

**ASSESSMENT OF LEFT ATRIAL STRUCTURE
AND FUNCTION IN THE SETTING OF ATRIAL
FIBRILLATION USING CARDIAC MAGNETIC
RESONANCE IMAGING**

A thesis submitted by

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Statement of originality

I, Payman Molaee certify that this work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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Payman Molaee

February 2012

Dedication

I dedicate this thesis to my beautiful wife Kamilia jaan, my dearest son William Ezzat joon, my dear parents Roya and Shahrooz Molae, my dear sister Elham jaan, my dear father-in-law Manouchehr Tai and my wonderful late mother-in-law dear Faezeh Tai. You have all been a great source of love, support and guidance to me.

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Thesis related publications

Wong CX*, Abed HS*, **Molaee P***, Nelson AJ, Brooks AG, Sharma G, Leong DP, Lau DH, Middeldorp ME, Roberts-Thomson KC, Wittert GA, Abhayaratna WP, Worthley SG, Sanders P. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *Journal of the American College of Cardiology* 2011; 57 (17): 1745-51.

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Abstracts

Molaee P, Teo K.S.L, Kuklik K, Worthley S.G, Sanders P. Atrial fibrillation ablation improves cardiac structure and function: A long-term cardiac magnetic resonance study. *Journal of the American College of Cardiology* 2009; 53: A112.

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Kuklik P, **Molaee P**, Brooks A.G, Young G.D, Worthley S, Sanders P. New Method of Quantitative Description of Regional Mechanics of Atria by Means of Electroanatomical Mapping. *Heart, Lung and Circulation 2009; 18: S154-S155.*

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Thesis summary

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with significant morbidity and mortality. As a result of AF, patients develop palpitations, syncope, cardiac failure and thromboembolic complications. The management of AF has revolved around the issues of rate versus rhythm control, and stroke prevention. Although rhythm control was thought to be the most desirable approach, several large randomised trials failed to show a significant difference between the two treatment strategies. In fact, rhythm control strategy may be associated with increased adverse outcomes. This has largely been attributed to the poor efficacy and significant toxicity of antiarrhythmic agents.

Since the seminal observation that the pulmonary veins play an important role in triggering AF, radiofrequency catheter ablation of AF has evolved rapidly. Although this is a potentially curative treatment for selected patients with AF, there are several issues that need to be addressed, including predictors of success of the procedure, effects of ablation on cardiac structure and function, and implications of AF ablation for long-term stroke risk.

Cardiac magnetic resonance imaging (CMR) is now regarded as the “gold standard” non-invasive imaging modality for the assessment of cardiac structure and function. It is thus an ideal tool for initial assessment and follow-up of patients with AF undergoing ablation. The chapters in this thesis are based on CMR studies in patients with AF.

Left atrial (LA) volume is an established prognostic marker. Currently, LA volume is commonly measured using the biplane area-length method and applying the method of discs. This involves geometric assumptions, which may introduce inaccuracies. In Chapter 3, the accuracy and reproducibility of biplane area-length method was compared with the “gold standard” volumetric measurement using CMR, in healthy controls and subjects with AF. The biplane area-length method correlated well with the volumetric method in healthy controls, but in subjects with AF, the correlation was less robust and the area-length method was less reproducible.

Traditionally, “lone” AF has been defined as the occurrence of AF in the absence of any cardiopulmonary disease. However, the CMR study presented in Chapter 4 demonstrates that despite having no evidence of cardiac abnormalities on echocardiography, subjects with “lone” AF have atrial functional abnormalities and ventricular structural changes compared with controls.

The success of AF ablation can be variable depending on the expertise of the centre, clinical and imaging characteristics. Predictors of success following AF ablation have not been well established. The clinical and CMR factors associated with medium-term outcomes following AF ablation are presented in Chapter 5. Following multivariate analysis, increased LA volume and female gender were the only predictors of AF recurrence at one year post-ablation.

In the study presented in Chapter 6, CMR was performed at baseline and 12-month follow-up to assess the impact of AF ablation on cardiac structure and function. In

subjects with successful ablation, there was evidence of reverse remodelling within the atria and ventricles, with reduction in chamber volumes post-ablation. Importantly, these changes associated with cardiac reverse remodelling after ablation may indeed contribute to the success of ablation.

CHAPTER 1

INTRODUCTION

1.1. Background

Atrial fibrillation (AF) is the most common arrhythmia (Go et al. 2001). It affects 1 in 10 Australians over the age of 75 years (AIHW 2008). It is associated with significant morbidity and mortality (Benjamin et al. 1998; Miyasaka et al. 2006). The most feared complication of AF is stroke, secondary to thromboembolism from the left atrium (LA) or left atrial appendage (Lip et al.). Stroke is the second leading cause of death in Australia (AIHW 2008). Around 1 in 5 cases of ischaemic stroke are attributable to AF (Wolf et al. 1991). These patients have a significantly worse prognosis than other stroke patients, with increased mortality, and patients who survive have loss of independence and requirement for a high level of care (Lamassa et al. 2001).

Another major comorbidity associated with AF is congestive heart failure (CHF). Indeed, AF and CHF have been identified as the 2 major epidemics of cardiovascular disease in the 21st century (Braunwald 1997). Congestive heart failure is a common clinical syndrome, affecting over 1 in 10 Australians \geq 65 years old (Krum et al. 2006). Atrial fibrillation can be caused by, or a cause of CHF, and their coexistence leads to a vicious cycle of decreased exercise capacity, worsening heart failure and increased morbidity and mortality (Dries et al. 1998).

With the ageing population in Australia, AF is becoming an increasingly important public health issue. In Australia, the number of hospitalisations with AF as the principal diagnosis has increased from about 27,000 in 1998 – 99 to over 47,000 in 2007 – 08 (AIHW 2008). This now accounts, in absolute number, for greater number of admissions to hospital than CHF. In addition, AF leads to significant utilisation of

primary health care resources due to regular monitoring of treatment. In recent years, various novel treatment strategies have evolved, which may potentially reduce the burden of morbidity in patients with AF. In order to assess the efficacy of these novel therapies, more sensitive imaging modalities can be helpful, particularly in assessing LA structure and function, and in monitoring these parameters in patients with AF, before and after various treatment strategies, and how they relate to cardiomyopathy and stroke risk, as well as overall morbidity and mortality.

1.2. Left atrium

The human LA has a variety of functions. It is an electrically active chamber that functions as a reservoir, conduit and a booster pump at various phases of the cardiac cycle (Poutanen et al. 2000). In addition, there is evidence of an endocrine role in regulating blood volumes through ANP. Until recently, the LA has largely been neglected while research has focussed on the left ventricle (LV). However, the importance of the LA has now been appreciated in numerous cardiac conditions and research involving LA anatomical, functional and electrophysiological abnormalities is gathering momentum.

1.2.1. Left atrial anatomy

The LA has a smooth, thin internal wall with a characteristic left atrial appendage (Lip et al.) located high in the body of the LA (Al-Saady et al. 1999; Ho et al. 2002). The muscular fibres are thin and longitudinally arranged, in keeping with the low pressures within the normal LA (Ho et al. 1999). The pulmonary veins (PVs) drain into the four corners of the posterior aspect of the LA, with significant variations having been

reported (Ho et al. 1999). Noteworthy neighbouring structures which surround the LA include the trachea and oesophagus posteriorly and the coronary sinus inferiorly (Ho et al. 2002).

Two structures associated with the LA have become the focus of attention; namely the LAA and the PVs. The LAA is a long, trabeculated, tubular structure with a constriction at its mouth (Ho et al. 1999). It lies in close proximity to the free wall of the LV and its function can be affected by the LV (Akosah et al. 1995). It is multilobular in 80% of cases, with 54% of the population having a bilobular LAA (Veinot et al. 1997). In rheumatic AF, 57% of thrombi are found in the LAA, whereas in nonrheumatic AF, 91% of thrombi are within the LAA (Blackshear and Odell 1996). This has significant implications in terms of imaging strategies and management of patients with cardiac thromboembolism. The PVs have sleeves of atrial myofibres with the superior PVs having longer sleeves (Ho et al. 2001). This has become particularly relevant since the recognition of initiation of AF through ectopic foci within the PVs and targeting of PVs in the treatment of AF (Haissaguerre et al. 1998).

1.2.2. Left atrial physiology

The LA has several functions that can be broadly categorised into haemodynamic, electrical and endocrine.

Haemodynamically, the LA functions as a reservoir (during systole), conduit (during diastole) and a booster pump (during late diastole) (Toma et al. 1987). Left ventricular filling is modulated by LA function. In early ventricular diastole, the mitral valve opens

due to an atrioventricular pressure gradient. The initial atrial to ventricular flow is through passive emptying which is attributed to the energy stored within the elastic LA wall during LV systole (Grant et al. 1964). The next phase involves active relaxation and the “sucking” effect of the LV. This phase is termed diastasis or the plateau phase, during which the LA acts as a conduit with little change in the LA volume (Matsuda et al. 1983). In the normal heart, most of the LV filling occurs in diastasis (Matsuda et al. 1983). In late diastole, the LA contracts and serves as a booster pump. Rapid LV filling occurs early in diastole, but in patients with a poorly compliant LV, there is an increased reliance on LA contraction for augmentation of LV filling (Hoit and Gabel 2000). LA contraction contributes from 10 - 30% of the cardiac output, with the “booster” role of the LA becoming more prominent in patients with LV abnormalities and with increasing age (Matsuda et al. 1983). In normal subjects, the relative contributions of the reservoir and conduit phases to LV filling are about 40% and 35% respectively. The contribution of LA contraction to LV stroke volume increases from 12% at age 20 years to 46% at 80 years, in normal subjects (Kuo et al. 1987).

LA reservoir and booster functions are accentuated during exercise, while the conduit function remains unchanged (Toutouzas et al. 1996). This leads to increased LV filling through maintenance of the atrioventricular pressure gradient in diastole and enhanced LA contraction secondary to increased preload (Toutouzas et al. 1996). The Frank-Starling mechanism is operative in the LA with enhanced contractility in the presence of increasing stretch levels (Matsuda et al. 1983; Yamaguchi et al. 1987). However, increased LA stretch is associated with electrical remodelling and increased risk of arrhythmias (Kalman and Sparks 2001).

In addition to studying the LA itself, the assessment of LAA has provided further insights into LA function and has been extensively investigated in the era of transoesophageal echocardiography (TOE). The flow pattern in the LAA has been described as quadriphasic in the majority of patients in sinus rhythm, with 2 diastolic emptying waves, each followed by a filling wave (Mikael Kortz et al. 1993). Biphasic, triphasic and even pentaphasic flow patterns have been reported (Zeppellini et al. 1995). It has been proposed that LV function plays an important role in LAA emptying and filling and that LV function may in fact have a greater impact than LAA function on these parameters (Akosah et al. 1995). There is an age dependent decline in LAA emptying and filling velocities, with the mean emptying velocity in normal subjects decreasing from 83 cm/s in the 45 – 54 year age group to 68 cm/s in the ≥ 85 year age group (Agmon et al. 2000). The LAA emptying and filling patterns and velocities in various disease states, specifically AF, will be discussed in detail later.

1.3. Atrial fibrillation

1.3.1. Epidemiology

Atrial fibrillation is the most common arrhythmia with a prevalence of 9% in people ≥ 80 years old, and is more common in males (Go et al. 2001). It is associated with an increased risk of systemic embolism, CHF and mortality (Benjamin et al. 1998).

1.3.2. Classification

Numerous definitions and classifications have been applied in the setting of clinical trials to describe various subsets of patients with AF. The most commonly adopted

classification of AF is that developed by the American College of Cardiology/American Heart Association/European Society of Cardiology 2006 guidelines (Fuster et al. 2006). Paroxysmal AF is defined as an episode that terminates spontaneously in < 7 days. Atrial fibrillation is persistent if it is sustained beyond 7 days. Permanent AF is present if the arrhythmia lasts > 1 year and cardioversion has either failed or not been attempted. “Lone” AF refers to a subset of patients < 60 years old, with no clinical or echocardiographic evidence of cardiopulmonary disease or hypertension. It should be noted that patients can move from one classification to another and that the above classification excludes AF due to reversible causes, where the underlying pathology is the focus of management.

1.3.3. Effects of atrial fibrillation on the left atrium

Tachycardia-mediated atrial cardiomyopathy is an increasingly recognised phenomenon (Zipes 1997). AF leads to atrial structural, mechanical and electrical remodelling, which can be reversible to some extent (Gosselink et al. 1993; Wijffels et al. 1995; Sanders et al. 2003b). At the gross structural level, pressure and volume overload lead to LA enlargement which predisposes to AF (Henry et al. 1976). In addition, AF itself can promote LA enlargement, while maintenance of sinus rhythm can prevent this phenomenon (Sanfilippo et al. 1990; Gosselink et al. 1993). Furthermore, extensive ultrastructural cellular changes, including myofibrillar loss, accumulation of glycogen, changes in mitochondrial shape and size, fragmentation of sarcoplasmic reticulum and dispersion of nuclear chromatin have been noted in animal models of sustained AF (Ausma et al. 1997).

Although atrial mechanical dysfunction could be explained, to some extent, by the previously described structural abnormalities, these processes are gradual and take weeks to develop, while atrial mechanical dysfunction has been observed with short durations of AF, suggesting a cellular functional mechanism underlying its development (Daoud et al. 1999). Atrial fibrillation related atrial contractile dysfunction is attenuated by verapamil (Leistad et al. 1996; Daoud et al. 1999), increased extracellular calcium levels (Schotten et al. 2001), pacing and isoproterenol (Sanders et al. 2003b). Thus, it has been postulated that calcium and/or cellular calcium handling, particularly the L-type calcium channel, play a vital role in the process of reversible atrial mechanical dysfunction in the setting of AF (Leistad et al. 1996; Daoud et al. 1999; Schotten et al. 2001). Moreover, the duration of AF is an important determinant of the extent of recovery of atrial mechanical function following cardioversion (Shapiro et al. 1988; Manning et al. 1994). Patients with more prolonged AF (≥ 3 years) have a more attenuated response to pacing and isoproterenol compared to those with a shorter duration of AF (1 – 6 months) (Sanders et al. 2003b). This may be related to the degree of atrial structural remodelling, myocardial cell death, and fibrosis, which are more extensive with prolonged AF and less likely to be reversible (Ausma et al. 1997; Aïme-Sempe et al. 1999; Sanders et al. 2003b).

Activation of the renin-angiotensin-aldosterone system has been implicated in AF and associated atrial fibrosis (Goette et al. 2000). In particular, angiotensin II, through its type 1 receptor, may mediate atrial fibrosis (Goette et al. 2000). Blockade of the renin-angiotensin-aldosterone system was initially found to reduce the occurrence of AF following myocardial infarction with associated LV dysfunction (Pedersen et al. 1999).

Although subsequent animal studies found a reduction in atrial structural remodelling using angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists (Li et al. 2001; Kumagai et al. 2003), and human studies assessing the effects of renin-angiotensin-aldosterone blockade on AF occurrence, as a concomitant endpoint, have been confirmatory (Maggioni et al. 2005; Wachtell et al. 2005; Ducharme et al. 2006), a large randomised controlled trial, using valsartan was negative (Disertori et al. 2009). Despite this, the renin-angiotensin-aldosterone system does appear to play a significant role in LA remodelling and the genesis and maintenance of AF.

Atrial fibrillation is also associated with electrical remodelling, involving a marked reduction in the atrial effective refractory period and loss of the physiologic lengthening of the refractory period at slower heart rates, which can all be reversed with restoration of sinus rhythm (Wijffels et al. 1995; Hobbs et al. 2000). The proposed mechanism for these electrophysiologic changes is rate induced cytosolic calcium overload caused by rapid atrial depolarisation (Goette et al. 1996; Leistad et al. 1996). Ion channel remodelling with a decrease in the protein content of the L-type calcium channel and down-regulation of the number or function of L-type calcium channels has been observed in AF (Bosch et al. 1999; Van Wagoner et al. 1999; Brundel et al. 2001). In addition, several important changes in intercellular ion channels at gap junctions have been observed in the setting of AF, including an increased expression of connexin 43 and heterogeneity in the distribution of connexin 40 (Elvan et al. 1997; van der Velden et al. 2000). This has been termed gap junctional remodelling. Furthermore, sinus node dysfunction with prolonged corrected sinus node recovery time and an increase in P

wave duration and intra-atrial conduction time have been demonstrated in AF (Elvan et al. 1996). These changes reverse gradually following conversion of AF to sinus rhythm (Elvan et al. 1996). Interestingly, a recent study found that even in patients with “lone” AF, who are presumed to have structurally normal hearts, there are significant structural and electrophysiologic abnormalities, which predispose to AF development and progression (Stiles et al. 2009).

The aforementioned atrial structural and electrophysiologic changes play an important role in initiation and maintenance of AF and are being studied as potential targets for the treatment of AF. One of the studies presented in this thesis (Chapter 4) involves the investigation of LA structure and function in patients with “lone” AF, in order to gain a better understanding of the changes in such patients and its relationship to AF initiation and progression.

1.3.4. Effects of atrial fibrillation on the left ventricle

Atrial fibrillation induced cardiomyopathy has long been recognised, but it was not until recently, that this field was revisited (Grogan et al. 1992). Both AF and CHF are common conditions, which increase in frequency with ageing (Go et al. 2001; Krum et al. 2006). Atrial fibrillation induced cardiomyopathy has been found in about 25% of patients with AF who were referred for atrioventricular node ablation and pacing (Redfield et al. 2000). In a retrospective study of patients hospitalised with CHF and associated AF, tachycardia-mediated cardiomyopathy was thought to be the underlying cause of CHF in 29% of patients with no previous known structural heart disease (Fujino et al. 2007). Atrial fibrillation can be a cause or consequence of CHF. Previous

studies have found normalisation of LV systolic function in patients with AF and LV dysfunction following cardioversion to sinus rhythm (Grogan et al. 1992), atrioventricular node ablation and pacing (Redfield et al. 2000), and more recently catheter ablation of AF (Hsu et al. 2004). These observations lend support to the concept of tachycardia-mediated cardiomyopathy and the fact that AF can lead to LV dysfunction.

Mechanistically, AF is associated with significant adverse haemodynamic consequences, which manifest as a reduction in cardiac output and can lead to progressive heart failure (Grogan et al. 1992). The underlying reasons for the haemodynamic changes observed in AF include the associated tachycardia, which when prolonged leads to tachycardia-mediated cardiomyopathy (Coleman et al. 1971); variable cycle length, which has a deleterious effect on cardiac output independent of the heart rate (Clark et al. 1997); loss of synchronised atrial contraction, which leads to a reduction in ventricular filling and a resultant decrease in cardiac output by about 20% (Morris et al. 1965; Naito et al. 1983); neurohumoral activation, involving the renin-angiotensin-aldosterone system (Boldt et al. 2003) and catecholamine secretion (Wichmann et al. 1983), which lead to a reduction in coronary blood flow (Wichmann et al. 1983) and promote ventricular hypertrophy and fibrosis (Young et al. 1994).

On the other hand, LV dysfunction significantly increases the risk of AF (Benjamin et al. 1994). The prevalence of AF increases from 4% in patients with New York Heart Association (NYHA) class I heart failure (The SOLVD Investigators 1992) to 50% in patients with NYHA class IV heart failure (The CONSENSUS Trial Study Group

1987). In addition, patients with diastolic dysfunction are also at an increased risk of developing AF, with the risk increasing with severity of diastolic dysfunction (Tsang et al. 2002). Pathophysiologically, LV systolic and diastolic dysfunction are associated with elevated LA pressures and stretch. Left atrial stretch leads to electrophysiologic and structural alterations including stimulation of stretch activated channels (Bode et al. 2000), shortening of atrial effective refractory period and lengthening of atrial conduction time (Solti et al. 1989), and fibrosis (Shinagawa et al. 2002). In addition to these, significant cellular electrophysiologic changes occur in atrial myocytes in the setting of CHF, including reduced density of L-type calcium, transient outward potassium, and delayed rectifier potassium currents (Li et al. 2000). Furthermore, CHF is associated with neurohumoral activation, particularly the renin-angiotensin-aldosterone system, which in turn leads to atrial fibrosis (Sadoshima and Izumo 1993). These pathophysiologic changes in CHF set up the substrate for AF, which frequently complicates CHF.

The above discussion outlines the complex relationship between AF and CHF. It has been suggested that in patients with no underlying structural heart disease, AF, particularly with suboptimal rate control, can lead to some degree of LV dysfunction, which is often clinically under-recognised. Furthermore, in patients with underlying structural heart disease, AF can cause significant haemodynamic deterioration, as described, and lead to decompensated heart failure.

1.3.5. Effects of atrial fibrillation on the right atrium and ventricle

There is a paucity of data regarding the effects of AF on the right heart. Although intuitively, the process of structural and electrical remodelling occurring in the left heart is also likely to be present in the right heart, there are indeed few studies that have investigated this hypothesis. One small study in patients with “lone” AF, and normal atrial size at baseline, who were followed up over a mean of 20.6 months, found a significant increase in both left and right atrial (RA) size, with the extent of enlargement being the same in both atria (Sanfilippo et al. 1990). The implications of this study are that AF leads to atrial structural remodelling, which occurs to a similar degree in both atria. At the cellular level, histopathologic examination of human RA appendages, in patients undergoing open heart surgery, has revealed a significant burden of apoptotic myocytes with myolysis contributing to cellular remodelling in the setting of AF and dilated atria (Aime-Sempe et al. 1999). Furthermore, RA fibrosis has been demonstrated in a dog model of induced AF with and without concomitant pacing induced ventricular dysfunction (Avitall et al. 2008).

Despite evidence demonstrating the prognostic significance of right ventricular (RV) size and function in various settings (Otasevic et al. 2005; La Vecchia et al. 2006; Sade et al. 2009), there is little data regarding the effects of AF on RV structure and function and its prognostic implications. This may partly be due to the limitations of conventional imaging modalities in assessing RV structure and function. Thus, there is a clear need for studies to fill this knowledge gap and allow a better understanding of the effects of AF on overall cardiac structure and function.

1.3.6. Clinical consequences of atrial fibrillation

Atrial fibrillation carries a significant burden of morbidity and mortality (Benjamin et al. 1998). In the Framingham Heart Study, AF was associated with increased mortality with an odds ratio of 1.5 in males and 1.9 in females, after adjustment for pre-existing cardiovascular disease (Benjamin et al. 1998). Although this may partly be attributable to increased stroke and CHF risk, AF may also be associated with underlying confounding factors, which increase mortality, rather than being a causal factor.

The clinical presentation of AF can be highly variable with some episodes being highly symptomatic, while others may be largely asymptomatic and only detected through monitoring (Page et al. 1994). In some cases, AF can be associated with disabling symptoms such as palpitations, dyspnoea, exercise intolerance, exacerbation of angina, CHF, and thus lead to a noticeable impairment in quality of life (Hamer et al. 1994).

Stroke is the most feared complication of AF, with the overall risk being about 5% per year in the setting of nonvalvular AF (Wolf et al. 1991). The underlying mechanisms of thromboembolism in the setting of AF are rather complex. Traditionally, stasis associated with AF has been thought to promote thrombus formation, which usually occurs within the LAA (Black et al. 1991). More recently, other potential contributing factors have emerged. Numerous studies have found a systemic hypercoagulable state in patients with AF. Soluble P-selectin, a marker of platelet activation, and plasma von Willebrand factor, a marker of endothelial damage/dysfunction, have been shown to be elevated in AF patients with established thromboembolic risk factors (Conway et al. 2002). Furthermore, another study confirmed evidence of intravascular thrombogenesis

with increased levels of fibrinogen and fibrin D-dimer (Lip et al. 1996). In fact, the markers of platelet aggregation and coagulation appear to correlate with the duration of AF (Sohara et al. 1997). Regional activation of the coagulation system has been found in patients with AF in the setting of rheumatic mitral stenosis, with increased levels of fibrinopeptide A, thrombin-antithrombin III complex and prothrombin fragment F1.2 in the LA (Yamamoto et al. 1995; Peverill et al. 1996). These findings suggest that the underlying pathophysiology of thromboembolism in the setting of AF is likely to be multifactorial. The effects of various treatment strategies on these underlying abnormalities are not well understood and are currently under investigation.

1.3.7. Rhythm versus rate control in atrial fibrillation

The issue of rhythm versus rate control is rather controversial. The theoretical and haemodynamic advantages of a rhythm control strategy are appealing. As discussed earlier, AF is associated with atrial electrical and structural remodelling that promotes further AF, leading to the dictum of “AF begets AF” (Wijffels et al. 1995). Rhythm control has long been advocated as it was thought to lead to restoration of normal haemodynamics, reduction in AF related symptoms, improvements in exercise tolerance and quality of life, possible amelioration of thromboembolic risk obviating the need for long-term anticoagulant therapy, prevention of cardiac electrical and structural remodelling, and even improvement in survival (Waldo 1999).

Over the last decade, several randomised trials have addressed the question of rhythm versus rate control in AF (Hohnloser et al. 2000; Van Gelder et al. 2002; Wyse et al. 2002; Carlsson et al. 2003; Opolski et al. 2004). The results have largely dampened the

enthusiasm surrounding a rhythm control strategy due to a lack of any demonstrable benefit and a possible tendency towards increased adverse events with a rhythm control strategy (Hohnloser et al. 2000; Van Gelder et al. 2002; Wyse et al. 2002; Carlsson et al. 2003; Opolski et al. 2004).

