycle length. The cSNRT was repeated 3 times and averaged.

4.2.3 Electroanatomic Mapping

CARTO electroanatomic voltage and activation maps were created of the right atrium using a 3.5 mm ablation catheter (2–5–2 mm interelectrode spacing; Biosense-Webster, Johnson & Johnson, Diamond Bar, CA, USA). This was performed during constant pacing from the proximal coronary sinus (CSp) at 600 ms cycle length to standardize both cycle length and direction of wavefront propagation. Endocardial contact during mapping was ensured by: electrogram characteristics, fluoroscopic visualization of catheter mobility in relation to cardiac motion and the catheter icon on the 3-dimensional navigation system. Atrial points were then acquired if the stability criteria in space (≤6 mm) and in local activation time (≤5 ms) were met. Mapping density was uniform across the RA endocardium and the point density determined at a fill threshold of 15 mm. Editing of points was performed offline. The RA was divided into 4 segments for offline analysis: posterior, anterior, septal and lateral. Local activation time was manually annotated to the beginning of the first deflection from the isoelectric line on bipolar electrograms. Electrogram voltage was defined as the amplitude of the peak positive to the peak negative deflections. Where
a >25% variance in the maximum beat-to-beat voltage occurred, poor contact was inferred and the points excluded.

Assessment of Complex Signals

Fractionated signals during sinus rhythm were defined as signals with ≥3 deflections >50 ms duration; double potential were defined as those with 2 separate deflections separated by an isoelectric interval (410). The percentage of complex signals was calculated by dividing the number of complex signals by the total number of signals in each segment (124).

Voltage Analysis

Local voltage was defined as the amplitude from the peak-positive to the peak-negative deflection of the local bipolar electrogram. Low voltage areas were defined as contiguous areas ≤0.5 mV on bipolar voltage maps. Electrically silent areas (scar) were defined as an absence of recordable activity or a bipolar voltage amplitude ≤0.05 mV. Regional voltage was determined by averaging the bipolar voltage from the posterior, anterior, septal, and lateral regions of the RA. The proportion of low-voltage signals was calculated for each segment by dividing the number of low-voltage signals by the total number of signals for that segment.

Assessment of Conduction

Isochronal activation maps of the atria were created and regional conduction velocity (CV) was determined in the direction of the wave-front propagation as previously
described (366). The EA mapping system calculates the CV by expressing the linear distance between 2 points as a function of the difference in the local activation times (LAT). Points are selected perpendicular to isochrones created at 3 ms intervals in LAT to determine regional CV. Conduction was determined as the mean of 5 pairs of points along the activation front through regions of least isochronal crowding.

4.2.4 Statistical Analysis

All continuous variables are expressed as mean ± SD and categorical variables as number of subjects (%). Comparisons between groups were performed by an unpaired Student’s t-test. Categorical variables were compared using Fisher’s exact test. A P < 0.05 was considered statistically significant.

4.3 RESULTS

4.3.1 Baseline and Clinical Characteristics

The baseline patient characteristics are shown in Table 1. The patients were well matched for age, with no significant differences in gender, presence of hypertension and diabetes, left ventricular dimensions and left ventricular function between the groups. Patients with AF had a non-significant trend toward longer documented arrhythmia duration compared with AFL patients.
4.3.2 Atrial Refractoriness

There was a trend to shorter atrial refractory periods at all sites and all pacing cycle lengths in patients with atrial flutter compared to patients with atrial fibrillation (Figure 1). This achieved statistical significance when pacing from the coronary sinus and high septal right atrium at pacing cycle length of 600ms.

4.3.3 Sinus Node Recovery Time

There was a non-significant increase in the sinus node recovery time in patients with atrial flutter compared to patients with atrial fibrillation (CSNRT 341msec ± 183 v 231 ± 161, p=0.1).

4.3.4 Voltage Analysis

A total of 203 ± 96 points per patient were analyzed in the right atrial electroanatomic maps. Mean global voltage was 2.2mV ± 0.7 in patients with AF, compared to 1.9mV ± 0.5 in patients with atrial flutter, p=0.4. There was a non-significant trend towards a lower voltage in all pre-specified atrial regions in patients with atrial flutter compared to controls (Figure 2).

At both the global and regional RA assessments, there was an increase in the proportion of low voltage areas in patients with AFL compared to patients with AF (Global % low voltage signals: AF 10 ± 8% v AFL 19 ± 8%, p=0.02). These differences were significant in all atrial regions excluding the anterior region (Figure 3). In patients with AFL, approximately one-quarter of signals in the posterior right atrium were classified as low voltage.
Two patients with AFL had areas of electrical silence in the posterior and lateral RA regions. No patient with AF was found to have areas of electrical silence (Figure 4A and 4B- CARTO map).

4.3.5 Assessment of Complex Signals

Patients with AFL were found to have a significantly higher proportion of complex signals in the RA overall (%FS/DP AFL: 17 ± 5% v AF 7 ± 5%, p=0.0002). The proportion of complex signals was higher in all atrial regions excluding the anterior region where there was a non-significant trend (Figure 5).

4.3.6 Assessment of Atrial Conduction

Total right atrial activation times were significantly longer in patients with chronic AFL compared to patients with AF (146msec ± 28 v 106msec ± 18msec, p=0.0005). In all pre-defined anatomic segments, there was a progressive prolongation in activation times in patients with AFL compared to patients with AF, significant in the septal and anterior regions (Table 2).

4.4 DISCUSSION

This study provides insights into the relative differences in atrial substrate that may be associated with the preferential expression of either AF or AFL in individual patients. The following changes were observed in patients with AFL compared to patients with AF:
i. A reduction in tissue voltage and an increase in the proportion of low voltage areas;

ii. A higher proportion of complex signals;

iii. Evidence of diffuse conduction slowing with marked regional abnormalities.

In addition, patients with AFL had significantly shorter atrial refractory periods.

**Relationship between Atrial Fibrillation and Atrial Flutter**

Atrial fibrillation and atrial flutter have an important clinical inter-relationship. Approximately three-quarters of patients with AFL have co-existent AF (107) and up to 82% of patients with AFL who have undergone successful radiofrequency ablation will also manifest AF over long term follow up (210, 269, 270). In the majority of patients with AF, however, this occurs in isolation (179), suggesting that both fundamental similarities and differences in atrial substrate and arrhythmogenesis are present. Importantly, it is not clear why some patients with atrial arrhythmias develop sustained atrial flutter, while in others the only sustained clinical arrhythmia observed is atrial fibrillation.

The mechanism of atrial flutter is well established to be a macroreentrant circuit confined within the right atrium and which may be viewed as rotating around the tricuspid annulus. Requisite for reentry to occur is the presence of a second posterior barrier to prevent a short-circuiting of the dominant peri-tricuspid wavefront. Stability of the circuit will be dependent on the size of the excitable gap, which is a function of refractory period, conduction velocity and the length of the posterior barrier. In the sterile canine pericarditis model, spontaneous conversion of AF to AFL is contingent upon an increase in the length of the line of functional block in the lateral RA (214).
In human electrophysiologic studies, the occurrence of functional conduction block at the crista terminalis was found at longer coupling in patients with AFL compared to patients with AF (108). Waldo et al described a plausible mechanistic relationship unifying the 2 arrhythmias: during AF a critical functional line of block is formed between the vena cavae thus establishing the necessary boundary for reentry (107). In some patients this line of block may be relatively fixed with minimum requirement for extension.

In human studies, Roithinger et al also observed that onset of atrial flutter occurred following a period of atrial fibrillation. Mapping demonstrated the requirement for a critical increase in CL of AF and a period of lateral RA electrical silence. However, the study did not address why this is more likely to occur in some AF patients than others (215).

Mechanisms of “disorganization” of AFL to AF have also been proposed. Importantly, AFL may “degenerate” into AF through loss of integrity of functional barriers resulting in wave front short-circuiting and generation of daughter wavelets (411-413).

Prior studies of atrial remodeling in atrial fibrillation and atrial flutter have demonstrated reduction in regional voltage, an increase in low voltage areas, slowed conduction and an increase in complex and fractionated signals. Studies in both atrial fibrillation and atrial flutter patients have shown a concentration of abnormal signals in the posterior right atrium in the region of the crista terminalis (366, 409).

The results from our study are consistent with, and further develop these observations by providing a direct comparison between the 2 arrhythmias. We found substrate abnormalities in both AF and AFL patients. However, for most measures remodeling
was more marked in patients with atrial flutter than in AF patients of similar arrhythmia duration. Voltage reduction and low voltage regions were more prevalent in flutter than fibrillation patients. Similarly conduction slowing was more marked and refractory period shorter suggesting a wider excitable gap to stabilize a flutter circuit. Importantly, the prevalence of complex signals (fractionation and double potentials indicating regional slowed conduction) was most markedly different posteriorly in the right atrium in the region of the crista terminalis; suggesting a more extensive region of functional conduction block in flutter patients.

4.5 STUDY LIMITATIONS

Although we have observed more marked atrial remodeling in flutter patients than in patients with atrial fibrillation of similar duration, the reason for these differences is unclear. It is possible that the more marked remodeling is a consequence of atrial flutter. However, it is reasonable to expect that atrial fibrillation of similar duration would similarly cause atrial remodeling.

4.6 CONCLUSIONS

Patients with AFL as a sustained clinical arrhythmia show more marked right atrial remodeling than patients in whom the persistent clinical arrhythmia is atrial fibrillation. Changes included more profound conduction slowing, shorter refractory periods and higher prevalence of complex signals. All of these changes facilitate the stabilization of atrial flutter and may explain why some patients are more likely to develop atrial flutter as a sustained clinical arrhythmia.
Table 1: Baseline and Clinical Characteristics

<table>
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<th>AF</th>
<th>AFL</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>60 ± 7</td>
<td>65 ± 9</td>
<td>0.1</td>
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<tr>
<td>Male</td>
<td>10 (77%)</td>
<td>10 (100%)</td>
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<tr>
<td>Symptom Duration (y)</td>
<td>6 ± 4</td>
<td>3 ± 4</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 (31%)</td>
<td>5 (50%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
<td>0.4</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59 ± 7</td>
<td>55 ± 9</td>
<td>0.6</td>
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<td>LA diameter (mm)</td>
<td>44 ± 7</td>
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<td>Left ventricular end-diastolic dimension (mm)</td>
<td>50 ± 5</td>
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<td>0.7</td>
</tr>
<tr>
<td>Left ventricular end-systolic dimension (mm)</td>
<td>32 ± 6</td>
<td>35 ± 8</td>
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</tr>
<tr>
<td>Interventricular septum (mm)</td>
<td>10 ± 2</td>
<td>11 ± 1</td>
<td>0.3</td>
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</table>

AF: atrial fibrillation; AFL: atrial flutter; LA: left atrial; LVEF: left ventricular ejection fraction
Table 2: Atrial Activation Times

<table>
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<th>AF</th>
<th>AFL</th>
<th>p</th>
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<tr>
<td>Total LAT (msec)</td>
<td>106 ± 18</td>
<td>146 ± 28</td>
<td>0.0005</td>
</tr>
<tr>
<td>Septal LAT (msec)</td>
<td>61 ± 19</td>
<td>88 ± 18</td>
<td>0.003</td>
</tr>
<tr>
<td>Lateral LAT (msec)</td>
<td>83 ± 24</td>
<td>91 ± 33</td>
<td>0.6</td>
</tr>
<tr>
<td>Anterior LAT (msec)</td>
<td>65 ± 25</td>
<td>98 ± 23</td>
<td>0.004</td>
</tr>
<tr>
<td>Posterior LAT (msec)</td>
<td>86 ± 20</td>
<td>99 ± 26</td>
<td>0.2</td>
</tr>
</tbody>
</table>

AF: atrial fibrillation; AFL: atrial flutter; LAT: local activation time.
Atrial Refractoriness

Figure 1: Atrial effective refractory periods. There was a trend to a decrease in atrial ERP’s in patients with AFL compared to AF.

AF: atrial fibrillation; AFL: atrial flutter; CS: coronary sinus; HSRA: high septal right atrium
Global and Regional Voltage

Figure 2: Global and regional voltage comparison. There was a trend to a decrease in tissue voltage in patients with AFL at a global and regional level.

AF; atrial fibrillation; AFL: atrial flutter
Proportion of Low Voltage and Electrically Silent Areas

**Figure 3:** Proportion of low voltage and electrically silent areas were significantly increased in patients with AFL.

AF: atrial fibrillation; AFL: atrial flutter
Electroanatomic Voltage Mapping
Figure 4: Bipolar voltage mapping in LAO and PA orientation. The left panel is representative of a patient with atrial fibrillation; the right panel represents a patient with atrial flutter. Areas of low voltage (<0.5mV) are represented by red, and areas of high voltage represented by blue and purple. Areas of electrical silence or scar are demonstrated in grey; fractionated signals in pink; and double potentials in light blue. Compared to patients with AF, patients with AFL demonstrated a greater proportion of low voltage areas; fractionated signals and double potentials; and scar.

DP= double potentials; FS= fractionated signals; IVC= inferior vena cava; LAO= left anterior oblique. PA= posteroanterior; SVC= superior vena cava.
Complex Signals

Figure 5: Patients with AFL demonstrated a significantly increased number of fractionated signals and double potentials compared to patients with AF.

AF: atrial fibrillation; AFL: atrial flutter; DP: double potential; FS: fractionated signals
CHAPTER 5

High Prevalence of Early Cognitive Impairment in a Low-Risk Adult Population of Patients with Atrial Fibrillation
5.1 INTRODUCTION

Atrial fibrillation (AF) is the most common sustained arrhythmia seen in clinical practice, and is a major risk factor for stroke and silent cerebral infarction. Atrial fibrillation increases the age-adjusted incidence of stroke 4.8-fold. In addition, up to 15-25% of patients with AF have radiologic evidence of one or more silent cerebral infarcts, in the absence of a history of frank stroke or identifiable neurologic deficits (414). However, there is increasing evidence that these infarcts may not be truly “silent”, as they have been associated with an increased rate of dementia and mortality in elderly patients (415), and an acceleration of cognitive decline in Alzheimer’s disease (416).

Observational and longitudinal population analyses have shown an association between AF and the development of cognitive dysfunction (417, 418). However, in patients with AF without a history of stroke, who are young and otherwise classified as having “lone AF” or who have a CHADS$_2$ score $\leq 1$, the prevalence of cognitive impairment is uncertain.

We prospectively evaluated the prevalence of early cognitive impairment in a low-risk population of patients with paroxysmal and persistent atrial fibrillation (predominantly CHADS$_2$ score $\leq 1$) presenting for radiofrequency ablation. We compared them to a control group of patients with supraventricular tachycardia, in order to investigate the unique impact of AF on cognition.
5.2 METHODS

5.2.1 Study Population

We prospectively evaluated 90 patients scheduled for elective radiofrequency ablation (RFA) for symptomatic atrial fibrillation not controlled by or intolerant to medical therapy. An additional 26 age-matched patients with supraventricular tachycardia were recruited as an arrhythmia comparison group. Paroxysmal AF was defined as self-terminating AF episodes of brief duration (<7 days) (419). Persistent AF was defined as episodes of AF lasting >7 days that do not spontaneously terminate or are terminated by cardioversion (419). To avoid the confounding effects of co-existent AF in patients with SVT, a detailed history of symptoms was undertaken, previous electrocardiograms were sourced, and any patients with a history suggestive of AF were excluded. Any patient presenting for ablation of atrial flutter was also excluded because of the high association of coincident AF (420).

Ethics committee approval was granted, and written informed consent was obtained from all patients. Patients aged 18-80yrs scheduled for elective RFA were considered eligible for recruitment. Exclusion criteria included; pre-existing neurologic or clinically evident neurovascular disease including stroke; dementia (defined as a score of <26 on the Mini Mental State Examination); significant pre-morbid depression and/or anxiety; anticipated difficulty with neurocognitive assessment eg deafness, language difficulties; and geographical remoteness.

Cognitive function in these patients was evaluated by comparison of neuropsychologic test results with previously published normative data. Normative data used in this study was derived from population-based studies conducted to establish the normal range of performance in each test (421-423).
5.2.2 Cognitive Evaluation

The Mini Mental State Examination was administered at the commencement of neuropsychologic testing to screen for significant underlying cognitive impairment, and, if present, patients were excluded from the study protocol.

The presence of significant concurrent mood disorder (anxiety and/or depression) was evaluated at the time of neuropsychologic testing by Visual Analog Scales (VAS) (424). Patients completing the VAS questionnaire are asked to rate their levels of these conditions by indicating a position along a continuous line between two extremes at the end-points. Patients reporting significant mood symptoms consistent with a diagnosis of clinical anxiety or depression were not included in the study.

The patient’s highest education level was documented in order to appropriately stratify patients for comparison against an equivalent control group population. The National Adult Reading Test (NART) assessed pre-morbid intelligence, where a score is derived by the maximum number of words correctly pronounced from a list of 50 words, with gender and level of education taken into consideration (425).

Neuropsychologic testing consisted of 7 auditory and written tests based on the Canadian Study of Health and Aging (426), administered to patients by a trained interviewer, and described in detail in Table 1 (427).

Patients were also asked to subjectively rate their own memory ability by answering a yes or no response to a question on the presence of memory trouble in their everyday life; and to rate their memory ability as better; worse; or the same as other people their own age (428).

Previously published neuropsychologic test data in normative populations was used to define the normal range of performance in each test (421-423). Normative data
derives from the administration of standardized neuropsychologic tests to large numbers of individuals, and are used as the comparative standard against which individual performances can be measured. Individuals in the study groups were compared to population normative data, which takes into account the effects of age, gender and education on performance (423).

5.2.3 Definition and Classification of Cognitive Impairment

Cognitive test outcomes were evaluated on 2 levels:

1. Group Analysis
2. Individual Analysis

Group Analysis

A single mean score for each of the 7 neuropsychologic tests was calculated for each group (group mean scores). These 7 group mean scores were then compared to the mean scores of the normative population for the respective tests, and this was performed for each of the PAF, PeAF and SVT groups. This comparison gives an indication of any overall differences between each study group and the normative controls for each test. However, important differences in performance of individual study patients may be obscured. Therefore the primary outcome results of the study are the individual test results.
**Individual Analysis**

**Pre-Existing Cognitive Impairment**

Pre-Existing Cognitive Impairment (PreCI) for an individual patient was considered present when a patient was classified as impaired in 2 or more of the 7 neuropsychologic tests compared to the normative population (428, 429). Impairment in an individual test was considered to be present when a patient scored ≥2 SD below the mean of the normative population for that test (428, 429). For CERAD AVLT-Immediate, patients are assigned 3 scores for each of the 3 trials of this test. Patients were considered to be impaired in this test if the performance was ≥2 SD below the normative population scores on at least two of the three trials (423, 428).