The most compelling reason to adopt a rhythm control strategy would be a reduction in mortality and significant morbidity, such as stroke and CHF. The largest trial of rhythm versus rate control, with the longest period of follow-up, designed to address this question was the AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) study (Wyse et al. 2002). The trial involved over 4000 patients above the age of 65 years, or with risk factors for stroke, with a primary endpoint of overall mortality. After a mean follow-up of 3.5 years, there was no significant difference in overall mortality between the rhythm versus rate control arms (26.7% versus 25.9%, $P = 0.08$). However, there was a concerning, albeit small and nonsignificant, increase in mortality and stroke rate in the rhythm control group (Wyse et al. 2002). The nonsignificant increase in overall mortality in the rhythm control group in the AFFIRM study was particularly observed in older patients, those with CHF and coronary artery disease (Wyse et al. 2002). On *post hoc* analysis, the observed excess mortality in the rhythm control arm was attributable to the toxicity of the antiarrhythmic agents used in that group (Steinberg et al. 2004). These findings raise serious questions about the efficacy and safety of current medical rhythm control strategies. The increased occurrence of stroke in the rhythm control group runs contrary to the previously postulated benefits of a rhythm control strategy. A possible explanation for the nonsignificant increase in stroke rate in the rhythm control group is the occurrence of

asymptomatic AF following the cessation of therapeutic anticoagulation in this group, implying that patients with AF at high risk of thromboembolic events should remain anticoagulated despite being treated with a rhythm control strategy. Although the AFFIRM study did not directly address this issue, further *post hoc* analyses support this notion (Sherman et al. 2005).

The proposed positive effects of sinus rhythm maintenance in reducing the development and ameliorating the symptoms of CHF have not been confirmed in the rhythm versus rate control studies. There was no significant difference in the rate of development of new CHF between the 2 groups in the AFFIRM study (2.7% in the rhythm control group versus 2.1% in the rate control group) (Wyse et al. 2002). Furthermore, in the second largest randomised trial of rhythm versus rate control, the RACE (RATE Control versus Electrical cardioversion for persistent atrial fibrillation) study, there was no significant difference in CHF related hospitalisations (4.5% in the rhythm control group versus 3.5% in the rate control group) following 2.3 years of follow-up (Van Gelder et al. 2002). The issue of rhythm versus rate control in the setting of CHF was directly addressed in the AF-CHF (Atrial Fibrillation and Congestive Heart Failure) study (Roy et al. 2008). Over 1300 patients with LV ejection fraction of $\leq 35\%$, symptomatic CHF, and AF were randomised to pharmacological rhythm versus rate control groups. After a mean follow-up of 3.1 years, there was no significant difference in the primary endpoint of cardiovascular mortality (27% in the rhythm control group versus 25% in the rate control group). In addition, secondary endpoints including overall mortality, stroke and worsening CHF were similar between the two groups. In fact, there was an excess of hospitalisations in the rhythm control group, largely due to the need for repeat

cardioversions and modification of antiarrhythmic therapy. Thus, current evidence suggests that pharmacological rhythm control strategies do not lead to improvements in CHF related outcomes and could possibly cause increased morbidity due to antiarrhythmic related toxicity.

As discussed earlier, AF can be associated with significant symptoms and impairment in quality of life (Hamer et al. 1994). Although one would expect a rhythm control strategy to reduce AF related symptoms and hence improve quality of life, this has not been borne out in the aforementioned rhythm versus rate control trials (Hohnloser et al. 2000; Wyse et al. 2002; Carlsson et al. 2003; Hagens et al. 2004). In 2 of the smaller studies, rhythm control was found to improve exercise capacity, but this did not result in an improvement in the overall quality of life (Hohnloser et al. 2000; Opolski et al. 2004). These findings may again be due to the limited efficacy and significant toxicity of current antiarrhythmic therapies. In addition, quality of life depends on many variables and can be difficult to interpret. While there is no clear benefit of either rhythm or rate control strategy in symptom management and quality of life in numerous studies, this finding cannot be extrapolated to an individual patient, who may derive significant improvement in symptoms with a rhythm control strategy. Hence, this issue remains unresolved and patients with AF are often treated based on individual symptoms and preferences.

Overall, the results of randomised rhythm versus rate control studies have not only shown no significant difference in mortality, but suggest possibly increased mortality and hospitalisation with a rhythm control strategy (Van Gelder et al. 2002; Wyse et al.

2002). The theoretical benefits of maintenance of sinus rhythm may not have been realised in these studies, predominantly due to the disappointing performance of the current antiarrhythmic drugs. In the RACE study, only 39% of patients in the rhythm control group were in sinus rhythm at 2.3 years of follow-up (Van Gelder et al. 2002). In the AFFIRM study, there was a higher proportion of patients in the rhythm control group who were in sinus rhythm, however, it was still a modest 63% (Wyse et al. 2002). The proportion of patients remaining in sinus rhythm were likely to be overestimated as the patients were followed up symptomatically and had 12 lead electrocardiograms at follow-up visits (Van Gelder et al. 2002), which could have missed many asymptomatic episodes of AF recurrence. Thus the limited efficacy of the currently available antiarrhythmic drugs is a major obstacle in determining the effects of sinus rhythm maintenance on long-term outcomes. The toxicity of antiarrhythmic drugs used for rhythm control manifested as increased hospitalisations, QT interval prolongation and increased pulmonary events, which may have negated the potential beneficial effects of maintenance of sinus rhythm (Steinberg et al. 2004). Furthermore, the cessation of anticoagulation in some patients in the rhythm control group may have contributed to the excess stroke rate in this group (Wyse et al. 2002).

Finally, the two largest studies, AFFIRM and RACE, tended to include older, asymptomatic patients with underlying heart disease (Van Gelder et al. 2002; Wyse et al. 2002). Thus, the issue of rhythm control in younger, symptomatic patients with little or no underlying heart disease remains unanswered. In addition, the use of more efficacious and less toxic means of rhythm maintenance may lead to substantial benefits with a rhythm control strategy.

1.3.8. Atrial fibrillation ablation

Surgical AF ablation using the Cox-Maze procedure was initially introduced in 1987 (Cox et al. 1991). The theoretical basis behind the procedure was based on the fact that AF was initiated and maintained by macroreentrant circuits within the atria, which in turn could be terminated by creation of surgical incisions within the atria (Cox et al. 1991b; Cox et al. 1991a). Although this was a significant step in nonpharmacological rhythm maintenance, it was a highly invasive, technically demanding and time-consuming procedure, which was largely reserved for patients having concomitant heart surgery.

Early attempts at replicating the maze procedure using a less invasive transcatheter based approach, although initially encouraging (Haissaguerre et al. 1994; Swartz JF 1994), were hindered by prolonged procedures, complex catheter manipulation within the atria, high complication rates and ultimately limited efficacy (Gaita et al. 1998). The seminal work of Haissaguerre et al. demonstrating that PVs are a source of ectopic beats that initiate AF (Haissaguerre et al. 1998), has led to a revolution in the field of AF ablation. Over the last decade, AF ablation has evolved from a largely experimental procedure to one that is commonly performed worldwide. While numerous modifications to the originally described ablation procedure have been developed over the last decade (Pappone et al. 2000), an essential component involves the complete electrical disconnection of the PVs from the LA (Jais et al. 2002). This leads to the elimination of the triggering factor and can be highly effective in maintaining sinus rhythm, particularly in the subset of patients with paroxysmal AF and little LA abnormality (Oral et al. 2003). However, in patients with persistent and permanent AF,

elimination of triggers is insufficient and significant modification of the arrhythmogenic substrate may be required (Nademanee et al. 2004; Haissaguerre et al. 2005; Haissaguerre et al. 2005; Sanders et al. 2007).

The rationale for performing AF ablation is essentially similar to the postulated benefits of a rhythm control strategy, including the alleviation of AF related symptoms and improvement in quality of life, establishment of normal haemodynamics, reduction in the risk of stroke and CHF, and ultimately decreased mortality. However, unlike the prior studies suggesting a lack of benefit of a rhythm control strategy, ablation provides the opportunity to eliminate the use of antiarrhythmic drugs; a known contributor to an adverse clinical outcome. Therefore, at least theoretically, there is a potentially significant advantage in such a strategy.

Currently, there is no standardised approach to trials involving AF ablation and hence interpretation of results can be difficult. One of the issues is the definition of a successful procedure. This has varied significantly between studies, with some defining success as freedom from symptomatic AF, while others have considered both symptomatic and asymptomatic recurrence, and yet others have defined it as a significant reduction in AF burden. Furthermore, the detection of asymptomatic AF is highly dependent on the intensity of monitoring. Other issues include the inclusion or exclusion of atrial flutter and other atrial arrhythmias as failure of therapy, duration of follow-up, the duration of the “blanking period” when early arrhythmia recurrences are not considered as treatment failure, and the reporting of success rates following several ablation procedures and/or on antiarrhythmic therapy. The heterogeneity of the patient

population in AF ablation trials has hindered interpretation and extrapolation of results to the clinical setting. It has now been established that the type of AF is an important determinant of outcomes, with patients in paroxysmal AF having better outcomes compared with those who have persistent or longstanding persistent AF (Berruezo et al. 2007). Other factors implicated in the recurrence of AF following ablation include increasing age, presence of hypertension, concomitant structural heart disease, features of the metabolic syndrome, elevated inflammatory markers, and left atrial dilatation (Berruezo et al. 2007; Abecasis et al. 2009; Letsas et al. 2009). Furthermore, differences in technique, local expertise, and volume of a centre can have a significant bearing on overall results. Given these limitations, concerted efforts are being made to improve the quality of published data in this field in order to guide future treatment and developments in AF ablation.

In the meantime, the available evidence supports AF ablation as being significantly superior to antiarrhythmic drug therapy for the prevention of recurrent AF, with consequent improvement in symptoms and quality of life (Wazni et al. 2005; Pappone et al. 2006; Oral et al. 2006b; Jais et al. 2008). However, there is a clear lack of randomised trial data assessing other endpoints. Early, nonrandomised, single centre studies have shown promising results (Pappone et al. 2003), but these need to be confirmed in multicentre, randomised trials.

The effects of AF ablation on long-term stroke risk have not been established. In a single centre, retrospective study involving 755 patients who had undergone AF ablation, 56% of whom had 1 or more risk factors for stroke, 1.1% had a

thromboembolic event (Oral et al. 2006). The majority of the thromboembolic events occurred in the first 2 weeks post-ablation and 2 later episodes occurred despite therapeutic anticoagulation. Following documentation of the lack of AF recurrence 3 - 6 months post-ablation, anticoagulation was ceased in 79% of patients without and 68% of patients with risk factors for stroke. In this cohort, patients > 65 years old and those with a prior history of stroke were less likely to have discontinuation of their anticoagulant therapy. During a mean follow-up period of 25 months, none of the patients in whom anticoagulation was ceased had thromboembolic events. While this preliminary data is very encouraging, there are several caveats to consider. The study was a retrospective analysis and prone to bias. Patients at higher risk, such as older patients and those with previous stroke, remained on anticoagulation. Hence, these findings are at best hypothesis generating and cannot be extrapolated to the wider population of patients undergoing AF ablation, particularly older patients and those who have experienced previous episodes of thromboembolism. Furthermore, there have been concerning reports of thromboembolism and LAA thrombus formation in patients who had remained in sinus rhythm post-AF ablation (Lombardo et al. 2006). Thus, randomised trials of long-term anticoagulation versus cessation of anticoagulation following AF ablation are required to provide more definitive answers to this important clinical question.

As described earlier, AF and CHF frequently occur together. AF leads to a deterioration in haemodynamics and symptoms, and could ultimately increase mortality in the setting of CHF (Dries et al. 1998). The potential benefits of sinus rhythm maintenance were not borne out with a pharmacological rhythm management strategy (Roy et al. 2008). As

discussed in detail earlier, the lack of benefit with maintenance of sinus rhythm is thought to be predominantly due to the limited efficacy and significant toxicity of the antiarrhythmic drugs. Thus, intuitively, rhythm control with a less toxic and more effective strategy, namely AF ablation, would be expected to improve outcomes in patients with AF and CHF. Several studies have supported this hypothesis (Hsu et al. 2004; Chen et al. 2004; Tondo et al. 2006; Gentlesk et al. 2007; Lutomsky et al. 2008; Khan et al. 2008). In a retrospective analysis, Chen et al. found a nonsignificant increase in LV ejection fraction of 4.6% and significant improvement in quality of life at 6 months post-ablation, in patients with impaired LV systolic function and AF (Chen et al. 2004). In their cohort, 73% of patients with impaired LV systolic function were free from AF recurrence at 14 months follow-up (Chen et al. 2004). In a prospective, nonrandomised study involving 58 consecutive patients with CHF having AF ablation, after a mean follow-up of 12 months, there was a marked improvement in LV ejection fraction of $21 \pm 13\%$, reduction in LV end diastolic dimension, overall symptoms, exercise capacity and quality of life (Hsu et al. 2004). In this study, 78% of patients were in sinus rhythm at 12-month follow-up with 69% being in sinus rhythm without using antiarrhythmic drugs. More recently, a multicentre randomised controlled study (PABA-CHF) published the findings comparing AF ablation with atrioventricular node ablation and biventricular pacing (optimal rate control) in patients with AF, LV ejection fraction $< 40\%$ and NYHA class II – III heart failure (Khan et al. 2008). At 6-month follow-up, 88% of patients in the AF ablation group were free from AF recurrence (71% without using antiarrhythmic drugs). In the AF ablation group, there was a significant improvement in LV ejection fraction (35% versus 28%, $P < 0.001$), 6-

minute walk distance and quality of life questionnaire scores, compared with the group undergoing atrioventricular node ablation and biventricular pacing (Khan et al. 2008).

In totality, the above results are consistent with the notion that in the setting of CHF, successful rhythm control, attained without the use of toxic antiarrhythmic drugs, can lead to beneficial effects. One of the important remaining questions in this field is the effect of AF ablation on the clinical endpoints of CHF hospitalisation and mortality, which needs to be addressed by large, multicentre, randomised trials.

Despite the widespread application of AF ablation, and its impressive reported success rates in maintaining sinus rhythm over medium term follow-up (Pappone et al. 2003), there are numerous limitations and gaps in our understanding, which require further study. The issues of thromboembolic risk and effects on LV structure and function in patients with CHF have been discussed previously. Pre-procedural predictors of success have not been clearly established. Limited studies have suggested a younger age (Gerstenfeld et al. 2006; Sauer et al. 2006), presence of paroxysmal AF (Gerstenfeld et al. 2006; Berruezo et al. 2007), shorter duration of AF (Matsuo et al. 2009), longer surface ECG AF cycle length (Matsuo et al. 2009), smaller LA (Abecasis et al. 2009) and LV size (Berruezo et al. 2007), absence of hypertension and obstructive sleep apnoea (Sauer et al. 2006) as being predictors of maintenance of sinus rhythm following AF ablation. In Chapter 5, we report the findings of a study investigating pre-procedural predictors of long-term maintenance of sinus rhythm following AF ablation.

Another pertinent question is the consequence of AF ablation on LA structure and function. AF ablation has consistently been found to lead to a reduction in LA size (Tsao et al. 2005; Jayam et al. 2005; Beukema et al. 2005; Perea et al. 2008). This observed reduction in LA size may be due to reverse remodelling or scarring associated with ablation. The latter has raised concerns about the impact of ablation induced LA scarring on LA function (Wylie et al. 2008). Preliminary data on the effects of AF ablation on LA function have been conflicting and inconclusive. An initial study of linear radiofrequency ablation in the setting of open heart surgery found a deleterious effect on LA volume and ejection fraction (Thomas et al. 2004). Several subsequent studies have yielded conflicting results with some suggesting preservation or improvement in LA function following percutaneous ablation (Reant et al. 2005; Verma et al. 2006; Perea et al. 2008; Tsao et al. 2009), while others have raised concerns about deterioration in LA function (Lemola et al. 2005; Wylie et al. 2008). These studies were associated with several limitations, including small sample size, lack of medium to long-term follow-up, and limitations of some imaging modalities to accurately determine chamber volume and function. The effect of AF ablation on LA function has important clinical implications. In particular, if AF ablation has a significant detrimental effect on LA function, thromboembolic risk may remain elevated despite the maintenance of sinus rhythm (Lombardo et al. 2006), thus necessitating continued anticoagulation. Therefore, further research is required in order to determine the effects of AF ablation on LA function and its clinical implications. The study presented in Chapter 6 explored the medium to long-term effects of AF ablation on cardiac structure and function, with particular emphasis on LA structure and function.

The ultimate question regarding AF ablation is whether it has an impact on mortality. In a preliminary, retrospective study involving 1,171 patients with AF, the outcomes of patients undergoing AF ablation were compared with those being treated with a pharmacological rhythm control strategy (Pappone et al. 2003). After a median follow-up period of 900 days, patients who had undergone AF ablation had improved survival, reduced morbidity and better quality of life (Pappone et al. 2003). Although these findings are encouraging, large randomised trials, which are adequately powered to address the effects of AF ablation on long-term morbidity and mortality need to be performed in order to conclusively answer these questions. In the meantime, the main indication for AF ablation remains the alleviation of symptoms and improvement in quality of life in patients with symptomatic AF, who have failed or are intolerant to antiarrhythmic drug therapy (Fuster et al.).

1.4. Assessment of left atrial structure and function

There is currently no “gold standard” non-invasive test to assess LA function. Clinically, the most commonly used imaging modality for the assessment of LA structure and function is echocardiography. Other modalities include CMR, computed tomography (CT) and LA catheterisation.

1.4.1. Implications of left atrial size and function

Left atrial dilatation results from pressure or volume overload. Pressure overload is seen with mitral stenosis and in conditions with elevated LV filling pressures, such as systolic and diastolic CHF. Volume overload occurs with mitral regurgitation and high cardiac output states (Stefanadis et al. 2001). Although initially atrial stretch can be an

adaptive response, augmenting LA output through the Frank-Starling mechanism (Yamaguchi et al. 1987; Matsuzaki et al. 1991), progressive dilatation of the LA leads to a pathologic response with a decline in LA contractile function (Anwar et al. 2007). Ultimately, LA dilatation leads to an increased risk of atrial arrhythmias, and in particular AF (Henry et al. 1976). There is a relationship between increased LA size and the risk of developing AF, with an antero-posterior LA dimension of >5.0 cm being associated with a fourfold risk of developing AF over a follow-up period of 3 years (Psaty et al. 1997).

Left atrial dilatation is a marker of cardiovascular disease burden and adverse outcomes, including AF, stroke, CHF and mortality (Gardin et al. 2001). As will be discussed in detail later, LA volume, being a more accurate measure of LA size, correlates more closely with adverse cardiovascular outcomes than LA dimension (Lester et al. 1999). The implications of LA size and function in the setting of AF have been discussed previously. However, LA size and function are of significance in other settings. Indeed LA dilatation is an important indicator of diastolic dysfunction (Paulus et al. 2007). In the absence of atrial pathology, congenital heart disease or mitral valve disease, LA volume is a good marker of the burden and chronicity of elevated LV filling pressure (Tsang et al. 2002). Left atrial volume increases with the severity of diastolic dysfunction and indicates the chronicity of the elevated filling pressures, in addition to being a marker of increased mortality in this setting (Tsang et al. 2002a; Pritchett et al. 2005). Furthermore, LA size is an independent predictor of stroke and all-cause mortality (Barnes et al. 2004). In a large retrospective study, involving a cohort of patients in sinus rhythm with no history of stroke, transient ischaemic attacks,

AF or valvular heart disease, indexed LA volume of $\geq 32 \text{ mL/m}^2$ was an independent predictor of first ischaemic stroke and all cause mortality (Barnes et al. 2004). Left atrial size has been found to correlate with cardiovascular and all-cause mortality in various settings including middle-aged (Benjamin et al. 1995; Laukkanen et al. 2005), and older individuals in the general population (Gardin et al. 2001), following acute myocardial infarction (Moller et al. 2003), and in patients with diastolic (Pritchett et al. 2005) and systolic CHF (Rossi et al. 2002). In addition, LA volume is a predictor of a first episode of CHF in a community setting, with the majority of these patients having preserved systolic function at the time of presentation with CHF (Takemoto et al. 2005). Interestingly, in some of the cited studies, when LV mass and markers of diastolic dysfunction were considered in a multivariate analysis, the effect of LA volume on mortality was either partially (Benjamin et al. 1995; Laukkanen et al. 2005) or completely (Gardin et al. 2001; Pritchett et al. 2005) abrogated. This suggests that at least some of the prognostic significance of LA size is related to LV diastolic dysfunction.

Data regarding LA function and its prognostic significance are much more scant. This is partly due to a lack of a recognised, quantitative “gold standard” method for the assessment of LA function. The literature in this field has mainly focussed on LAA function and spontaneous echo contrast (SEC), a swirling echodensity reflective of increased erythrocyte aggregation, presence of fibrinogen and a low flow state, associated with an increased risk of thrombus formation and systemic embolism (Sigel et al. 1983; Zabalgoitia et al. 1998). These indirect measures of LA function have been studied extensively and found to be predictive of adverse outcomes (Fatkin et al. 1994).

Left atrial appendage emptying velocity and SEC have been particularly well studied in the setting of AF (Mugge et al. 1994; Zabalgoitia et al. 1998).

The peak LAA emptying velocity (LAAEV), as measured by Doppler echocardiography, has been used as a marker of LAA mechanical function. It has been found to be predictive of cardiovascular outcomes in a number of settings. A low LAAEV (≤ 20 cm/s) is strongly correlated with the presence of SEC within the LA and increased risk of thrombus formation and systemic embolism in the setting of AF (Fatkin et al. 1994; Kamp et al. 1999). Following cardioversion of AF, LAAEV has been found to deteriorate initially, and improve towards normal within 1 week (Tabata et al. 1997), consistent with the well-described phenomenon of “stunning”, immediately following cardioversion, and associated with increased thromboembolic risk (Tabata et al. 1997; Sanders et al. 2003b). Furthermore, in a large, prospective, multicentre study, mean LAAEV of > 31 cm/s was an independent predictor of successful cardioversion (Palinkas et al. 2001). Following successful cardioversion, patients with a peak LAAEV > 40 cm/s have a higher likelihood of remaining in sinus rhythm at 1-year follow-up (Antonielli et al. 2002). More recently, a study in patients undergoing AF ablation has demonstrated that a lower peak LAAEV immediately post-ablation is predictive of AF recurrence within 6 months of ablation (Verma et al. 2004). A higher peak LAAEV, measured by intracardiac echocardiography during AF ablation, was found to be associated with good LA booster pump function recovery post-ablation (Donal et al. 2005). Apart from its prognostic implications in AF, LAAEV has also been studied in patients with dilated cardiomyopathy (Ito et al. 2000). In a small, retrospective,

observational study, a peak LAAEV < 50 cm/s in patients with dilated cardiomyopathy was an independent predictor of cardiovascular mortality (Ito et al. 2000).

In contrast to LAAEV, SEC is a rather qualitative measure of LA function (Fatkin et al. 1994). However, it has been extensively studied and validated, particularly in the setting of AF (Fatkin et al. 1994; Leung et al. 1994). The severity of SEC is inversely related to LAAEV, with patients who have the most severe degree of SEC and those with thrombus having a similarly low LAAEV (Fatkin et al. 1994). Clinically, SEC is graded semiquantitatively using a scale from 0 (none) to 4+ (severe) (Fatkin et al. 1994). Attempts have been made to quantitate the degree of SEC more objectively using integrated backscatter in patients with AF (Klein et al. 1996; Ito et al. 2000a) and those with rheumatic mitral stenosis (Ho et al. 2000). This has largely been restricted to the research setting due to limitations including artefacts and difficulties in data acquisition and interpretation.

In terms of its prognostic significance, SEC has been found to be a potent risk factor for thromboembolism in the setting of nonvalvular AF (Fatkin et al. 1994; Leung et al. 1994; SPAFIII 1998; Zabalgoitia et al. 1998), as well as mitral stenosis and mitral valve replacement (Black et al. 1991). In addition to being an independent marker of thromboembolic risk, SEC is correlated with clinical risk factors for thromboembolism, such as previous episodes of thromboembolism, LV dysfunction and hypertension (Zabalgoitia et al. 1998). SEC has been detected in over 80% of patients with AF who have had a recent thromboembolic event or confirmed LAA thrombus (Manning et al. 1995). More recently, patients with AF and dense SEC were noted to have increased

risk of clinically detectable and silent cerebral embolic events, despite continued anticoagulation (Bernhardt et al. 2005). Furthermore, in patients undergoing AF ablation, the use of higher intensity anticoagulation during the procedure in those with SEC at baseline, resulted in a significant reduction in the incidence of LA thrombus formation during the procedure (Ren et al. 2005). This demonstrates the prognostic utility and therapeutic implications of LA SEC in the setting of AF ablation.

There have been several interesting observations with regards to LA SEC. Left atrial SEC is found to a lesser extent in patients with coexistent mitral regurgitation and AF (Fatkin et al. 1994), consistent with previous studies that have shown a reduced risk of thromboembolism in patients with AF and associated mitral regurgitation (Blackshear et al. 1993). This is presumably due to reduced stasis within the LA in the setting of mitral regurgitation. In addition, treatment with anticoagulation does not influence the appearance of LA SEC (Black et al. 1991). This is not surprising as the underlying pathophysiologic mechanism for SEC is thought to be red cell aggregation in the setting of low shear, and indeed anticoagulation has not been found to influence red cell aggregation in vitro (Fatkin et al. 1997). However, anticoagulation is the currently preferred treatment strategy in high risk patients, as it has clearly been shown to reduce the risk of thromboembolic complications (SPAFIII 1998).

Over the years, there have been numerous imaging modalities that have been developed and used for the assessment of LA size and function. These will be discussed in detail below, elaborating on the specific methods for each imaging modality, and their relative merits.

1.4.2. Echocardiography

Echocardiography is a widely available, established, non-invasive imaging modality for assessing LA size and function. There are several parameters that can be measured using echocardiography. These will be discussed along with the implications and limitations of each of the methods.

1.4.2.1. Left atrial dimension

Left atrial dimension can be measured by M-mode and two-dimensional (2D) echocardiography. Parasternal long axis views are used for M-mode measurement of LA antero-posterior dimension. This is the smallest dimension of the LA. Although it is simple, convenient and highly specific, it is the least sensitive echocardiographic parameter for detection of LA dilatation (Lester et al. 1999). Left atrial dilatation can occur in the superior-inferior and medial-lateral axes, which are not reflected by this simple M-mode measurement of LA dimension.

Left atrial volume determinations are more accurate than linear dimensions (Lester et al. 1999). LA volume can be estimated using the cube formula, the ellipsoid model or Simpson's rule, the latter two being advocated by the American Society of Echocardiography (Lang et al. 2005). The cube formula is the simplest but least accurate method, which assumes the LA to be spherical and uses the LA antero-posterior dimension as its diameter (Khankirawatana et al. 2004). The ellipsoid model assumes the LA to be a prolate ellipse and uses 2 orthogonal short axis dimensions and one long axis dimension. The volumes determined using these linear dimensions are

highly dependent on the location and direction of the minor axis measurements, and tend to significantly underestimate LA volume (Khankirawatana et al. 2004). The biplane area-length formula substitutes area for length, in order to provide better LA volume estimation (Khankirawatana et al. 2004). LA volume can also be measured using 2D images in 2 orthogonal apical views (apical 4-chamber and apical 2-chamber) and applying the method of discs (Simpson's rule) to obtain an estimation of volume (Lester et al. 1999; Khankirawatana et al. 2004). All measurements are made at end-systole, which is echocardiographically determined to be the frame immediately preceding the opening of the mitral valve, with the LAA, PVs and mitral valve apparatus being excluded from LA volume estimations (Lang et al. 2005). The effect of body size on LA size is taken into account by indexing to body surface area (BSA) (Lang et al. 2005).

Although a more accurate and reproducible method for determination of LA size, the biplane method has several limitations. Apical views place the LA in the far field of the ultrasound beam with a resultant loss of lateral resolution and limited visualisation of the endocardium, planimetry of the LA requires estimation of posterior and lateral wall positions in order to exclude the PVs and LAA, and LA size changes with respiration (Lester et al. 1999). In addition, 2D echocardiographic measurements of LA volume make geometric assumptions, as outlined earlier, limiting their utility. Despite these limitations, the biplane echocardiographic estimation of LA volume is superior to M-mode echocardiography and has been validated using cine computed tomography (Kircher et al. 1991). Overall, echocardiographic measures underestimate LA volume compared with CT (Vandenberg et al. 1995) and magnetic resonance imaging (Rodevan

et al. 1999). It should be noted that there is slight underestimation of true LA volume by CMR, as shown in cadaveric LA cast studies (Jarvinen et al. 1994).

Recently, three-dimensional (3D) echocardiography has been found to be the most accurate echocardiographic means of LA volume estimation and has been validated using CMR (Keller et al. 2000). It has the least inter and intra-observer variability and volume underestimation (Jenkins et al. 2005). However, as 3D echocardiography is a relatively new technique, with small studies and limited availability, there is no clear consensus on the methods and comparisons with previously documented normal values. Thus, despite its demonstrated advantages, 3D echocardiographic measurements of LA volume are largely a research-based tool, while 2D biplane methods are used in routine clinical practice.

1.4.2.2. Left atrial phasic function

Numerous LA volume measurements can be used to assess LA phasic function (Toutouzas et al. 1996). Three volumes at different phases in the cardiac cycle are used to derive various LA phasic volumes. Maximum LA volume (V_{\max}) occurs at ventricular end-systole as the mitral valve opens. Minimum LA volume (V_{\min}) occurs at ventricular end-diastole, as the mitral valve closes. LA volume just prior to atrial contraction (V_p), corresponds to the onset of P wave on the electrocardiogram. The total LA emptying volume is an estimate of the reservoir volume and is the difference between the maximum and minimum LA volumes. LA passive emptying volume is the difference between maximal LA volume and the LA volume prior to atrial contraction. LA active emptying volume is the difference between the pre-atrial contraction volume

and the minimum LA volume. The LA active emptying fraction is defined as the LA active emptying volume/ V_p . The conduit volume is the difference between LV stroke volume and the total LA emptying volume.

The proportion of passive, conduit, and active LV filling largely depends on LV compliance. With ageing, there is an increase in the active LA contribution to LV filling to overcome the normal age related increase in LV stiffness, but the maximum LA volume does not increase (Thomas et al. 2003). In heart failure with preserved systolic function, there is LA enlargement and reduced LA active and passive emptying fractions (Melenovsky et al. 2007). Therefore, the measurement of these volumes can be used to assess LA phasic function in various disease states and the effects of treatments, such as radiofrequency catheter ablation (RFCA) of AF (Reant et al. 2005), on different phases of LA function.

Left atrial phasic volumes and function can also be assessed using automated border detection. Acoustic quantification is a technique used for automated border detection. It uses ultrasound backscatter to recognise the blood-tissue interface of a cardiac chamber, which allows the continuous online measurement of cardiac chamber area or volume over time that is represented in waveform (Waggoner et al. 1993). The waveforms are subsequently analysed using signal averaging to reduce noise, and parameters pertaining to the phasic function of the LA are determined (Spencer et al. 2001). Parameters derived include the maximum LA area (LA_{max}), minimum LA area (LA_{min}), LA area at the onset of atrial emptying (LA_{ae}), peak filling rate (PFR), peak passive emptying rate (PPER), and peak active emptying rate (PAER) (Spencer et al. 2001).

Reservoir function is determined using filling area ($LA_{max} - LA_{min}$), expansion index ($(LA_{max} - LA_{min})/LA_{min} \times 100$), and the PFR. The diastolic emptying index is defined as $LA_{max} - LA_{min}/LA_{max} \times 100$. The conduit function is assessed using the passive emptying percentage of total emptying ($(LA_{max} - LA_{ae})/(LA_{max} - LA_{min}) \times 100$), passive emptying index ($(LA_{max} - LA_{ae})/LA_{max} \times 100$) and the PPER (first derivative of the LA area). The active contractile component is represented by the active emptying percentage of total emptying ($(LA_{ae} - LA_{min})/(LA_{max} - LA_{min}) \times 100$), active emptying index ($(LA_{ae} - LA_{min})/LA_{ae} \times 100$) and the PAER (Spencer et al. 2001).

Studies using LA automated border detection have found that, on average, 66% of LA emptying occurs passively, while 34% is attributable to LA contraction (Spencer et al. 2001). Furthermore, there is an age-related decline in passive emptying and augmentation of active LA contraction, while LA filling is unchanged with age (Spencer et al. 2001). One study found that patients with AF have a reduced diastolic emptying index, while those with significant mitral regurgitation have a depressed expansion index and diastolic emptying index (Waggoner et al. 1993). However, automated border detection can be difficult, particularly for studying the thin-walled LA, and data analysis can be cumbersome (Keren et al. 1995). Therefore, this technique has largely been restricted as a research tool for the assessment of LA function.

1.4.2.3. *Transmitral flow*

Pulsed-wave Doppler echocardiography can be used to measure transmitral flow velocities. This is helpful in the assessment of LA function as well as LV diastology. The E wave in the pulsed-wave Doppler transmitral flow velocity curve corresponds to

the early diastolic phase, which involves passive LA emptying, while the A wave represents the late active diastolic filling phase due to LA contraction. The peak A wave velocity and A wave velocity-time integral (VTI) are markers of LA contractile function (Manning et al. 1994). However, these measures are dependent on loading conditions, heart rate, ventricular diastolic compliance (Choong et al. 1987), and ageing (Prasad et al. 2005), thus limiting their utility for the assessment of LA function.

The atrial filling fraction is another measure of LA contractile function. It estimates the LA contractile contribution to LV filling and is the fraction of A wave VTI to total mitral inflow VTI (Manning et al. 1994). This takes into consideration the variations in heart rate and is deemed to be a better marker of atrial contractile function than the A wave VTI.

The A wave VTI has been extensively used in the evaluation of LA contractile function recovery following cardioversion (Manning et al. 1994; Manning et al. 1995a), surgical ablation (Thomas et al. 2004) and RFCA of AF (Reant et al. 2005). The early studies of the effects of cardioversion of AF on LA function, using A wave VTI and atrial filling fraction, led to a better understanding of atrial stunning post-cardioversion and the time course of LA functional recovery, which is partly dependent on the duration of AF, taking up to 4 weeks in those with prolonged (> 6 weeks) AF (Manning et al. 1994).

1.4.2.4. Pulmonary vein flow

The non-invasive study of the PV flow pattern was initially described in 1985 using transthoracic echocardiography (Keren et al. 1985). Measurements of the PV flow

profile aid in the assessment of LA systolic performance (Oki et al. 1997), compliance, mean LA pressure (Kuecherer et al. 1990), prediction of LA functional recovery following AF ablation (Donal et al. 2005), and detection of PV stenosis post-AF ablation (Jander et al. 2005). In addition, PV flow patterns have been used for the assessment of LV diastolic function (Rakowski et al. 1996), estimation of LV filling pressures (Appleton et al. 1993), constrictive pericarditis (Schiavone et al. 1989), and mitral valve disease (Klein et al. 1991; Klein et al. 1993). The normal PV flow pattern is tri- or quadri-phasic (Bartzokis et al. 1991). The first systolic wave (S1) represents the flow from the PV to the LA during early ventricular systole. The second systolic wave (S2) represents late ventricular systole and isovolumic relaxation. In early diastole, a D wave is observed and in late diastole an atrial reversal (AR) wave, reflecting atrial systole is detected. Hence, in patients with AF, the AR wave is absent.

With the exception of S2, which reflects pressure propagation due to RV contraction, PV flow reflects phasic LA pressure and the parameters that influence it (Smiseth et al. 1999). The peak velocity and VTI of the PV systolic waves overall, are a reflection of LA reservoir function (Keren et al. 1985). The determinants of the PV systolic flow waves are LA relaxation for S1, and LA compliance and RV contraction for S2 (Smiseth et al. 1999). The peak velocity and VTI of the PV diastolic wave reflects LA conduit function and is determined by factors which affect LA afterload, such as LV relaxation, LV stiffness and mechanical obstruction due to mitral stenosis (Castello et al. 1991). The atrial reversal wave magnitude and duration reflect LA contractile function and LV chamber stiffness (Appleton 1997). Besides haemodynamic factors, several other physiologic factors influence PV flow, including age (Gentile et al. 1997),

preload (Hoit et al. 1992; Keren et al. 1996), heart rate and respiration (Appleton 1997). Thus, these factors need to be considered when assessing PV flow patterns.

Although TOE provides a comprehensive PV flow profile, particularly S1 and AR, improvements in equipment and technology have meant that in expert centres, transthoracic echocardiography can provide high quality PV flow recordings in up to 90% of patients (Jensen et al. 1997). Furthermore, contrast echocardiography has been utilised to improve the PV flow profile (Dini et al. 2000). Thus in routine clinical practice, transthoracic echocardiography can be used to assess PV flow with TOE reserved for assessing patients with complex haemodynamics and suboptimal PV flow recordings on transthoracic echocardiography.

1.4.2.5. Atrial ejection force

The atrial ejection force is an index of atrial systolic function, which is based on classic Newtonian mechanics. It is defined as the force exerted by the LA to accelerate blood into the LV during atrial systole (Manning et al. 1993). It can be measured non-invasively by 2D and Doppler echocardiography. It is the product of the acceleration and mass of blood going from the LA into the LV. The formula used to calculate atrial ejection force is as follows:

$$\begin{aligned} \text{Atrial ejection force} &= \text{mass} \times \text{acceleration} \\ &= 0.5 \times \rho \text{ (density of blood)} \times \text{mitral orifice area} \times V_A^2 \text{ (peak} \\ &\quad \text{transmitral A velocity)} \end{aligned}$$

The mitral valve orifice area is calculated in the apical 4-chamber view and is assumed to be circular, and the peak A velocity is measured at the level of the mitral annulus

(Manning et al. 1993). Atrial ejection force has been studied in patients following cardioversion for AF, demonstrating a much lower atrial ejection force initially post-cardioversion compared with normal controls, but a gradual improvement over weeks in patients who remained in sinus rhythm during follow-up (Manning et al. 1993). Atrial ejection force has also been used to investigate the effects of heart transplantation (Freimark et al. 1995), hypertension (Cioffi et al. 2004), antihypertensive therapy (Dernellis et al. 1996), mitral stenosis (Stefanadis et al. 1998), septal reduction therapy in hypertrophic cardiomyopathy (Nagueh et al. 1999), cardiac amyloidosis (Modesto et al. 2005), normal ageing (Thomas et al. 2002) and obesity (Chinali et al. 2006) on LA function. In a cohort of middle-aged and older adults with a high prevalence of hypertension and diabetes, atrial ejection force correlated with older age, higher body mass index, blood pressure, serum creatinine, glucose and insulin levels, and was an independent predictor of fatal and nonfatal cardiovascular events (Chinali et al. 2005). However, there are several limitations. Doppler measurements are angle-dependent and thus prone to underestimation of flow velocity if the Doppler sample is not aligned parallel to the direction of blood flow, the peak A velocity and mitral annular diameter are not measured concurrently, the reproducibility of these measurements may be questionable, and most importantly, the incremental value of this parameter over other measures of LA size and function have not been clearly established.

1.4.2.6. Pulsed-wave tissue Doppler imaging

Tissue Doppler imaging (Gardin et al.) allows quantitative assessment of myocardial contraction and relaxation, using low velocity pulsed-wave Doppler interrogation of the myocardium (Palka et al. 1995). For the assessment of LA contractile function, the

sample volume is placed on the atrial side of the mitral annulus, at the basal interatrial septum in the apical 4-chamber view and measurements are made at end-expiration to exclude respiratory variation (Thomas et al. 2003). The measurement of late diastolic peak mitral annulus velocity (A' velocity) using pulsed-wave tissue Doppler is an accurate marker of atrial contractile function (Thomas et al. 2003). A' velocity correlates well with other conventional measures of LA function (Hesse et al. 2004) such as peak A velocity, atrial emptying fraction and atrial ejection force, and has been found to increase with age, consistent with studies that used transmitral A wave velocity (Thomas et al. 2003). In addition, A' velocity is inversely associated with maximal LA volume (De Castro et al. 2008). A' velocity has also been shown to be of prognostic importance in a prospective study involving patients with a variety of cardiac disorders (Wang et al. 2003). Subjects were categorised based on tertiles of A' velocity (< 4, 4 – 7 and > 7 cm/s). After a mean follow-up of 23 months, there was a progressive increase in cardiac death in those with a lower A' velocity (hazard ratio 11.53, 95% confidence interval 4.10 - 32.39, when A' velocity was < 4 cm/s compared with > 7 cm/s) (Wang et al. 2003). These findings have been confirmed in the general population (Mogelvang et al. 2009) and in a small study of patients with aortic stenosis (Poh et al. 2008). Furthermore, A' velocity has been used as a measure of interatrial dyssynchrony by comparing the timing of onset of mitral and tricuspid annulus A' wave (Sakabe et al. 2009). In a small, prospective study, it was found that patients with paroxysmal AF who had a lower A' velocity at either the mitral or tricuspid annulus, and those with greater interatrial dyssynchrony (≥ 34 ms) had an increased likelihood of progressing to persistent AF (Sakabe et al. 2009). However, once again as Doppler measurements are angle-dependent, the accuracy and reproducibility of this parameter is highly reliant on

the beam being aligned parallel to the interatrial septum, thus limiting the utility of this parameter for assessment and serial follow-up of LA function. Furthermore, translational motion cannot be distinguished from myocardial contraction, and scarring in regions where the measurements are taken can influence the results. In an attempt to overcome these issues, multiple measurements, taken at the mitral annulus and averaged have been suggested (Mogelvang et al. 2009), but this is yet to be standardised.

1.4.2.7. Colour tissue Doppler imaging

Colour TDI allows simultaneous acquisition of myocardial velocities within various segments in the same view with subsequent measurements being made offline (Thomas et al. 2003). This method can be used to assess segmental LA contraction. The LA is divided into several segments at the annular, mid-atrial and superior levels in the apical 4-chamber and 2-chamber views (Thomas et al. 2003). It has been found that in the normal LA, there is an annular to superior segmental gradient, with the highest velocities in the segment adjacent to the annulus and little movement in the superior segment (Thomas et al. 2003). In addition, ageing is associated with a uniform increase in segmental velocities (Thomas et al. 2003). Following cardioversion of chronic AF, there is differential improvement in LA contractility at 1-week and 1-month follow-up, with recovery in the lateral, anterior and posterior annular segments being similar, while the annular septal segment is slower to recover, and the superior segment is relatively immobile compared to all other segments (Boyd et al. 2008). In a small cohort, segmental LA recovery predominantly occurred within 1-month of cardioversion, but did not normalise even at 6-month follow-up (Boyd et al. 2008). Interestingly, RA

segmental function, assessed by colour TDI, normalised at 1-month post-cardioversion (Boyd et al. 2008).

Colour TDI may be useful in assessing regional LA function in the setting of RFCA and surgical ablation for AF. In one study, following surgical linear ablation for chronic AF, velocities were found to be lower in all segments compared with patients who had been cardioverted and maintained in sinus rhythm for ≥ 6 months, who in turn had lower segmental velocities compared with normal controls (Boyd et al. 2009). In addition, in the surgical ablation group, there was a significantly lower velocity in the inferior and lateral segments compared with other segments (Boyd et al. 2009). Although this study was small, the findings are consistent with the postulated detrimental effects of scarring on LA contractility.

There are several caveats to using colour TDI for assessment of regional LA function. As mentioned previously, TDI is angle-dependent and hence the values obtained for peak velocity may be underestimated if the interrogating beam is not correctly aligned with the axis of movement of the LA wall. Furthermore, TDI cannot distinguish between passive translational motion secondary to tethering versus active contraction. Hence, the increased velocities noted in the LA segments adjacent to the annulus could be due to translational cardiac motion from the LV rather than a true difference in LA regional contractility. Importantly, the reproducibility of these measurements outside of experimental settings in expert centres has not been established. Despite these limitations, colour TDI provides a means of determining regional LA motion and

assessing the effects of different treatment strategies on segmental function, and may have implications for guiding the duration of anticoagulation following RFCA of AF.

1.4.2.8. Atrial strain and strain rate imaging

Strain is a measure of the change in myocardial fibre length compared with the original length. It is a reflection of deformation and describes the contraction and relaxation pattern of the myocardium (Urheim et al. 2000). Strain rate is the rate of deformation and is an index of contractility. Strain rate imaging involves subtraction of translational motion from regional thickening velocity (Heimdal et al. 1998). Strain and strain rate measurements have been applied in ventricular function analysis over the last decade (Urheim et al. 2000), however it was not until recently that their utility for the evaluation of LA function in various settings has been realised (Di Salvo et al. 2005). Strain analysis overcomes the problem of distinguishing between passive translatory motion and intrinsic myocardial motion associated with TDI (Di Salvo et al. 2005). Doppler based measurements are made using a narrow sector with a high frame rate (> 110 frames/s) with the LA wall aligned with the Doppler beam, and a narrow sample volume placed in the basal septal, inferior, lateral and anterior walls in the apical 4 and 2-chamber views (Thomas et al. 2007).

Atrial strain and strain rate (A-sr) have predominantly been studied in the setting of AF and conditions predisposing to AF. In a group of patients with lone AF of ≤ 3 months duration, multivariable analysis showed that atrial inferior wall peak systolic strain rate and septal peak systolic strain prior to cardioversion were the best predictors of maintenance of sinus rhythm at 9-month follow-up (Di Salvo et al. 2005). More

recently, in an observational study, Doppler derived A-sr following RFCA of AF was demonstrated to be a predictor of maintenance of sinus rhythm post-ablation (Schneider et al. 2008). In patients with chronic AF, A-sr post-cardioversion is significantly reduced immediately after cardioversion and improves over 4 weeks (Thomas et al. 2007). However, despite the maintenance of sinus rhythm for up to 6 months, A-sr remains lower than normal controls (Thomas et al. 2007). This is in contrast to previous studies that had shown normalisation of the peak A velocity on transmitral flow within 4 weeks of cardioversion (Manning et al. 1994).

Atrial strain rate has been used to assess atrial activation in the setting of AF (Thomas et al. 2007). Atrial activation can be measured as the time from aortic valve closure to peak A-sr. This has been found to be delayed following cardioversion for chronic AF, and remains essentially unchanged at 6-month follow-up, implying that atrial conduction remains prolonged despite the maintenance of sinus rhythm (Thomas et al. 2007). This may be secondary to a persistent atrial myopathic process and/or enlarged LA with delay in the time to peak A-sr. In addition to their applications in patients with AF and following ablation, LA strain and A-sr have been found to be early markers of LA dysfunction in the setting of hypertension (Kokubu et al. 2007; Eshoo et al. 2009), obesity (Di Salvo et al. 2008), diabetes (Muranaka et al. 2009), hypertrophic cardiomyopathy (Telagh et al. 2008), cardiac amyloidosis (Modesto et al. 2005) and atrial septal defect closure (Di Salvo et al. 2005).

Doppler derived atrial strain suffers from the limitation of angle dependence as outlined earlier. In particular, the angle of interrogation can be $> 30^\circ$ for the basal anterior and

lateral walls of the LA in a significant proportion of patients, thus rendering measurements at these sites unreliable (Thomas et al. 2007). In recent years, another method of strain analysis, speckle tracking, has been developed and validated (Langeland et al. 2005). This technique is independent of the angle of insonation, overcoming the limitations of Doppler derived strain indices (Langeland et al. 2005). While many studies have investigated speckle tracking for the assessment of LV function, there is a paucity of data for assessment of LA function, largely due to the technical difficulties associated with applying speckle tracking for a thin-walled chamber such as the LA. Speckle tracking 2D strain echocardiography has been used to demonstrate depressed LA contractile function at baseline and following cardiac resynchronisation therapy in patients with idiopathic dilated cardiomyopathy compared with those with ischaemic cardiomyopathy, implying possible LA involvement in the myopathic process and perhaps increased levels of diastolic dysfunction in the group with idiopathic dilated cardiomyopathy (D'Andrea et al. 2007). Peak LA wall strain during LV systole, derived using 2D speckle tracking, has been found to be inversely correlated with LV end-diastolic pressure using invasive haemodynamic measurements (Wakami et al. 2009). Speckle tracking has also been used to evaluate the effects of ageing (Okamatsu et al. 2009) and percutaneous atrial septal defect closure (Di Salvo et al. 2009) on LA function. Although speckle tracking is highly promising, both from a research and clinical perspective, it is limited by its dependency on the 2D echocardiographic image quality, in particular frame rate, which is lower compared with Doppler derived strain, and image resolution (Notomi et al. 2005; Amundsen et al. 2006). There is a trade-off between these 2 parameters. While a low frame rate leads to excessive change in the speckle pattern from one frame to the next and makes the

speckle pattern difficult to analyse and interpret, a high frame rate is associated with reduced scan line density and image resolution. The use of speckle tracking for the evaluation of LA function is an evolving field and is currently utilised within the realms of research, although this is likely to change with improvements in technique and expertise.

1.4.2.9. Blood flow within the left atrium

Blood flow within the LA has not been well studied. As mentioned earlier, studies have shown that SEC within the LA is strongly associated with stroke risk in AF (Tsai et al. 1992). One study in patients with AF or atrial flutter, investigated blood flow velocity at several sites within the LA and LAA using TOE, and related this to stroke risk (Shively et al. 1996). The lowest velocities were in the posterior region of the LA and in the LAA. There was a sharp increase in stroke risk associated with lower velocities in the posterior region of LA, and a nonsignificant increase in stroke risk in patients with low LAA velocities. In 13 out of 15 patients with cardioembolic stroke, blood flow velocity was ≤ 15 cm/s in the posterior LA and/or LAA. Low posterior LA velocities were associated with SEC, mitral stenosis, large LA, large LV, LV dysfunction, and reduced LA ejection fraction. LA blood flow velocities were higher in patients with typical atrial flutter compared with atypical atrial flutter or AF, and in patients with significant mitral regurgitation. This study suggests that stroke risk is more strongly associated with stasis within the LA body and, to a lesser extent, with velocities in the LAA (Shively et al. 1996). Furthermore, it appears that the risk of atrial stasis is highest when a low stroke volume and LV dilatation accompany LA dilatation (Shively et al. 1996). These findings were not confirmed in another study, which measured blood flow velocity at

only 1 site within the body of the LA, the mid LA (Heppell et al. 1997). Blood flow within the LA is rather complex, with a 3D vortical pattern of flow (Fyrenius et al. 2001), which will be discussed later. Therefore, echocardiographic measurements of blood flow velocity in one region may not be reflective of the true haemodynamic status within the LA.

1.4.3. Computed tomography

Since the advent of RFCA for the management of AF, CT is being commonly used in the assessment of LA structure and function, and in delineation of the complex and variable anatomy of the PVs and neighbouring structures, such as the oesophagus. Electron beam CT (EBCT) and multislice CT (MSCT) have been studied in this context. Electron beam CT has the advantage of a reasonably high temporal resolution with prospective electrocardiographic (ECG) triggering, and allows cine imaging at a rate of 17 frames/s, however, it has limited spatial resolution and a low contrast-to-noise ratio (Wiese et al. 2004). Multislice CT offers high volume coverage, excellent spatial resolution and retrospective ECG gating, but it has limited temporal resolution and higher radiation exposure, although with improvements in technique the radiation dose can be significantly reduced (Hunold et al. 2003).

Cine CT provides accurate estimation of LA volume (Kircher et al. 1991). Electron beam CT has been used to assess LA function in a subset of patients post-AF ablation, showing a significant improvement in LA size and ejection fraction (Verma et al. 2006). Furthermore, in a small comparative study involving patients with AF undergoing cardioversion, EBCT identified LAA thrombus with high sensitivity

(100%), but reduced specificity (87%) compared with TOE (Achenbach et al. 2004). However, these data are preliminary at best, and EBCT is not routinely used due to the stated limitations.