**Amnestic Mild Cognitive Impairment**

Amnestic Mild Cognitive Impairment (aMCI) was considered present when a patient manifested both an objective and subjective memory impairment on neuropsychologic testing. Objective memory impairment was considered present when a patient scored ≥1.5 SD below the normative population in the CERAD AVLT-Immediate and/or Delayed test. In the case of CERAD AVLT-Immediate, to be classified as impaired required a decrease in ≥2 of the 3 trials for this test (428, 430). Subjective memory impairment was considered present when a patient answered “yes” to the question “do you have trouble with your memory in everyday life?” (428).
5.2.4 Statistical Analysis

Comparison of groups was made using independent t tests for continuous variables, and chi-squared or Fishers exact test for dichotomous parameters. Statistical significance was established at p<0.05. Effect size for the differences in means was performed using Cohen’s d, a standardized index that quantifies the magnitude of difference between the populations. d was defined as the mean of the study group minus the mean of the control group and divided by the standard deviation of the control group (431). In interpreting Cohen’s d, an effect size of < 0.1 was considered trivial; 0.1 - 0.3 a small effect; 0.3 - 0.5 moderate; and > 0.5 a large difference effect.

5.3 RESULTS

5.3.1 Baseline and Clinical Characteristics

From January 2009 through December 2010, a total of 116 patients with either paroxysmal AF, persistent AF or SVT were recruited for analysis. Baseline and clinical characteristics were similar between the 3 groups, except for a lower proportion of male patients with SVT (p<0.001) and are shown in Table 2. Of note, the CHADS\textsubscript{2} score was identical between the 3 groups, and reflected a low-risk population. There was a relatively higher prevalence of hypertension in patients with paroxysmal AF and a higher prevalence of previous TIA in persistent AF patients.

The presenting arrhythmia in the patients with SVT was; AVNRT (13 patients); AVRT due to accessory pathway (6 patients); atrial tachycardia (5 patients); and multiple tachycardia mechanisms in 2 patients (accessory pathway and atrial tachycardia, n=1; AVNRT and atrial tachycardia, n=1).
5.3.2 Pre-Morbid Mood and Intelligence Quotient

Pre-morbid levels of anxiety and depression were similar between the 3 patient study groups (Figure 1). Intelligence quotient as assessed by the National Adult Reading Test was also similar (Figure 2).

5.3.3 Group Analysis

Group mean scores on neuropsychologic tests are presented in Table 3. Effect size differences between group means (Cohen’s d) between the study groups and the normative data are presented below. Values shown in parentheses are the range of Cohen’s d results.

Overall, the most significant differences between the study population and the normative data were seen in the results of the CERAD AVLT test (memory test). Cohen’s d indicated a large difference between PAF patients and controls in the CERAD AVLT- Immediate after taking into consideration the effect of age, gender and level of education (0.71-2.94). Lower mean CERAD AVLT- Immediate scores relative to controls were also seen in patients with persistent AF (0.35- 1.28) and in SVT patients (0.63- 1.23). Effect size difference was also large for these groups, however less than those seen for patients with PAF.

There was a moderate-large difference in mean results of the grooved pegboard (dominant) test in patients with PAF and PeAF compared to controls (PAF 0.25-0.78; PeAF 0.69-0.85). A smaller difference observed in patients with SVT (0.32-0.49). This pattern was reflected in the grooved pegboard non-dominant test (PAF 0.57-0.85; PeAF 0.45-0.98; and SVT 0.46-0.61). Differences between all groups reflected a
worse performance relative to controls, indicated by larger raw scores (longer time taken to complete task).

There was a mild effect size difference between PAF patients and controls in the trail-making tests (TMT A: 0.11-0.15; TMT B: 0.1-0.13). Raw scores indicate an impaired performance in PAF (longer time taken to complete the task). Younger patients with PeAF demonstrated a large (1.07) and moderately (0.3) worse performance in the TMTA and TMTB tasks, respectively, with a longer time taken to complete the task. Older PeAF patients performed similar to controls (TMTA: 0.04; TMTB: 0.07). Mixed results were seen in SVT patients; younger patients performed moderately better than controls in the TMT B (0.25) reflected by a lower raw score and shorter time taken to complete the task. The other SVT groups performed worse than controls (0.34-0.73).

There was no abnormality seen in the verbal fluency tests in PAF, PeAF or SVT patients.

5.3.4 Individual Analysis

Pre-Existing Cognitive Impairment

The results of the individual patient performance in each neuropsychologic test are shown in Table 4. Overall, patients with both PAF and PeAF performed worse than patients with SVT, particularly in the trail-making test part A (p=0.05), and in the grooved pegboard (non-dominant) test (p=0.07). Pre-existing cognitive impairment was present in a total of 5/60 (8%) patients with PAF; 6/30 (20%) patients with PeAF; and 0/26 (0%) patients with SVT (p=0.035).
Amnestic Mild Cognitive Impairment (aMCI)

A total of 34/60 (57%) patients with PAF, 10/30 (33%) patients with PeAF, and 6/26 (23%) patients with SVT were classified as aMCI (p=0.007), having satisfied the subjective and objective criteria.

Presence of Both PreCI and aMCI

Overall, 35/60 (58%) patients with PAF and 14/30 (47%) patients with PeAF were classified as having either PreCI, aMCI or both. The majority of patients were defined as having aMCI, with a smaller proportion of patients classified as PreCI or an overlapping syndrome of both aMCI and PreCI (Figure 3). Of the patients with PAF as a whole, 30/60 (50%) patients were classified as aMCI only; 1/60 (2%) patients were classified as having PreCI only; and 4/60 (7%) patients were classified as having both PreCI and aMCI. Of the patients with PeAF, 8/30 (27%) patients were classified as aMCI only, 4/30 (13%) patients were classified as PreCI only; and 2/30 (7%) were classified as both PreCI and aMCI. In patients with SVT, 6/26 (23%) patients were classified as aMCI only, and no patients satisfied the criteria for PreCI. This resulted in a negative diagnosis of PreCI and/or aMCI (i.e. normal test results) in 42% patients with PAF; 53% patients with PeAF; and in 77% patients with SVT, p=0.01.

5.4 DISCUSSION

Our results indicate that in a low risk cohort of patients with atrial fibrillation (predominantly CHADS\textsubscript{2}≤1) pre-existing cognitive impairment is present in 10-20%. These findings were reinforced by the observation that in a similar low-risk cohort of
patients with SVT, PreCI was not detected. In addition, we identified a proportion of patients classified as aMCI who may have an elevated risk for the future progression of cognitive impairment and development of dementia (430). The current population had symptomatic AF for approximately 6-7 years prior to neuropsychologic testing indicating that this duration may be sufficient to result in cognitive impairment in some patients.

**Relationship of Atrial Fibrillation to Cognitive Impairment and Dementia**

There is accumulating evidence of an increased risk of development of cognitive impairment and dementia in patients with atrial fibrillation. In a cross-sectional study of over 6500 patients with AF, a positive association was found between AF and dementia (OR 2.3, 95% CI 1.4-3.7); and impaired cognitive function (OR 1.7, 95% CI 1.2-2.5) (294). Recently, longitudinal studies have followed patients with AF after diagnosis, and described the rate of development of cognitive impairment. In a large community-based cohort of elderly patients, (mean age 71 ± 15y), patients with AF were found to have a cumulative rate of dementia of 22.5 per 1000 person-years, compared to an incidence of 6.8 per 1000 person-years in the general population (417). In addition, several studies have shown that the presence of AF is a predictor of developing post-stroke dementia (432, 433). One study examined the relationship between AF and dementia in patients without clinically evident stroke and observed a similar association (434).
Potential Pathophysiologic Mechanisms of Cognitive Decline in AF

The mechanisms by which AF leads to cognitive impairment are likely to include, but may not be fully explained by, stroke and silent cerebral infarction. In the Baltimore Longitudinal Study of Aging Autopsy program, symptomatic and asymptomatic brain infarcts were shown to significantly increase the odds of dementia (435). It appears that for macroscopic infarcts, the number and size of infarcts and a hemispheric location showed the strongest correlation with dementia (435). Microscopic infarcts may also be a significant cause of dementia (435). Whilst macroscopic and microscopic lesions frequently co-exist, microscopic lesions independently increased the odds of dementia, particularly when also distributed in the cerebral hemispheres.

Several antemortem studies have provided a link between radiologic surrogates of these cerebral pathologic changes and the prevalence of cognitive impairment. White matter hyperintensities (WMH) are seen on T2 weighted MRI sequencing, and are accepted markers of subclinical microvascular brain injury (436). WMH are related to clinical stroke as well as to conventional stroke risk factors (437), with the most consistent being that of age and hypertension (438). These lesions are located deep in the white matter, and are thought to be secondary to accompanying adjacent small vessel disease (301). The affected vessels are presumed to induce the white matter lesions through chronic ischaemia, and by damage mediated by an abnormal leaking of plasma into the white matter (439, 440). Meta-analysis of large population-based studies suggests a significant association between WMH and the occurrence of Alzheimer’s disease and vascular dementia (441). In patients with documented WMH and baseline neurologic impairment, an increase in WMH lesions has been associated with a higher conversion rate to dementia (442). Studies looking at the relationship of
WMH to decline in cognitive performance have found a positive association in the general population, and in patients with MCI or cerebrovascular disease (441).

Notwithstanding the critical role clinical and subclinical stroke plays in the pathogenesis of cognitive impairment in patients with AF, there may exist other contributing mechanisms. Aside from what may be ascribed to the co-existence of conventional risk factors in AF patients, such as hypertension, there may be a unique haemodynamic and coagulopathic milieu associated with AF that augments this neurologic damage. Beat-to-beat fluctuations in stroke volume may cause disruptions in cerebral blood flow, resulting in chronic cerebral hypoperfusion (306). Endothelial dysfunction in patients with AF increases the risk for thromboembolism by inducing a hypercoagulable state (313). The effects of endothelial dysfunction are mediated by the release of prothrombotic and proinflammatory molecules, including von Willebrand factor (vWF), adhesion molecules and selectins. In patients with AF, elevated plasma vWF levels have been detected (314), and correlate to a higher risk of cardiovascular events (315). In AF patients, elevated levels of vWF are independently associated with left atrial/appendage thrombus and spontaneous echo contrast (316). Elevated levels of vWF mediate platelet aggregation and adhesion to the vascular endothelium, leading to platelet and fibrin thrombi, and potentially to brain infarction.

Amnestic Cognitive Impairment and Atrial Fibrillation

Amnestic mild cognitive impairment encompasses subjective memory complaints, objective memory impairment, and an absence of functional decline, and is associated in some patients with progression to dementia (443). It therefore may enable early identification of patients who are at risk of further deterioration. We observed a 40-
80% increase in the prevalence of aMCI in patients with persistent and paroxysmal AF relative to patients with SVT. In these patients, AF represents a potentially modifiable risk factor providing an impetus toward curative management. However, whether interventional ablation will reduce the prevalence of aMCI in this group remains speculative and requires further study.

Prevalence studies have detected aMCI in approximately 14-18% of individuals aged 70 years and older (430). In our study, although PreCI was not present in any of the SVT patients, this group had a prevalence of aMCI of 26%. The reason for this surprisingly high figure is unclear. It is unlikely that this group represents a truly “normal” population even though the arrhythmia present in these patients is benign.

Although the conversion rate from aMCI to dementia has been reported up to 10-15% per year, there is considerable heterogeneity in the progression of the disease, with a proportion of patients stable or improved at long-term follow up (295).

In patients with mild cognitive impairment, atrial fibrillation has been significantly associated with conversion to dementia, with a hazard ratio of 4.63 (295).

5.5 CONCLUSIONS

We observed a prevalence of pre-existing cognitive impairment in a low-risk AF population of 10-20%; and in no patients with SVT. The prevalence of amnestic mild cognitive impairment was also increased in patients with AF. These findings highlight the potential for subtle neurocognitive sequelae even in AF patients at low thrombo-embolic risk. Additional studies evaluating the very-long term outcomes of these patients are justified to determine whether these subtle cognitive changes are progressive.
Table 1: Description of Neuropsychologic Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Cognitive Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERAD Auditory Verbal Learning Test (AVLT)- Immediate</td>
<td>Patients are read a list of 10 words, and are asked to recall as many words as possible. The maximum number of correct words recalled is documented. This is repeated a further 2 times, however the word order is changed each time. The results of each individual trial are taken as the scores for this test.</td>
<td>Memory</td>
</tr>
<tr>
<td>CERAD Auditory Verbal Learning Test (AVLT)- Delayed</td>
<td>After a 15-minute delay after completion of the CERAD AVLT- Immediate test, patients are asked to recall as many of the 10 words as possible without further prompting or re-reading of the list. The maximum number of correct words remembered is taken as the score.</td>
<td>Memory</td>
</tr>
<tr>
<td>Trail Making Task Part A</td>
<td>Consists of 25 circles distributed over a sheet of paper numbered 1 – 25. The patient is instructed to draw lines to connect the numbers in ascending order as quickly as possible. The time taken to complete the task is taken as the score.</td>
<td>Executive Functioning</td>
</tr>
<tr>
<td>Trail Making Task Part B</td>
<td>Consists of 25 circles distributed over a sheet of paper, the circles include both numbers (1 – 13) and letters (A – L). The patient is instructed to draw lines to connect the circles in an ascending pattern, but with the added task of alternating between numbers and letters (i.e., 1-A-2-B-3-C, etc.). The time taken to complete the task is taken as the score.</td>
<td>Executive Functioning</td>
</tr>
<tr>
<td>Test</td>
<td>Description</td>
<td>Test Type</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Controlled Oral Word Association Test</td>
<td>Patients are instructed to say as many words as possible starting with a given letter within 60 seconds. F; A; and S are tested.</td>
<td>Verbal fluency test, measuring frontal and temporal lobe function (executive function)</td>
</tr>
<tr>
<td>CERAD Semantic Fluency Test</td>
<td>Patients are instructed to generate a list of as many words as possible from a predefined category (animals) within 60 seconds. The number of correct answers is taken.</td>
<td>Verbal fluency test of semantic memory, measuring temporal and frontal lobe function</td>
</tr>
<tr>
<td>Grooved Pegboard Test (Dominant hand)</td>
<td>Requires patients to insert 25 keyed pegs into a specially designed pegboard with randomly positioned slots. Pegs must be rotated to match the hole before they can be inserted. The duration taken to complete the task in seconds is taken.</td>
<td>Requires complex visual-motor coordination and evaluates lateralized injury</td>
</tr>
<tr>
<td>Grooved Pegboard test (Non-Dominant hands)</td>
<td>Requires patients to insert 25 keyed pegs into a specially designed pegboard with randomly positioned slots. Pegs must be rotated to match the hole before they can be inserted. The duration taken to complete the task in seconds is taken.</td>
<td>Requires complex visual-motor coordination and evaluates lateralized injury</td>
</tr>
</tbody>
</table>

CERAD: The Consortium to Establish a Registry for Alzheimer’s Disease; AVLT: Auditory Verbal Learning Test
Table 2: Baseline and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PAF</th>
<th>PeAF</th>
<th>SVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>58 ± 9</td>
<td>53 ± 10</td>
<td>57 ± 12</td>
</tr>
<tr>
<td>Males (n, %)</td>
<td>45 (75%)</td>
<td>28 (93%)</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Symptom Duration (mth)</td>
<td>84 ± 72</td>
<td>81 ± 71</td>
<td>101 ± 88</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59 ± 8</td>
<td>55 ± 8</td>
<td>59 ± 8</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>31 (52%)</td>
<td>10 (33%)</td>
<td>8 (31%)</td>
</tr>
<tr>
<td>DM</td>
<td>5 (8%)</td>
<td>1 (3%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>CAD</td>
<td>6 (10%)</td>
<td>1 (2%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>2 (3%)</td>
<td>3 (10%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>13 (22%)</td>
<td>8 (27%)</td>
<td>6 (23%)</td>
</tr>
<tr>
<td>BMI</td>
<td>30 ± 6</td>
<td>28 ± 3</td>
<td>32 ± 7</td>
</tr>
<tr>
<td>Smoker/Ex-smoker</td>
<td>13 (22%)</td>
<td>5 (17%)</td>
<td>6 (23%)</td>
</tr>
<tr>
<td>CHADS&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0.7 ± 0.8</td>
<td>0.7 ± 0.9</td>
<td>0.7 ± 0.8</td>
</tr>
<tr>
<td>ACEI/A2RB</td>
<td>22 (37%)</td>
<td>8 (27%)</td>
<td>6 (23%)</td>
</tr>
<tr>
<td>CCB</td>
<td>13 (22%)</td>
<td>6 (20%)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>β- Blocker</td>
<td>10 (17%)</td>
<td>8 (27%)</td>
<td>5 (19%)</td>
</tr>
<tr>
<td>AAD (including sotalol)</td>
<td>45 (75%)</td>
<td>13 (43%)</td>
<td>11 (42%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>24 (40%)</td>
<td>22 (73%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>33 (55%)</td>
<td>6 (20%)</td>
<td>7 (27%)</td>
</tr>
</tbody>
</table>

AAD; anti-arrhythmic drug: ACEI; angiotensin-converting enzyme inhibitor
angiotensin 2 receptor blocker: BMI; body mass index: CAD; coronary artery
CCB; calcium channel blocker: CHADS<sub>2</sub>; congestive
failure/hypertension/age>75y/diabetes mellitus/stroke 2 points: DM;
mellitus: LVEF; left ventricular ejection fraction: PAF: paroxysmal atrial fibr
PeAF: persistent atrial fibrillation; SVT; supraventricular tachycardia TIA;
ischaemic attack
Table 3: Comparison of Group Scores with Normative Values