Multislice CT has been extensively used for LA and PV imaging pre- and post-RFCA of AF, due to its ability to provide excellent anatomical detail. It allows clear identification of the posterior LA and the complex and variable PV anatomy, which provides a roadmap prior to AF ablation (Marom et al. 2004). These images can be merged with electroanatomic data using proprietary software to reduce fluoroscopy times, arrhythmia recurrence, and improve rates of sinus rhythm restoration (Kistler et al. 2006). In addition, accurate localisation of the oesophagus may improve the safety of the procedure, by limiting the extent of ablation in regions that are in close proximity to the oesophagus and hence reduce the risk of atrio-oesophageal fistula formation (Sanchez-Quintana et al. 2005). Recently, MSCT has been shown to have a high negative predictive value in identifying SEC or thrombus in the LAA prior to AF ablation (Kim et al. 2007). However, other studies have been conflicting, some suggesting high inter-observer variability, with poor sensitivity and specificity for the detection of LAA thrombus (Gottlieb et al. 2008), while others have found high sensitivity but poor specificity (Feuchtner et al. 2008). Further studies are required to determine the value of MSCT for the detection of LAA thrombus, but currently TOE remains the “gold standard” for exclusion of LAA thrombus prior to AF ablation.

Multislice CT is also an important diagnostic tool following AF ablation. It can detect complications including PV stenosis (Robbins et al. 1998) and atrio-oesophageal fistula

formation (Pappone et al. 2004). In addition, MSCT can be used to detect remodelling of the PVs in patients with AF and has been used to document a reduction in PV diameter post-ablation (Scharf et al. 2003).

Advantages of MSCT over CMR in this setting include short image acquisition times, with images being acquired during 1 breath hold. In addition, patients with metallic devices (eg. pacemakers) can be examined without problems. However, radiation and contrast exposure are major limitations of MSCT, particularly for patients who have repeat ablation procedures and CT scans pre- and post-ablation.

1.4.4. Cardiac magnetic resonance imaging

Bloch and Purcell independently described the fundamentals of nuclear magnetic resonance in 1946 (Bloch 1946; Purcell et al. 1946), but it was first utilised for imaging in 1973. Since then, magnetic resonance imaging (MRI) has evolved rapidly. Although imaging of the heart posed a number of challenges, particularly due to its constant motion, there have been rapid advances over the past decade in the technical aspects of CMR, leading to significant improvements in acquisition speed and image quality, such that CMR can now provide comprehensive, high resolution non-invasive assessment of cardiac structure and function. CMR has numerous advantageous properties that make it the ideal tool for the assessment of patients with AF, both in the clinical and research setting. These include the absence of ionising radiation, high spatial resolution, excellent soft tissue contrast, large field of view in virtually any plane, the ability to accurately measure flow, as well as being the “gold standard” non-invasive imaging modality for volumetric assessment without geometric assumptions (Worthley et al.

2000). The basic principles of CMR, various anatomic and functional imaging sequences, and specific use of CMR in the setting of AF and AF ablation will be discussed below.

1.4.4.1. Basic principles of magnetic resonance imaging

Although comprehensive coverage of MRI physics is beyond the scope of this introductory chapter, a brief description of the fundamental aspects of MRI is appropriate. MRI exploits the abundant presence of hydrogen atoms within the human body to produce high resolution images. An MRI scan consists of a strong magnet, which produces an external magnetic field. The hydrogen atoms within the body have one proton, which spins in a random direction. When exposed to a strong external magnetic field, these spins align parallel to the long axis of the magnetic field, like compass needles, and revolve or precess with a specific frequency, the Larmor frequency. The frequency of precession increases with the strength of the magnetic field.

Following exposure to the magnetic field, the protons can then be stimulated with brief radiofrequency pulses of a specific frequency, corresponding to the Larmor frequency of the hydrogen protons. This causes a momentary flip in the direction of proton spins, which is no longer aligned with the magnetic field. Following excitation, the spins eventually return to their original resting (lower energy) orientation and in the process emit a radio signal, which is used for image generation through Fourier transformation.

An important concept in MRI is T1 and T2 relaxation. When the spins are excited, their magnetisation has longitudinal and transverse vector components. As the spins relax, the longitudinal magnetisation increases towards the resting state, while the transverse component gradually disappears. These processes have been termed T1 and T2 relaxation respectively. The times for T1 and T2 relaxation are specific to each tissue and are fundamental to the image contrast produced by different tissues, and tissue characterisation in MRI.

1.4.4.2. Anatomic and functional imaging

There are two broad groups of sequences commonly used in CMR, spin-echo and gradient-echo. Spin-echo pulse sequences involve an initial 90° pulse, which rotates the magnetisation in the XY plane. The transverse magnetisation subsequently begins to dephase and a 180° pulse is used to rephase the magnetisation and produce a signal (Haddad et al. 1995). Spin-echo sequences produce a “black blood” image, which is used for anatomic assessment of cardiac and vascular structures. Traditionally, spin-echo imaging has been limited by motion artefacts (Winterer et al. 1999). Currently, breath hold segmented fast spin-echo sequences are used for higher resolution images, with rapid nonbreath hold acquisitions being routinely performed using single-shot spin-echo sequences to define the relationship of the great vessels and details of the vessel walls (Stehling et al. 1996). The major disadvantage of breath hold spin-echo imaging remains the length of the sequence, particularly when T1 is prolonged (Simonetti et al. 1996).

One of the major strengths of CMR is its ability to demonstrate cardiac function with excellent spatial resolution, using cine imaging. Initially, this was acquired using a gradient-echo sequence, which produced a “bright blood” image. This involved the application of a slice-selective radiofrequency pulse and gradient, followed by a phase-encoding gradient and finally a frequency-encoding gradient, with production of an echo (Alfakih et al. 2003). The bright blood signal was due to the inflow of moving blood, thus making the sequence susceptible to flow related artefacts with difficulty in delineating blood and myocardium, particularly in cases of slow blood flow. The advent of steady state free precession (SSFP) sequences, has led to a dramatic improvement in cine image quality and better definition of the blood-myocardium interface, in a shorter time compared with gradient-echo based sequences (Pereles et al. 2001). Steady state free precession sequences are dependent on the T2/T1 ratio of the imaged tissue rather than blood inflow characteristics (Reeder et al. 2004). Steady state free precession sequences allow accurate visualisation of ventricular wall motion, as well as volumetric quantification of all chambers. In fact, CMR is currently regarded as the “gold standard” non-invasive imaging modality for cardiac chamber volume and function analysis (Pennell 2001).

Despite its many advantages, SSFP is limited by the data being acquired over several cardiac cycles and combined to produce an image. Thus, irregularities in heart rate or rhythm, such as AF or frequent ectopy, lead to significant degradation in image quality. This can be overcome to some extent by using prospective triggering, which essentially commences imaging from the R wave on the ECG for a predetermined time, up to about mid-diastole, as heart rate irregularity usually affects diastole. Although this can

improve the quality of the images, the latter part of diastole is not captured and hence the chamber volumes and ejection fractions derived using prospective triggering are significantly reduced compared with retrospectively gated imaging (Sievers et al. 2005). Other options in cases of arrhythmias hindering ECG gating include real time imaging, with a lower spatial resolution, but it does allow visual analysis of wall motion and estimation of function, and use of arrhythmia detection algorithms, which can prohibitively lengthen scan times and associated breath holds.

1.4.4.3. Measurement of Blood Flow

Blood flow can be accurately assessed using velocity encoded cine (VENC), otherwise known as phase contrast sequences (Underwood et al. 1987). This is based on the principle that the phase of flowing spins in a magnetic field will change in direct proportion to their flow velocity. Two sequential gradients, composed of 2 lobes with opposite polarities are applied. The first pulse leads to a phase shift, which is reversed by the second. Thus, stationary spins have no net phase, while flowing spins acquire a net phase change that is dependent on the direction and flow of the spins.

Anatomical information is provided in the magnitude images, while phase images encode velocity information. Aliasing occurs if the maximum flow velocity exceeds the encoded velocity range selected by the operator. The velocity range is usually set just above the expected maximum velocity, in order to avoid aliasing and at the same time obtain the most accurate measurement of flow velocity. Velocity can be encoded in planes perpendicular (through-plane), or parallel (in-plane) to the direction of flow (Pennell 2001). More recently, time resolved 3D velocity encoding sequences have

been described (Bock et al. 2009). Flow measurements can be particularly useful for determination of severity of stenoses (Eichenberger et al. 1993) and assessment of flow through vasculature (Kondo et al. 1991). The specific applications in the setting of AF ablation will be discussed later.

1.4.4.4. Magnetic Resonance Angiography

Several magnetic resonance angiography (MRA) techniques have been described, namely time of flight, phase contrast and contrast enhanced (CE) MRA. The time of flight technique is limited by the duration of image acquisition and associated artefacts (Chiesa et al. 1993). Contrast enhanced MRA is a robust technique that can provide high quality images, in a single breath hold, and is now the most commonly used MRA technique.

Contrast enhanced MRA is performed using intravenous gadolinium based contrast agents. This leads to a significant increase in blood signal. The timing of the scan in relation to Gd injection is important for appropriate data collection (eg. arterial or venous phase). A small test bolus is administered initially to estimate the contrast arrival time at the target vessel and hence determine the optimal timing of image acquisition (Hany et al. 1997). A T1 weighted, spoiled gradient echo sequence can be used to acquire multiple thin slices in a 3D volumetric data set, with the ability to reformat the images in any plane. Although the in-plane resolution, slice thickness and volume of coverage can be selected by the operator, higher image resolution does come at the cost of longer breath holds, which may not be tolerated by patients. Thus, the set

parameters require a compromise between image resolution and scan duration. The value of CE-MRA in AF ablation will be discussed in detail later.

At this stage, it is important to cover some salient features of MRI contrast agents, as CE-MRA is performed using intravenous contrast agents. MRI contrast agents have paramagnetic moieties, which influence tissue relaxation parameters. Gadolinium-based MRI contrast agents chelated with ligands such as diethylenetriaminepentaacetate (DTPA), in order to render them nontoxic, were first used in clinical practice in the late 1980's (Stack et al. 1988). These agents act by significantly reducing T1 relaxation time, which is subsequently exploited by using heavily T1 weighted imaging sequences that depict tissues, including blood, containing a higher concentration of Gd as bright. The cardiovascular applications of contrast agents in MRI includes MRA (Wang et al. 1998) and scar imaging (Kim et al. 1999).

The safety and efficacy of MRI contrast agents has been demonstrated in various settings over many years. However, over recent years, a link between a severe, disabling and untreatable condition causing systemic fibrosis in patients with severe renal dysfunction, called nephrogenic systemic fibrosis (NSF) and Gd-based contrast agent use has been reported (Grobner 2006). Subsequent histopathologic studies have confirmed the presence of Gd within tissues of patients with NSF (High et al. 2007). This has prompted the American Food and Drug Administration and other regulatory authorities worldwide to issue warnings against the use of Gd-based contrast agents in patients with acute or severe chronic renal dysfunction (glomerular filtration rate < 30 mL/min/1.73 m²), and renal dysfunction of any severity in patients with the hepatorenal

syndrome or in the perioperative liver transplant period (FDA 2006). The risk of NSF with each individual agent is unknown, but factors that increase risk include multiple or higher than recommended doses of Gd-based contrast agents, linear Gd chelates, and the severity of renal dysfunction (Zou et al.). Overall, it has been estimated that the risk of NSF in patients with severe renal dysfunction following Gd administration is about 4% (Marckmann et al. 2006). There is currently no specific treatment for NSF, and although early dialysis following Gd administration has been suggested, the effect of such measures on the risk of NSF is unknown (FDA 2006). To date, two cases of NSF have been reported in. The risk in patients with estimated glomerular filtration rate between 30 – 60 mL/min/1.73 m² is unclear, but appears to be very low. The current recommendations in patients with glomerular filtration rates of 30 – 60 mL/min/1.73 m² are to exercise caution and use the lowest possible dose of Gd when necessary (FDA 2006).

1.4.4.5. Scar imaging

A unique capability of CMR is its ability to provide accurate, high resolution imaging of scarred myocardium (Kim et al. 1999). Areas of scarring demonstrate different contrast kinetics compared with normal myocardium, with increased extracellular space and volume of distribution for Gd (Rehwald et al. 2002). Thus, areas of scarring will have a higher concentration of Gd at 5 – 10 minutes following Gd administration (Rehwald et al. 2002). In order to highlight areas of scarring, which appear as areas of delayed enhancement, a gradient-echo based sequence with an inversion prepulse is used to produce a heavily T1 weighted image (Simonetti et al. 2001). The inversion pulse flips the magnetisation 180°. Areas of scarring, with an increased concentration of

Gd have a shorter T1 relaxation time, thus the recovery of longitudinal magnetisation back to baseline will be more rapid compared with normal myocardium. The image acquisition is timed in relation to the inversion pulse, such that the normal myocardium is at the zero line, while the scarred myocardium will have moved above the zero crossing line and towards baseline due to its shorter T1 relaxation time. This results in maximal signal suppression from normal myocardium, called nulling, and maximal signal intensity from areas of scarring with high Gd concentration. Scarred areas will therefore appear bright, while the normal myocardium is black.

Scar imaging uses a segmented inversion recovery sequence, acquiring images at alternate heartbeats in order to allow recovery of magnetisation in the normal myocardium to baseline prior to applying the next inversion pulse. The images are of high quality, but can be limited by difficulties with breath holding and presence of arrhythmias. In such cases, single shot, SSFP inversion recovery sequences can be used to acquire delayed enhancement images in a shorter time. Although the contrast to noise ratio and the sensitivity for scar detection are slightly reduced, the SSFP based sequence has an excellent correlation with segmented inversion recovery sequences, and is a reasonable alternative in cases where conventional sequences cannot be performed (Huber et al. 2006).

Scar imaging has been used for the assessment of myocardial infarction (Kim et al. 1999), viability (Kim et al. 2000), cardiac amyloidosis (Maceira et al. 2005), cardiac sarcoidosis (Smedema et al. 2005), myocarditis (Friedrich et al. 1998), and differentiation of ischaemic from idiopathic dilated cardiomyopathy (McCrohon et al.

2003). Recently, technological advances have enabled scar imaging of the LA in the setting of AF and RFCA (Peters et al. 2007). This will be discussed in greater detail later.

1.4.4.6. Assessment of left atrial volume

Human cadaveric LA cast studies have shown an excellent correlation between CMR measured and true LA volumes ($r = 0.99$, $P = 0.009$), with a minor, but consistent underestimation of true LA volume by CMR (-1.7 ± 2.1 mL, $P = 0.005$) (Jarvinen et al. 1994). In comparison, echocardiography can underestimate LA volume by up to 47% when compared with CMR (Rodevan et al. 1999). While 3D echocardiography has improved the accuracy of LA volume determination using echocardiography, CMR remains the most accurate imaging modality for LA volume determination and the standard against which all other imaging modalities are compared (Keller et al. 2000).

Several methods of LA volume measurement using CMR have been reported. The simplest, but least reproducible method involves the extension of the biplane area-length method used in echocardiography (Hudsmith et al. 2007). However, the area-length method has been found to slightly, but significantly, overestimate LA volume in one study (Sievers et al. 2004). Three dimensional volumetric measurements, applying Simpson's rule, produce the most accurate LA volumes (Jarvinen et al. 1994). It has been suggested that imaging in the long axis planes may provide more accurate and reproducible results, as the mitral valve plane is clearly visible in these views (Jarvinen et al. 1994). However, there have been no comparative studies using different imaging planes, and the best imaging plane and parameters are yet to be clearly established.

Previous CMR studies have documented a significant reduction in LA volume following AF ablation (Tsao et al. 2005; Jayam et al. 2005; Perea et al. 2008). However, Jayam et al. and Tsao et al. used LA dimensions, derived from MRA, to estimate LA volume, thus making geometric assumptions. Although MRA based measurements of LA volume correlate well with SSFP based volumetric measurements, there is a significant underestimation of LA size with MRA and wide limits of agreement (Hauser et al. 2004). Ideally, volumetric measurements applying Simpson's rule should be used, particularly in research settings and when serial follow-up of LA volume is required. This would improve the power of the studies and substantially reduce the sample size (Bellenger et al. 2000) required to demonstrate an effect following interventions such as AF ablation.

1.4.4.7. Evaluation of left atrial function

Volumetric measurements can be used to derive phasic LA function, including LA maximum and minimum volumes, reservoir volume, conduit volume, stroke volume and LA ejection fraction (Jarvinen et al. 1994). As previously described, LA function is multiphasic and complex, with no currently accepted "gold standard" for assessment of LA function. Recent CMR studies have used LA ejection fraction as a marker of global LA contractile function (Perea et al. 2008; Wylie et al. 2008). Perea et al. found a nonsignificant decline in mean LA ejection fraction in patients who remained in sinus rhythm post-AF ablation at 12-month follow-up, while there was a significant decrease in the mean LA ejection fraction in the group with recurrent AF (Perea et al. 2008). Similarly, another study found that, at short-term follow-up, there was a significant

reduction in LA ejection fraction in a cohort of patients with paroxysmal and persistent AF who had undergone AF ablation (Wylie et al. 2008).

Although the normal range for LA ejection fraction in males and females were published a number of years ago (Hudsmith et al. 2005), the clinical implications and prognostic value of LA ejection fraction has not been determined to date. Further studies are required in order to demonstrate the clinical significance of changes in LA ejection fraction as it pertains to thromboembolic risk and its implications for anticoagulation. In the meantime, LA ejection fraction is a robust, clearly defined parameter and appears to be a reasonable tool for non-invasive assessment of global LA contractile function.

Another potentially valuable means of assessing LA function is the measurement of regional LA contractility. While preliminary studies have been performed using echocardiography, as described previously, there are no validated CMR techniques. One small study evaluated segmental LA wall motion by dividing the LA into numerous segments and measuring the distance from these segments to a fixed reference point at 3 phases of the cardiac cycle (Nori et al. 2009). There was deterioration in regional motion in all segments of the LA in patients with paroxysmal AF post-ablation, with the deterioration in lateral wall motion reaching statistical significance. In the group with persistent AF, there was an improvement in LA wall motion in all segments, reaching statistical significance in the posterior, inferior and septal segments. These results appear counterintuitive as patients with persistent AF underwent more extensive ablation procedures, and would be expected to have greater

scarring and hence deterioration in regional LA function. However, several cautionary notes are required. Firstly, patients with persistent AF were scanned in AF and hence by definition would be expected to have poor LA contractility at baseline, and improvement with reversion to sinus rhythm post-ablation. Secondly, the assessment of regional LA wall motion was crude at best, and measurement of LA wall motion is subject to translational effects from LV contraction and mitral valve apparatus motion. Finally, the sample size was small with 16 patients in the paroxysmal and 13 patients in the persistent AF groups. Therefore, while the concept of the study is very interesting and relevant in the era of AF ablation, its implementation and design have numerous limitations that prohibit any firm conclusions being drawn. Further studies, with refinements in techniques of LA segmental function analysis, and improved study design would provide more insight to the effects of RFCA on regional LA function.

1.4.4.8. Left atrial scar imaging

An exciting and rapidly evolving field in CMR is LA scar imaging in the setting of AF ablation (Peters et al. 2007). Until recently, scar imaging using late gadolinium enhancement had been limited to the ventricles and particularly the LV. Until recently, LA scarring was not well defined using conventional delayed enhancement sequences due to its thin wall. However, technical advances have enabled the application of a navigator-gated, free breathing, 3D, gradient-echo inversion recovery delayed enhancement sequence, which provides high spatial resolution images of the LA and PVs (Peters et al. 2007).

The first published study in this field demonstrated evidence of new PV ostial scarring in all patients following AF ablation, with the extent of scarring decreasing over time (Peters et al. 2007). The same group showed that, in patients undergoing AF ablation, the degree of deterioration in LA ejection fraction post-ablation is correlated with the extent of LA scarring associated with the ablation procedure, raising concerns about the potential implications for thromboembolic risk (Wylie et al. 2008). In addition, it has been found that the extent of late gadolinium enhancement early post-ablation (within 24 hours) is greater than that seen at a later time (3 and 9 months) (Badger et al. 2009). This is thought to reflect the presence of the inflammatory process early post-ablation, with resolution of inflammation and scar maturation being complete by 3 months and remaining stable at 9 months follow-up (Badger et al. 2009). These findings are consistent with the clinical observations that early arrhythmia recurrence post-ablation may not necessarily signify long-term procedural failure (Oral et al. 2002), and supports the current guideline recommendation of a 3-month “blinking period” when arrhythmia recurrence within 3 months post-ablation is not considered as treatment failure (Calkins et al. 2007b).

More recent studies have focussed on the implications of LA scarring on clinical outcomes. One study found that patients with more extensive LA scarring post-ablation were less likely to have arrhythmia recurrence at 3-month follow-up (McGann et al. 2008). A subsequent study confirmed these findings with longer-term follow-up (6.7 ± 3.6 months), demonstrating a negative association between AF recurrence and the degree of LA and PV scarring on CMR (Peters et al. 2009). Interestingly, this finding was particularly significant for the right inferior PV. The extent of LA scarring prior to

ablation in patients with AF has been found to be the strongest predictor of outcomes at medium-term follow-up (mean 9.6 ± 3.7 months), with up to 75% of those with extensive LA scarring pre-ablation having AF recurrence at follow-up (Oakes et al. 2009).

Future applications in this promising field include the assessment of the effects of various interventions (eg. antihypertensive therapy) on LA scarring and real-time CMR assessment of LA and PV scarring during AF ablation procedures and their relation to long-term outcomes.

1.4.4.9. Blood flow within the left atrium

Blood flow within the LA has a complex 3D pattern (Fyrenius et al. 2001). Cardiac magnetic resonance imaging can be used to demonstrate the pattern of flow within the LA as shown in a study involving healthy humans, which used time resolved 3D phase contrast MRI and particle trace visualisation to analyse blood flow within the LA (Fyrenius et al. 2001). Time resolved phase contrast MRI permits accurate flow velocity measurements without constraints to flow direction or imaging planes (Fyrenius et al. 1999). Vortical flow was observed within the LA with the predominant volume of blood within the vortices being from the left sided PVs. Vortices are energy preserving structures which maintain the momentum of flowing blood by preventing deceleration and reacceleration (Fyrenius et al. 2001). In addition, vortices may play an important role in the avoidance of stasis within the LA and prevention of thromboembolism. Further studies in this area have been hampered by technical limitations in acquiring 3D

flow data in a timely manner. However, the development of 3D flow sequences (Bock et al. 2009) will enable future studies to focus on the pattern of blood flow within the LA in various disease states, particularly AF, and its implications for thromboembolic risk.

1.4.4.10. Imaging in atrial fibrillation ablation

Cardiac magnetic resonance imaging is an ideal, non-invasive imaging modality for patients undergoing AF ablation, as it can provide useful anatomical and functional information in pre- and post-ablation studies, enabling assessment of the LA and PVs, and detection of complications post-ablation. One of the major advantages of CMR compared with CT is the lack of ionising radiation, which is particularly relevant in this setting as patients may require multiple scans for follow-up surveillance and repeat procedures, which would expose them to excessive doses of radiation with CT.

Beyond the numerous applications of CMR in the setting of AF ablation described above, CMR can provide high resolution anatomical images of the LA and PVs and an anatomical roadmap prior to AF ablation, using CE-MRA (Wittkamp et al. 2003). As with CT, MRA images can be integrated with electro-anatomic mapping information to guide AF ablation (Dong et al. 2006). Previous studies have demonstrated that PV anatomy is highly variable with potential implications for AF ablation (Kato et al. 2003; Mansour et al. 2004). The PVs in patients with AF have been found to be ovoid (Wittkamp et al. 2003), with dynamic changes in size and location throughout the cardiac cycle (Lickfett et al. 2005). Earlier studies using CMR have shown that the superior PVs in patients with AF are larger and more elliptical in shape compared with

controls (Tsao et al. 2001). Furthermore, PV dilatation is associated with LA dilatation, particularly affecting the LA transverse, rather than the antero-posterior or longitudinal dimensions (Tsao et al. 2001). Following successful AF ablation, there is reverse remodelling of the PVs with a reduction in size and a more rounded shape, in patients without AF recurrence (Tsao et al. 2005). Cardiac magnetic resonance imaging can also be used to determine the location of neighbouring structures, particularly the oesophagus, prior to ablation in order to reduce the risk of atrio-oesophageal fistula formation (Kenigsberg et al. 2007).

Cardiac magnetic resonance imaging provides valuable information following AF ablation. MRA is an accurate method for detecting PV stenosis post-ablation (Dill et al. 2003). The 3D dataset can be manipulated in any orientation, which allows accurate assessment of the PV ostium and severity of stenosis. The most reproducible assessment of PV size has been found to be the measurement of major and minor axes of the PV ostia in the sagittal plane, where the PVs separate from the LA and each other (Hauser et al. 2004). One study, using MRA as one of the imaging modalities found that a significant proportion of patients with severe PV stenosis are asymptomatic, and there is a higher risk of PV stenosis with distal ablation inside smaller PVs (Arentz et al. 2003). Such observations have led to changes in ablation techniques with the placement of ablation lesions more proximally within the LA reducing the incidence of severe PV stenosis. In addition to providing high resolution anatomic images, CMR of the PVs can also provide haemodynamic information using VENC sequences to assess flow within the PVs (Valsangiaco et al. 2003). Furthermore, CMR can be used to assess lung perfusion in cases of severe PV stenosis (Kluge et al. 2004). Such versatility, as well as

the avoidance of radiation exposure, makes CMR the non-invasive modality of choice for PV assessment following ablation.

A rare, yet devastating complication of AF ablation is atrio-oesophageal fistula formation (Pappone et al. 2004). Patients with atrio-oesophageal fistulae usually present about 2 – 4 weeks post-ablation with fever, chills and recurrent cerebral embolic events (Cummings et al. 2006). Septic shock can also be a presenting feature. Unfortunately, most cases are fatal (Cummings et al. 2006). As described earlier, CMR allows localisation of the oesophagus prior to ablation, in order to aid planning of the procedure and reduce the risks. In patients suspected of having an atrio-oesophageal fistula, CMR and CT are the best imaging modalities for early detection and intervention in order to potentially improve outcomes (Calkins et al. 2007b).