<table>
<thead>
<tr>
<th>TEST</th>
<th>Published Norms:</th>
<th>PAF</th>
<th>PeAF</th>
<th>SVT</th>
<th>Cohen's d (PAF)</th>
<th>Cohen's d (PeAF)</th>
<th>Cohen's d (SVT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n) Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CERAD AVLT Immediate (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12y education &lt;69y</td>
<td>23     8.1 (1.3)</td>
<td>6.5 (1.6)</td>
<td>6.5 (1.2)</td>
<td>7.4 (0.9)</td>
<td>1.1</td>
<td>1.28</td>
<td>0.63</td>
</tr>
<tr>
<td>&lt;12y education ≥70y</td>
<td>23     7.6 (1.9)</td>
<td>6.0 (1.4)</td>
<td>-</td>
<td>4.0 (0.0)</td>
<td>0.96</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥12y education males &lt;69y</td>
<td>61     8.0 (1.3)</td>
<td>7.0 (1.5)</td>
<td>7.2 (1.3)</td>
<td>6.2 (1.6)</td>
<td>0.71</td>
<td>0.62</td>
<td>1.23</td>
</tr>
<tr>
<td>≥12y education males ≥70y</td>
<td>66     7.7 (1.5)</td>
<td>6.5 (0.7)</td>
<td>-</td>
<td>-</td>
<td>1.03</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥12y education females &lt;69y</td>
<td>151    8.8 (1.0)</td>
<td>6.0 (0.9)</td>
<td>8.5 (0.7)</td>
<td>7.9 (1.6)</td>
<td>2.94</td>
<td>0.35</td>
<td>0.67</td>
</tr>
<tr>
<td>≥12y education females ≥70y</td>
<td>89     8.2 (1.4)</td>
<td>-</td>
<td>-</td>
<td>7.0 (1.4)</td>
<td>-</td>
<td>-</td>
<td>0.86</td>
</tr>
<tr>
<td>CERAD AVLT Delayed (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;12y education &lt;69y</td>
<td>23     7.0 (1.9)</td>
<td>3.2 (2.1)</td>
<td>4.4 (2.4)</td>
<td>4.9 (2.2)</td>
<td>1.9</td>
<td>1.2</td>
<td>1.02</td>
</tr>
<tr>
<td>&lt;12y education ≥70y</td>
<td>23     6.7 (1.9)</td>
<td>4.1 (1.4)</td>
<td>-</td>
<td>2.0 (0.0)</td>
<td>1.62</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥12y education males &lt;69y</td>
<td>61     7.0 (2.1)</td>
<td>4.6 (1.7)</td>
<td>4.2 (2.3)</td>
<td>3.2 (2.1)</td>
<td>1.26</td>
<td>1.27</td>
<td>1.81</td>
</tr>
<tr>
<td>≥12y education males ≥70y</td>
<td>66     6.3 (1.8)</td>
<td>3.0 (0.0)</td>
<td>-</td>
<td>-</td>
<td>2.59</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>≥12y education females &lt;69y</td>
<td>151    7.9 (1.6)</td>
<td>4.8 (1.9)</td>
<td>7.0 (2.8)</td>
<td>5.0 (2.3)</td>
<td>1.76</td>
<td>0.39</td>
<td>1.46</td>
</tr>
<tr>
<td>≥12y education females ≥70y</td>
<td>89     6.9 (1.7)</td>
<td>-</td>
<td>-</td>
<td>4.0 (1.4)</td>
<td>-</td>
<td>-</td>
<td>1.86</td>
</tr>
<tr>
<td>TMT Part A (sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-age 30-49y</td>
<td>30     27.6 (9.4)</td>
<td>29.3 (13.5)</td>
<td>37.9 (9.8)</td>
<td>33.3 (5.9)</td>
<td>0.15</td>
<td>1.07</td>
<td>0.73</td>
</tr>
<tr>
<td>-age 50-69y</td>
<td>30     36.7 (13.7)</td>
<td>38.0 (10.3)</td>
<td>36.2 (12.0)</td>
<td>42.4 (19.5)</td>
<td>0.11</td>
<td>0.04</td>
<td>0.34</td>
</tr>
<tr>
<td>TMT Part B (sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-age 30-49y</td>
<td>30     61.3 (17.9)</td>
<td>63.7 (29.8)</td>
<td>66.5 (16.3)</td>
<td>57.6 (10.9)</td>
<td>0.1</td>
<td>0.3</td>
<td>0.25</td>
</tr>
<tr>
<td>-age 50-69y</td>
<td>30     77.0 (30.5)</td>
<td>80.6 (25.9)</td>
<td>74.8 (31.7)</td>
<td>85.2 (23.9)</td>
<td>0.13</td>
<td>0.07</td>
<td>0.3</td>
</tr>
<tr>
<td>COWAT (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-age &lt;70y</td>
<td>220    38.5 (13.7)</td>
<td>42.3 (12.0)</td>
<td>41.8 (11.2)</td>
<td>41.4 (10.5)</td>
<td>0.3</td>
<td>0.57</td>
<td>0.24</td>
</tr>
<tr>
<td>-age 70-79y</td>
<td>334    34.8 (12.8)</td>
<td>39.5 (15.3)</td>
<td>-</td>
<td>58 (19.6)</td>
<td>0.33</td>
<td>-</td>
<td>1.4</td>
</tr>
<tr>
<td>CERAD Semantic Fluency (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-age &lt;70y</td>
<td>92     17.6 (4.7)</td>
<td>19.9 (4.9)</td>
<td>20.4 (5.1)</td>
<td>22.0 (4.5)</td>
<td>0.5</td>
<td>0.57</td>
<td>0.96</td>
</tr>
<tr>
<td>-age 70-79y</td>
<td>228    16.1 (4.0)</td>
<td>20.3 (3.5)</td>
<td>-</td>
<td>26.3 (12.1)</td>
<td>1.12</td>
<td>-</td>
<td>1.13</td>
</tr>
<tr>
<td>GP Dominant (sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-age 10-59y</td>
<td>1460   65.1 (9.2)</td>
<td>73.1 (11.3)</td>
<td>73.2 (9.8)</td>
<td>69.4 (8.3)</td>
<td>0.78</td>
<td>0.85</td>
<td>0.49</td>
</tr>
<tr>
<td>-age &gt;60y</td>
<td>100    82.7 (18.7)</td>
<td>86.8 (13.0)</td>
<td>99.3 (28.3)</td>
<td>88.2 (15.0)</td>
<td>0.25</td>
<td>0.69</td>
<td>0.32</td>
</tr>
<tr>
<td>GP Non Dominant (sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-age 10-59y</td>
<td>1460   70.0 (10.3)</td>
<td>83.9 (20.6)</td>
<td>82.5 (14.9)</td>
<td>76.2 (10.1)</td>
<td>0.85</td>
<td>0.98</td>
<td>0.61</td>
</tr>
<tr>
<td>-age &gt;60y</td>
<td>100    88.0 (26.2)</td>
<td>102.0 (22.5)</td>
<td>102.9 (38.4)</td>
<td>101.6 (32.8)</td>
<td>0.57</td>
<td>0.45</td>
<td>0.46</td>
</tr>
</tbody>
</table>
Data are presented as mean (SD).

Test results are presented as either number of correct answers given (n) or time taken to complete the task (sec). This is indicated after the name of the test in the table, and explained below.

The CERAD AVLT Immediate and Delayed; COWAT; and CERAD Semantic Fluency tests are graded as the number of correct answers given (n). For these tests, a higher raw score indicates a better performance, i.e. a higher score indicates a greater number of correct answers given.

The TMT Part A and B; and the Grooved Pegboard Dominant and Non-Dominant Hands are timed tasks (sec): lower raw scores indicate a better performance, i.e. a shorter time taken to complete the test.

**Abbreviations listed in table**

CERAD AVLT: Consortium to Establish a Registry for Alzheimer’s Disease Auditory Verbal Learning Test; COWAT: Controlled Oral Word Association Test; education: representing highest level of education received (years); GPD: Grooved Pegboard Test, Dominant; GPND: Grooved Pegboard Test, Non-Dominant; TMTA: Trail-making Test Part A; TMTB: Trail-making Test Part B.

**Interpretation of Effect Size (Cohen’s d) Results**

Cohen’s d, a standardized index that quantifies the magnitude of difference between the populations was used to compare the mean scores of the normative data with the mean scores of the 3 study populations. A summary of analysis of the effects size (Cohen’s d) is presented below. A detailed explanation is included in the text.

**CERAD AVLT- Immediate test:** Cohen’s d range indicated a large difference between PAF patients and the normative population (0.71-2.94), representing a large and significantly worse performance by PAF patients compared to controls. Cohen’s
d range for PeAF (0.35-1.28) and SVT patients (0.63-1.23) also indicates a large difference effect, but less than that seen for PAF patients.

**CERAD AVLT- Delayed test:** All groups performed worse relative to controls. The magnitude of difference was largest for PAF patients (PAF 1.26-2.59; PeAF 0.39-1.27; SVT 1.02-1.86).

**TMT Part A and Part B:** PAF patients demonstrated a mild effect size difference to controls (TMT A: 0.11-0.15; TMT B: 0.1-0.13) indicating a worse performance. Younger patients with PeAF demonstrated a large (1.07) and moderately worse performance in the TMTA and TMTB tasks, respectively. Older patients performed similar to controls (TMTA 0.04; TMTB 0.07). Mixed results were seen in SVT patients; younger patients performed moderately better than controls in the TMT B (0.25). Other groups performed worse than controls (0.34-0.73).

**COWAT and CERAD semantic fluency tests:** No abnormality detected in PAF, PeAF or SVT patients. Raw scores indicate number of correct answers given is higher than control patients.

**Grooved Pegboard Dominant and Non-Dominant tests:** PAF and PeAF patients demonstrated a moderate-large difference compared to controls (GPD: PAF 0.25-0.78; PeAF 0.69-0.85. GPND 0.57-0.85; PeAF 0.45-0.98). Abnormal results were seen in patients with SVT, with effect size smaller compared to patients with AF (GPD 0.32-0.49; GPND 0.46-0.61).
Table 4: Prevalence of Impairment in Individual Neuropsychologic Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Impaired Performance, n (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PAF (n=60)</td>
<td>PeAF (n=30)</td>
</tr>
<tr>
<td>CERAD AVLT, n</td>
<td>6 (10%)</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>TMT Part A, sec</td>
<td>2 (3.3%)</td>
<td>5 (16.7%)</td>
</tr>
<tr>
<td>TMT Part B, sec</td>
<td>4 (6.7%)</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>COWAT, n</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>CERAD semantic fluency, n</td>
<td>1 (1.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>GP Dominant, sec</td>
<td>6 (10%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>GP Non Dominant, sec</td>
<td>11 (36.7%)</td>
<td>8 (26.7%)</td>
</tr>
<tr>
<td>OVERALL PreCI</td>
<td>5/60 (8%)</td>
<td>6/30 (20%)</td>
</tr>
</tbody>
</table>

CERAD AVLT: The Consortium to Establish a Registry for Alzheimer’s Disease Auditory Verbal Learning Test; COWAT: Controlled Oral Word Association Test; GP; Grooved Pegboard; PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; PreCI: Pre-Existing Cognitive Impairment; SVT: supraventricular tachycardia; TMT: Trail Making Task.
Visual Analog Scale Scores for Anxiety and Depression

Figure 1: Visual Analog Scale (VAS) scores for anxiety and depression. There were no significant differences in mean scores between study populations.

PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; SVT: supraventricular tachycardia; VAS: visual analog scale
Figure 2: Intelligence Quotient (IQ) as assessed by the National Adult Reading Test (NART). There was no significant difference in mean NART scores between the study populations.

NART: national adult reading test; PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; SVT: supraventricular tachycardia
Prevalence of Pre-Existing Cognitive Impairment and Amnestic Mild Cognitive Impairment

**PAF**

- Normal
- aMCI
- PreCl
- aMCI and PreCl

**PeAF**

- Normal
- aMCI
- PreCl
- aMCI and PreCl
Figure 3: Patients who were classified as having amnestic mild cognitive impairment (aMCI), pre-existing cognitive impairment (PreCI), or both.

aMCI: amnestic mild cognitive impairment; PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; PreCI: pre-existing cognitive impairment; SVT: supraventricular tachycardia
CHAPTER 6

Subtle Cognitive Dysfunction following Atrial Fibrillation Ablation
6.1 INTRODUCTION

Ablation for atrial fibrillation (AF) is a highly effective strategy in the management of this common arrhythmia. However, the procedure carries a risk of major complications, including a 0.5-1% risk of transient ischaemic attack or stroke (287). Prolonged placement of left atrial catheters, and atrial endocardial damage caused by ablation may trigger thrombus formation despite use of anticoagulation. Recent MRI studies have demonstrated the development of new cerebral lesions following irrigated AF ablation in 10-15% of apparently asymptomatic patients (335, 444).

Whether subtle neurocognitive dysfunction may occur following AF ablation procedures has not been well established.

We evaluated the incidence of post-operative cognitive dysfunction (POCD) in patients following radiofrequency ablation (RFA) for atrial fibrillation, and compared this with a non-procedural control population of age-matched patients with AF. We also studied a group of matched patients with supraventricular tachycardia undergoing ablation as an arrhythmia comparison group.

6.2 METHODS

6.2.1 Patient Selection

The study consisted of a total of 150 patients in 4 groups: (1) 60 patients with paroxysmal AF undergoing radiofrequency ablation (RFA) for drug-refractory AF; (2) 30 patients with persistent AF undergoing RFA for drug-refractory AF; (3) 30 patients with supraventricular tachycardia (SVT) undergoing RFA; and (4) 30 patients with AF awaiting RFA for symptomatic drug-refractory AF (control group). These
patients were studied during the waiting period prior to scheduled ablation. They were of similar age and met the inclusion and exclusion criteria described below.

Consecutive patients presenting for RFA of AF and SVT were approached for inclusion into the study. The protocol was approved by the Melbourne Health Research and Ethics committee, and written informed consent was obtained from all patients. Exclusion criteria included; pre-existing neurologic or clinically evident neurovascular disease; significant pre-morbid depression and/or anxiety; anticipated difficulty with neurocognitive assessment eg deafness, language difficulties; and geographical remoteness.

6.2.2 Ablation Procedures

For paroxysmal AF patients, the ablation strategy consisted of wide encirclement of the PV antra without additional adjunctive ablation (5, 114). The endpoint was demonstration of PV entrance and exit block. Patients with persistent AF had adjunctive ablation at the discretion of the treating electrophysiologist.

In patients receiving anticoagulation therapy prior to PVAI, warfarin was stopped five days before the procedure and low molecular weight heparin was commenced. All anti-arrhythmic agents except amiodarone were discontinued for at least five half-lives before the procedure. Transesophageal echocardiography (TOE) was performed in all patients immediately prior to the procedure to rule out atrial or atrial appendage thrombus. A decapolar catheter was positioned in the coronary sinus and a quadripolar catheter in the His bundle position. Two 8.5F long sheaths (SL1, St. Jude Medical, MN, USA) were introduced into the left atrium with trans-septal puncture performed under fluoroscopic and TOE guidance. A Lasso circular mapping catheter
(Biosense Webster, CA, USA) or a Reflexion spiral catheter (St. Jude Medical, MN, USA) was introduced through the SL1 sheath into the left atrium for electrical mapping of the pulmonary veins. An irrigated ablation catheter (4 mm, D curve, Navistar Thermocool and Thermocool, Biosense Webster, MN, USA) was introduced through the SL1 sheath into the left atrium for ablation (maximum power 30-35W). Sheaths were continuously irrigated at 3mL/min, increasing to 17mL/min during RF delivery. Patients received intravenous heparin to maintain an activated clotting time (ACT) of 300-350 seconds throughout the procedure.

Following ablation warfarin was commenced and enoxaparin was administered in full dose (1mg/kg BD) commencing 6 hours after the procedure. Enoxaparin was continued until a therapeutic INR (2.0-3.0) was attained. Warfarin was administered for at least three months or indefinitely in patients with a CHADS2 score ≥ 2. Anti-arrhythmic therapy was restarted immediately after the procedure and continued for 3 months. No new antiarrhythmic therapy was commenced in the post-operative period and drug therapy remained constant for the duration of the protocol.

Patients with SVT received RFA targeted at the specific underlying arrhythmia.

6.2.3 Anaesthesia

All AF and SVT patients underwent RFA under general anaesthetic. Patients were given induction anaesthesia with a combination of propofol, midazolam and fentanyl. General anaesthetic was maintained throughout the procedure using volatile anaesthetic agents (sevoflurane or desflurane). Routine measures of oxygenation and temperature monitoring were documented. Bispectral Index (BIS®) monitors were used to estimate depth of anaesthesia throughout the procedure. Arterial blood gas
measurements were taken at random intervals throughout the procedure to measure intra-procedural factors such as pH, glucose and lactate that may potentially modify assessments of post-operative cognitive dysfunction.

6.2.4 Post-operative Cognitive Dysfunction (POCD) and Neuropsychologic Testing

Neuropsychologic testing comprised of 8 tests based on The Canadian Study of Health and Aging administered to all patients by a trained interviewer (426). The results are given as the number of correct answers or the time taken to complete the test. Testing was administered at 3 timepoints:

1. Baseline Tests, administered within 7 days prior to the procedure;
2. Post-procedure Tests, administered 24-48 hrs post-procedure; and
3. Late post-procedure Tests, administered 3 months post-procedure.

The individual tests consisted of 8 auditory and written tests, described in Table 1. These tests included:

1. The Consortium to Establish a Registry for Alzheimer’s Disease (CERAD) Auditory Verbal Learning Test
2. Trail Making Task Part A
3. Trail Making Task Part B
4. Digit Symbol Substitution Test
5. Controlled Oral Word Association Test (COWAT)

6. CERAD Semantic Fluency Test

7. Grooved Pegboard Test (Dominant hand)

8. Grooved Pegboard test (Non-Dominant hands)

Absolute test scores were reversed for timed tasks (Trail Making Task Part A and B; Grooved Pegboard Test (Dominant and Non-Dominant hands), so that a decrease in test score reflected cognitive decline for all tests.

In addition to the neuropsychologic tests, patients were also administered the following tests;

1. Mini Mental State Examination (MMSE) to exclude pre-existing cognitive impairment at baseline; and to exclude post-procedural delirium.

2. The National Adult Reading Test (NART) was administered to estimate baseline intelligence quotient (IQ).

3. Visual analog scales were administered to assess the presence of mood disorder and fatigue levels that may affect the diagnosis of POCD. Patients were asked to mark an ungraded line (10 cm in length) anchored by 0 and 100 at each end to estimate their current levels of anxiety; depression; and fatigue.

Test scores were analyzed to identify POCD using the reliable change index (RCI). The RCI rule was calculated following the procedure outlined by Rasmussen et al (445). Briefly, RCIs were determined by subtracting the preoperative score ($X_1$) from the postoperative score ($X_2$), giving $\Delta_x$ for each individual participant for a given task. The mean expected change for the controls, $\Delta_{xc}$, calculated in the same way,
was then subtracted from this, removing any practice effect. This score was then divided by the standard deviation for the change in test results of the control group, \( \text{SD}(\Delta X_c) \), controlling for the expected variability. These scores were then used to create a combined test score (\( \Sigma Z_{\text{combined}} \)) using the sum of \( z \) scores for each test (\( \Sigma Z_{a,b,c,d,\text{etc.}} \)) divided by the standard deviation of this summation in the control group (\( \text{SD}[\Sigma Z_{\text{control}}] \)). POCD was defined in an individual when their RCI score was less than -1.96 on \( \geq 2 \) tests and/or their combined \( z \) score was less than -1.96. This classifies POCD on the basis of a substantial failure on \( \geq 2 \) tests, or a more pervasive subtle decline across the neuropsychological test battery (428, 445).