1.5. Aims of the thesis

The focus of this thesis is the non-invasive assessment LA structure and function in patients with AF and the effects of AF ablation on subsequent structure and function, using CMR. In particular, the aims are to:

1. Assess the accuracy of the biplane area-length method for measuring LA volume in normal and abnormal atria.
2. Determine if there are subtle differences in cardiac structure and function in patients with “lone” AF, who have previously been thought to have no structural abnormalities using conventional imaging.
3. Determine imaging markers that are predictive of AF recurrence following radiofrequency catheter ablation.

4. Evaluate the medium to long-term effects of AF ablation on cardiac structure and function.

1.6. Conclusions

The accurate assessment of LA structure and function is becoming increasingly important in the current practice of cardiology, due to an “epidemic” of AF and the evolution of catheter ablation techniques, which can potentially be curative in select cases. Although AF ablation has been found to be a promising treatment strategy, numerous questions remain regarding its impact on cardiac (particularly LA) structure and function, and its implications for long-term outcomes in patients with AF. In order to address these issues, robust, non-invasive, and safe imaging modalities are required, which can assess anatomical and functional characteristics in patients with AF undergoing ablation. Cardiac magnetic resonance imaging satisfies all these criteria, being a non-invasive, safe, high resolution imaging modality, without ionising radiation. Thus, CMR is ideally suited for both research and clinical purposes in this setting, and is the imaging modality utilised for the studies that were performed as part of this thesis.

CHAPTER 2

COMMON METHODOLOGIES

2.1. Introduction

The methods presented in this chapter are common to the studies presented in Chapters 3 – 6. Previously established techniques are appropriately referenced, while new techniques are described in detail in the relevant chapters.

2.2. Subjects

2.2.1. Normal control subjects

Healthy subjects aged > 18 years with no history of cardiorespiratory disorders, hypertension, obstructive sleep apnoea or obesity were recruited.

2.2.2. Subjects with atrial fibrillation

Consecutive subjects, aged > 18 years, with “lone”, paroxysmal or persistent AF undergoing radiofrequency catheter ablation were enrolled in the studies presented in this thesis, following written, informed consent. The classifications of AF have previously been described in Chapter 1 and in detail elsewhere (Fuster et al. 2006).

2.2.3. Exclusion criteria

Exclusion criteria were contraindications to undergoing CMR or having gadolinium contrast agents. Subjects with AF or other significant arrhythmias at the time of any CMR scan were excluded. As stipulated by the institutional ethics committee, subjects with a creatinine clearance < 60 mL/min were excluded from the component of the CMR study involving gadolinium administration.

2.3. Ethics approval

The Royal Adelaide Hospital Human Research Ethics Committee and the Investigational Drug Subcommittee approved all study protocols. All subjects provided written informed consent and were free to withdraw at any stage during the study.

2.4. Cardiac magnetic resonance imaging

Imaging of all subjects was performed using a 1.5 Tesla Siemens Avanto MRI scanner (Siemens Medical Solutions, Erlangen, Germany), fully equipped with cardiac imaging capabilities, including a phased array chest coil. Subjects were scanned in the supine position.

2.4.1. Ventricular structure and function

2.4.1.1. Image acquisition

Left and right ventricular structure and function were assessed using a balanced SSFP sequence. Localiser images were used to acquire long and short axis (SA) scout images. Subsequently long axis scout images were used to prescribe the imaging planes for the SA cine volume stack, with the first basal slice being placed at, and parallel to, the atrioventricular groove in the end-diastolic frame of the long axis images. The ventricles were imaged in the SA plane, with 6 mm slice thickness and 4 mm interslice gaps, proceeding apically to cover the entire ventricular volume as described previously (Alfakih et al. 2003). Typical imaging parameters included echo time 1.2 ms, repetition time 63.7 ms, flip angle 80°, matrix size 192 × 156, field of view 360 - 440 mm. Images were acquired using surface electrocardiogram based retrospective gating, at end-

expiration. Retrospective gating was used to enable image acquisition throughout diastole as opposed to prospective gating, where images are acquired until early to mid-diastole. The loss of the terminal phase of diastole with prospective gating leads to underestimation of ventricular end-diastolic volume (EDV) and ejection fraction, as well as maximum LA volume and ejection fraction (Sievers et al. 2005). Imaging was performed at end-expiration for a more reproducible breath hold.

2.4.1.2. *Image analysis*

Image analysis was performed using proprietary software (Argus, Siemens Medical Solutions, Erlangen, Germany), in a blinded manner. Ventricular volumes were calculated by manually tracing the endocardial contours in the SA views, at end-diastole (onset of R wave) and end-systole (smallest cavity volume), and applying Simpson's rule. Papillary muscles and trabeculations were excluded from the ventricular volume if they were contiguous with the ventricular wall. The basal slice for the LV was selected when at least 50% of the blood pool was surrounded by ventricular myocardium. The apical slice was defined as the last slice with visible intracavity blood pool. For the RV, volumes below the pulmonary valve were included. Trabeculations were excluded from RV volume measurement (Hudsmith et al. 2005). Measurements were normalised to body surface area.

Ventricular ejection fractions were calculated using the formula; (maximum volume – minimum volume)/maximum volume × 100 (%). Left ventricular mass was measured by multiplying the LV myocardial volume by 1.05 g/cm³ (specific density of myocardium).

2.4.2. Atrial structure and function

2.4.2.1. Image acquisition

The atria were imaged in 3 perpendicular planes, SA, horizontal long axis (Modesto et al.) and vertical long axis (Otasevic et al.). Images were acquired with 6 mm slice thickness and no interslice gaps, providing a comprehensive 3D dataset (Teo et al. 2008). Otherwise, imaging parameters were as described above with images obtained during end-expiratory breath hold, using retrospective gating.

2.4.2.2. Image analysis

As described earlier, image analysis was performed using proprietary software (Argus, Siemens Medical Solutions, Erlangen, Germany), in a blinded manner. Atrial volumes were calculated using a 3D technique (Teo et al. 2008). Endocardial contours were manually traced at maximal (ventricular end-systole) and minimal (ventricular end-diastole) LA volumes, for every slice in the HLA projection, and modified Simpson's rule was applied (Figure 2.1). The PVs were excluded, and the atrial appendages were included if present on the images (Teo et al. 2008). Atrial ejection fractions were calculated using the formula; $(\text{maximum volume} - \text{minimum volume}) / \text{maximum volume} \times 100 (\%)$.

2.5. Radiofrequency catheter ablation

2.5.1. Ablation procedure

All patients were therapeutically anticoagulated for at least 1 month using warfarin (INR 2.0 – 3.0) and subsequently switched to low molecular weight heparin, with the

last dose administered on the evening prior to the ablation. Patients underwent transoesophageal echocardiography within 7 days of RFCA to exclude LAA thrombus.

Electrophysiological study was performed in the post-absorptive state with sedation utilising midazolam and fentanyl. The LA was accessed using a single conventional transeptal puncture using an SLO sheath and BRK1 needle (St Jude Medical) following which a bolus of unfractionated heparin 100IU/kg was administered followed by repeated bolus unfractionated heparin to maintain the activated clotting time between 300-350 seconds. The following catheters were positioned: 10 pole catheter within the CS, 10 pole Variable Lasso catheter (Biosense-Webster) to map the pulmonary veins with the assistance of an SLO sheath, and 3.5mm tip externally irrigated ablation catheter (Navi-Star or Thermocool, Biosense-Webster) with an Agilis sheath (St Jude Medical). Circumferential ablation of the pulmonary veins was undertaken with an endpoint of pulmonary vein electrical isolation. Ablation was performed using a delivered power of 30W with irrigation rates of 30-60mL/min. Additional substrate modification was performed in patients with episodes of AF \geq 48 hours, LA size \geq 57mm (longest diameter) or evidence of structural heart disease. This took the form of linear ablation along the LA roof and/or mitral isthmus and/or ablation of complex fractionated atrial electrograms (CFAE). Cavo-tricuspid isthmus ablation with an endpoint of bi-directional isthmus block was performed only in patients with a history of typical flutter or if mapping confirmed cavo-tricuspid isthmus dependent flutter during the procedure. Linear ablation was performed with a delivered power of 30-35W with irrigation rates of 30-60mL/min. In all cases electroanatomic mapping (CARTO, Biosense-Webster; or NavX, St Jude Medical) was used (Figure 2.2).

2.5.2. Follow-up

All patients were maintained on antiarrhythmic drugs for a 6-week period. Patients were reviewed with clinical history, physical examination, ECG and 7-day continuous Holter monitoring at 3 monthly intervals for 12 months and then 6 monthly. A 3-month “blinking period” was applied as per the current consensus guidelines (Calkins et al. 2007). Patients with any atrial arrhythmias lasting > 30 seconds were deemed to have failed AF ablation. In patients with a CHADS2 score ≤ 1 anticoagulation was discontinued after 3 months. However, in those with a CHADS2 score ≥ 2 anticoagulation was continued for a minimum of 12 months, after which in the absence of arrhythmia, discontinuation of anticoagulation was only performed by individual discussion of the risks associated with cessation of anticoagulation. Follow-up CMR scans were performed at 12 months post-ablation.

2.6. Statistical analysis

Data are presented as mean \pm standard deviation (SD). Comparisons between pre- and post-ablation atrial and ventricular volumes, LV mass, and atrial and ventricular ejection fractions, were made using a two-tailed, paired t test for normally distributed data, and the Wilcoxon matched pairs nonparametric test for data that were not normally distributed. Comparisons of atrial and ventricular volumes and ejection fractions, between normal controls and subjects with AF were made using a two-tailed, unpaired t test. Statistical significance was taken at $P < 0.05$. Other statistical tests, specific to each study are described in the relevant chapters. A statistician provided formal statistical support.

Inter- and intra-observer variability were assessed using the Bland and Altman method (Bland and Altman 1986). The coefficient of variation was calculated as the SD of the differences between the two sets of measurements divided by the mean value of the parameter.

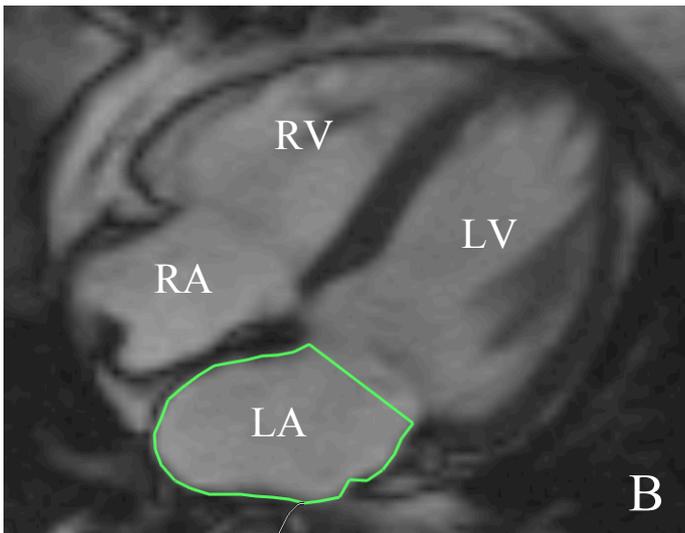
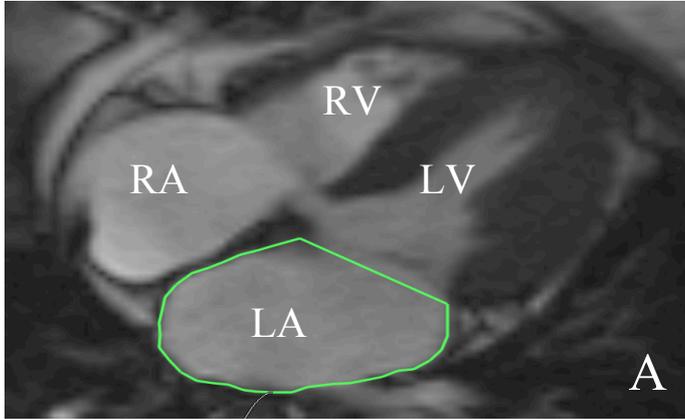


Figure 2.1. Left atrial endocardial contours manually traced at end-systole (A) and end-diastole (B). LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle

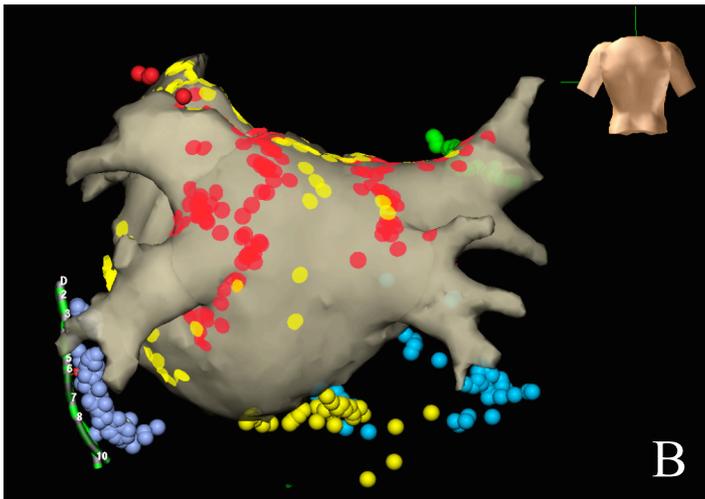
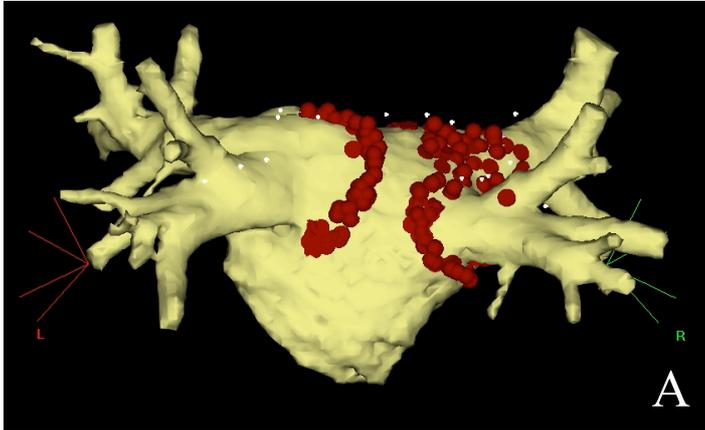


Figure 2.2. CARTO (Biosense Webster) map of circumferential pulmonary vein isolation in a patient with paroxysmal AF (A). NavX (Endocardial Solutions) image demonstrating extensive ablation in a patient with persistent AF (B).

CHAPTER 3

Accuracy of the Biplane Area-Length Method for Assessing Left Atrial Volume in Subjects with Normal and Dilated Left Atria: A Comparative Study Using Cardiac Magnetic Resonance Imaging

3.1. Summary

Left atrial volume is an important prognostic marker in various cardiac disorders. The biplane area-length method is a simple and rapid means of measuring LA volume in clinical practice. The accuracy of this method, particularly in patients with dilated LA, has not been well studied. Fifteen healthy controls (7 male; mean age 54.3 ± 6.4 years) and 56 subjects with AF (37 male; mean age 58.8 ± 8.5 years; 43 paroxysmal) were studied. Comprehensive clinical and CMR assessment was performed. All subjects were in sinus rhythm at the time of the CMR scan. Maximal LA volume was calculated from the horizontal and vertical long axis images using the biplane area-length method. This was compared with the volume derived using the “gold standard” CMR based three-dimensional volumetric data set applying Simpson’s rule. Measurements were made in a blinded manner. Overall, there was a moderate correlation ($r = 0.76$) between the biplane area-length method and the volumetric measurement, with the mean difference (± 2 SD) between the two methods being 2.3 ± 41.1 mL. In healthy controls, there was a strong correlation between the two methods ($r = 0.92$), with a mean difference (± 2 SD) of 6.3 ± 19.9 mL. However, in subjects with AF, the correlation between the methods was only moderate ($r = 0.72$), with a mean difference (± 2 SD) of 1.3 ± 45.0 mL. In conclusion, the biplane area-length method correlates well with true volumetric measurements of LA volume in subjects with normal atria. However, in subjects with LA dilatation, the biplane area-length method is not an accurate measure of LA volume.

3.2 Introduction

Left atrial dilatation is associated with an increased risk of developing atrial arrhythmias, particularly AF (Henry et al. 1976). In addition, subjects with LA dilatation have increased cardiovascular morbidity and mortality (Gardin et al. 2001). Left atrial volume has been found to be a more sensitive and accurate measure of LA dilatation compared with the antero-posterior dimension (Lester et al. 1999). Current guidelines advocate the biplane area-length method and application of the method of discs for deriving LA volume (Lang et al. 2005). Although this method has been validated using cine computed tomography (Kircher et al. 1991) and is relatively easy to perform, it involves geometric assumptions that may not be valid, particularly in cases of significant LA dilatation.

Cardiac magnetic resonance imaging is the currently accepted “gold standard” non-invasive imaging modality for assessment of cardiac chamber volume, measuring true three-dimensional volume without geometric assumptions (Bellenger et al. 2000). Specifically, cadaveric cast studies have shown that CMR is highly accurate for measuring LA volume (Jarvinen et al. 1994). However, in clinical practice, true volumetric measurements can be time consuming and hence the biplane area-length method is frequently used to determine LA volume. The accuracy of the biplane area-length method, particularly in patients with significant LA dilatation, has not been well studied. The aim of this CMR-based study was to compare LA volume derived using the biplane area-length method with the well-established, highly accurate true volumetric measurement of LA volume using Simpson’s rule, in a population with normal and dilated left atria.

3.3. Methods

3.3.1 Study population

Healthy control subjects (> 18 years old) with no documented cardiopulmonary disease, hypertension, diabetes mellitus, thyroid, renal, or hepatic disorder, by appropriate testing, were recruited and a comprehensive CMR scan was performed. In addition, subjects with AF were recruited and underwent a similar CMR examination. Exclusion criteria were AF at the time of the CMR examination and contraindications to undergoing a CMR scan. The study protocol was approved by the Royal Adelaide Hospital research ethics committee, and written informed consent was obtained from all subjects.

3.3.2. Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed using a 1.5 Tesla scanner (Siemens Avanto, Siemens Medical Solutions, Erlangen, Germany). Comprehensive atrial imaging was performed as described previously (Teo et al. 2008). In brief, SSFP cine images of the LA (6 mm slice thickness, no interslice gaps) and LV (6 mm slice thickness, 4 mm interslice gaps) were acquired in the SA plane. Subsequently, detailed imaging of the LA was undertaken in the HLA and VLA planes (6 mm slice thickness, no interslice gaps). Images were acquired using surface electrocardiogram based retrospective gating, at end-expiration. Typical imaging parameters were: echo time 1.2 ms, repetition time 63.7 ms, flip angle 80°, matrix size 192 × 156, field of view 360 - 440 mm. All images were acquired during the same scan thus controlling for haemodynamic status.

3.3.3. Image analysis

3.3.3.1. Volumetric method

Image analysis was performed using proprietary software (Argus, Siemens Medical Solutions, Erlangen, Germany), in a blinded manner. Atrial volumes were calculated using a three-dimensional technique, previously described by our group (Teo et al. 2008). The endocardial contours were manually traced at ventricular end-systole (maximal LA volume), just prior to the opening of the mitral valve leaflets, in each of the slices in the HLA projection, and modified Simpson's rule was applied. The pulmonary veins (PVs) were carefully excluded, and the LAA was included. The volumetric method was used as the "gold standard" for LA volume determination.

3.3.3.2. Biplane area-length method

The HLA (4-chamber view) and VLA (2-chamber view) projections were used to measure maximal LA volume, at ventricular end-systole just prior to mitral valve leaflet opening, by applying the biplane area-length method (Wang et al. 1984). The PVs were excluded and the LAA was included in these measurements (Hudsmith et al. 2005). Left atrial volume was calculated using the formula $8 \times A_1 \times A_2 / 3 \times \pi \times L$, where A_1 and A_2 are maximal LA areas in the HLA and VLA projections respectively, and L is the shortest of the two lengths measured from the LA back wall to the line across the hinge point of the mitral valve, in the HLA and VLA projections (Figure 3.1) (Wang et al. 1984). The volumes derived using the biplane method were subsequently compared with the three-dimensional volumetric measurements.

3.3.4. Reproducibility

Intra- and inter-observer variability of LA volume measurements were assessed in 10 randomly selected subjects, with separate measurements performed by two blinded observers.

3.3.5. Statistical analysis

Data are presented as mean \pm SD. Initially all subjects were analysed as a single group. In order to assess the influence of LA dilatation on LA volumes derived using the two methods, the subjects were divided into two groups, those with no cardiac abnormalities and those with a history of AF. The relationship between the volumes derived using the biplane area-length method and the three-dimensional volumetric method was assessed using a Pearson correlation coefficient (r). Furthermore, Bland and Altman analysis was performed to assess the limits of agreement between the two methods for deriving LA volume (Bland and Altman 1986). These results are presented as the mean difference and the limits of agreement. The Bland and Altman method was also used to determine intra- and inter-observer variability. Statistical significance was taken at $P < 0.05$.

3.4. Results

3.4.1. Subject characteristics

Fifteen healthy subjects (7 male; mean age 54.3 ± 6.4 years) and 56 subjects with AF (37 male; mean age 58.8 ± 8.5 years; 43 paroxysmal) were studied.

3.4.2. Left atrial volume in the overall group

The mean LA volume in the total study population was 101.4 ± 29.7 mL using the volumetric method and 103.7 ± 30.5 mL using the biplane area-length method. There was a moderate correlation between the LA volumes measured using the three-dimensional volumetric and the biplane area-length methods ($r = 0.76$, $P < 0.0001$) (Figure 3.3A). The Bland-Altman analysis showed a mean difference of 2.3 mL between the biplane area-length and volumetric LA volume measurements with the limits of agreement being ± 41.1 mL (Figure 3.3B).

3.4.3. Left atrial volume in subjects with atrial fibrillation

The subjects were divided into 2 groups, healthy controls and those with AF, in order to assess the effects of LA abnormality on the correlation between the volumetric and biplane methods of LA volume estimation. In subjects with AF, the correlation between the biplane area-length method and three-dimensional volumetric method was again moderate ($r = 0.72$, $P < 0.0001$) (Figure 3.4A). The Bland-Altman analysis revealed a mean difference of 1.3 mL between the biplane area-length and volumetric LA volume estimations with the limits of agreement being ± 45.0 mL (Figure 3.4B).

3.4.4. Left atrial volume in healthy control subjects

In the healthy control group, there was a strong correlation between the LA volume derived using the biplane area-length and the volumetric methods ($r = 0.92$, $P < 0.0001$) (Figure 3.5A). The Bland-Altman analysis demonstrated a mean difference of 6.3 mL between the biplane area-length and the volumetric methods with limits of agreement ± 19.9 mL (Figure 3.5B).

3.4.5. Reproducibility

Intra- and inter-observer variability for LA volumes derived using the two methods are presented in Table 3.1. Overall, there was excellent intra- and inter-observer agreement for the volumetric method, while the biplane area-length method was associated with greater inter-observer variability.

3.5. Discussion

3.5.1. Main findings

This study demonstrates that there is only a moderate correlation between the widely used biplane area-length method and the “gold standard” volumetric method for LA volume measurement in subjects with LA abnormality. However, in healthy control subjects, there is a strong correlation between these two methods for LA volume estimation.

3.5.2. Volumetric versus biplane area-length method

The volumetric method using CMR requires no geometric assumptions and is a true measure of LA volume. It has been shown to be highly accurate and reproducible in cadaveric cast studies with only minor underestimation of true LA volume (Jarvinen et al. 1994). However, this method requires a longer imaging protocol and image analysis is time consuming. Furthermore, many of the established normal reference values for LA volume are based on the biplane area-length method from echocardiographic measurements (Wang et al. 1984; Thomas et al. 2002; Lang et al. 2005). Echocardiographic measurement of LA volume derived using the biplane area-length method has been found to be an important prognostic marker, predicting cardiovascular

adverse events and mortality (Tsang et al. 2001; Tsang et al. 2003; Barnes et al. 2004). Therefore, this method has been firmly established in clinical practice and is routinely used in trials.

However, echocardiographic LA volume estimations using the biplane area-length method are based on geometric assumptions and significantly underestimate LA volume (Rodevan et al. 1999). Interestingly, in this study the biplane area-length method led to a small overestimation of LA volume in the overall cohort, and more so in the healthy control subjects. Consistent with the present study, another CMR-based study, found that the biplane area-length method was associated with a small overestimation of LA volume compared with the volumetric method (Sievers et al. 2004). This apparent discrepancy between echocardiographic and CMR studies comparing the biplane area-length and volumetric methods of LA volume estimation may be due to the fact that during echocardiography, apical views place the LA in the far field of the ultrasound beam with a resultant loss of lateral resolution and limited visualisation of the endocardium. Hence, planimetry of the LA requires estimation of posterior and lateral wall positions. In addition, the LA is often foreshortened in the apical views, leading to underestimation of LA volume.

This study confirms that while there is a strong correlation between LA volumes derived using the biplane area-length and the volumetric methods in healthy controls, the correlation is weaker in subjects with LA abnormality, such as those with AF. This can be explained by the asymmetric changes in LA geometry with LA dilatation rendering volume estimations based on geometric assumptions inaccurate. In addition,

there is wide inter-observer variability using the biplane area-length method in subjects with diseased LA. The lack of reproducibility of the biplane area-length method is a significant limitation of this technique.

3.5.3. Implications

This study supports the notion that as part of a comprehensive CMR assessment, patients should ideally have a volumetric measurement of LA volume. However, this can be time consuming, both in terms of image acquisition and analysis, and the biplane area-length method is a reasonable alternative in patients who are not known to have conditions affecting LA size. In the research setting, particularly in follow-up studies, CMR volumetric measurement of LA volume should be used, as it reduces the chances of a type II error due to inaccurate measurements. In the meantime, CMR-based studies are required to establish a normal range for LA volume based on the volumetric method.