This evaluation identifies any change in performance over time, compared to baseline performance. As described above, this was considered present with either a severe deterioration in a few tests, or a less severe deterioration in many tests, relative to baseline functioning. The presence or absence of deficits in AF non-procedural patients over time (D2 and D90) was also assessed to verify the performance of the control population.

### 6.2.5 Statistical Analysis

Group comparisons were made using unpaired t tests or one-way analysis of variance (ANOVA) for continuous variables, and chi-squared test for dichotomous variables. Associations were determined using univariable analysis and multivariable logistic regression with a probability value of <0.2 set for entry into the multivariable regression models.
6.3 RESULTS

6.3.1 Baseline Characteristics

The baseline and clinical characteristics of the patients with PAF, PeAF, SVT and the control population are shown in Table 2. The mean age of patients was similar across the 4 groups. There was a higher proportion of males in patients with AF compared to SVT. Other baseline characteristics, including CHADS2 risk factors, were comparable between the groups. Baseline medications are also shown in Table 2. A higher proportion of patients with paroxysmal AF were taking aspirin and a higher proportion of persistent AF patients were taking warfarin prior to the ablation procedure. Use of anti-arrhythmic drugs and angiotensin-converting enzyme inhibitors/angiotensin 2 receptor blockers was higher in patients with PAF. The proportions of patients taking β-Blockers were not significantly different between the 4 groups.

6.3.2 Procedural Characteristics

In patients with paroxysmal AF, successful pulmonary vein isolation was achieved in 59/60 patients (98%), and in 29/30 patients with persistent AF (97%), p=1.0). 10/30 (33%) patients with persistent AF had adjuvant linear ablation, including 2/10 patients who also received adjuvant ablation of complex fractionated electrograms. Of the control patients, AV node reentrant tachycardia (AVNRT) was present in 14 patients; AV reentrant tachycardia (AVRT) in 7 patients; atrial tachycardia (ATc) in 5 patients; and multiple tachycardia mechanisms were present in 4 patients (2 patients with AVNRT and ATc; 1 patient with AVRT and ATc, and 1 patient with multiple AVRT pathways).
A comparison of procedural parameters is shown in Table 3. There was no difference between patients with PAF, PeAF and SVT when comparing depth of anaesthesia (as measured by BIS score); mean systolic blood pressure; and intraprocedural pH and glucose levels. The peri-procedural ACT was significantly greater in patients undergoing AF ablation, but not between patients with paroxysmal and persistent atrial fibrillation. Compared to SVT patients with left-sided tachycardia, patients with paroxysmal and persistent AF had significantly longer left atrial access time, longer RF time and fluoroscopy times. There was no significant difference between these parameters in patients with paroxysmal compared to persistent AF (p=0.5, p=0.3 p=0.2, for LA time, RF time and fluoroscopy time respectively). Patients with persistent AF received a significantly higher mean number of cardioversions during the procedure than patients with PAF or SVT (1.4±1.2 vs. 0.3±0.8 vs. 0±0, p<0.0001).

No patient developed a stroke, TIA, or other clinical embolic phenomenon post-procedure.

6.3.3 Clinical Outcomes

Baseline Demographics and Patient Characteristics

The results of scores in anxiety, depression and fatigue are presented in Figures 1-3. There were no differences in anxiety levels between the 4 groups at the 3 timepoints assessed. In the assessment of depression, patients with persistent AF demonstrated an increased score at the D2 testing timepoint only. Patients with persistent AF rated their levels of fatigue higher than the other 3 study populations at baseline and day 90. Estimated intelligence quotient as measured by the National Adult Reading Test was
6.3.4 Neuropsychologic Test Outcomes

Immediate (D2 Post-operative) Neuropsychologic Test Results

Testing was performed between 24-48 hours after RFA in patients with AF and SVT undergoing RFA (mean testing time 36 ± 10hrs) and at 24-48 hours after baseline testing in the AF control population (39 ± 18hrs). The incidence of POCD was 13% (4/30) in patients with SVT; 28% (17/60) in patients with PAF; and 27% (8/30) in patients with PeAF (p=0.04). No AF control patient deteriorated at this time compared with baseline to qualify for classification of POCD.

Long-Term (D90 Post-operative) Neuropsychologic Test Results

At 3 months, no control (non-procedural) AF patient had developed an abnormality in neuropsychologic testing compared with baseline testing. The incidence of POCD in patients with SVT was 3% (1/30), in patients with PAF 13% (8/60), and patients with PeAF 20% (6/30); p=0.007). When analyzing the 3 procedural groups together, 29/150 (19%) patients manifest POCD at day 2 and 15/120 (10%) at day 90 post ablation procedure; p=0.029.

When comparing POCD outcomes for impairment (z scores <-1.96 below controls for that test) on individual tests, the highest frequencies were seen in the Trail Making Test B, the CERAD AVLT Word Learning Test, and the Controlled Oral Word Learning Test (COWAT) (Table 4). Impairment was detected across the entire range.
of tests in patients with PAF and PeAF reflecting a generalized deficit in multiple
tests in these patients. Abnormalities in patients with SVT were seen in only 3 of 8
tests. One patient with SVT had evidence of neurocognitive decline at D90 compared
with baseline. This was a 67 year old male with hypertension and diabetes who
underwent ablation of a left anterolateral pathway. During the procedure, left atrial
access time was 56 mins, with 1.5 minutes of radiofrequency ablation time. Of the 30
AF control patients, an abnormality in 1 test was seen in 2 patients only (Table 4).

Factors associated with POCD

The patient data at D2 and D90 was analysed by univariate analysis to identify
associations between the development of POCD and other variables (Tables 5-6). All
baseline clinical and cardiovascular risk factors were included in the univariate
analysis. At D2, every minute increase in LA access time was associated with POCD
on univariate analysis (p=0.02). At D90, increasing left atrial access time remained
significantly associated (Table 6). Persistent AF and male gender were associated
with a higher odds ratio of POCD at D90, with borderline statistical significance.

6.4 DISCUSSION

The major findings of this study are as follows:

1. POCD occurs with a frequency of 13-20% at 90 days following AF ablation
   with both paroxysmal and persistent AF

2. An increased left atrial access time is the most powerful predictor of POCD at
   the early (D2) and long-term (D90) assessments
3. Impairment in cognitive performance at long-term follow up is seen with an increased prevalence in persistent vs. paroxysmal AF patients

4. POCD at late follow up is rarely observed in patients with SVT undergoing RFA.

**Cerebral Complications of Atrial Fibrillation Ablation**

The combined risk of stroke/transient ischaemic attack with current procedural and anticoagulation practices in AF ablation has been reported at approximately 1% in a large survey (287). However, it is increasingly recognized that silent cerebral embolic events may occur more frequently than overt stroke. MRI studies have shown an incidence of approximately 10-15% of new apparently asymptomatic cerebral lesions post ablation (335, 444). In the series by Gaita et al, periprocedural symptomatic stroke occurred with a frequency of 0.4%. However, postprocedural cerebral MRI was positive for new embolic lesions in 14% patients who underwent irrigated RF ablation. These emboli were heterogeneous in size, including some very large defects, ranging from 3-35mm (335). Whether these emboli are truly silent is unclear and is likely to be determined by their size and number, and also the anatomic region. Emboli to the motor cortex are more likely to produce detectable clinical symptoms than emboli affecting areas responsible for cognition (446). The sequelae of silent cerebral infarction (SCI) may include subtle neurocognitive impairment, and an increased lifetime risk of cognitive impairment and dementia.
Aetiology of POCD

The aetiology of POCD is likely to be multifactorial. The surgical procedure, the anaesthetic and patient susceptibility, are all likely to influence the vulnerability to POCD (428). In the current study, we compared post-procedural cognitive function at day 2 and day 90 with cognitive function immediately prior to the ablation. We observed an overall incidence of POCD at D2 of 19% and at D90 of 10%. The higher early incidence may in part reflect the reversible impact of anaesthesia (447) on cognitive function. In patients undergoing cardiac surgery, this effect is most pronounced at hospital discharge, and has been reported to improve by the time of late testing after 6 weeks (355). Late improvement may also be related to time dependent improvement in cognition after an initial event.

Late post-procedural cognitive impairment (D90) is more likely to directly reflect any intra-procedural cerebral insult, including subclinical cerebral ischaemia (360). In a randomized study of 100 patients undergoing cardiac surgery, Pugsley et al found patients randomized to an arterial line filter had a significantly lower number of cerebral microembolic events, and were significantly less likely to have POCD at 8 week follow up (360).

Neurocognitive dysfunction after coronary artery bypass grafting is thought to be due predominantly to cerebral microembolism (446), primarily originating from disruption of aortic atherosclerotic lesions (448, 449), as well as recirculated lipid matter from the pericardial aspirate (450), and air entering the bypass circuit (429). Damage to small cerebral vessels from lipogenous material has been found at autopsy in patients after bypass surgery (429). In addition, cerebral injury is thought to be exacerbated by the systemic inflammatory response and mediator release activated by cardiopulmonary bypass, and ischaemia/reperfusion injury (451, 452).
We observed no instances of time-dependent (over 3 months) cognitive decline in a non-procedural AF population. In contrast, the AF procedural groups had a significantly higher incidence of late POCD (D90), the strongest association being with LA access time. Prolonged access to the systemic circulation with the potential for microembolism, may play an important role in development of POCD. In a study of post-AF ablation MRI lesions, Gaita et al found that cardioversion and procedural ACT <250, were the only factors associated with the development of new lesions on imaging (335). Interestingly, in an analysis of patients with persistent AF undergoing cardioversion alone, no silent embolic lesions were detected (335). This raises the suggestion that the prothrombotic milieu induced by catheter ablation is an important factor in the thromboembolic risk associated with cardioversion. In our population with a target ACT of 300-350 there was no association between either ACT or incidence of cardioversion and the risk of POCD.

Interestingly, in our relatively low risk population, we found that POCD occurs independently of conventional cardiovascular risk factors. Different results may have been obtained if predominantly higher risk patients with CHADS2 score of ≥ 2 had been studied. Nevertheless, similar results were reported by Evered et al in an analysis of POCD in patients undergoing cardiac and orthopaedic surgery (428). The reasons behind this remain speculative, but other factors not routinely screened for may play a role. Cerebral haemodynamics, platelet function (453) and systemic inflammation (454) have been shown to be abnormal in patients with AF, and variability in these parameters may affect cognitive reserve and susceptibility to POCD (428).

Intraprocedureal hypotension may directly cause cerebral injury, or may also exacerbate cerebral injury due to microembolism (446). However, haemodynamic effects are unlikely to have played a major role in POCD in our population, as the
majority of patients had normal left ventricular function and were normotensive throughout the procedure.

We observed only 1 patient in the SVT group with evidence of late cognitive dysfunction. This patient was a 67 year old male who underwent transeptal puncture for a left anterolateral pathway ablation. One can speculate that a combination of procedural (left atrial access) and patient related factors (age, diabetes and hypertension) contributed to the development of cognitive dysfunction post procedure in this individual. This patient was borderline abnormal in only 2 of 8 tests.

Prior Studies of Cognitive Dysfunction Following Cardiac Procedures

Post-operative cognitive dysfunction (POCD) has been most extensively studied in patients following coronary artery bypass grafting. POCD has been documented in approximately 53% patients at hospital discharge, 36% at 6 weeks post-operatively, and in 24% 6 months post-operatively (355). Although there is attenuation in the incidence of POCD in the short-intermediate period after cardiac surgery, POCD at hospital discharge was significantly associated with both the severity and incidence of cognitive decline at 5 years (355).

In a prior small series, Schwarz et al compared the results of neurocognitive testing of 23 patients with AF undergoing ablation with either RFA or cryoablation, to healthy community-based volunteers (361). By comparison, the patients with AF as a group declined in scores of verbal memory post ablation. Overall 56.5% of ablation patients deteriorated from baseline in the verbal memory tests, which comprised 1 of 5 cognitive domains tested, compared to 17% of controls.
Clinical Implications

The study demonstrates that AF ablation may be associated with subtle neurocognitive impairment that persists at 3 months following the procedure. The strongest predictor of POCD was LA access time. Further studies are required to determine whether these subtle abnormalities will be associated with an increased lifetime risk of cognitive impairment and dementia. Alternately, cure of AF may in itself be protective in the longer term. The long-term cognitive implications will be an important determinant of procedural safety. Furthermore, strategies which reduce the LA access time, optimize anticoagulation approach and address timing of DC reversion may have an impact on the prevalence of POCD.

6.5 STUDY LIMITATIONS

Recently many departments have adopted an approach of performing AF ablation with a therapeutic INR. This may potentially reduce the prevalence of POCD.

All procedures were performed under general anaesthesia and these results may not necessarily be applicable to patients who undergo the procedure under conscious sedation. Nevertheless, POCD persisted well beyond the time when the effects of anaesthesia may continue to effect cognitive function.

6.6 CONCLUSIONS

Ablation for AF is associated with a 13-20% incidence of POCD in patients with AF at long-term follow up. These results were seen in a population of predominantly
CHADS$^2$ 0-1 patients who represent the majority of patients undergoing AF ablation. The long-term implications of these subtle changes require further study and may ultimately be an important determinant of procedural safety.
**Table 1: Description of Neuropsychologic Tests**

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Cognitive Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERAD Auditory Verbal Learning Test- Immediate</td>
<td>Patients are read a list of 10 words, and are asked to recall as many words as possible. The maximum number of correct words recalled is documented. This is repeated a further 2 times, however the word order is changed each time. The results of each individual trial are taken as the scores for this test.</td>
<td>Memory</td>
</tr>
<tr>
<td>CERAD Auditory Verbal Learning Test- Delayed</td>
<td>After a 15-minute delay after completion of the CERAD AVLT- Immediate test, patients are asked to recall as many of the 10 words as possible without further prompting or re-reading of the list. The maximum number of correct words remembered is taken as the score.</td>
<td>Memory</td>
</tr>
<tr>
<td>Trail Making Task Part A</td>
<td>Consists of 25 circles distributed over a sheet of paper numbered 1 – 25. The patient is instructed to draw lines to connect the numbers in ascending order as quickly as possible. The time taken to complete the task is taken as the score.</td>
<td>Executive Functioning</td>
</tr>
<tr>
<td>Trail Making Task Part B</td>
<td>Consist of 25 circles distributed over a sheet of paper, the circles include both numbers (1 – 13) and letters (A – L). The patient is instructed to draw lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The time taken to complete the task is taken as the score.</td>
<td>Executive Functioning</td>
</tr>
<tr>
<td>Digit-Symbol Substitution Test</td>
<td>Requires patients to reproduce on paper, within 90 sec, as many coded symbols as possible within blank boxes beneath randomly generated digits, according to a coding scheme for pairing digits with symbols. The number of correct symbols reproduced in 90 sec is taken as</td>
<td>Memory and Processing Function</td>
</tr>
<tr>
<td>Test Description</td>
<td>Instructions</td>
<td>Test Purpose</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>CERAD Semantic Fluency Test</strong></td>
<td>Patients are instructed to generate a list of as many words as possible from a predefined category (animals) within 60 seconds. The number of correct answers is taken.</td>
<td>Verbal fluency test of semantic memory, measuring temporal and frontal lobe function</td>
</tr>
<tr>
<td><strong>Grooved Pegboard Test (Dominant hand)</strong></td>
<td>Requires patients to insert 25 keyed pegs into a specially designed pegboard with randomly positioned slots. Pegs must be rotated to match the hole before they can be inserted. The duration taken to complete the task in seconds is taken.</td>
<td>Requires complex visual-motor coordination and evaluates lateralized injury</td>
</tr>
<tr>
<td><strong>Grooved Pegboard test (Non-Dominant hands)</strong></td>
<td>Requires patients to insert 25 keyed pegs into a specially designed pegboard with randomly positioned slots. Pegs must be rotated to match the hole before they can be inserted. The duration taken to complete the task in seconds is taken.</td>
<td>Requires complex visual-motor coordination and evaluates lateralized injury</td>
</tr>
</tbody>
</table>

CERAD: The Consortium to Establish a Registry for Alzheimer’s Disease
Table 2: Baseline and Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PAF</th>
<th>PeAF</th>
<th>SVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>57 ± 9</td>
<td>53 ± 10</td>
<td>56 ± 11</td>
</tr>
<tr>
<td>Males (n, %)</td>
<td>45 (75%)</td>
<td>28 (93%)</td>
<td>13 (43%)</td>
</tr>
<tr>
<td>Symptom Duration (mth)</td>
<td>84 ± 72</td>
<td>81 ± 75</td>
<td>92 ± 180</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59 ± 8</td>
<td>55 ± 8</td>
<td>59 ± 5</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>31 (52%)</td>
<td>10 (33%)</td>
<td>9 (27%)</td>
</tr>
<tr>
<td>DM</td>
<td>5 (8%)</td>
<td>1 (3%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>CAD</td>
<td>6 (10%)</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Previous TIA</td>
<td>2 (3%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>13 (22%)</td>
<td>8 (27%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>Smoker/Ex-smoker</td>
<td>13 (22%)</td>
<td>4 (13%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>CHADS2</td>
<td>0.75 ± 0.8</td>
<td>0.70 ± 0.9</td>
<td>0.67 ± 0.7</td>
</tr>
<tr>
<td>ACEI/A2RB</td>
<td>22 (37%)</td>
<td>6 (20%)</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>CCB</td>
<td>13 (22%)</td>
<td>6 (20%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>β- Blocker</td>
<td>10 (17%)</td>
<td>8 (27%)</td>
<td>8 (27%)</td>
</tr>
<tr>
<td>AAD (including sotalol)</td>
<td>43 (72%)</td>
<td>13 (43%)</td>
<td>12 (40%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>22 (37%)</td>
<td>22 (73%)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>32 (53%)</td>
<td>5 (17%)</td>
<td>5 (17%)</td>
</tr>
</tbody>
</table>

AAD: anti-arrhythmic drug; ACEI: angiotensin-converting enzyme inhibitor; A2RB: angiotensin 2 receptor blocker; BMI: body mass index; CAD: coronary artery disease; CCB: calcium channel blocker; CHADS2: congestive heart failure/hypertension/age>75y/diabetes mellitus/stroke 2 points; DM: diabetes mellitus; TIA: transient ischaemic attack; LVEF: left ventricular ejection fraction; PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; SVT: supraventricular tachycardia
Table 3: Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Paroxysmal AF</th>
<th>Persistent AF</th>
<th>SVT</th>
<th>P (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left Atrial Access Time</strong></td>
<td>159±35</td>
<td>166±42</td>
<td>92±45*</td>
<td>0.0007</td>
</tr>
<tr>
<td><strong>RF Duration (min)</strong></td>
<td>50±19</td>
<td>47±20</td>
<td>9±10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Fluoroscopy Time</strong></td>
<td>41±10</td>
<td>44±13</td>
<td>20±13</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>ACT (mean)</strong></td>
<td>312 ± 31</td>
<td>311 ± 20</td>
<td>170 ± 32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>BIS® Score</strong></td>
<td>42 ± 6</td>
<td>38 ± 8</td>
<td>43 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td><strong>SBP (mean)</strong></td>
<td>110 ± 8</td>
<td>111 ± 7</td>
<td>115 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>7.4 ± 0.1</td>
<td>7.3 ± 0.1</td>
<td>7.4 ± 0.1</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td>6.2 ± 1.0</td>
<td>6.4 ± 0.9</td>
<td>6.7 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td><strong>DCR (n)</strong></td>
<td>0.3±0.8</td>
<td>1.4±1.2</td>
<td>0±0,</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

ACT: activated clotting time; AF: atrial fibrillation; BIS: BiSpectral Index; DBP: diastolic blood pressure; DCR: direct current cardioversion; RF: radiofrequency; SBP: systolic blood pressure; SVT: supraventricular tachycardia

* In patients who required LA access as part of the clinically indicated ablation procedure
<table>
<thead>
<tr>
<th></th>
<th>PAF</th>
<th>PeAF</th>
<th>SVT</th>
<th>Controls</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CERAD-AVLT n (%)</td>
<td>6 (10%)</td>
<td>3 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.09</td>
</tr>
<tr>
<td>TMTA n (%)</td>
<td>4 (7%)</td>
<td>3 (10%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>0.3</td>
</tr>
<tr>
<td>TMTB n (%)</td>
<td>2 (3%)</td>
<td>5 (17%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>0.02</td>
</tr>
<tr>
<td>DSST n (%)</td>
<td>3 (5%)</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0.6</td>
</tr>
<tr>
<td>COWAT n (%)</td>
<td>7 (12%)</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0.2</td>
</tr>
<tr>
<td>CERAD fluency n (%)</td>
<td>1 (2%)</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>0.4</td>
</tr>
<tr>
<td>GPD n (%)</td>
<td>3 (5%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.4</td>
</tr>
<tr>
<td>GPND n (%)</td>
<td>2 (3%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0.6</td>
</tr>
</tbody>
</table>

AVLT: Auditory Verbal Learning Test; CERAD: Consortium to Establish a Registry for Alzheimer’s Disease; COWAT: Controlled Oral Word Association Test; DSST: Digit-Symbol Substitution Test; GPD: Grooved Pegboard Test, Dominant; GPND: Grooved Pegboard Test, Nondominant; PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; SVT: supraventricular tachycardia; TMTA: Trail-making Test Part A; TMTB: Trail-making Test Part B.
Table 5: Univariate Analyses at D2 Assessment

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA Access Time (every min increase)</td>
<td>1.008</td>
<td>1.001-1.014</td>
<td>0.02</td>
</tr>
<tr>
<td>Age (every 1 yr increase)</td>
<td>1.0</td>
<td>0.94-1.03</td>
<td>0.4</td>
</tr>
<tr>
<td>Male Gender</td>
<td>1.0</td>
<td>0.39-2.56</td>
<td>1.0</td>
</tr>
<tr>
<td>AF vs. SVT</td>
<td>0.4</td>
<td>0.13-1.26</td>
<td>0.1</td>
</tr>
<tr>
<td>Cardioversion</td>
<td>0.9</td>
<td>0.67-1.31</td>
<td>0.7</td>
</tr>
<tr>
<td>RFA in AF</td>
<td>1.0</td>
<td>0.39-2.37</td>
<td>0.9</td>
</tr>
<tr>
<td>Increase in symptom duration</td>
<td>1.0</td>
<td>0.99-1.01</td>
<td>0.8</td>
</tr>
<tr>
<td>IQ</td>
<td>0.9</td>
<td>0.95-1.02</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.6</td>
<td>0.25-1.46</td>
<td>0.3</td>
</tr>
<tr>
<td>CAD</td>
<td>0.4</td>
<td>0.05-3.64</td>
<td>0.4</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.5</td>
<td>0.06-4.39</td>
<td>0.5</td>
</tr>
<tr>
<td>OSA</td>
<td>1.9</td>
<td>0.58-6.20</td>
<td>0.3</td>
</tr>
<tr>
<td>CHADS2</td>
<td>1.0</td>
<td>0.58-1.75</td>
<td>1.0</td>
</tr>
<tr>
<td>ACEI/A2RB</td>
<td>1.5</td>
<td>0.56-3.83</td>
<td>0.4</td>
</tr>
<tr>
<td>Statin</td>
<td>2.8</td>
<td>0.76-10.02</td>
<td>0.1</td>
</tr>
<tr>
<td>B Blocker</td>
<td>0.50</td>
<td>0.20-1.26</td>
<td>0.1</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.210</td>
<td>0.085-.0519</td>
<td>0.001</td>
</tr>
<tr>
<td>ACT level</td>
<td>1.003</td>
<td>0.99-1.01</td>
<td>0.3</td>
</tr>
<tr>
<td>RFA Time</td>
<td>1.009</td>
<td>0.991-1.027</td>
<td>0.333</td>
</tr>
</tbody>
</table>

ACEI: angiotensin-converting enzyme inhibitor; ACT: activated clotting time; AF: atrial fibrillation; A2RB: angiotensin 2 receptor blocker; CAD: coronary artery disease; CHADS2: congestive heart failure/hypertension/age>75y/diabetes mellitus/stroke 2 points; IQ: intelligence quotient; LA: left atrial; OSA: obstructive sleep apnoea; RFA: radiofrequency ablation; SVT: supraventricular tachycardia
<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA Access Time (every min increase)</td>
<td>1.0</td>
<td>1.00-1.02</td>
<td>0.03</td>
</tr>
<tr>
<td>Age (every 1 yr increase)</td>
<td>1.0</td>
<td>0.96-1.09</td>
<td>0.5</td>
</tr>
<tr>
<td>Male Gender</td>
<td>6.1</td>
<td>0.77-48.67</td>
<td>0.09</td>
</tr>
<tr>
<td>AF vs. SVT</td>
<td>5.3</td>
<td>0.67-42.48</td>
<td>0.1</td>
</tr>
<tr>
<td>PAF vs. SVT</td>
<td>4.5</td>
<td>0.53-37.47</td>
<td>0.17</td>
</tr>
<tr>
<td>PeAF vs. SVT</td>
<td>7.25</td>
<td>0.82-64.46</td>
<td>0.07</td>
</tr>
<tr>
<td>Cardioversion</td>
<td>1.0</td>
<td>0.71-1.51</td>
<td>0.8</td>
</tr>
<tr>
<td>RFA in AF</td>
<td>2.1</td>
<td>0.70-6.26</td>
<td>0.2</td>
</tr>
<tr>
<td>Increase in symptom duration</td>
<td>1.0</td>
<td>0.99-1.01</td>
<td>1.0</td>
</tr>
<tr>
<td>Intelligence Quotient</td>
<td>1.0</td>
<td>0.96-1.07</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.5</td>
<td>0.18-1.60</td>
<td>0.3</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.2</td>
<td>0.03-0.79</td>
<td>0.03</td>
</tr>
<tr>
<td>Obstructive sleep apnoea</td>
<td>0.3</td>
<td>0.08-1.08</td>
<td>0.07</td>
</tr>
<tr>
<td>CHADS2</td>
<td>1.6</td>
<td>0.82-2.99</td>
<td>0.18</td>
</tr>
<tr>
<td>ACEI/A2RB</td>
<td>0.6</td>
<td>0.19-1.83</td>
<td>0.4</td>
</tr>
<tr>
<td>Statin</td>
<td>1.1</td>
<td>0.28-4.10</td>
<td>0.9</td>
</tr>
<tr>
<td>B Blocker</td>
<td>0.6</td>
<td>0.19-1.90</td>
<td>0.4</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0.6</td>
<td>0.19-1.66</td>
<td>0.3</td>
</tr>
<tr>
<td>Activated Clotting Time (ACT) level</td>
<td>1.0</td>
<td>1.00-1.02</td>
<td>0.1</td>
</tr>
<tr>
<td>RFA Time</td>
<td>1.0</td>
<td>0.99-1.04</td>
<td>0.2</td>
</tr>
</tbody>
</table>

ACEI: angiotensin-converting enzyme inhibitor; AF: atrial fibrillation; A2RB: angiotensin 2 receptor blocker; CAD: coronary artery disease; CHADS2: congestive heart failure/hypertension/age>75y/diabetes mellitus/stroke 2 points; LA: left atrial; PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; RFA: radiofrequency ablation; SVT: supraventricular tachycardia
Visual Analog Scale: Anxiety

**Figure 1:** Visual Analog Scale (VAS) scores for anxiety at baseline, day 2 and day 90 tests. There was no difference in reported anxiety levels between the patient groups.

PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; SVT: supraventricular tachycardia
Figure 2: Visual Analog Scale (VAS) scores for depression at baseline, day 2 and day 90 tests. Patients with persistent AF reported higher levels of depression at day 2 only. There was no other difference in reported levels of depression between the patient groups.

PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; SVT: supraventricular tachycardia
**Figure 3:** Visual Analog Scale (VAS) scores for fatigue at baseline, day 2 and day 90 tests. Patients with persistent AF reported higher levels of fatigue at all timepoints relative other groups.

PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; SVT: supraventricular tachycardia
CHAPTER 7

Multifrequency Transcranial Doppler Measurement of Microembolic Signals during Pulmonary Vein Isolation: A Characterization of Solid and Gaseous Emboli
INTRODUCTION

Pulmonary vein isolation (PVI) has resulted in cure or significant symptom palliation in many patients with drug-refractory paroxysmal and persistent atrial fibrillation (4, 5, 114, 455-457). Although the risk of major complications in experienced centers is low, there is still concern regarding the prevalence and significance of microemboli. Prolonged placement of left atrial sheaths and catheters, and extensive atrial endocardial ablation creates a potentially prothrombotic environment. With contemporary ablation techniques and anticoagulation management, large worldwide surveys have reported the incidence of stroke or transient ischaemic attack at 0.9-1% after PVI (287). However, recent magnetic resonance imaging (MRI) studies have reported a higher incidence (7-15% using irrigated ablation catheters) of apparently silent cerebral lesions (335, 336, 444).

Prior studies using transcranial Doppler monitoring of the cerebral circulation have identified large numbers of microembolic signals (MES) in the majority of patients undergoing PVI, primarily during delivery of ablation (343-345). These signals were not associated with overt clinical events. However, those studies were unable to discriminate between gaseous and solid emboli. In the present study we prospectively evaluated the prevalence of micro-embolic signals measured using trans-cranial Doppler in patients undergoing ablation of paroxysmal or persistent AF. We used a new software algorithm capable of discriminating between solid and gaseous emboli.
METHODS

Study Population

The study included 55 consecutive consenting patients with symptomatic drug-refractory atrial fibrillation scheduled for elective radiofrequency ablation. Patients with a prior AF ablation were excluded. A total of 37 patients with paroxysmal AF and 18 patients with persistent AF were included. Paroxysmal AF was defined as self-terminating AF episodes of brief duration (< 7 days). AF was defined as persistent when episodes were >7 days and did not spontaneously terminate (419). Patients were excluded if left atrial or left atrial appendage thrombus was detected on pre-procedure transoesophageal echocardiogram. Patients were assessed for any neurologic deficits after recovery from anaesthesia and at day 1 post procedure by a specialist physician. All patients provided written informed consent, and the study protocol was approved by the Melbourne Health Research and Ethics Committees.

Ablation Strategy and Procedure Endpoints

The ablation strategy consisted of wide encirclement of the PV antra without additional adjunctive left atrial ablation in patients with PAF. Patients with PeAF received additional substrate ablation at the discretion of the treating electrophysiologist. Ipsilateral pairs of the PV antra were widely encircled, and, depending on the individual anatomy, each PV isolated individually. The endpoint was demonstration of PV entrance block (evidenced by elimination or dissociation of all high-frequency PV potentials within the encircled area) and PV exit block (evidenced by capture of PV potentials during pacing within the PV with dissociation.
from the atrium) (5, 114). All antiarrhythmic agents except amiodarone were discontinued for at least 5 half-lives before the procedure. The ablation procedure was conducted under general anaesthesia. Transoesophageal echocardiography (TOE) was performed in all patients immediately prior to the procedure to rule out atrial or atrial appendage thrombus.

Two 8.5 F long sheaths (SL1, St. Jude Medical, St. Paul, MN, USA) were introduced into the left atrium with transeptal puncture performed under fluoroscopic and TOE guidance. A Lasso circular mapping catheter (Biosense Webster, Diamond Bar, CA, USA) or a Reflexion spiral catheter (St. Jude Medical) was introduced through the SL1 sheath into the left atrium for electrical mapping of the pulmonary veins. An irrigated ablation catheter (4 mm, D curve, Navistar Thermocool and Thermocool, Biosense Webster) was introduced through the SL1 sheath into the left atrium for ablation (maximum power 30–35 W). The sheaths were continuously irrigated at 3mL/min at baseline, increasing to 17mL/min during power delivery. Left atrial geometry was created using a 3-dimensional electroanatomic mapping system (CARTO-XP, Biosense-Webster or NavX, St. Jude Medical).

**Procedural Anticoagulation**

In patients receiving anticoagulation therapy prior to PVAI, warfarin was stopped 5 days before the procedure and low molecular weight heparin was commenced. Patients received a 5000u heparin bolus upon completion of the first transeptal puncture, and were administered intravenous heparin after completion of the second transeptal puncture to maintain a target activated clotting time (ACT) of 300-350 seconds.
**Transcranial Doppler Monitoring**

Transcranial Doppler (TCD) monitoring was performed by insonation of the right middle cerebral artery via the temporal window, utilizing the Compumedics™ DWL Doppler Box®. The probe was placed over the temporal bone and stabilized using a specially designed probe holder (Lam rack). This device inserts into the ears and has an anchoring point over the nose, enabling the probe to be fixed and for adjustment of the probe's position and angle. A segment of the right proximal middle cerebral artery (MCA) was insonated for the duration of left atrial access time. The insonation depth for spectrogram recording was between 45 to 65 mm. (At this location, the MCA is approximately 50mm from the temporal window where the probe sits as the temporal bone may be up to 5mm thick). A multifrequency transcranial Doppler (EmboDop, DWL) was used that simultaneously insonates at 2.0 and 2.5- MHz frequencies. The detection and discrimination of Doppler signals using this system have previously been described in detail (352, 458). In brief, emboli are differentiated from artifacts on the basis of 4 parameters in a binary decision tree; quarter Doppler shift, maximum duration limits, reference gate, and bidirectional enhancement (458). Differentiation of solid and gaseous microemboli is based on the difference between the embolus-to-blood ratio (EBR) at 2.5-MHz insonation frequency and the EBR at 2.0-MHz insonation (dEBR). Solid microemboli exhibit a relatively constant dEBR between 2 and 2.5-MHz compared to gaseous emboli. The dEBR limit for detection of solid is set between -0.83 and 2.05 dB, based on in vitro studies (338), and where embolic signals fall outside of this range they are classified as gaseous emboli.

All discrimination of emboli composition was performed using the automatic discrimination software of the multifrequency Doppler. No reliable conclusion as to the composition and the size of an embolus can be drawn from the appearance of the
embolus’ signal (459). Solid emboli of different composition (ie platelet vs. atheroma) give rise to MES of varying intensity; and the size of MES that results in detectable MES is dependent on the material (459). Therefore no attempt was made to classify emboli composition based on visual appearance.

A trained operator was present during the duration of the procedure to document the phases of the ablation procedure for offline-correlation with events. Data was recorded continuously and stored digitally on the computer hard disk, and archived for off-line analysis. Offline analysis was preformed to confirm that automatically detected high intensity signals conformed to the definition of a microembolus based on the International Consensus on Microembolus Detection Criteria (460, 461). These criteria include: 1. The signal was of short duration (<300 millisecond); 2. The signal was unidirectional; and 3. There was an increase in intensity at least 3 dB above the background blood flow signal.

Transcranial Doppler monitoring was continuous from 10 minutes period prior to transeptal puncture, until completion of the procedure and withdrawal of catheters from the left atrium. The duration of monitoring was divided into 4 periods for analysis: 1. Baseline; consisting of intracardiac catheter placement prior to transeptal puncture; 2. Left atrial access time; including transeptal puncture, flushing of sheaths and introduction of catheters, 3. Left atrial mapping; creation of left atrial geometry by 3-D mapping systems; 4. Ablation; the time from the commencement of isolation of pulmonary veins to the completion of the procedure, including adjunctive substrate ablation where performed.

Microembolic signals are reported as number of events during the entire procedure, and in the 4 pre-specified timepoints described above. Microembolic patterns were classified into 3 groups: Type 1; Isolated MES that were not continuous; Type 2;
Moderate MES that were continuous but not dense in appearance; and Type 3; Shower of MES that were continuous and dense in appearance (343, 350).

Statistical Analysis

All continuous variables are expressed as mean ± SD and categorical variables as number of subjects (%). Comparisons of continuous variables were made using analysis of variance and Student’s t-test as appropriate. Categorical variables were compared using Fisher’s exact test. P value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 55 patients were included in the study; 37 patients with PAF and 18 patients with PeAF. The baseline and clinical characteristics are presented in table 1. There were no differences in any of the baseline clinical parameters between patients with PAF and PeAF.

Procedural Characteristics

Successful isolation of the pulmonary veins was achieved in all patients. A total of 6/18 patients with persistent AF had adjunctive left atrial ablation. This included 5 patients with linear ablation of the left atrial roof connecting the left and right superior pulmonary veins; and 1 patient who underwent roofline ablation and ablation of
complex fractionated electrograms within the left atrium. Patients with persistent AF had longer LA access time, RF ablation times and fluoroscopy time compared to patients with PAF, however the differences were modest and did not reach statistical significance (Table 2). A significantly higher proportion of patients with PeAF was in AF during ablation, and had a significantly higher number of cardioversions during the procedure. There was no difference between the level of anticoagulation achieved during the procedure between the 2 groups.