3.5.4. Study limitations

The CMR images were acquired during breath holding at end-expiration. Respiratory phases can influence LA volumes (Poutanen et al. 2000). However, image acquisition for the volumetric and biplane area-length methods, for each subject, was performed under the same conditions, at end-expiration. Thus, this should not affect the comparison of these two methods. In addition, the sample size of healthy controls was rather small, but despite this, it was clearly evident that the correlation between the two methods of LA volume estimation was stronger in the healthy controls, with no LA abnormalities, compared with AF subjects.

3.6. Conclusions

In subjects without LA abnormalities, the biplane area-length method correlates well with CMR volumetric measurement of LA volume, with small overestimation of LA volume. However, in subjects with LA abnormalities, this correlation is only moderate. In the research setting, particularly where serial follow-up measurements are required, the volumetric method should be used for improved accuracy.

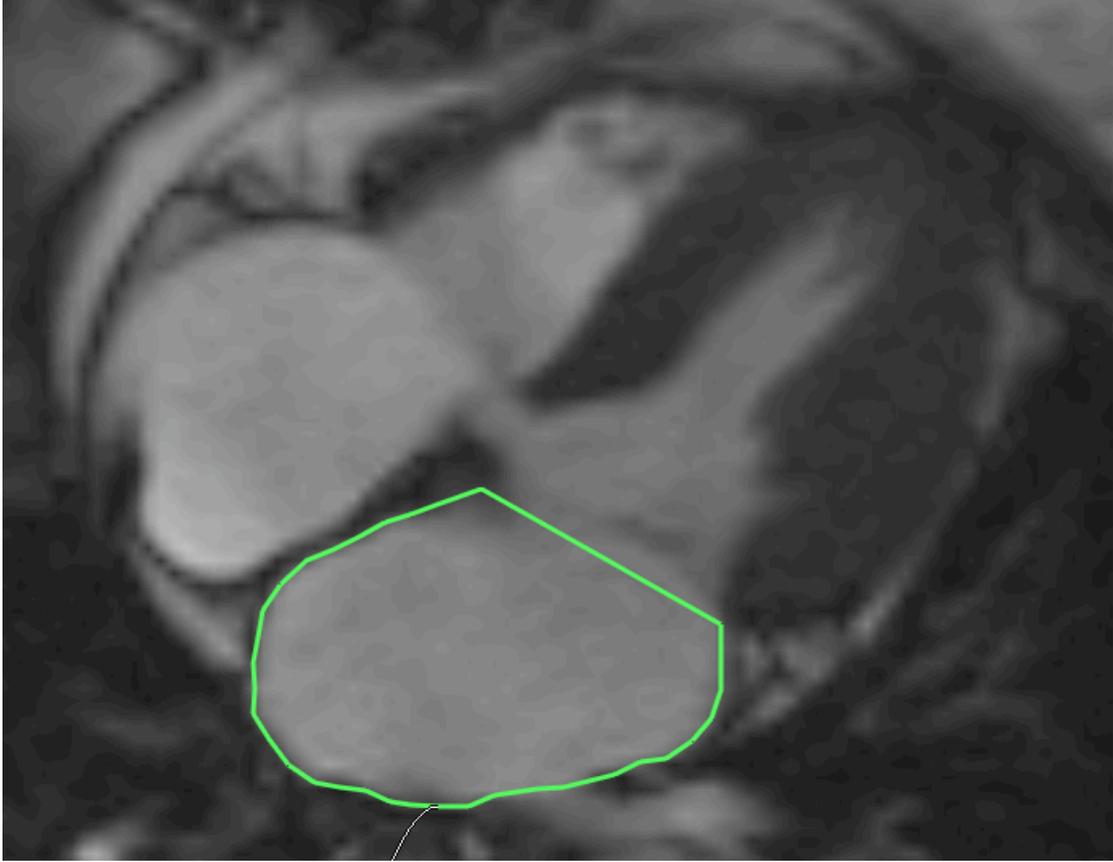


Figure 3.1. Volumetric method for measuring LA volume. Left atrial endocardial contours were manually traced at maximal LA size (ventricular end-systole) in every slice in the horizontal long axis projection and Simpson's rule was applied to derive maximal LA volume.

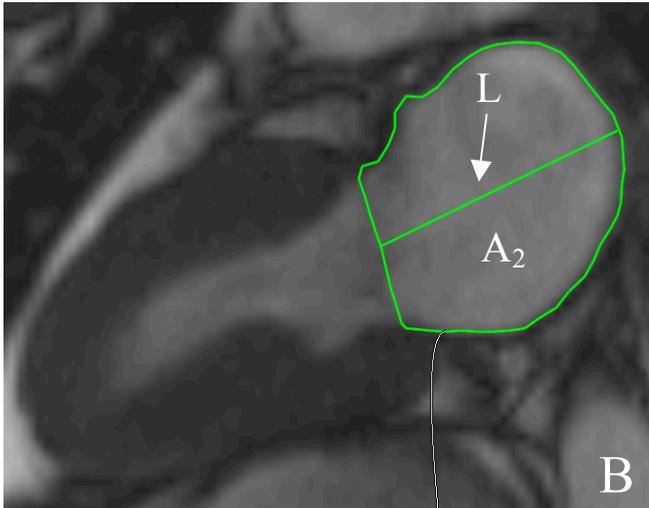
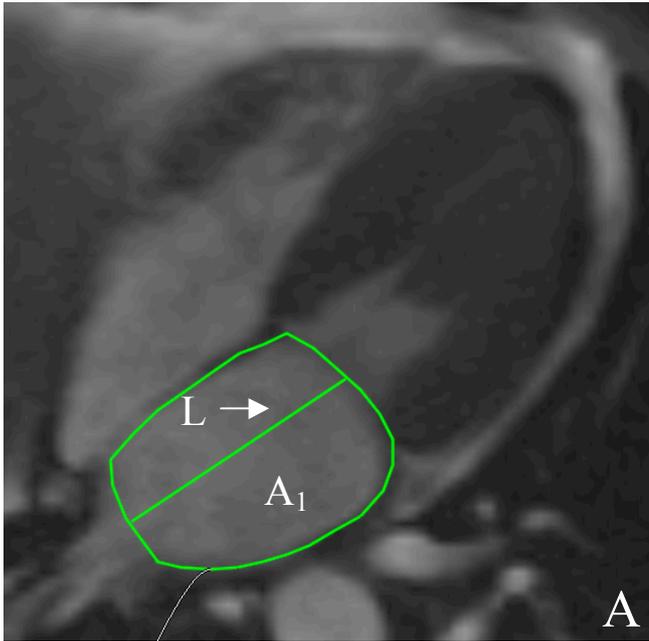
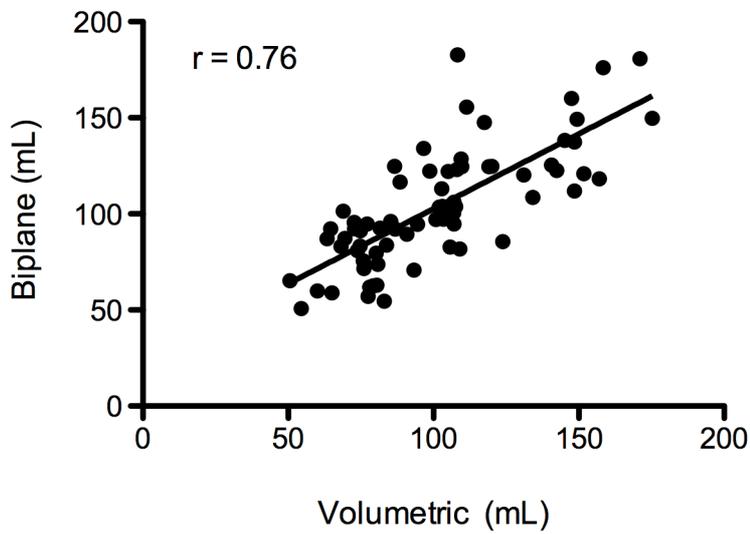


Figure 3.2. Biplane area-length method for measuring LA volume. Endocardial contours were traced in the horizontal long axis (A) and vertical long axis (B) projections at maximal LA size (ventricular end-systole) to determine LA areas (A_1 and A_2). The length (L) is measured from the back wall of the LA to the mitral annular plane, with the shorter L used in the equation as described in the text, to calculate LA volume.

A



B

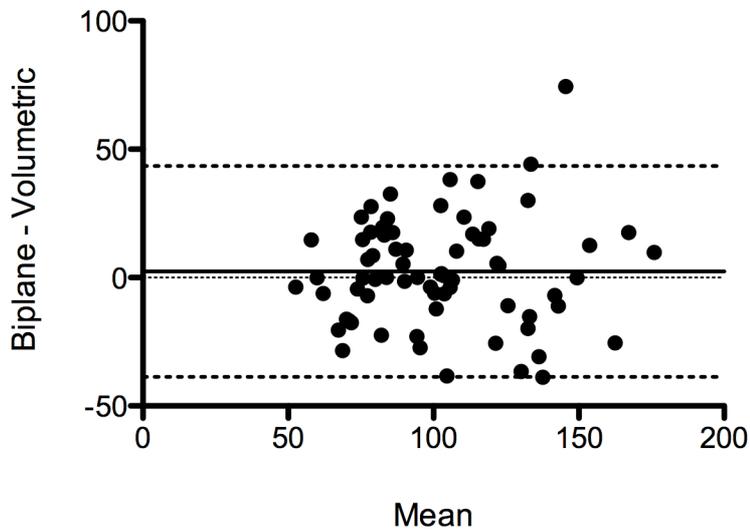
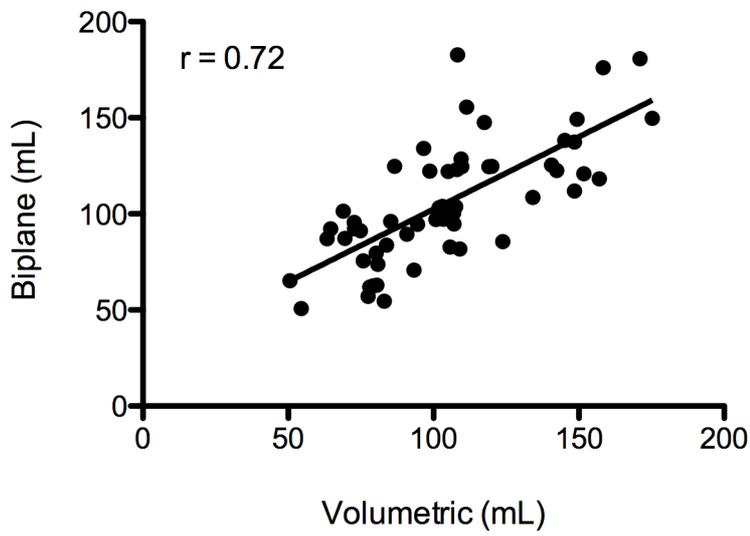


Figure 3.3. Overall cohort. Relationship between LA volumes measured using the biplane area-length and the volumetric methods (A); Bland-Altman plot comparing the biplane area-length and the volumetric methods (B). Solid line in (B) represents the bias and the dotted lines represent 95% limits of agreement.

A



B

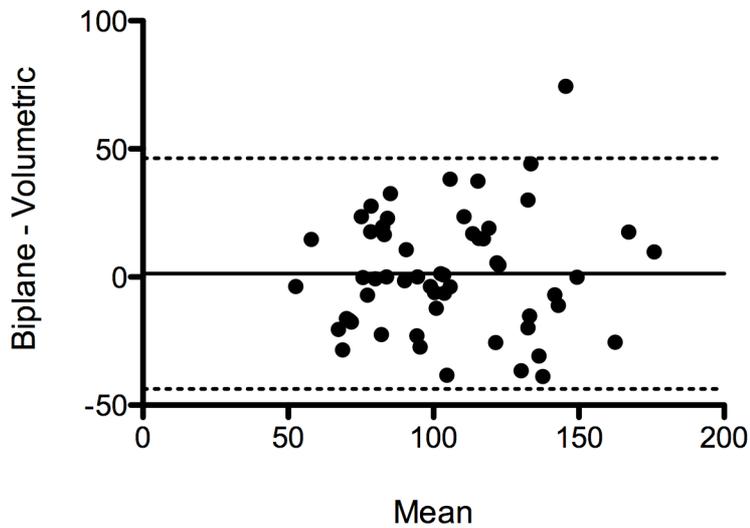
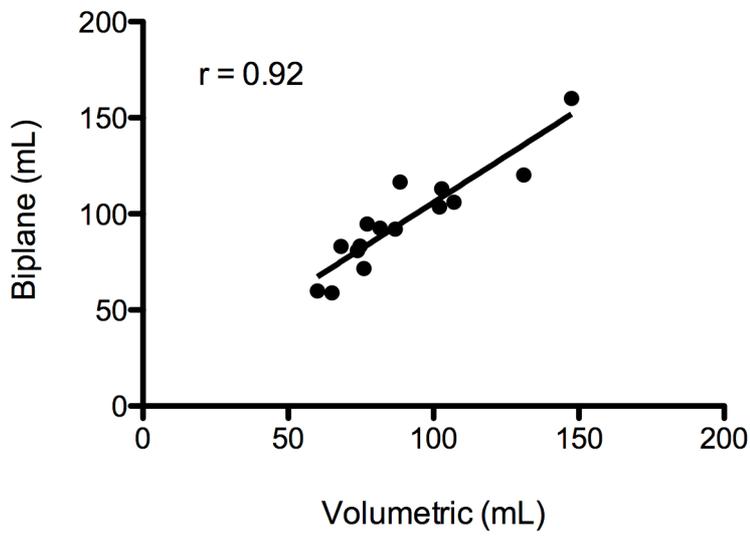


Figure 3.4. Atrial fibrillation subjects. Relationship between LA volumes measured using the biplane area-length and the volumetric methods (A); Bland-Altman plot comparing the biplane area-length and the volumetric methods (B). Solid line in (B) represents the bias and the dotted lines represent 95% limits of agreement.

A



B

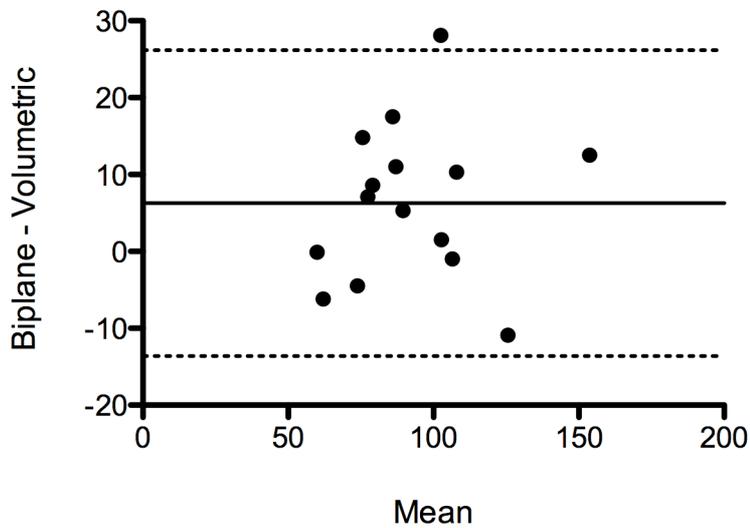


Figure 3.5. Healthy control subjects. Relationship between LA volumes measured using the biplane area-length and the volumetric methods (A); Bland-Altman plot comparing the biplane area-length and the volumetric methods (B). Solid line in (B) represents the bias and the dotted lines represent 95% limits of agreement.

Table 3.1. Reproducibility of left atrial volume measurements.

	Intra-observer	Inter-observer
	Bias (95% Limits of agreement)	Bias (95% Limits of agreement)
Volumetric	-1.7 (-10.6 – 7.2)	-0.9 (-17.4 – 15.6)
Biplane	-2.2 (-9.3 – 4.9)	-11.0 (-76.5 – 54.6)

CHAPTER 4

Atrial Functional Abnormalities in Patients with Lone Atrial Fibrillation

4.1. Summary

Cardiac structure and function in patients with “lone” AF have not been well studied. Twenty-six consecutive subjects with “lone” AF and 15 control subjects underwent comprehensive CMR assessment. All subjects were in sinus rhythm at the time of the scan. Atrial and ventricular volumes and ejection fractions were calculated in a blinded manner. Subjects with “lone” AF had a significantly lower left and right atrial ejection fraction compared with controls (LA ejection fraction; $48.5 \pm 8.5\%$ vs. $54.0 \pm 6.6\%$ respectively, $P = 0.04$, RA ejection fraction; $42.6 \pm 7.5\%$ vs. $49.2 \pm 10.1\%$ respectively, $P = 0.02$). In addition, subjects with “lone” AF had significantly increased indexed left and right ventricular EDVs and LV mass compared with controls (indexed LV EDV; $81.7 \pm 14.2 \text{ mL/m}^2$ vs. 73.4 mL/m^2 , $P = 0.006$, indexed RV EDV; $98.1 \pm 21.4 \text{ mL/m}^2$ vs. $78.6 \pm 16.9 \text{ mL/m}^2$, $P = 0.005$, indexed LV mass; $67.5 \pm 13.6 \text{ g/m}^2$ vs. $58.9 \pm 10.7 \text{ g/m}^2$ respectively, $P = 0.04$). There were no significant differences in left and right atrial maximal volumes, or left and right ventricular ejection fractions between the groups. In conclusion, patients with “lone” AF have demonstrable abnormalities in atrial function, ventricular volumes and ventricular mass. These structural and functional abnormalities may have important implications in the pathogenesis, progression and management of patients with “lone” AF.

4.2. Introduction

“Lone” AF constitutes 3 – 11% of all cases of AF and has traditionally been considered a relatively benign condition, with a low risk of thromboembolism and good prognosis (Kopecky et al. 1987). Despite the favourable outlook of these patients, in a long-term

follow-up study, 31% of patients with paroxysmal or persistent “lone” AF progressed to permanent AF over 25 years (Jahangir et al. 2007). The pathophysiologic basis of “lone” AF is not well understood. Although triggering factors were initially thought to play the most important role in this subgroup of AF patients, with the substrate being less important, a recent electrophysiologic study found a clearly abnormal substrate in patients with “lone” paroxysmal AF that could potentially promote further disease progression (Stiles et al. 2009). Furthermore, other studies have implicated increased atrial fibrosis (Frustaci et al. 1997), LV diastolic dysfunction (Jais et al. 2000), inflammation (Chung et al. 2001), and atrial coronary artery microvascular dysfunction (Skalidis et al. 2008) as pathophysiologic correlates of “lone” AF.

In the era prior to echocardiography, “lone” AF was defined as the presence of the arrhythmia in young patients without clinical cardiovascular disease, hypertension or thyrotoxicosis (Evans and Swann 1954). In the modern era, the definition of “lone” AF has been refined to include the absence of structural heart disease based on echocardiography (Fuster et al. 2006). However, it is well known that the assessment of LA structure and function by conventional two-dimensional echocardiography is limited (Kircher et al. 1991). Thus, subtle cardiac structural and functional abnormalities in patients with “lone” AF that may be associated with disease progression, may go undetected using conventional imaging techniques. Over the last decade, CMR has been clearly established as a “gold standard” technique for measuring cardiac chamber volumes and function, and has been validated as an accurate tool for the measurement of LA volume (Jarvinen et al. 1994). We therefore set out to

determine whether there were any differences in cardiac structure and function in patients with “lone” AF compared with healthy controls, using CMR.

4.3. Methods

4.3.1. Study population

Consecutive patients with “lone” AF, who were free from arrhythmia in the preceding week, had CMR in sinus rhythm. The classification of “lone” AF was based on current guideline definitions, with patients having no cardiopulmonary abnormalities on history, examination, electrocardiography, chest X-ray and echocardiography, and absence of hypertension, thyroid disorder, diabetes mellitus, alcohol or substance abuse and electrolyte disturbances by appropriate tests (Fuster et al. 2001). Coronary artery disease was excluded by history, electrocardiography and stress test criteria where indicated. Healthy control subjects had no documented cardiopulmonary disease, hypertension, thyroid, renal or hepatic disorder, diabetes mellitus, and had a comprehensive CMR scan. Exclusion criteria for both groups included AF during scanning, significant renal dysfunction (creatinine clearance < 60 mL/min) or contraindications to undergoing a CMR scan. The study protocol was approved by the Royal Adelaide Hospital research ethics committee, and written informed consent was obtained from all subjects.

4.3.2. Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed using a 1.5 Tesla scanner (Siemens Avanto, Siemens Medical Solutions, Erlangen, Germany). Comprehensive atrial and ventricular CMR imaging was performed as described previously (Teo et al. 2008). In

brief, steady state free precession cine images of the LA (6 mm slice thickness, no interslice gaps) and LV (6 mm slice thickness, 4 mm interslice gaps) were acquired in the SA plane. Subsequently, detailed imaging of the atria was undertaken in the HLA and VLA planes (6 mm slice thickness, no interslice gaps). Images were acquired using surface electrocardiogram based retrospective gating, at end expiration. Typical imaging parameters were: echo time 1.2 ms, repetition time 63.7 ms, flip angle 80°, matrix size 192 × 156, field of view 360 - 440 mm.

4.3.3. Image analysis

Image analysis was performed using proprietary software (Argus, Siemens Medical Solutions, Erlangen, Germany), in a blinded manner. Ventricular volumes were calculated by manually tracing the endocardial contours in the SA views, at end-diastole (onset of R wave) and end-systole (smallest cavity volume), and applying Simpson's rule. Papillary muscles and trabeculations were excluded from the ventricular volume if they were contiguous with the ventricular wall. The basal slice for the LV was selected when at least 50% of the blood pool was surrounded by ventricular myocardium. The apical slice was defined as the last slice with visible intracavity blood pool (Hudsmith et al. 2005). For the RV, volumes below the pulmonary valve were included. Trabeculation was excluded from RV volume measurement (Hudsmith et al. 2005).

Atrial volumes were calculated using a three dimensional technique (Teo et al. 2008). The endocardial contours were manually traced in the HLA views, and modified Simpson's rule was applied. The pulmonary veins (PVs) were carefully excluded, and

the LAA was included if present in the images. All volumes were indexed to body surface area. Atrial and ventricular ejection fractions were calculated using the formula; (maximum volume – minimum volume)/maximum volume × 100 (%). Atrial ejection fraction was used as a marker of global LA contractile function (Wylie et al. 2008) and ventricular ejection fraction as a marker of ventricular systolic function.

4.3.4. Reproducibility

Intra- and inter-observer variability for atrial and ventricular measurements in our CMR unit have been previously reported (Teo et al. 2008). In brief, the intraclass correlation coefficients for intra-observer variability were: maximum LA volume 0.84, maximum RA volume 0.98, LV EDV 0.95, LV ejection fraction 0.91, RV EDV 0.89, RV ejection fraction 0.77. The intraclass correlation coefficients for inter-observer variability were: maximum LA volume 0.87, maximum RA volume 0.92, LV EDV 0.96, LV ejection fraction 0.94, RV EDV 0.93, RV ejection fraction 0.7.

4.3.5. Statistical analysis

Data are presented as mean ± SD. Comparisons of atrial and ventricular volumes, LV mass and atrial and ventricular ejection fractions between subjects with “lone” AF and healthy controls were made using a two-tailed, unpaired t test for normally distributed data and the Mann Whitney test for data that were not normally distributed. Statistical significance was taken at $P < 0.05$.

4.4. Results

4.4.1. Baseline characteristics

The baseline characteristics are presented in Table 4.1. Twenty-six consecutive subjects with “lone” AF (23 males, mean age 50.8 ± 11.3 years) were included in this study. Fifteen healthy subjects (7 males, mean age 54.3 ± 6.4 years) were studied as controls.

4.4.2. Atrial structure and function

There was no significant difference in indexed LA volume between the “lone” AF and control groups (51.8 ± 12.1 mL/m² vs. 46.9 ± 8.7 mL/m² respectively, $P = 0.2$). Similarly, the indexed RA volumes were comparable between the two groups (57.4 ± 15.6 mL/m² in the “lone” AF group vs. 51.5 ± 14.8 mL/m² in the control group, $P = 0.2$). However, the LA ejection fraction was significantly lower in the “lone” AF group compared with controls ($48.5 \pm 8.5\%$ vs. $54.0 \pm 6.6\%$ respectively, $P = 0.04$). Right atrial ejection fraction was also significantly less in the “lone” AF group compared with normal controls ($42.6 \pm 7.5\%$ vs. $49.2 \pm 10.1\%$ respectively, $P = 0.02$) (Table 4.2).

4.4.3. Ventricular structure and function

The indexed left and right ventricular EDVs were significantly higher in the “lone” AF group compared with the control group (indexed LV EDV: 81.7 ± 14.2 mL/m² in “lone” AF group vs. 73.4 ± 31.4 mL/m² in control group, $P = 0.006$; indexed RV EDV: 98.1 ± 21.4 mL/m² in “lone” AF group vs. 78.6 ± 16.9 mL/m² in control group, $P = 0.005$). Subjects with “lone” AF had a significantly higher indexed LV mass than controls (67.5 ± 13.6 g/m² vs. 58.9 ± 10.7 g/m² respectively, $P = 0.04$) (Table 4.2).

Left and right ventricular ejection fractions were similar between the two groups (LV ejection fraction: $70.3 \pm 6.0\%$ in “lone” AF group vs. $69.6 \pm 5.5\%$ in control group, $P = 0.7$; RV ejection fraction: $55.7 \pm 12.1\%$ in “lone” AF group vs. $60.3 \pm 4.8\%$ in control group, $P = 0.3$).

4.5. Discussion

4.5.1. Major findings

In this study, several significant cardiac structural and functional abnormalities were demonstrated in patients with “lone” AF. The study showed that compared with normal controls, subjects with “lone” AF have; 1) significantly reduced LA and RA contractile function, 2) increased LV and RV EDVs, and 3) increased LV mass.