**Cerebral Microembolic Events**

Microemboli were detected in all patients who underwent PVAI. The mean number of total microemboli detected in all patients was 368 ± 338. Figure 1 shows the proportion of embolic signals occurring during the sequential periods of the procedure. The majority of MES (71% total, mean 238 ± 309) occurred during the RF ablation period, and during the period following transeptal puncture and establishment of left atrial access (24% total, mean 125 ± 129). Relatively fewer emboli were seen during the period of mapping and creation of 3-D geometry (5% total, mean 28 ± 39), and no emboli were detected during the baseline monitoring period.

The dEBR (difference between the embolus-to-blood ratio between 2.5-MHz insonation frequency and the EBR at 2.0-MHz insonation), calculated by the Doppler system software, was used to classify MES as solid or gaseous in composition. Overall, the majority of cerebral MES were classified as gaseous (89% total MES) compared to solid emboli (11% total MES). This represented a mean of 328 ± 301 gaseous MES/patient and mean of 40 ± 45 solid MES/patient, respectively, p<0.0001.
The relative proportion of solid: gaseous emboli was consistent throughout the components of the procedure, with the proportion of solid MES comprising 13.2%; 10.5%; and 12.0% MES during the transeptal puncture period; mapping period and ablation period respectively (Table 3).

**MES counts in PAF and PeAF**

When comparing patients with PAF and PeAF, there was no difference between the mean number of gaseous or solid microemboli observed between the 2 groups (Gaseous MES: PAF; 327 ± 323 vs. PeAF; 330 ± 265, p=0.9. Solid MES: PAF; 36 ± 36 vs. PeAF; 48 ± 60, p=0.4). There were no significant differences between solid or gaseous MES between patients with PAF and PeAF during any of the pre-specified procedural phases (Table 4).

Type 3 MES showers (continuous and dense MES) were seen following injection of contrast or saline with a representative example shown in Figure 2. Type 2 (continuous but not dense MES) were also observed during RF ablation (Figure 3). Type 1 single gaseous and/or solid emboli (isolated MES) were also observed intermittently throughout the duration of left atrial access (Figures 4-5).

There was a significant increase in both solid and gaseous MES count with increasing RF time. For RF time, Solid MES counts were 20 ± 18; 42 ± 48; 47 ± 31 for ablation times <40 mins; 40-60 mins; and >60 mins, respectively, p=0.055. Gaseous MES counts were 163 ± 108; 378 ± 280; 386 ± 357 for RF times <40 mins; 40-60 mins; >60 mins, respectively, p=0.02.

For LA access time, there was a trend to an increase in solid and gaseous MES counts as LA time increased. Solid MES counts were 33 ± 28; 38 ± 53; and 53 ± 56, with LA
access times <150 mins; 150-200 mins; and >200 mins, respectively, p=0.6. Gaseous MES counts were 285 ± 317; 324 ± 249; and 385 ± 356, with LA access times <150 mins, 150-200 mins, and >200 mins, respectively, p=0.6.

There was no association between increased solid or gaseous MES counts with a range of clinical variables including gender; increasing age; type of AF; cardioversion or rhythm (AF/SR) during the procedure; hypertension; diabetes mellitus; or CHADS₂ score (Table 4).

Procedural Complications

No patient developed a stroke or transient neurologic deficit post-procedure. There were no other major complications including cardiac perforation and tamponade, myocardial infarction, major bleeding or vascular complications.

DISCUSSION

Main Findings

This study presents novel information on the characteristics of cerebral microembolic events seen during pulmonary vein isolation for atrial fibrillation. We found that all patients undergoing PVI demonstrated MES, with the majority of events occurring during RF ablation. Relatively fewer MES counts occurred during transeptal puncture/LA contrast injection, and during LA mapping, respectively. The majority (~90%) of these cerebral MES represented gaseous emboli. However a substantial number of solid embolic events occur during AF ablation. We did not find a difference between total or solid embolic counts between patients with PAF or PeAF
with similar LA access and ablation times. However, persistent AF population in this study was relatively young with a low prevalence of associated structural heart disease. An increase in RF ablation time in both PAF and PeAF patients was associated with a trend towards an increase in both solid and gaseous MES. No patients developed a clinical neurologic complication as a procedural complication.

**Source of Embolization in AF Ablation**

Gaseous emboli may result from microbubbles injected into the left atrium via contrast medium during transeptal puncture or pulmonary venography; within saline flushing of intra-atrial sheaths; as a result of catheter irrigation; or from air inadvertently entrained into the left atrium during catheter and sheath manipulation. Intracardiac echocardiography (ICE) has established that microbubble formation is also a frequent by-product of radiofrequency ablation per se. In an experimental study of porcine atrium, Wood et al describe a step-wise increase in the stream of microbubble formation occurring in parallel with increasing tissue temperatures, relating microbubble formation to excessive thermal injury (349). In a related study, Bruce et al described the relationship between catheter and tissue temperatures and microbubble formation in dogs undergoing irrigated radiofrequency ablation. They demonstrated that intermittent microbubble formation occurs over a wide range of tissue temperatures, and found that continuous microbubble formation occurred at elevated tissue temperature and likely reflects tissue damage and steam formation (350). Natale and coworkers demonstrated that RFA using ICE-guided imaging with power titration according to the presence of microbubbles was associated with a reduction in char and soft thrombus to conventional RF temperature control energy delivery (462). Microbubble formation during ablation may also occur at times of
suboptimal catheter tip-tissue contact (351). In that study embolic showers were the precursor to coagulum formation on the catheter tip, relating poor tissue contact with the formation of thrombus. Kilicaslan et al found that 97% of microbubbles formed during RF and seen on ICE were immediately followed by an appearance of MES on transcranial Doppler, with the number of ICE- detected microbubbles correlating positively with MES volume, linking the two phenomena (343).

**Significance of Cerebral Microemboli**

The clinical significance of MES detected by transcranial ultrasound is not fully understood. There have been conflicting reports on the relationship between intraoperative MES and clinical endpoints such as post-procedural cognitive dysfunction (POCD) (359). A major limitation in the interpretation of these studies has been the variability in the methodology of neuropsychologic testing and also technical differences in the detection of MES by TCD. The detection of cerebral microembolization and the associated sequelae have been explored most extensively after cardiac and carotid surgery, where MES are a common finding. Following cardiac bypass surgery, there is strong evidence that MES are associated with POCD. Elevated numbers of MES have been correlated with neurologic events including transient ischaemia attack, stroke and cognitive decline (360). In a randomized study of 100 patients undergoing cardiac surgery, Pugsley et al found patients randomized to an arterial line filter had a significantly lower number of cerebral MES, and were significantly less likely to have POCD at 8 week follow up (360). However, the relative prevalence of solid and gaseous emboli was not reported in this study.
Animal studies have provided evidence for the harmful effects of solid microemboli. In one study, atheromatous emboli 200-500 µm were introduced into the systemic circulation in rats and resulted in disseminated neuronal cell death (463).

Gas embolism may be catastrophic when large, and gas microembolization may also cause pathologic damage through complex mechanisms. Gas emboli lodging in small cerebral arteries may result in ischaemia by compromising distal perfusion, and through inciting an inflammatory response. The bubble distorts as it travels through the microvasculature, resulting in an increased surface area of the bubble in contact with the endothelium. The surface of the bubble elicits a foreign body inflammatory response resulting in neuronal cell injury and oedema, and provokes arteriolar vasoconstriction (464, 465).

Pathologic studies have identified thousands of cerebral microemboli in patients who died soon after cardiopulmonary bypass (357). The walls of the affected arterioles were stretched and the appearance of suggests the effect of microembolic occlusion with subsequent resolution of the embolus (464). These microvascular lesions represent widespread microembolism to the brain during bypass surgery, and increase in volume in concert with a longer procedure duration. Although solid emboli are assumed to pose a greater risk and to cause more persistent neurologic damage, these pathologic studies suggest that large volumes of gaseous emboli may also induce cerebral pathology. Skjelland et al reported both solid and gaseous microemboli were independently associated with procedure-related ischaemic strokes and new DW-MRI lesions in patients undergoing carotid endarterectomy and stenting (466). The ability of MES to cause microinfarction and potentially neurocognitive sequelae may also relate to other factors such as cerebral flow velocities. Orlandi and coworkers found cerebral MES were correlated with cerebral ischaemic events when there was also
low flow velocity in the middle cerebral artery, suggesting patients with reduced cerebral perfusion are more susceptible to microinfarction through impaired washout of emboli (467, 468)

**Solid Embolism During AF Ablation and Silent Cerebral Ischaemia**

An ongoing concern during AF ablation procedures is the risk of thrombus formation and embolic events. Endocardial disruption of the LA during RF may lead to platelet adhesion and activation (348), the conversion of prothrombin to thrombin, and a triggering of the intrinsic pathway of coagulation. “Soft thrombus” formation consisting of denatured and aggregated proteins may also form and adhere to the catheter tip and dislodge from the surface during catheter and sheath manipulation (469). Such emboli may be the cause of new and apparently silent cerebral lesions identified on diffusion-weighted MRI in up to 15% patients after irrigated AF ablation (334-336, 444). In the series by Gaita et al, periprocedural symptomatic stroke occurred with a frequency of 0.4%, whilst post-procedural cerebral MRI demonstrated new lesions in 14% patients. These emboli were heterogeneous in size, but not associated with overt clinical events in the majority of patients.

**Number of Cerebral MES**

In the present study, we observed a lower median number of MES signals during PVI compared to other groups, where very large numbers even exceeding those seen during coronary artery bypass surgery have been reported (339, 343-345). Sauren et al found a mean of 5 MES during epicardial PVI procedure versus 3908 MES with endocardial ablation (345). For endocardial procedures significantly higher embolic
counts were observed using a conventional radiofrequency catheter (3908 cerebral MES) compared to an irrigated RF tip catheter (1404 MES) or to cryoballoon ablation (935 MES) (344). In the present study, the lower observed MES counts may be related to the low-risk population studied and high target ACT levels (300-350).

STUDY LIMITATIONS

Patients in this study were overall low risk for thromboembolism in AF (predominantly CHADS2 score 0 or 1), and may not be representative of embolic risk in older patients with structurally abnormal hearts.

The significance of apparently solid emboli using this TCD technique remains uncertain. Further studies correlating these signals with MRI findings and detailed neuro-cognitive evaluation are required.

CONCLUSIONS

Cerebral MES are universal in patients undergoing pulmonary vein isolation for AF, and occur principally during ablation. The majority are gaseous but solid microemboli comprise a small but significant proportion and may occur in the absence of overt neurologic complication. Although the clinical significance of these signals requires further study they may represent a potentially useful safety marker during the evaluation of new AF ablation techniques.
<table>
<thead>
<tr>
<th></th>
<th>PAF</th>
<th>PeAF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (y)</strong></td>
<td>56 ± 8</td>
<td>55 ± 11</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Male (%)</strong></td>
<td>30 (81%)</td>
<td>17 (94%)</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Duration of AF (mths)</strong></td>
<td>92 ± 71</td>
<td>81 ± 72</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>LVEF &gt;59% (n,%)</strong></td>
<td>36 (97%)</td>
<td>15 (83%)</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>LA diameter (mm)</strong></td>
<td>4.3 ± 0.3</td>
<td>4.3 ± 0.4</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>Hypertension (%)</strong></td>
<td>15 (41%)</td>
<td>6 (33%)</td>
<td>0.8</td>
</tr>
<tr>
<td><strong>CAD (%)</strong></td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>DM (%)</strong></td>
<td>2 (5%)</td>
<td>2 (11%)</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>BMI (%)</strong></td>
<td>28.7</td>
<td>27.9</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>TIA/Stroke (%)</strong></td>
<td>1 (3%)</td>
<td>2 (11%)</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>CHADS2 (n)</strong></td>
<td>0.7 ± 0.6</td>
<td>0.8 ± 0.7</td>
<td>0.3</td>
</tr>
</tbody>
</table>

BMI: body mass index; CAD: coronary artery disease; CHADS$_2$: congestive heart failure/hypertension/age>75y/diabetes mellitus/stroke 2 points; DM: diabetes mellitus; LA: left atrial; LVEF: left ventricular ejection fraction; PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; TIA: transient ischaemic attack
Table 2: Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PAF</th>
<th>PeAF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA access time (mins)</td>
<td>159 ± 45</td>
<td>175 ± 42</td>
<td>0.2</td>
</tr>
<tr>
<td>Total RF time (mins)</td>
<td>49 ± 18</td>
<td>58 ± 24</td>
<td>0.1</td>
</tr>
<tr>
<td>RF ablation left-sided PV’s (mins)</td>
<td>19 ± 10</td>
<td>23 ± 13</td>
<td>0.3</td>
</tr>
<tr>
<td>RF ablation right-sided PV’s (mins)</td>
<td>22 ± 14</td>
<td>24 ± 12</td>
<td>0.7</td>
</tr>
<tr>
<td>Fluoroscopy time (mins)</td>
<td>40 ± 11</td>
<td>45 ± 17</td>
<td>0.2</td>
</tr>
<tr>
<td>ACT (sec)</td>
<td>313 ± 22</td>
<td>312 ± 21</td>
<td>0.9</td>
</tr>
<tr>
<td>Cardioversions (mean/pt)</td>
<td>0.3 ± 1.1</td>
<td>1.5 ± 2.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Ablation Performed in SR (n)</td>
<td>26 (70%)</td>
<td>4 (22%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

LA access time: defined as the period from first successful transeptal puncture to withdrawal of catheters and sheaths from the LA.

ACT: activated clotting time (sec); LA: left atrial; PAF: paroxysmal atrial fibrillation; PeAF: persistent atrial fibrillation; PV: pulmonary vein; RF: radiofrequency; SR: Sinus Rhythm
Table 3: Total Procedural Emboli Count

<table>
<thead>
<tr>
<th></th>
<th>Solid MES</th>
<th>Gaseous MES</th>
<th>Solid Emboli Ratio, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total procedural count</strong></td>
<td>40 ± 45</td>
<td>328 ± 301</td>
<td>12%</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td><strong>Transeptal Puncture and Pulmonary Vein Injection</strong></td>
<td>15 ± 14</td>
<td>110 ± 117</td>
<td>13.2%</td>
</tr>
<tr>
<td><strong>3-Dimensional Mapping</strong></td>
<td>3 ± 6</td>
<td>25 ± 34</td>
<td>10.5%</td>
</tr>
<tr>
<td><strong>Radiofrequency Ablation</strong></td>
<td>26 ± 39</td>
<td>212 ± 276</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

Data are presented as mean and standard deviation in parentheses

MES: microembolic signal
Table 4: MES Discrimination in PAF and PeAF

<table>
<thead>
<tr>
<th></th>
<th>PAF</th>
<th>PeAF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Combined Solid and Gaseous MES Count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total MES</td>
<td>363 ± 354</td>
<td>377 ± 318</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Solid MES Count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Solid MES</td>
<td>36 ± 36</td>
<td>48 ± 60</td>
<td>0.4</td>
</tr>
<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Transeptal</td>
<td>13 ± 13</td>
<td>17 ± 16</td>
<td>0.4</td>
</tr>
<tr>
<td>Mapping</td>
<td>2 ± 6</td>
<td>3 ± 4</td>
<td>0.8</td>
</tr>
<tr>
<td>RFA</td>
<td>23 ± 27</td>
<td>30 ± 56</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Gaseous MES Count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Gaseous MES</td>
<td>327 ± 323</td>
<td>330 ± 265</td>
<td>0.9</td>
</tr>
<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Transeptal</td>
<td>105 ± 123</td>
<td>119 ± 110</td>
<td>0.7</td>
</tr>
<tr>
<td>Mapping</td>
<td>27 ± 41</td>
<td>22 ± 15</td>
<td>0.7</td>
</tr>
<tr>
<td>RFA</td>
<td>215 ± 286</td>
<td>207 ± 265</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Data are presented as mean and standard deviation in parentheses

MES: microembolic signal; RFA: radiofrequency ablation
Table 5: Analysis of Solid and Gaseous Embolic Counts

<table>
<thead>
<tr>
<th></th>
<th>Solid MES</th>
<th>p (ANOVA)</th>
<th>Gaseous MES</th>
<th>p (ANOVA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>43 ± 48</td>
<td>0.4</td>
<td>355 ± 315</td>
<td>0.1</td>
</tr>
<tr>
<td>No</td>
<td>26 ± 19</td>
<td></td>
<td>176 ± 130</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50y</td>
<td>42 ± 54</td>
<td>0.1</td>
<td>329 ± 272</td>
<td>0.2</td>
</tr>
<tr>
<td>50-60y</td>
<td>28 ± 41</td>
<td></td>
<td>253 ± 272</td>
<td></td>
</tr>
<tr>
<td>&gt;60y</td>
<td>46 ± 30</td>
<td></td>
<td>460 ± 406</td>
<td></td>
</tr>
<tr>
<td><strong>PeAF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>48 ± 60</td>
<td>0.4</td>
<td>330 ± 265</td>
<td>0.9</td>
</tr>
<tr>
<td>No</td>
<td>36 ± 36</td>
<td></td>
<td>327 ± 323</td>
<td></td>
</tr>
<tr>
<td><strong>Cardioversion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>49 ± 65</td>
<td>0.5</td>
<td>337 ± 282</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>36 ± 37</td>
<td></td>
<td>339 ± 345</td>
<td></td>
</tr>
<tr>
<td><strong>Rhythm during RF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>33 ± 40</td>
<td>0.7</td>
<td>274 ± 214</td>
<td>0.5</td>
</tr>
<tr>
<td>SR</td>
<td>39 ± 37</td>
<td></td>
<td>348 ± 346</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>32 ± 28</td>
<td>0.4</td>
<td>344 ± 348</td>
<td>0.9</td>
</tr>
<tr>
<td>No</td>
<td>43 ± 49</td>
<td></td>
<td>332 ± 283</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40 ± 13</td>
<td>0.6</td>
<td>334 ± 188</td>
<td>0.9</td>
</tr>
<tr>
<td>No</td>
<td>37 ± 40</td>
<td></td>
<td>327 ± 314</td>
<td></td>
</tr>
<tr>
<td><strong>CHADS2 score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>51 ± 55</td>
<td></td>
<td>375 ± 318</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>31 ± 29</td>
<td>0.6</td>
<td>343 ± 353</td>
<td>0.9</td>
</tr>
<tr>
<td>2 or more</td>
<td>29 ± 21</td>
<td></td>
<td>234 ± 106</td>
<td></td>
</tr>
<tr>
<td><strong>LA time duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150mins</td>
<td>32 ± 28</td>
<td></td>
<td>285 ± 317</td>
<td></td>
</tr>
<tr>
<td>150-200mins</td>
<td>38 ± 53</td>
<td>0.6</td>
<td>324 ± 249</td>
<td>0.6</td>
</tr>
<tr>
<td>&gt;200mins</td>
<td>53 ± 56</td>
<td></td>
<td>385 ± 356</td>
<td></td>
</tr>
<tr>
<td><strong>RF Time</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40 mins</td>
<td>20 ± 18</td>
<td></td>
<td>163 ± 108</td>
<td></td>
</tr>
<tr>
<td>40-60 mins</td>
<td>42 ± 48</td>
<td>0.055</td>
<td>378 ± 280</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;60 mins</td>
<td>47 ± 31</td>
<td></td>
<td>386 ± 360</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as mean and standard deviation in parentheses.

CHADS2: congestive heart failure/hypertension/age>75y/diabetes mellitus/stroke 2 points; LA: left atrial; RF: radiofrequency
Cerebral MES Count According to Procedural Component

**Figure 1**: Figure depicting the total number of microembolic signals according to each time period during the AF ablation procedure. The majority of cerebral MES occurred during the time of radiofrequency ablation within the left atrium; followed by the period of transeptal puncture and injection of saline and contrast into the left atrium. There were no events seen at baseline.
Type 3 MES Pattern: Embolic Shower

**Figure 2:** Transcranial Doppler showing a Type 3 MES pattern (shower of continuous and dense MES) during injection of contrast. The multifrequency TCD was used to discriminate embolic composition based on the dEBR (difference between the embolus-to-blood ratio (EBR) at 2.5-MHz insonation frequency and the EBR at 2.0-MHz insonation). In this example, MES were classified as gaseous.
Type 2 MES Pattern

**Figure 3**: Transcranial Doppler showing a Type 2 MES pattern (continuous but not dense MES pattern) during injection of contrast. The multifrequency TCD was used to discriminate embolic composition based on the dEBR (difference between the embolus-to-blood ratio (EBR) at 2.5-MHz insonation frequency and the EBR at 2.0-MHz insonation). In this example, MES were classified as gaseous.
Type 1 MES Pattern: Gaseous

Figure 4: Type 1 (isolated) pattern of MES. This example shows a gaseous MES.

Note, it is not possible to classify MES based on visual appearance alone.
Type 1 MES Pattern: Solid

Figure 5: Type 1 (isolated) pattern of MES. This example shows a solid MES. Note, it is not possible to classify MES based on visual appearance alone.
CHAPTER 8

Tachycardia-Mediated Cardiomyopathy

Secondary to Focal Atrial Tachycardia: Long-term Outcome After Catheter Ablation
8.1 INTRODUCTION

Tachycardia-mediated cardiomyopathy (TCM) is an important reversible cause of left ventricular (LV) dysfunction that may complicate both supraventricular and ventricular arrhythmias (470, 471). Catheter ablation is highly effective in providing long-term success for the majority of patients with supraventricular arrhythmias (220, 244). The mechanistic insights into the pathophysiology of TCM are based on animal models in which rapid right atrial and ventricular pacing has been used to induce heart failure. Prior animal studies have demonstrated a relationship between an increasing tachycardia rate and duration and increased severity of LV dysfunction (472). Although TCM is known to occur secondary to incessant supraventricular arrhythmias, there is a paucity of data describing the characteristics of focal atrial tachycardia that lead to TCM.

The aim of the present study was to determine the incidence of TCM among patients presenting with focal atrial tachycardia (AT), the electrophysiologic characteristics of focal AT associated with the development of reversible LV dysfunction, and the long-term clinical outcome after successful catheter ablation.

8.2 METHODS

8.2.1 Study Population

The study population consisted of a consecutive series of 345 patients undergoing radiofrequency ablation (RFA) for focal AT between January 1997 and July 2008. All patients had clinically documented paroxysmal or incessant AT. Comparison of P-wave morphology with the sinus rhythm P-wave was made to identify ectopic AT. The lower atrial rate was 100 beats/min with a change or distinct difference in the P-
wave morphology to the typical sinus P-wave important in the diagnosis of focal AT. Tachycardia was defined by the presence of $\geq 10$ consecutive tachycardia beats on 12-lead electrocardiogram or Holter monitor. Incessant tachycardia was defined as continuous tachycardia or continuous paroxysms of tachycardia separated by $\leq 2$ sinus beats (218). Patients had failed therapy with a mean of 1.5 ± 1.2 antiarrhythmic drugs before the procedure. Patients routinely undergo echocardiography before electrophysiology (EP) study and RFA. Left ventricular dysfunction was defined as left ventricular ejection fraction (LVEF) of $<50\%$. Patients were considered to have pre-existing LV dysfunction when cardiomyopathy occurred in the context of known significant coronary artery disease, valvular heart disease, congenital heart disease, or inherited cardiomyopathy; cardiomyopathy has been documented before the onset of tachycardia; or the echocardiographic abnormalities were segmental or of a pattern attributable to another cause. These patients (n=14) were excluded from the analysis. Comparisons were made between patients with TCM (n=30) and without TCM (n=301).

Of the patients with TCM, 27 of 30 (90\%) were in tachycardia at the time of baseline (pre-ablation) echocardiogram, and 3 of 30 (10\%) were in sinus rhythm. At the time of echocardiography, the mean heart rate in the incessant population was 114± 16 beats/min versus 69 ± 9 beats/min in the sinus rhythm population (p<0.0001).

### 8.2.2 Electrophysiologic Study

All patients underwent EP study in the fasting state with minimal use of sedation, and after the provision of informed written consent. All antiarrhythmic drugs were discontinued a minimum of 5 half-lives before the procedure.
**Catheter Positioning**

Catheter positioning and the approach used in our laboratory for ablation of focal AT have been previously described in detail (473). In brief, catheters were positioned in the following manner: 1) coronary sinus catheter (10-pole) positioned with the proximal bipole at the ostium of the coronary sinus; 2) crista terminalis catheter (20-pole) positioned along the crista terminalis; 3) His bundle electrogram catheter; and 4) mapping and ablation catheter. When necessary, the 3-dimensional electroanatomic mapping system was used.

**Mapping and Definition of Focal AT**

Diagnosis of focal AT was made using the standard electrophysiologic criteria (232). Anatomic localization of the atrial focus was performed during tachycardia or atrial ectopy by analysis of the following: 1) surface electrogram P-wave morphology (223); 2) right atrial endocardial activation sequence during tachycardia (224, 225); 3) conventional point-by-point mapping; and 4) when necessary, the 3-dimensional electroanatomic mapping system. Definitions of anatomic locations of tachycardia origin within the atria have been previously described (218, 224, 225, 232). In the right atrium, these foci tend to occur along the crista terminalis (109), tricuspid annulus (225), ostium of the coronary sinus, and the perinodal region. In the left atrium, foci occur predominantly at the pulmonary vein ostia and less commonly at the mitral annulus, left atrial appendage, and left-sided septum.

Tachycardia-cycle length was assessed by calculating the mean cycle length of 10 consecutive tachycardia beats from intracardiac electrograms recorded at the time of EP/RFA, and is a measure of the atrial rate in tachycardia. The tachycardia cycle
length (TCL) is expressed in milliseconds. Ventricular rate was assessed by calculating the mean heart rate of 10 consecutive QRS complexes in tachycardia recorded during EP/RFA. Ventricular rate is expressed as beats/min. Patients with incessant tachycardia had a tachycardia pattern described in the preceding text. One patient had incessant atrial ectopy with persistent atrial bigeminy or trigeminy and was included in this group.

8.2.3 Radiofrequency Ablation

RFA was performed with continuous temperature feedback control of power output to achieve a target temperature of 50° to 60° for a maximum power of 40 to 50 W. The power was reduced to 30 W for tachycardia sites at the pulmonary vein ostia and within the atrial appendages. Irrigated ablation was used where adequate power could not be achieved. Acute procedural success was defined by the absence of tachycardia or ectopy 30 mins after ablation despite infusion of isoproterenol (≤6 µg/min) and burst atrial pacing.

8.2.4 Follow-up

Patients were followed up by the treating electrophysiologist and by telephone interview. Any patient with symptoms suggestive of recurrent tachycardia was reviewed by the treating electrophysiologist, and attempts were made to document the rhythm. The patients with impaired LV function underwent repeat echocardiography after successful ablation.
8.2.5 Statistical Analysis

All continuous variables are expressed as mean ± SD. Comparisons between groups were performed with an unpaired Student t test or Mann-Whitney U test. Categorical variables, expressed as numbers and percentages, were compared with a chi-squared test. A value of p<0.05 was considered statistically significant.

8.3 RESULTS

8.3.1 Patient Characteristics

The study population included 345 patients (40% male; mean age 50 ± 18 years, range 9 to 85 years). Left ventricular dysfunction was present in 44 patients. Fourteen of 44 patients had prior structural heart disease secondary to ischaemic (n=10), congenital (n=2), dilated cardiomyopathy (n=1), and valvular heart disease (n=1). These patients were excluded owing to alternate potential mechanisms of impaired LV function. Therefore, 30 of 331 (10%) patients demonstrated cardiomyopathy secondary to focal AT. Of the patients considered to have TCM, the mean LVEF was 35 ± 11%. Echocardiographic assessment of LV function was undertaken during tachycardia in 27 of 30 patients. Of the 30 patients with TCM, 12 underwent echocardiography within 48 hours after the ablation procedure. Eleven of 12 patients were in tachycardia during the pre-ablation echocardiogram, and all post-ablation echocardiograms were performed in sinus rhythm. The mean heart rate during the pre-ablation echocardiogram for these 12 patients was 110 ± 19 beats/min. There was no significant difference between LVEF pre-ablation versus the immediate post-ablation echocardiogram (LVEF 36 ± 10% vs. 39 ± 10%, p=0.5). The clinical characteristics of the patient population with TCM are presented in Table 1.
8.3.2 Tachycardia Characteristics

Comparisons between patients with and without TCM are presented in Table 2. The TCM group was younger (mean age of 39 ± 22 years, range 9 to 81 years, vs. 51 ± 17 years, range 15 to 85 years; p=0.0006) and was significantly more likely to be male (60% vs. 38%, p<0.001) (Table 2). There was no significant difference in symptom duration or use of antiarrhythmic drugs between the 2 groups.

There were significant differences in the TCL of the ectopic AT, and also of the ventricular rate during tachycardia, between patients with and without TCM. Patients with TCM had a longer mean atrial TCL and slower ventricular rate during tachycardia than did patients without TCM (TCL 502 ± 131 ms vs. 402 ± 105 ms, p<0.0001; and ventricular rate117 ± 21 beats/min vs. 141 ± 33 beats/min, p=0.0007) (Table 2).

Incessant or frequent paroxysmal tachycardia was significantly associated with TCM compared with patients who had normal LV function (100% vs. 20%, p<0.001). Incessant tachycardia was present in 27 of 30 patients with TCM: very frequent paroxysmal tachycardia separated by short episodes (>2beats) of sinus rhythm was present in 2 patients, and 1 patient had LV dysfunction (EF 36%) after a 5-year history of incessant atrial ectopy with normal ventricular function. This unusual presentation followed persistent atrial bigeminy/trigeminy on electrocardiography and Holter monitoring, although sustained tachycardia was not present. After the development of cardiomyopathy, catheter ablation was performed at the ostium of the coronary sinus. After successful ablation of the ectopic foci, there was complete recovery of LV function in this patient with frequent isolated ectopy.
Sixteen of the 30 foci that resulted in TCM originated from either the atrial appendages (n=8) or the pulmonary veins (n=8). This reflected the frequent occurrence of incessant tachycardia from these anatomic sites.

### 8.3.3 Incessant Atrial Tachycardia

Overall, incessant AT occurred in 82 of 331 (25%) patients (Table 3). The TCM occurred in 30 of 82 (37%) patients with incessant tachycardia. A comparison of the characteristics of patients with incessant AT who had TCM with those of patients who also had incessant AT but did not have TCM showed the following: 1) incessant AT patients with TCM were similar in age (mean age 39 ± 22 years) and sex (60% male) to incessant AT patients without TCM (mean age 45 ± 18 years, p=0.2; 54% male, p=0.8); 2) symptom duration was not significantly different between incessant AT patients with TCM (6 ± 7 years) and without TCM (4 ± 6 years, p=0.5); and 3) in incessant AT patients with TCM, the TCL was longer (502 ± 131 ms) and ventricular response rate was slower (mean heart rate 117 ± 21 beats/min) than in patients who did not have TCM (TCL 446 ± 106 ms, p=0.05; and heart rate 132 ± 33 beats/min, p=0.05).

The incidence of incessant AT and incidence of TCM as per anatomic site of origin is presented in Table 3. Common anatomic sites of incessant tachycardia were the atrial appendages (n=16 of 19; 84%) and pulmonary vein ostia (n=26 of 44; 59%) (Figure 1). These sites also had a high incidence of associated TCM (Table 3). Cardiomyopathy developed in 8 of 19 (42%) patients with tachycardia originating from the right or left atrial appendages, and in 8 of 44 (18%) patients with a
pulmonary vein origin, significantly higher than from other anatomic locations (14 of 238; 6%; p=0.008).

8.3.4 Radiofrequency Ablation

Catheter ablation was attempted in 303 of 345 patients. Ablation was not attempted in the remaining 42 owing to insufficient activity (n=22), close proximity to the atrioventricular node (n=12), and multiple changing morphologies (n=8). Acute success in patients for whom RF was pursued was achieved in 272 of 303 (90%) patients. In patients with TCM, success without use of medication was achieved in 26 of 30 (87%) patients at mean follow-up of 23 ± 21 months. Of the other 4 patients, 2 with right atrial appendage tachycardia had recurrence of tachycardia post-ablation and are now successfully controlled with drugs with normalization of LV function; 1 patient had incessant multifocal tachycardia unable to be mapped and eliminated with RFA, and this patient has been only partially controlled with medication; and 1 83-year old patient had subsequent pacemaker implantation and AV node ablation.

8.3.5 Recovery of LV Function

Left ventricular function returned to normal in 29 of 30 (97%) patients at 2.8 ± 2 months after successful ablation (Figure 2). One now 20 year old male who presented with incessant tachycardia soon after birth has persistent LV dysfunction. Previous attempts at RFA were unsuccessful owing to multiple changing foci of tachycardia. Partial control of tachycardia with medical therapy has led to an improvement in LV function, from severe (LVEF 22%) to mildly impaired (LVEF 40% to 59%). There
have been no instances of syncope or sudden cardiac death in the TCM group at a
mean follow-up of 20 ± 28 months.

8.4 DISCUSSION

This study provides a detailed description of cardiomyopathy secondary to focal atrial
tachycardia in a large patient cohort with long-term follow-up. The important findings
were as follows:

1) 30 of 82 (37%) patients with incessant tachycardia presented with a TCM (30
of 331 patients, representing 10% of the atrial tachycardia cohort);
2) Anatomic sites with a predilection for incessant tachycardia (the atrial
appendages and pulmonary veins) were most frequently complicated by LV
dysfunction; and
3) Successful catheter ablation was achieved in 26 of 30 patients. Successful
control with drugs was achieved in 3 of the 4 remaining patients; an 83-year
old patient with an incessant parahisian tachycardia proceeded to pacemaker
implantation and AV node ablation. Therefore, complete recovery of LV
function was obtained in 29 of 30 (97%) patients. There were no late adverse
events in long-term follow-up.

**Animal Studies of Tachycardia-Induced Cardiomyopathy**

In tachypacing-induced animal models of heart failure, an increasing rate, longer
duration, and type of tachycardia are primarily responsible for the development of
myopathic change (474). Constant or incessant rapid pacing at a pre-defined fixed rate
is generally used for the induction of the cardiomyopathic state. In contrast,
tachyarrhythmias in humans, even when incessant, demonstrate significant variability related to diurnal variation and autonomic tone. This is an important consideration when bridging the gap from “bench to bedside” in interpreting the findings from animal models (471). Notwithstanding these limitations, important insights into the pathophysiology of TCM have been determined.

**Human Studies of Tachycardia-Induced Cardiomyopathy**

Tachycardia has been well described as an important cause of reversible LV dysfunction (475-477). The incidence of TCM is poorly defined and likely underestimated. In patients with unexplained cardiomyopathy, approximately 50% have been classified as idiopathic (478, 479). Kasper et al reported that, of 673 consecutive patients with presumed dilated cardiomyopathy, 1 case was attributed to tachycardia (478). This is likely to be an underestimate, particularly among patients with atrial fibrillation and dilated cardiomyopathy in whom uncontrolled tachycardia may cause or exacerbate heart failure (480). In addition, children with permanent junctional reciprocating tachycardia appear vulnerable to the development of LV dysfunction, with 24 of 85 (28%) children affected in 1 series (481). TCM has also rarely been reported to complicate other frequent paroxysmal or persistent supraventricular tachycardias, including AV nodal re-entry tachycardia and AV re-entrant tachycardias (470, 476, 482). The diagnosis of AT may be challenging, particularly at ventricular rates of 110 beats/min as presented in the current study. Differentiating sinus tachycardia from AT may be difficult, with tachycardia considered an “appropriate” compensatory response to LV dysfunction. In the majority of instances, an analysis of P-wave morphology will readily rule out a sinus mechanism. However, foci arising from the crista terminalis or from right-sided
pulmonary veins may have a P-wave morphology indistinguishable from a sinus P-wave and lead to an incorrect diagnosis of compensatory sinus tachycardia (223).

In the present study, cardiomyopathy developed in one-third of patients with incessant AT. When compared with all patients with AT who did not have a cardiomyopathy, patients with TCM demonstrated a longer atrial TCL and slower ventricular response. Patients with rapid paroxysmal AT may be more likely to be symptomatic with palpitations and more aware of tachycardia episodes. More rapid tachycardia is likely to be appropriately diagnosed and not mistaken for sinus tachycardia. Patients with rapid AT may, therefore, be recognized earlier and given more rapid treatment, leaving less time for TCM to develop. By contrast, patients with slower, incessant tachycardia may not present early with palpitations, but rather, later with symptoms of cardiac failure.

When a comparison was made between patients with incessant tachycardia in whom cardiomyopathy did or did not develop, similar differences in cycle length and ventricular response were observed. Symptom duration (although notoriously difficult to assess), age at presentation, and sex were not significantly different. Alternate factors beyond tachycardia rate (and possibly duration) are likely important in the predisposition to LV dysfunction.