4.5.2. Atrial abnormalities in “lone” atrial fibrillation

Traditionally, “lone” AF has been considered to be a benign condition with no associated cardiac abnormalities (Kopecky et al. 1987). However, recent studies have demonstrated that while initially at low risk, over the long-term, a significant proportion of patients with paroxysmal or persistent “lone” AF progress to permanent AF and the risk of thromboembolism increases over time (Jahangir et al. 2007). This has raised an important question regarding the potential role of an abnormal substrate leading to AF progression in this population. Numerous studies have suggested that patients with “lone” AF indeed have atrial abnormalities at the cellular (Frustaci et al. 1997), structural (Sitges et al. 2007), and electrophysiologic (Zimmermann et al. 1998; Stiles et al. 2009) levels. Moreover, detailed electrophysiologic analyses in patients with

“lone” AF have found significant conduction abnormalities, sinus node dysfunction, as well as areas of low voltage signifying atrial fibrosis (Stiles et al. 2009).

Echocardiographic studies in patients with “lone” AF have been conflicting with regards to LA size and function (Kosmala et al. 2006; Sitges et al. 2007). Although some have demonstrated a larger LA volume in patients with “lone” AF compared with controls (Phang et al. 2004; Sitges et al. 2007), others have found no significant difference in LA volume between these two groups (Kosmala et al. 2006). However, echocardiography has several well-recognised limitations in accurately and reproducibly quantifying chamber volumes and function (Ujino et al. 2006). In our study, using the currently accepted “gold standard” imaging modality for chamber volume measurement, there was no significant difference in LA volume between subjects with “lone” AF and controls. However, LA ejection fraction was significantly lower in the “lone” AF group compared with controls. Our findings for the RA were consistent with those of the LA, showing no significant difference in RA volume between subjects with “lone” AF and controls, but a significantly lower RA ejection fraction in the “lone” AF group. In contrast, Kosmala et al. found no significant difference in LA ejection fraction between patients with “lone” AF and controls, although they did demonstrate LA functional abnormalities on PV flow analysis (Kosmala et al. 2006). Others have found LA functional abnormalities in patients with “lone” AF using tissue Doppler analysis of peak early systolic velocity of the lateral mitral annulus (Sitges et al. 2007), and spontaneous echo contrast on transoesophageal echocardiography (Di Angelantonio et al. 2005). Thus, there is agreement between

studies that patients with “lone” AF have atrial functional abnormality when more sensitive indices are used to evaluate such patients.

4.5.3. Ventricular changes in “lone” atrial fibrillation

In this study, there were significantly higher left and right ventricular EDVs and LV mass in patients with “lone” AF. Left and right ventricular systolic function was preserved in patients with “lone” AF. Previous studies have not found a difference in LV size between patients with “lone” AF and controls (Kosmala et al. 2006; Sitges et al. 2007). However, these studies used LV end-diastolic dimension on echocardiography, which is a less sensitive measure of LV size. Furthermore, RV assessment was not performed in these studies. In the above studies, LV mass was assessed in one (Sitges et al. 2007), while interventricular septum thickness was used as a marker of LV mass in the other (Kosmala et al. 2006). In both studies, there was no significant difference between patients with “lone” AF and controls. However, Sitges et al. found a nonsignificantly elevated indexed LV mass in patients with “lone” AF (Sitges et al. 2007). The absence of a significant difference in LV mass between the two groups in these studies is likely due to the technical limitations of the measurements whereas CMR has been demonstrated to be a reproducible method of LV mass determination (Bellenger et al. 2000). Possible underlying mechanisms that could lead to larger ventricular size and greater LV mass in patients with “lone” AF include neurohumoral activation, particularly involving the renin-angiotensin-aldosterone system (Boldt et al. 2003) or a generalised cardiomyopathic process, similar to that involving the atrial myocardium (Frustaci et al. 1997). Further studies are required to

elucidate the underlying factors contributing to ventricular dilatation and increased LV mass in patients with “lone” AF.

4.5.4. Implications

Overall, our findings suggest that “lone” AF is associated with LA functional abnormalities. This is consistent with an atrial myopathic process as observed in previous studies (Todd et al. 2003; Stiles et al. 2009). The fact that this functional atrial abnormality was seen in “lone” AF patients during stable sinus rhythm points to an abnormal substrate, which may be responsible for disease progression in this population (Jahangir et al. 2007). This could have important implications in the management of patients with “lone” AF in the era of AF ablation, as additional ablation strategies aimed at substrate modification may be warranted in this subset of patients. Furthermore, the increased ventricular volumes and LV mass in patients with “lone” AF may respond to early interventions targeting potential neurohumoral mechanisms, such as blockade of the renin-angiotensin-aldosterone system (Boldt et al. 2006).

4.5.5. Study limitations

The sample size in this study was small, but “lone” AF, by strict definition is uncommon, thus limiting the potential study population. However, we used the “gold standard” non-invasive imaging modality for chamber quantification. Cardiac magnetic resonance imaging, due to its high image quality, accuracy and reproducibility has been shown to detect differences in volume and mass with only a small sample size as opposed to traditional imaging techniques (Bellenger et al. 2000). Our control group

had a similar mean age and body mass index, but there were a higher proportion of females in the control group compared with the “lone” AF group. Males have a higher indexed LV mass compared with females, however, indexed atrial (Lang et al. 2005) and ventricular volumes (Teo et al. 2008), and atrial (Hudsmith et al. 2005) and ventricular (Teo et al. 2008) ejection fractions are not significantly different between adult males and females. Thus, the greater proportion of females in the control group should not have an impact on the results, with the exception of the LV mass. Furthermore, the difference in LV mass between the groups cannot be explained by body size as the values were indexed to body surface area. Finally, CMR is not the ideal imaging modality for assessing diastolic function. Hence, in our study we did not assess diastology using CMR. Diastolic dysfunction could be an important contributing factor in patients with “lone” AF, and could affect some of the measured parameters, although we did not observe a significant difference in LA volume between the groups, which would usually be expected with diastolic abnormalities.

4.6. Conclusions

Patients with “lone” AF, despite normal findings on echocardiography, demonstrate subtle, but significant abnormalities in atrial function, ventricular EDV and LV mass when assessed by CMR. These changes could have important implications in the pathogenesis, disease progression and management of patients with “lone” AF.

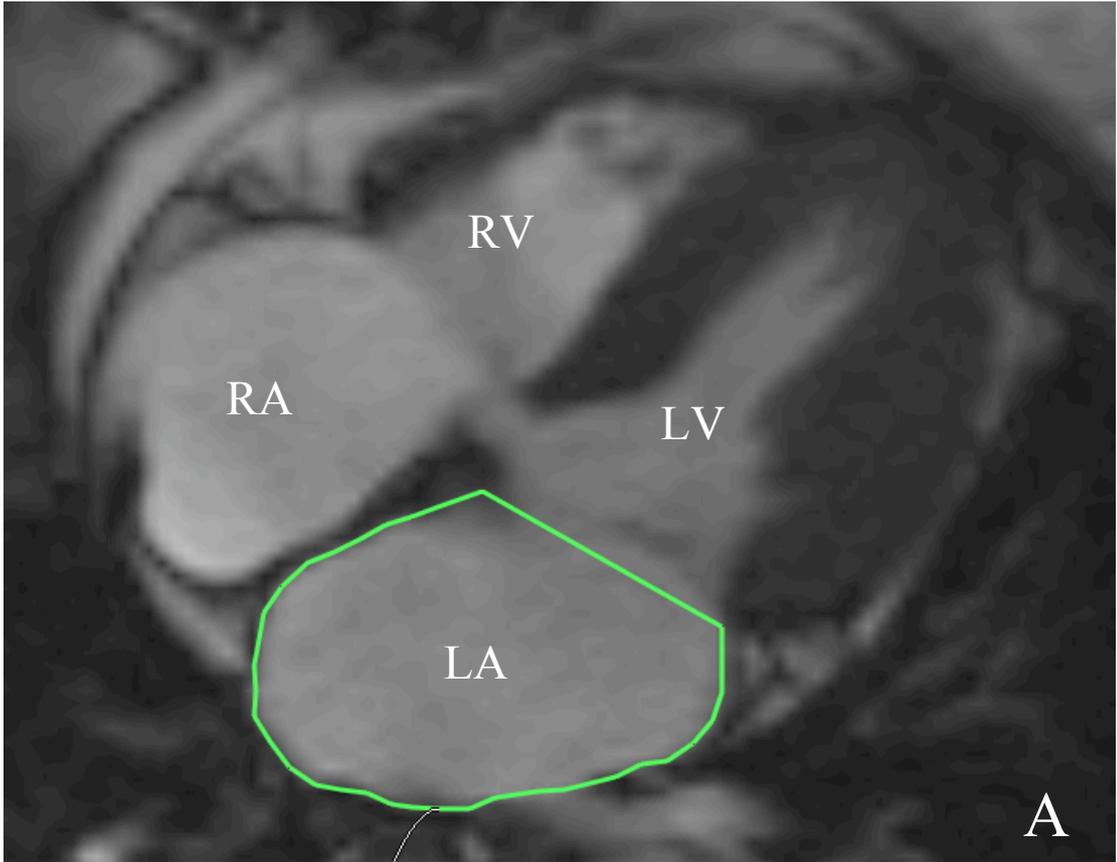
Table 4.1. Baseline characteristics

	Patients (n = 26)	Controls (n = 15)
Age (years)	50.8 ± 11.3	54.3 ± 6.4
Gender (M : F)	23 : 3	7 : 8
Body mass index	26.9 ± 4.5	26.2 ± 4.2
Paroxysmal : Persistent AF	25 : 1	-
Median AF history (months)	54	-

Table 4.2. Cardiac chamber volumes, mass and function in patients and controls

	Patients (n = 26)	Controls (n = 15)	<i>P</i> Value
Maximum LA volume/BSA (mL/m²)	51.8 ± 12.1	46.9 ± 8.7	0.2
LA ejection fraction (%)	48.5 ± 8.5	54.0 ± 6.6	0.04
Maximum RA volume/BSA (mL/m²)	57.4 ± 15.6	51.5 ± 14.8	0.2
RA ejection fraction (%)	42.6 ± 7.5	49.2 ± 10.1	0.02
LVEDV/BSA (mL/m²)	81.7 ± 14.2	73.4 ± 31.4	0.006
LV ejection fraction (%)	70.3 ± 6.0	69.6 ± 5.5	0.7
LV mass/BSA (g/m²)	67.5 ± 13.6	58.9 ± 10.7	0.04
RVEDV/BSA (mL/m²)	98.1 ± 21.4	78.6 ± 16.9	0.005
RV ejection fraction (%)	55.7 ± 12.1	60.3 ± 4.8	0.3

BSA, body surface area; LA, left atrial; RA, right atrial; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; RV, right ventricular; RVEDV, right ventricular end-diastolic volume.



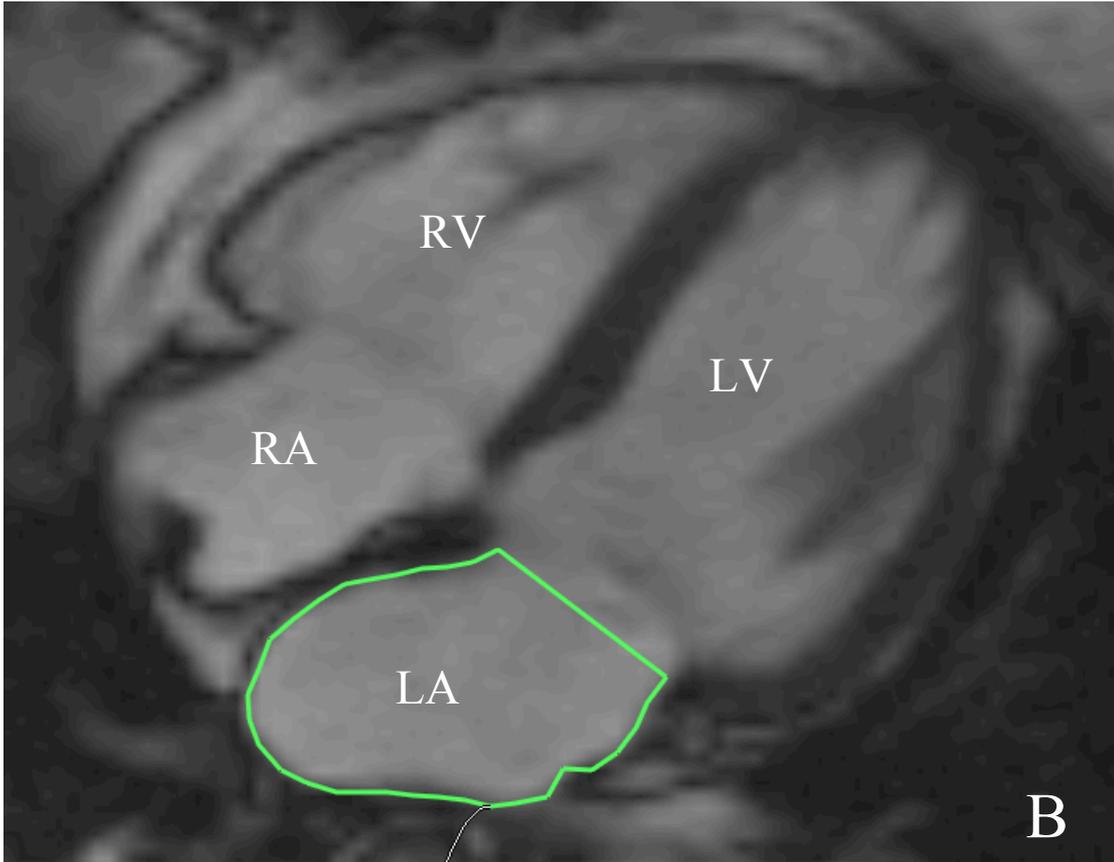


Figure 4.1. Horizontal long axis image. Left atrial endocardial contours drawn at maximal volume in end-systole (A) and minimal volume in end-diastole (B). LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle.

CHAPTER 5

Predictors of Recurrent Atrial Fibrillation Following Radiofrequency Catheter Ablation

5.1. Summary

The success rate of RFCA for AF can be variable. Pre-procedural factors that affect outcomes of AF ablation have not been well established. A cohort of 138 patients (61 males (70%), mean age 57.2 ± 10.5 years, 66 (76%) with paroxysmal AF) undergoing RFCA for drug refractory AF over a 12-month period were included in this study. All patients had comprehensive clinical and CMR assessment at baseline, and were in sinus rhythm at the time of the CMR scan. Atrial and ventricular volumes and ejection fractions were calculated in a blinded manner. Follow-up was performed at 3, 6, 9 and 12 months with history, physical examination, ECG and 7 days of continuous Holter monitoring to detect symptomatic and asymptomatic AF recurrence. There were 87 patients with complete follow-up data out of the 138 patients. At 12 months post-ablation, following a single procedure, 54 patients (62%) were in sinus rhythm without the use of antiarrhythmics and an additional 5 patients (6%) were in sinus rhythm on antiarrhythmic therapy. On multivariate analysis, the only independent predictors of AF recurrence at 12 months were female gender (OR 3.09; 95% CI 1.09 – 8.7; $P = 0.03$) and increased maximal LA volume (OR 1.04; 95% CI 1.004 – 1.08; $P = 0.03$). In conclusion, female gender and LA dilatation are independent predictors of recurrent AF following a single ablation procedure.

5.2. Introduction

Radiofrequency catheter ablation is being increasingly performed for the management of AF and is a potentially curative treatment strategy in selected patients (Haissaguerre et al. 1998; Pappone et al. 2003). However, it is an invasive treatment strategy

associated with several serious complications including stroke, cardiac tamponade, pulmonary vein stenosis and the rare, but almost universally fatal, atrio-oesophageal fistula (Cappato et al. 2009). Accordingly, the current primary indication for RFCA is symptomatic AF, refractory to at least one antiarrhythmic agent, although these indications are expanding based on new developments in the field (Calkins et al. 2007b).

The reported rates of freedom from AF at medium-term follow-up in patients undergoing RFCA have varied widely (Pappone et al. 2006; Cheema et al. 2006). To a great extent, this disparity may be attributed to procedural factors as well as the lack of a universally accepted definition of success and standardised follow-up in the published literature. In addition to these factors, another important determinant of outcomes appears to be the patient characteristics (Berruezo et al. 2007). The determination of pre-procedural predictors of outcome can aid in patient selection, counselling and risk-benefit analysis. However, as yet, such pre-procedural prognostic factors have not been fully elucidated. Previous studies have assessed baseline echocardiographic (Berruezo et al. 2007) and computed tomographic (Hof et al. 2009) parameters, but echocardiography is limited by geometric assumptions in determining volumes and computed tomography is not an ideal modality for the assessment of function. Cardiac magnetic resonance imaging is widely regarded as the “gold standard” for determining chamber volume and function (Bellenger et al. 2000) and is the ideal tool for assessing cardiac structure and function in patients undergoing RFCA for AF. The aim of this study was to determine pre-procedural clinical and CMR-based prognostic factors in patients undergoing RFCA for AF.

5.3. Methods

5.3.1. Study population

Patients undergoing their first RFCA for symptomatic, drug refractory AF were recruited over a period of 12 months. Comprehensive clinical and CMR data were collected. Patients with contraindications for CMR (such as pacemakers, implantable cardioverter-defibrillators, significant claustrophobia) were excluded. The study protocol was approved by the Royal Adelaide Hospital research ethics committee, and written informed consent was obtained from all subjects.

5.3.2. Ablation procedure

All patients were therapeutically anticoagulated for at least 1 month using warfarin (INR 2.0 – 3.0) and subsequently switched to low molecular weight heparin, with the last dose administered on the evening prior to the ablation. Patients underwent TOE within 7 days of RFCA to exclude LAA thrombus.

Electrophysiological study was performed in the post-absorptive state with sedation utilising midazolam and fentanyl. The LA was accessed using a single transeptal puncture using an SLO sheath and a BRK1 needle (St Jude Medical). Following transeptal access, a bolus of 100IU/kg of unfractionated heparin was administered, with repeated boluses to maintain the activated clotting time between 300-350 seconds. The following catheters were utilised: 10 pole catheter within the coronary sinus; 10 pole Variable Lasso catheter (Biosense-Webster) used with the SLO sheath for mapping the pulmonary veins; and a 3.5 mm tip externally irrigated (Navi-Star or Thermocool, Biosense-Webster). Circumferential ablation was performed of the pulmonary veins

with an endpoint of isolation. Ablation of the pulmonary veins was performed using a delivered power of 30W with irrigation rates of 30-60mL/min. Additional substrate modification was performed in patients with an episode of AF \geq 48 hours, LA size \geq 57mm (longest diameter) or with evidence of structural heart disease. This took the form of linear ablation along the LA roof and/or mitral isthmus and/or ablation of CFAE. Cavo-tricuspid isthmus ablation with an endpoint of bi-directional isthmus block was performed only in patients with a history of typical flutter or if mapping confirmed typical flutter during the procedure. Linear ablation was performed with a delivered power of 30-35W with irrigation rates of 30-60mL/min. In all cases electroanatomic mapping (CARTO, Biosense-Webster; or NavX, St Jude Medical) was used. The endpoint of linear ablation was the demonstration of bi-directional conduction block based on previously established criteria.

5.3.3. Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed using a 1.5 Tesla scanner (Siemens Avanto, Siemens Medical Solutions, Erlangen, Germany). Steady state free precession cine images of the LA (6 mm, contiguous slices) and LV (6 mm slices with 4 mm interslice gaps) were acquired in the SA, VLA and HLA planes. Images were acquired using surface electrocardiogram based retrospective gating, at end expiration. Typical imaging parameters were: echo time 1.2 ms, repetition time 63.7 ms, flip angle 80°, matrix size 192 × 156, field of view 360 - 440 mm.

5.3.4. Image analysis

Image analysis was performed using proprietary software (Argus, Siemens Medical Solutions, Erlangen, Germany), in a blinded manner. Ventricular volumes were calculated by manually tracing the endocardial contours in the SA views, at end-diastole (onset of R wave) and end-systole (smallest cavity volume), and applying Simpson's rule. Papillary muscles and trabeculations were excluded from the ventricular volume if they were contiguous with the ventricular wall. The basal slice for the LV was selected when at least 50% of the blood pool was surrounded by ventricular myocardium. The apical slice was defined as the last slice with visible intracavity blood pool. For the RV, volumes below the pulmonary valve were included. Trabeculation was excluded from RV volume measurement.

Atrial volumes were calculated using a three dimensional technique (Teo et al. 2008). The endocardial contours were manually traced in the HLA views, and modified Simpson's rule was applied. The PVs were excluded, and the LAA was included if present on the images. Atrial and ventricular ejection fractions were calculated using the formula; $(\text{maximum volume} - \text{minimum volume}) / \text{maximum volume} \times 100 (\%)$.

5.3.5. Follow-up

All patients were maintained on antiarrhythmic drugs for a 6-week period. Patients were reviewed with history, physical examination, ECG and 7-day continuous Holter monitoring at 3 monthly intervals for 12 months and thereafter 6 monthly. A 3-month "blinking period" was applied as per the HRS consensus guidelines (Calkins et al. 2007). Patients with any atrial arrhythmias lasting > 30 seconds were deemed to have

failed AF ablation. In patients with a CHADS2 score ≤ 1 anticoagulation was discontinued after 3 months. However, in those with a CHADS2 score ≥ 2 anticoagulation was continued for a minimum of 12 months, after which in the absence of arrhythmia, discontinuation of anticoagulation was only performed by individual discussion of the potential risks associated with cessation of anticoagulation.

5.3.6. *Statistical analysis*

Statistical analysis was performed using SAS 9.2 (SAS Institute Inc, Cary, NC, USA). Continuous variables are presented as mean \pm SD or median and interquartile range, where indicated. Categorical variables are presented as counts and percentages. The association between baseline clinical and CMR parameters and outcome was assessed using logistic regression analysis with recurrence at 12 months as the outcome. A univariate regression analysis was performed initially, followed by a multivariate regression analysis. A t test was used for continuous variables and chi-square test for discrete variables. Variables were included in the multivariate analysis if P was < 0.1 on the univariate analysis. A two-tailed P value < 0.05 was required for statistical significance on multivariate analysis.

5.4. Results

5.4.1. *Patient characteristics*

In total, 138 patients underwent RFCA for AF over a period of 12 months. Eighty-seven patients were included in this study as 51 had incomplete data. Baseline clinical characteristics and CMR parameters are presented in Tables 5.1 and 5.2, respectively.

5.4.2. Ablation outcomes

At 12 months post-ablation, 54 patients (62%) were AF free without antiarrhythmic agents following a single procedure. An additional 5 patients (6%) were free of AF recurrence on antiarrhythmic therapy. Furthermore, an additional 11 patients were AF free without antiarrhythmic therapy after a second procedure (75% of the cohort). Details of the extent of ablation are provided in Table 5.3.

5.4.3. Predictors of recurrent atrial fibrillation

Clinical and CMR parameters at baseline were analysed using univariate and multivariate models. Table 5.4 demonstrates the univariate variables that were evaluated to determine success after RFCA. On univariate analysis, predictors of AF recurrence included female gender and indexed maximal LA volume (Table 5.4). On multivariate analysis, indexed maximal LA volume (OR 1.04; 95% CI 1.004 – 1.08, $P = 0.033$) and female gender (OR 3.09; 95% CI 1.09 – 8.7, $P = 0.030$) were the only independent predictors of AF recurrence at 12 months post-ablation (Table 5.5).

5.5. Discussion

5.5.1. Main findings

This study demonstrates that female gender and maximum LA volume are associated with AF recurrence at 12 months post-RFCA. In this cohort, the type and duration of AF, hypertension, structural heart disease and LV size and function were not associated with AF recurrence.

5.5.2. Clinical predictors of recurrent atrial fibrillation

In the pre-ablation era, the only clinical predictor of maintenance of sinus rhythm at 1 year following cardioversion for AF was the duration of AF, with patients who have a history of AF for greater than 1 year having a low likelihood of remaining in sinus rhythm (Dittrich et al. 1989). Although RFCA has been shown to be highly effective at maintaining sinus rhythm at medium-term follow-up, a notable proportion of patients require repeat procedures in order to maintain sinus rhythm (Oral et al. 2003; Oral et al. 2006b). Apart from the procedural technique, previous studies have suggested several clinical variables as being important predictors of outcome in patients undergoing RFCA for AF. These include age, hypertension and presence of persistent or permanent AF (Berruezo et al. 2007; Abecasis et al. 2009; Arya et al.). Interestingly, the duration of AF has not been shown to be associated with outcomes. This may be due to the asymptomatic nature of many AF episodes, which could lead to inaccuracies in the estimation of AF duration.

In this study, the only independent pre-procedural clinical predictor of recurrent AF was female gender. Interestingly, in a multicentre study of patients undergoing AF ablation, female gender was found to be a significant predictor of secondary recurrence (Bhargava et al. 2009). The reasons underlying the female preponderance for AF recurrence following ablation have not been fully explored and require further investigation. The evidence in the field of AF suggests that women with AF appear to have a worse prognosis as demonstrated by increased stroke and bleeding risks (Fang et al. 2005; Shireman et al. 2006). Furthermore, female gender is a recognised predictor of periprocedural complication following AF ablation (Shah et al. 2012). Further studies to

assess the substrate for AF in females and factors impacting on the efficacy of AF ablation are warranted.

Age, hypertension and the type of AF were not predictive of AF recurrence. It should be noted that the majority of patients in this study were aged 70 years or younger, thus making it difficult to comment on outcomes of RFCA in an older population. Although intuitively, the type of AF is thought to have an impact on ablation outcomes, this has not been consistently shown in previous studies. Some studies have found increased AF recurrence in patients with nonparoxysmal AF on unadjusted and multivariate analyses (Cheema et al. 2006), while in other studies nonparoxysmal AF was only a significant predictor on univariate but not multivariate analyses (Berruezo et al. 2007). A recent study found that there was no significant association between the type of AF and recurrence following ablation (Cha et al. 2008). These inconsistent findings may be due to heterogeneity of the study population, under-representation of females and the elderly, varying definitions of outcomes, and durations of follow-up. The low numbers of patients with nonparoxysmal forms of AF may explain the lack of an association between AF type and outcome in this study.