In the present study, foci arising from the atrial appendages and pulmonary veins were frequently incessant; however, there was no significant difference in the likelihood of TCM developing according to site of origin if tachycardia was incessant. This observation suggests that the predilection for TCM to develop relates to the incessant nature of the focus rather than to the anatomical site of origin. Genetic factors influencing predisposition for TCM to develop may play an important role. Angiotensin-converting enzyme gene polymorphisms have been associated with TCM
A genotype containing a deletion allele is associated with elevated angiotensin-converting enzyme and angiotensin II concentrations (484). Deshmukh et al described an increase in the deletion/deletion genotype in incessant tachycardia patients with cardiomyopathy compared with normal LV function (483). This overexpression of the renin-angiotensin system may account for an individual predisposition to develop cardiomyopathy in the context of incessant tachycardia in some patients.

A high burden of ventricular ectopic activity has been shown to result in LV dysfunction (485). In the present study, 1 patient had impaired ventricular function in response to frequent or “incessant” atrial ectopy. This is a highly unusual and rare case of frequent atrial ectopics resulting in cardiomyopathy, and this patient does not reflect the clinical outcomes of patients who have a high burden of atrial or ventricular ectopy seen on Holter monitoring.

**Clinical Implications**

In our study population, incessant tachycardia occurred in approximately 25% of patients with focal AT, and TCM developed in approximately one-third of these patients. These tachycardia foci predominantly originated from the atrial appendages and from the pulmonary vein ostia. Successful RFA of atrial tachycardia foci was possible for the vast majority of these patients and resulted in complete reversibility of tachycardia-induced LV dysfunction. At a mean follow-up of almost 2 years, there were no late sudden deaths among this population.

Recovery of LV function after control of persistent tachycardia has been demonstrated for a range of different tachycardia mechanisms (475-477, 486). However, recent data have suggested that there may be a persistence of structural
abnormalities even with return to normal ventricular function. Nerheim et al reported the long-term outcomes of 24 patients with complete recovery from TCM after control of differing cardiac arrhythmias (487). Five patients who had recurrence of atrial fibrillation had a very rapid recurrence of heart failure, suggesting that some structural LV abnormalities may have persisted. Three other patients, all of whom had recurrence of atrial fibrillation (1 had undergone AV node ablation), died suddenly months to several years later despite apparent preservation of LV function, again raising the possibility of persistent LV structural abnormalities (487). We cannot rule out the presence of persistent occult LV abnormalities in our population. However, our data suggest that, for patients undergoing curative ablation of focal AT, late arrhythmia recurrence is rare and the long-term prognosis is excellent.

**STUDY LIMITATIONS**

The calculation of LV systolic function in the presence of a shortened diastolic filling time may result in an underestimate of LVEF. In this clinical study, we were unable to control for the effects of differences in heart rhythm in the assessment of LV function at baseline and after successful catheter ablation. In 27 of 30 (90%) patients, the echocardiography determination of baseline LV function was performed during tachycardia. We have included the findings from 12 patients in incessant AT who underwent an early repeat echocardiogram within 48 hours after the restoration of sinus rhythm by catheter ablation. There was no significant difference between pre-ablation LVEF (36 ± 10%) and immediate post-ablation LVEF (39 ± 10%; p=0.5).
CONCLUSIONS

TCM occurred in 10% of patients with focal atrial tachycardia. Incessant tachycardia is necessary for the development of TCM, and was seen in approximately one-third of the total population of patients with focal atrial tachycardia. Incessant tachycardias characteristically originated from the atrial appendages and pulmonary veins and had a significantly longer cycle length than did paroxysmal tachycardia’s, which did not result in cardiomyopathy. Long-term restoration of left ventricular function can be achieved with successful control or elimination of tachycardia in the majority of patients.
Table 1: Clinical and Tachycardia Characteristics in Patients With TCM

<table>
<thead>
<tr>
<th>Anatomic Site</th>
<th>Age (yrs)</th>
<th>Male (% n)</th>
<th>Symptom Duration (yrs)</th>
<th>TCL (msec)</th>
<th>Ventricular Rate (beats/min)</th>
<th>Pre-Ablation LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV (n=8)</td>
<td>36 ± 24</td>
<td>63 (5)</td>
<td>7 ± 8</td>
<td>407 ± 121</td>
<td>125 ± 14</td>
<td>34 ± 11</td>
</tr>
<tr>
<td>AA (n=8)</td>
<td>24 ± 7</td>
<td>88 (7)</td>
<td>3 ± 5</td>
<td>616 ± 137</td>
<td>103 ± 19</td>
<td>34 ± 10</td>
</tr>
<tr>
<td>Perinodal (n=2)</td>
<td>61 ± 28</td>
<td>100 (2)</td>
<td>0.8 ± 0.4</td>
<td>502 ± 45</td>
<td>123 ± 11</td>
<td>38 ± 11</td>
</tr>
<tr>
<td>CS (n=1)</td>
<td>67 ± 0</td>
<td>100 (1)</td>
<td>5 ± 0</td>
<td>N/A*</td>
<td>89#</td>
<td>36</td>
</tr>
<tr>
<td>CT (n=3)</td>
<td>41 ± 4</td>
<td>0 (0)</td>
<td>5 ± 5</td>
<td>413 ± 54</td>
<td>145 ± 23</td>
<td>40 ± 9</td>
</tr>
<tr>
<td>TA (n=3)</td>
<td>44 ± 22</td>
<td>33 (1)</td>
<td>10 ± 13</td>
<td>406 ± 115</td>
<td>151 ± 49</td>
<td>45 ± 0</td>
</tr>
<tr>
<td>Multifocal (n=5)</td>
<td>49 ± 28</td>
<td>40 (2)</td>
<td>7 ± 9</td>
<td>522 ± 32</td>
<td>116 ± 6</td>
<td>34 ± 13</td>
</tr>
</tbody>
</table>

Values are mean ± SD or %(n). *Premature atrial complex 37% total beats. #Mean rate Holter monitor.

AA - atrial appendage; CS - coronary sinus; CT - crista terminalis; LVEF - left ventricular ejection fraction; N/A - not applicable; PV - pulmonary vein; TA - tricuspid annulus; TCL - tachycardia cycle length; TCM - tachycardia-mediated cardiomyopathy.
Table 2: Clinical Characteristics of Patients With and Without TCM

<table>
<thead>
<tr>
<th></th>
<th>TCM (n=30)</th>
<th>No TCM (n=301)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>39 ± 22</td>
<td>51 ± 17</td>
<td>0.0006</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>60</td>
<td>38</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Incessant/very frequent paroxysmal</strong></td>
<td>100</td>
<td>20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Antiarrhythmic drugs</strong></td>
<td>1.4 ± 1.3</td>
<td>1.5 ± 1.1</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Symptom duration, years</strong></td>
<td>6 ± 7</td>
<td>6 ± 8</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>TCL, ms</strong></td>
<td>502 ± 131</td>
<td>402 ± 105</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>HR, beats/min</strong></td>
<td>117 ± 21</td>
<td>141 ± 33</td>
<td>0.0007</td>
</tr>
<tr>
<td><strong>Pre-ablation LVEF, %</strong></td>
<td>35 ± 11</td>
<td>59 ±1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are % or mean ± SD.

HR: heart rate; LVEF: left ventricular ejection fraction; TCL: tachycardia cycle length; TCM: tachycardia-mediated cardiomyopathy
Table 3: Anatomic Site of Origin of Focal Atrial Tachycardia

<table>
<thead>
<tr>
<th></th>
<th>PV (n=44)</th>
<th>MA (n=13)</th>
<th>AA (n=19)</th>
<th>Perinodal (n=40)</th>
<th>CS (n=27)</th>
<th>CT (n=85)</th>
<th>TA (n=53)</th>
<th>Multifocal (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>50 (22)</td>
<td>8 (1)</td>
<td>79 (15)</td>
<td>45 (18)</td>
<td>59 (16)</td>
<td>18 (15)</td>
<td>47 (25)</td>
<td>36 (10)</td>
</tr>
<tr>
<td>Age, years</td>
<td>38 ± 16</td>
<td>53 ± 16</td>
<td>33 ± 18</td>
<td>50 ± 14</td>
<td>40 ± 22</td>
<td>56 ± 13</td>
<td>48 ± 20</td>
<td>57 ± 14</td>
</tr>
<tr>
<td>Incessant</td>
<td>59 (26)</td>
<td>0 (0)</td>
<td>84 (16)</td>
<td>20 (8)</td>
<td>11 (3)</td>
<td>6 (5)</td>
<td>32 (17)</td>
<td>25 (7)</td>
</tr>
<tr>
<td>Tachycardia-mediated cardiomyopathy</td>
<td>18 (8)</td>
<td>0 (0)</td>
<td>42 (8)</td>
<td>5 (2)</td>
<td>4 (1)</td>
<td>4 (3)</td>
<td>6 (3)</td>
<td>18 (5)</td>
</tr>
</tbody>
</table>

Values are % (n) or mean ± SD.

AA-atrial appendage; CS- coronary sinus; CT-crista terminalis; MA- mitral annulus; PV-pulmonary vein; TA-tricuspid annulus
Tachycardia and Sinus Rhythm P Waves

**Figure 1: Tachycardia P Waves With Sinus Rhythm in 2 Patients With Incessant Atrial Tachycardia**

[Atrial Tachycardia: (Left):] This patient was a 53-year old man with a history of palpitations. LVEF was normal. In atrial tachycardia (AT), the P wave is broad, inverted and notched in leads V1 and V2 and positive in leads II, III, and avF. Electrophysiology study revealed an origin at the base of the right atrial appendage (RAA), and RFA was successful in terminating the tachycardia. (Right): This patient was a 32-year old asymptomatic woman in incessant tachycardia. The P wave in tachycardia is bifid positive in the inferior leads, broad and positive in leads V1 through V6, and negative in lead I. Tachycardia was successfully ablated at the origin of the left atrial appendage (LAA). AT: atrial tachycardia; LVEF: left ventricular ejection fraction; SR: sinus rhythm
A total of 27 of 30 patients with tachycardia-mediated cardiomyopathy (TCM) were in tachycardia during the initial echocardiographic assessment of left ventricular function. Pre-ablation left ventricular ejection fraction (LVEF) was 35 ± 11%, improving to 59 ± 3% at 2.8 ± 2 months post-ablation.
CHAPTER 9

Final Discussion
This thesis provides important original insights into both the electrical and structural remodeling responsible for atrial arrhythmias; and to the therapeutic implications for a procedure targeting this arrhythmia that is becoming increasingly performed in an expanding patient population.

Atrial arrhythmias result in electrical remodeling, which forms the basis for the seminal observation that “AF begets AF”. However electrical remodeling does not explain the stabilization of AF or late recurrences when atrial refactororiness has recovered. A second factor with a slower time course has been invoked and is likely to be structural change. This also explains the limited efficacy of antiarrhythmic medication particularly in AF of longer duration. Results from the rapid atrial pacing model provide insight into how AF modulates atrial electrical properties to maintain its own perpetuation but does not explain why certain pathophysiologic states are more vulnerable to AF. The thesis addressed the effects of hypertension and pulmonary hypertension, conditions known to be associated with AF, and gives insight into the underlying substrate before it is modified by the arrhythmia itself. This has been recognized as “atrial remodeling of a different sort”.

The relationship between hypertension and atrial fibrillation is well recognised and takes on added significance in the context of altering world population demographics. Hypertension is the most prevalent, independent and potentially modifiable risk factor for atrial fibrillation. In addition, in patients with AF, hypertension increases the stroke rate 2-3 fold. The electrophysiologic and structural effects of long standing chronically treated hypertension were studied. In addition, we studied a population of patients with idiopathic pulmonary hypertension to study the atrial effects of pulmonary hypertension in the absence of the confounding effects of other disease states, such as obstructive sleep apnoea and chronic obstructive pulmonary disease. A
better understanding of the atrial effects of pulmonary hypertension may help dissect out the relevant pathophysiologic factors responsible for the vulnerability to AF in these varied clinical conditions.

In Chapter 2 conventional electrophysiologic studies were performed in patients with no prior history of atrial fibrillation. Hypertension was associated with prolongation of atrial refractoriness; significant reduction in atrial conduction as assessed by electrophysiologic and electroanatomic studies; functional conduction delay at the crista terminalis; and increase in areas of low voltage; and an increase in the propensity and duration of atrial fibrillation. In Chapter 3 idiopathic pulmonary hypertension was associated with prolongation of sinus node recovery times; a reduction in tissue voltage with an increase in areas of low tissue voltage and electrically silent areas; an increase in the number of complex fractionated activity particularly in the region of the posterior right atrium; atrial conduction slowing with a significant reduction in conduction velocity and an increase in activation times at a global and regional level; and an increase in AF inducibility. Reductions in atrial voltage are likely to represent fibrosis. Therefore Chapters 2 and 3 demonstrate that hypertension and pulmonary hypertension are associated with atrial remodeling characterised by widespread conduction slowing as well as anatomically determined functional conduction delay and block; prolongation of atrial refractoriness and reductions in voltage with discrete regions of low voltage. These electrical and structural changes may in part be responsible for the increase in the incidence of atrial arrhythmias.

In Chapter 4 the comparison of atrial substrate changes between patients with atrial fibrillation and atrial flutter are presented. Atrial fibrillation and atrial flutter are the most common sustained arrhythmias seen in clinical practice. Whilst there may be
alternate expression of both AF and AFL in an individual patient, clinically one of these arrhythmias often predominates. Although it has been well recognised that both arrhythmias are associated with atrial substrate remodeling, there has been no direct comparison of atrial substrate changes in patients with AFL vs. AF. We found that the following changes were observed in patients with AFL compared to patients with AF: a reduction in tissue voltage and an increase in the proportion of low voltage areas; a higher proportion of complex signals; evidence of diffuse conduction slowing with marked regional abnormalities. In addition, patients with AFL had significantly shorter atrial refractory periods.

Radiofrequency ablation procedures have emerged as highly effective strategies in the management of patients with symptomatic paroxysmal and persistent atrial fibrillation. The procedure is evolving, and the optimal ablation strategy (particularly in patients with persistent atrial fibrillation), as well as a comprehensive understanding of the complications of the procedure, has lagged behind the technical advances in ablative strategies. We sought to define the cerebral complications of AF ablation with a focus on neurocognitive function.

Chapter 5 describes the baseline analysis of neurocognitive abnormalities in patients with atrial fibrillation (PAF and PeAF) in comparison with an age-matched population of patients with supraventricular tachycardia. Our results indicate that in patients with atrial fibrillation who are young and an otherwise healthy low-risk population, the prevalence of pre-existing cognitive impairment is approximately 10-20%. In addition, we have prospectively identified a further significant proportion of patients classified as aMCI, who have an elevated risk for the future development of cognitive impairment and dementia. These findings were reinforced by the
observation that in a similar low-risk cohort of patients with SVT, pre-existing cognitive impairment was not detected.

Chapter 6 describes the change in neurocognitive outcomes after ablation for AF in patients with PAF and PeAF and in patients with ablation for supraventricular tachycardia, in comparison to patients with AF without RF ablation. Patients with PAF and PeAF had a prevalence of early (day 2) post-operative cognitive dysfunction of approximately 25%. An increased left atrial access time was the most powerful predictor of post-operative cognitive dysfunction at early (day 2) and long-term (day 90) assessments. An impairment in cognitive performance at day 90 was seen with an increased prevalence in persistent compared to paroxysmal AF patients; and cognitive dysfunction was seen infrequently in patients with supraventricular tachycardia undergoing radiofrequency ablation at long-term follow up.

The aetiology of post-operative cognitive dysfunction after AF ablation is complex, but may relate in part to cerebral microembolism occurring during the procedure. Chapter 7 describes the prevalence of cerebral microembolism occurring during AF ablation. Importantly, and a highly original finding, we report the composition of cerebral emboli (gaseous vs solid) using a multi-frequency transcranial Doppler ultrasound. We found that all patients undergoing AF ablation demonstrated cerebral microembolic signals, and the majority of events were gaseous, and occurred during application of radiofrequency energy. We did not find a difference between total or solid embolic counts between patients with PAF or PeAF with similar LA access and ablation times. However, an increase in LA access and RF ablation time, however, in patients with both PAF and PeAF, trended towards an increase in both solid and gaseous MES.
A significant part of this thesis details the formation of the atrial substrate which supports atrial fibrillation yet triggers from rapidly firing foci in the right and left atrium may be responsible for the initiation of focal atrial tachycardia. Whilst focal atrial tachycardia is often benign, a proportion of patients may develop tachycardia-mediated cardiomyopathy as a consequence of focal atrial tachycardia. In Chapter 8, the incidence of tachycardia-induced cardiomyopathy among patients with focal atrial tachycardia is presented, with the electrophysiologic characteristics and the long-term clinical outcomes after successful catheter ablation. We found that approximately 1/3 of patients with incessant atrial tachycardia presented with a tachycardia-induced cardiomyopathy; anatomic sites with a predilection for incessant tachycardia (the atrial appendages and pulmonary veins) were most frequently complicated by left ventricular dysfunction; and that complete recovery of left ventricular function was achieved in the vast majority of patients, with no long-term events at long-term follow-up.
CHAPTER 10

Future Directions
An appreciation of the therapeutic implications of electrical and structural remodeling is important in attempting to improve current results with pharmacologic and invasive ablation strategies. There have been considerable advances in ablation techniques aimed at treating and potentially curing atrial fibrillation. To date success has been achieved predominantly in patients with paroxysmal atrial fibrillation with structurally normal hearts where presumably the triggers are more important than the substrate. The developments of technology and ablation techniques are currently evolving more rapidly than an understanding of their impact on the remodeled atria. It remains unclear whether “sinus rhythm begets sinus rhythm” a key premise in AF ablation strategies. In animal studies reverse structural remodeling is a very slow process which to date has been incomplete with similar information lacking in humans. Detailed information on the electrophysiologic properties of the left atrium and in particular the pulmonary veins which make an individual susceptible to atrial fibrillation also require ongoing attention.

The future direction of pharmacologic therapies for AF is also changing. Antiarrhythmic medication is of limited efficacy particularly in patients with structural heart disease or longer duration atrial fibrillation. Structural remodeling and conduction slowing are important factors limiting their effectiveness. A shift in the paradigm to the pharmacologic management of AF that targets the underlying substrate rather than the electrophysiologic properties of atrial refractoriness is evolving. Pre- existent agents with anti-inflammatory, anti-oxidant or anti-fibrotic effects are currently under investigation with promising preliminary results.

Atrial fibrillation has been described as an evolving epidemic in the setting of an ageing population. Ongoing research into the atrial substrate responsible for maintaining atrial fibrillation is fundamental to therapeutic advances.
Catheter ablation strategies must balance effectiveness in symptomatic benefit with minimal complications. Further progress into the understanding of the significance of solid and cerebral microemboli will assist in the evaluation of the safety implications of this procedure. The very-long term neurocognitive outcomes of patients undergoing ablation for AF are also of importance given increases in procedure volumes and the expanding indications.
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