5.5.3. Imaging predictors of recurrent atrial fibrillation

Left atrial size has been found to be an important factor in the maintenance of sinus rhythm in patients with AF, both in the setting of cardioversion (Verhorst et al. 1997) and following RFCA (Berruezo et al. 2007; Abecasis et al. 2009; Hof et al. 2009; Arya et al.). This study confirms the prognostic importance of LA volume. However, ventricular volumes and ejection fraction were not associated with ablation outcomes in

this study. In contrast, Berruezo et al. found that increased LV end-systolic diameter was a predictor of outcomes following RFCA on univariate analysis (Berruezo et al. 2007). In their study, Berruezo et al used echocardiographic measurements with associated limitations in accuracy and reproducibility, while CMR volumetric measurements are much more robust and reproducible. Furthermore, the majority of patients in our cohort had preserved systolic function and normal LV chamber volumes, thus preventing extrapolation of these results to populations with significant structural heart disease.

5.5.4. Implications

The clinical implications of this study are numerous. Although AF ablation can be highly successful in alleviating the symptoms of AF, a significant proportion of patients have recurrent AF following ablation and require multiple procedures. The findings of this study offer clinical and imaging markers that can be used for patient counselling prior to an ablation procedure and guide decision-making. While AF ablation could still be offered to patients with less favourable clinical and imaging markers, patients can be appropriately informed of the increased likelihood of recurrence and the need for repeat procedures. In addition, such patients may be treated with a tailored ablation strategy in order to improve procedural success. Future studies of different ablation strategies, based on such pre-procedural markers, could be useful in guiding the management of patients with higher likelihood of AF recurrence, and conversely in limiting the amount of ablation and its potential complications in patients who have a more favourable risk profile.

5.5.5. Study limitations

In this study, procedural success was defined as the absence of symptomatic and asymptomatic AF on 7-day Holter monitoring at 12 months follow-up with a 3-month “blinking period” as recommended in the current guidelines (Calkins et al. 2007b). However, it is possible that asymptomatic recurrences were undetected, which could influence the results. Multiple variables in treatment could have an impact on the outcomes, particularly given the heterogeneity of the study population in terms of AF type. The cohort of patients in this study is representative of the “real world” setting, however, the absolute number of patients who were older, and those with nonparoxysmal AF, congestive heart failure and valvular heart disease were low. A larger sample size could have overcome this limitation, and may have found an association between these baseline parameters and ablation outcomes.

5.6. Conclusions

Female gender and increased LA volume were independent predictors of recurrent AF at 12 months post-RFCA. These clinical and imaging markers can be used in informing patients about the likelihood of procedural success, patient selection and planning of ablation strategies. Furthermore, this study emphasises the important role of CMR as a pre-procedural imaging modality for patients undergoing AF ablation.

Table 5.1. Baseline clinical characteristics of patients included in the study

	AF Free*	AF Recurrence
Patients	54	33
Age (years)	58.0 ± 9.0	55.9 ± 12.5
Gender (M : F)	40 : 14	21 : 12
AF type:		
Paroxysmal	42 (78%)	24 (73%)
Persistent	12 (22%)	9 (27%)
Permanent	-	-
AF duration (months)	Median 48 (interquartile range 22-96)	Median 66 (interquartile range 33-114)
Hypertension	25 (46%)	16 (48%)
Structural heart disease	8 (15%)	2 (6%)

*Free from atrial fibrillation at 12 months post-ablation without antiarrhythmic therapy

Table 5.2. Baseline imaging characteristics of patients included in the study

	AF Free*	AF Recurrence
Maximum LA volume/BSA (mL/m ²)	50.4 ± 12.1	57.5 ± 14.9
LA ejection fraction (%)	46.4 ± 9.3	43.9 ± 13.8
LV end-diastolic volume/BSA (mL/m ²)	76.8 ± 15.1	78.9 ± 16.6
LV ejection fraction (%)	71.7 ± 8.5	69.7 ± 10.3
LV mass/BSA (g/m ²)	67.2 ± 13.2	62.1 ± 12.8

BSA, body surface area

* Free from atrial fibrillation at 12 months post-ablation without antiarrhythmic therapy

Table 5.3. Ablation procedure details

Procedure	Number (%)
Circumferential pulmonary vein isolation	87 (100%)
Roofline	57 (66%)
Cavotricuspid isthmus	16 (18%)
Complex fractionated atrial electrogram	15 (17%)
Mitral isthmus	8 (9%)
Coronary sinus	13 (15%)

Table 5.4. Univariate analysis of pre-procedural variables and the risk of AF recurrence

	OR (95% CI)	<i>P</i> Value
Age (years)	0.99 (0.95 – 1.03)	0.541
Female gender	2.41 (0.92 – 6.29)	0.072*
Hypertension	1.042 (0.42 – 2.57)	0.929
Structural heart disease	4.86 (0.58 – 40.42)	0.144
Paroxysmal AF	0.93 (0.33 – 2.65)	0.897
AF duration (months)	1.002 (0.997 – 1.006)	0.491
Indexed maximum LA volume (mL/m ²)	1.03 (0.999 – 1.069)	0.058*
LA ejection fraction (%)	0.98 (0.94 – 1.02)	0.231
Indexed LV EDV (mL/m ²)	1.009 (0.981 – 1.039)	0.520
LV ejection fraction (%)	0.97 (0.92 – 1.01)	0.152
Indexed LV mass (g/m ²)	0.97 (0.934 – 1.006)	0.102

*Included in multivariate analysis.

Table 5. Multivariate analysis of pre-procedural variables and the risk of AF recurrence

	OR (95% CI)	<i>P</i> Value
Female gender	3.088	0.033
Indexed maximum LA volume	1.042	0.030

CHAPTER 6

STRUCTURAL AND FUNCTIONAL REVERSE REMODELLING AFTER ATRIAL FIBRILLATION ABLATION: IMPLICATIONS FOR CLINICAL OUTCOMES

6.1. Summary

Transient arrhythmias have been observed after AF ablation. However, the reasons for their disappearance are not fully understood. Indeed, in persistent AF, the mechanisms that lead to a successful outcome have been incompletely explored; in particular the role of reverse remodelling is not known. We hypothesise that these phenomena may, in part, be a consequence of reverse remodelling of cardiac structure and function after AF ablation.

Of 90 consecutive patients undergoing primary RFCA who underwent detailed CMR before and 12 months post-ablation, 56 were in sinus rhythm at both CMR studies and formed the study cohort. The following were determined by investigators blinded to the knowledge of the procedure or clinical outcomes: atrial and ventricular volumes and ejection fractions, and ventricular mass. Ablation comprised circumferential pulmonary vein isolation in all and left atrial substrate modification in 63%. Clinical and 7-day continuous ambulatory monitoring was performed every 3 months with a failure considered as any atrial arrhythmia of > 30 seconds duration.

At 12 months post-procedure, 38 patients (68%) were in sinus rhythm after 1.3 ± 0.4 procedures, without the use of any antiarrhythmic agents, and a further 3 (5%) with antiarrhythmic drugs. In the LA, there was a significant reduction in volume post-ablation (105 ± 30 mL vs. 92 ± 25 mL; $P < 0.0001$). In the RA there was a similar reduction of volume (102 ± 33 mL vs. 88 ± 24 mL; $P < 0.0001$) with improvement in the ejection fraction ($41 \pm 10\%$ vs. $45 \pm 8\%$, $P = 0.004$) despite the absence of ablation in this

chamber. In the LV there was a significant reduction in end-diastolic volume (152 ± 37 mL vs. 137 ± 34 mL; $P < 0.0001$) and mass (134 ± 38 g vs. 128 ± 37 g, $P = 0.02$) post-ablation with no change in the ejection fraction. In the RV there was a significant reduction in end-diastolic volume (179 ± 51 vs. 159 ± 40 mL, $P < 0.0001$) and improvement in ejection fraction ($56\pm 11\%$ vs. $60\pm 10\%$, $P = 0.01$) following ablation.

In conclusion, ablation of AF with the maintenance of sinus rhythm, possibly with the cessation of antiarrhythmic drugs, is associated with marked reverse remodelling of cardiac structure and function. The reversal of remodelling in chambers where ablation had not been performed, particularly the RA, implicates an important role for reverse remodelling in the success of AF ablation and argues in favour of a “blanking period” during which further ablation should be avoided.

6.2. Introduction

Atrial fibrillation is the most common arrhythmia, with studies indicating that its frequency has reached epidemic proportions and is likely to increase further in this century (Go et al. 2001). It is well recognised that several conditions predispose to AF. The atrial remodelling forming the substrate for AF in a number of these conditions have been well characterised (Lau et al.; Lau et al.; Lau et al.; Li et al. 1999; Sanders et al. 2003; Verheule et al. 2003; Kistler et al. 2004; Sanders et al. 2004; Kistler et al. 2006; John et al. 2008; Roberts-Thomson et al. 2009). A common feature of many of these conditions is LA stretch (Ravelli and Allessie 1997). Indeed, increased atrial size has been characterised as a predictor for developing AF (Henry et al. 1976). Recent studies have also suggested that “lone” AF, when there is no identifiable structural heart

disease, is associated with significant atrial remodelling (Stiles et al. 2009). Atrial fibrillation itself is known to result in atrial structural, electrical and mechanical remodelling, which in part has been implicated in the progression of the AF disease process (Morillo et al. 1995; Wijffels et al. 1995; Ausma et al. 1997; Schotten et al. 2001).

In addition, AF leads to reduced ventricular filling, cardiac output and tachycardia-mediated cardiomyopathy (Grogan et al. 1992; Daoud et al. 1996). Although numerous studies have evaluated the impact of AF ablation on the LA using a variety of imaging modalities, there is a paucity of data regarding the impact on other cardiac chambers. Indeed, even the data presented on the atria have been quite variable, perhaps partly as a result of the imaging modality and techniques utilised. The long-term effects of AF ablation on cardiac structure and function have not been clearly established.

Catheter ablation of AF is increasingly applied as an effective strategy for rhythm control. However, there is a spectrum of targets with consensus only reached on the incorporation of pulmonary vein isolation (Calkins et al. 2007b). Techniques to individualise the ablation procedure remain elusive. It has been observed that patients may develop transient arrhythmias following ablation, which may have no consequence in the long-term (Oral et al. 2002). Indeed, the current expert consensus statement on AF ablation has recommended a 3-month “blanking period” during which ablation is avoided (Calkins et al. 2007a). The reasons for the disappearance of these arrhythmias are unknown; however, a variety of mechanisms, including tissue injury, resolution of

oedema, and “lesion maturation” have been proposed (Schwartzman et al. 2001; Okada et al. 2007; Badger et al. 2009).

Cardiac magnetic resonance imaging is now established as the “gold standard” for the non-invasive assessment of cardiac chamber volume, structure and function, due to its independence from geometric assumptions, high spatial resolution and high reproducibility (Bellenger et al. 2000). In this prospective clinical study, we used CMR to characterise the remodelling that occurs in each chamber of the heart after ablation of AF.

6.3. Methods

6.3.1. Study population

The study comprised 90 consecutive patients undergoing ablation of AF. All patients underwent detailed CMR study at baseline and 12 months post-ablation. Patients were excluded from the study if they had a contraindication for undergoing CMR imaging. In order to eliminate the effect of heart rhythm on CMR image quality and analysis, only patients in sinus rhythm at the time of both studies were included in the study cohort. The Royal Adelaide Hospital research ethics committee approved the study protocol, and written informed consent was obtained from all subjects.

6.3.2. Cardiac magnetic resonance imaging

Cardiac magnetic resonance imaging was performed using a 1.5 Tesla scanner (Siemens Avanto, Siemens Medical Solutions, Erlangen, Germany). Steady state free precession cine images of the LA (6 mm, contiguous slices) and LV (6 mm slices with 4 mm

interslice gaps) were acquired in the SA, and HLA planes. Images were acquired using surface electrocardiogram based retrospective gating, at end expiration. Typical imaging parameters were: echo time 1.2 ms, repetition time 63.7 ms, flip angle 80°, matrix size 192 × 156, field of view 360 - 440 mm.

6.3.3. Image analysis

Image analysis was performed using proprietary software (Argus, Siemens Medical Solutions, Erlangen, Germany). A single investigator blinded to the patient's clinical history, procedure and clinical outcome performed all CMR analyses. Ventricular volumes, mass and ejection fraction were measured as described previously (Hudsmith et al. 2005). Briefly, ventricular volumes were calculated by manually tracing the endocardial contours in the short axis views, at end-diastole (onset of R wave) and end-systole (smallest cavity volume), and applying Simpson's rule. Papillary muscles and trabeculations were excluded from the ventricular volume if they were contiguous with the ventricular wall. The basal slice for the LV was selected when at least 50% of the blood pool was surrounded by ventricular myocardium. The apical slice was defined as the last slice with visible intracavity blood pool. For the RV, volumes below the pulmonary valve were included. Trabeculation was excluded from RV volume measurement.

Atrial volumes were calculated using a three dimensional technique (Teo et al. 2008). The endocardial contours were manually traced in the HLA views, and modified Simpson's rule was applied. The PVs were excluded, and the LAA was included where

present on the images. Atrial and ventricular ejection fractions were calculated using the formula; (maximum volume – minimum volume)/maximum volume × 100 (%).

The intra- and inter-observer variability in our CMR unit have previously been reported (Teo et al. 2008). The intraclass correlation coefficients for intra-observer variability were: maximum LA volume 0.84, maximum RA volume 0.98, LV EDV 0.95, LV ejection fraction 0.91, RV EDV 0.89, RV ejection fraction 0.77. The intraclass correlation coefficients for inter-observer variability were: maximum LA volume 0.87, maximum RA volume 0.92, LV EDV 0.96, LV ejection fraction 0.94, RV EDV 0.93, RV ejection fraction 0.7.

6.3.4. Electrophysiology study

All patients were therapeutically anticoagulated for at least 1 month using warfarin (INR 2.0 – 3.0) and subsequently switched to low molecular weight heparin, with the last dose administered on the evening prior to the ablation. Patients underwent transoesophageal echocardiography within 7 days of RFCA to exclude LAA thrombus.

Electrophysiological study was performed in the post-absorptive state with sedation utilising midazolam and fentanyl. The LA was accessed using a single transeptal puncture using an SLO sheath and a BRK1 needle (St Jude Medical). Following transeptal access, a bolus of 100IU/kg of unfractionated heparin was administered, with repeated boluses to maintain the activated clotting time between 300-350 seconds. The following catheters were utilised: 10 pole catheter within the coronary sinus; 10 pole Variable Lasso catheter (Biosense-Webster) used with the SLO sheath for mapping the

pulmonary veins; and a 3.5 mm tip externally irrigated (Navi-Star or Thermocool, Biosense-Webster). Circumferential ablation was performed of the pulmonary veins with an endpoint of isolation. Ablation of the pulmonary veins was performed using a delivered power of 30W with irrigation rates of 30-60mL/min. Additional substrate modification was performed in patients with an episode of AF \geq 48 hours, LA size \geq 57mm (longest diameter) or with evidence of structural heart disease. This took the form of linear ablation along the LA roof and/or mitral isthmus and/or ablation of CFAE. Cavo-tricuspid isthmus ablation with an endpoint of bi-directional isthmus block was performed only in patients with a history of typical flutter or if mapping confirmed typical flutter during the procedure. Linear ablation was performed with a delivered power of 30-35W with irrigation rates of 30-60mL/min. In all cases electroanatomic mapping (CARTO, Biosense-Webster; or NavX, St Jude Medical) was used (Figure 6.1). The endpoint of linear ablation was the demonstration of bi-directional conduction block based on previously established criteria.

6.3.5. Follow-up

All patients were maintained on antiarrhythmic drugs for a 6-week period. Patients were reviewed with history, physical examination, ECG and 7-day continuous Holter monitoring at 3 monthly intervals for 12 months and then 6 monthly.. A 3-month “blinking period” was applied as per the current consensus guidelines (Calkins et al. 2007a). Patients with atrial arrhythmias lasting $>$ 30 seconds were deemed to have failed AF ablation. In patients with a CHADS2 score \leq 1, anticoagulation was discontinued after 3 months. However, in those with a CHADS2 score \geq 2, anticoagulation was continued for a minimum of 12 months, after which in the absence

of arrhythmia, discontinuation of anticoagulation was only performed by individual discussion regarding the risk of anticoagulation cessation. Follow-up CMR scans were performed at 12 months post-ablation.

6.3.6. *Statistical analysis*

Data are presented as mean \pm SD. Comparisons between pre- and post-ablation atrial and ventricular volumes, LV mass and atrial and ventricular ejection fractions, were made using a two-tailed, paired t test for normally distributed data, and the Wilcoxon matched pairs nonparametric test for data that were not normally distributed. Statistical significance was taken at $P < 0.05$.

6.4. Results

6.4.1. *Patient characteristics*

Thirty-four of 90 patients were excluded from the analysis, as they were not in sinus rhythm at the time of the baseline and/or follow-up CMR scan. A total of 56 patients, 37 male, with a mean age of 58.8 ± 8.5 years undergoing RFCA for paroxysmal (43 patients) or persistent (13 patients) AF were included in the study. Baseline characteristics are outlined in table 6.1. Mean follow-up was 12.7 ± 3.3 months. At follow-up, 38 patients (68%) were in sinus rhythm without the use of antiarrhythmic agents, with an additional 3 (5%) in sinus rhythm on antiarrhythmic therapy. Fourteen patients (25%) had circumferential pulmonary vein isolation (CPVI) only, with the majority having more extensive ablation (Table 6.2). On average, there were 1.3 ± 0.4 ablation procedures performed per patient.

6.4.2. Atrial volumes and function

There was a significant reduction in LA volume from 104.6 ± 30.3 mL at baseline to 92.4 ± 24.7 mL post-ablation ($P < 0.0001$) (Table 6.3 and Figure 6.2). In addition, RA volume was reduced by a similar extent (101.5 ± 33.3 mL pre-ablation vs. 88.3 ± 23.7 mL post-ablation, $P < 0.0001$). There was a significant decline in LA ejection fraction following AF ablation ($47.0 \pm 8.4\%$ pre-ablation vs. $40.0 \pm 9.0\%$ post-ablation, $P < 0.0001$). The RA ejection fraction improved significantly post-ablation ($41.3 \pm 10.9\%$ pre-ablation vs. $44.5 \pm 7.9\%$ post-ablation, $P = 0.004$).

6.4.3. Ventricular volumes, mass and function

There were significant reductions in LV (151.5 ± 37.3 mL pre-ablation vs. 136.6 ± 33.8 mL post-ablation, $P < 0.0001$) and RV (178.6 ± 50.5 mL pre-ablation vs. 158.8 ± 40.4 mL post-ablation, $P < 0.0001$) end-diastolic volumes following ablation (Table 6.3). Moreover, there was a significant improvement in RV ejection fraction ($56.4 \pm 10.6\%$ pre-ablation vs. $59.9 \pm 9.5\%$ post-ablation, $P = 0.01$). Left ventricular ejection fraction remained unchanged post-ablation ($73.7 \pm 7.3\%$ pre-ablation vs. $74.1 \pm 6.6\%$ post-ablation, $P = 0.7$). Interestingly, LV mass was significantly reduced following AF ablation (133.5 ± 37.5 g pre-ablation vs. 128.0 ± 36.9 g post-ablation, $P = 0.02$).

6.5. Discussion

In this study, we demonstrated that successful AF ablation leads to; 1) significant reduction in all cardiac chamber volumes, 2) improvement in right heart function, 3) no

significant change in LV function, and 4) decrease in LA ejection fraction, at medium-term follow-up.

6.5.1. Reverse remodelling following ablation

Atrial fibrillation leads to progressive LA electrical, mechanical and ultrastructural abnormalities (Wijffels et al. 1995; Ausma et al. 1997). Reversal of LA electrical and mechanical remodelling has been previously noted following cardioversion to sinus rhythm (Everett et al. 2000; Sanders et al. 2003). This has been thought to be due to the maintenance of sinus rhythm. The significant reduction in LA size post-ablation demonstrated in this study is consistent with several previous studies in patients undergoing AF ablation (Jayam et al. 2005; Reant et al. 2005; Perea et al. 2008). This finding may be secondary to reverse remodelling and/or scar formation following AF ablation. However, in our study, the changes were uniformly observed in left and right heart chambers, where ablation was not performed, thus supporting the former mechanism.

The temporal course of reverse remodelling following AF ablation was not directly investigated in this study. Delayed enhancement CMR has been used to assess the extent of scarring in the LA in the setting of AF ablation (Peters et al. 2007; McGann et al. 2008). It has been shown that early changes of LA injury, within 24 hours following AF ablation, do not correlate with the extent of scarring found at 3 months post-ablation (Badger et al. 2009). However, after 3 months, the extent of delayed enhancement appears to be stable, as demonstrated by repeat delayed enhancement CMR scans at 6 – 9 months post-ablation (Badger et al. 2009). These findings suggest that stable LA scar

can take up to 3 months to develop, and that in the early post-ablation phase, there is significant inflammation and oedema associated with acute tissue injury. It has long been recognised that early AF recurrence following ablation is common (Oral et al. 2002). Furthermore, the majority of patients experiencing early arrhythmia recurrence have no further arrhythmias after the initial months post-ablation (Oral et al. 2002; Bertaglia et al. 2005). Hence, the current guidelines recommend a 3-month “blinking period” during which arrhythmias are not considered as treatment failure (Calkins et al. 2007). Our study provides a possible mechanistic explanation in support of this clinical observation. The reverse remodelling detected in all cardiac chambers following AF ablation in this study suggests that this may play an important role in the maintenance of sinus rhythm in the medium to long-term.

6.5.2. Left atrial function following ablation

We found a significant, albeit small, reduction in LA ejection fraction following AF ablation. Studies assessing the effects of AF ablation on LA function have yielded conflicting results. Some have reported an improvement or stabilisation of LA function (Reant et al. 2005; Verma et al. 2006; Perea et al. 2008), while others found deterioration in LA function post-ablation (Lemola et al. 2005; Wylie et al. 2008; Rodrigues et al. 2009). This is partly attributable to the heterogeneity of patients, AF ablation procedures, duration of follow-up, and methods used for the assessment of LA function in different studies. The patients in our study had extensive substrate modification in addition to CPVI, which could lead to more extensive scarring and impairment of LA mechanical function. We used CMR to assess LA volumes and ejection fraction, which is a highly accurate and reproducible method for the

measurement of LA volumes and ejection fraction (Therkelsen et al. 2005). Whether LA ejection fraction is a good measure of global LA function is debatable. However, it has been used in numerous studies (Hudsmith et al. 2005; Perea et al. 2008; Wylie et al. 2008), and in the absence of a “gold standard”, is thought to be an acceptable measure of LA function. Further studies are required to clarify the overall effects of AF ablation on LA function and its clinical implications.

6.5.3. Clinical implications

Atrial fibrillation ablation has rapidly become a treatment of choice in selected patients. This study implicates reverse remodelling as an important factor in the maintenance of sinus rhythm following AF ablation. This could have potential implications in terms of stroke risk, the incidence and severity of heart failure associated with AF, and ultimately cardiovascular mortality in this population. Further studies are required to assess the impact of AF ablation on these hard clinical endpoints.

6.5.4. Study limitations

This was not a randomised study and involved a select cohort, who had successful RFCA and were imaged in sinus rhythm at baseline and follow-up. The exclusion of patients with AF at the time of the baseline and/or follow-up scan is a significant limitation of this study. As discussed previously, this was done due to suboptimal image quality in AF, and the issues involved in comparing results obtained using prospective gating in AF and retrospective gating in sinus rhythm. Furthermore, in addition to CPVI, extensive substrate modification was performed in a significant proportion of patients in this study. Thus, extrapolation of these results to the general population of

patients undergoing AF ablation should be performed cautiously. The outcome measures in this study were surrogate imaging markers with no hard clinical endpoints. Future multicentre, randomised controlled trials are required to determine whether the improvements in cardiac structure and function, found in this study and others, will translate to improved outcomes.

6.6. Conclusions

Successful AF ablation is associated with significant reverse remodelling of all cardiac chambers at medium-term follow-up. The remodelling of chambers other than LA, where ablation had not been performed, implicates a possible role for reverse remodelling following successful AF ablation.

Table 6.1. Patient characteristics

Age (years)	58.8 ± 8.5
Gender (M:F)	37:19
Paroxysmal: Persistent AF	43:13
Hypertension	31 (55%)
Structural heart disease	24 (43%)
Coronary artery disease	7 (13%)
Diabetes mellitus	3 (5%)

Table 6.2. Ablation procedures

Ablation procedure	Number
Circumferential pulmonary vein isolation	56 (100%)
Roofline	35 (63%)
Cavotricuspid isthmus	11 (20%)
Complex fractionated atrial electrogram	7 (13%)
Mitral isthmus	5 (9%)
Coronary sinus	7 (13%)
Superior vena cava	3 (5%)

Table 6.3. Cardiac chamber volumes and function at baseline and 12 months post-ablation

	Pre-ablation	Post-ablation	<i>P</i> value
Maximum LA volume (mL)	104.6 ± 30.3	92.4 ± 24.7	< 0.0001
LA ejection fraction (%)	47.0 ± 8.4	40.0 ± 9.0	< 0.0001
Maximum RA volume (mL)	101.5 ± 33.3	88.3 ± 23.7	< 0.0001
RA ejection fraction (%)	41.3 ± 9.8	44.5 ± 7.9	0.004
LVEDV (mL)	151.5 ± 37.3	136.6 ± 33.8	< 0.0001
LV ejection fraction (%)	73.7 ± 7.3	74.1 ± 6.6	0.7
LV mass (g)	133.5 ± 37.5	128.0 ± 36.9	0.02
RVEDV (mL)	178.6 ± 50.5	158.8 ± 40.4	< 0.0001
RV ejection fraction (%)	56.4 ± 10.6	59.9 ± 9.5	0.01

LA, left atrial; RA, right atrial; LV, left ventricular; RV, right ventricular; LVEDV, LV end-diastolic volume; RVEDV, RV end-diastolic volume.

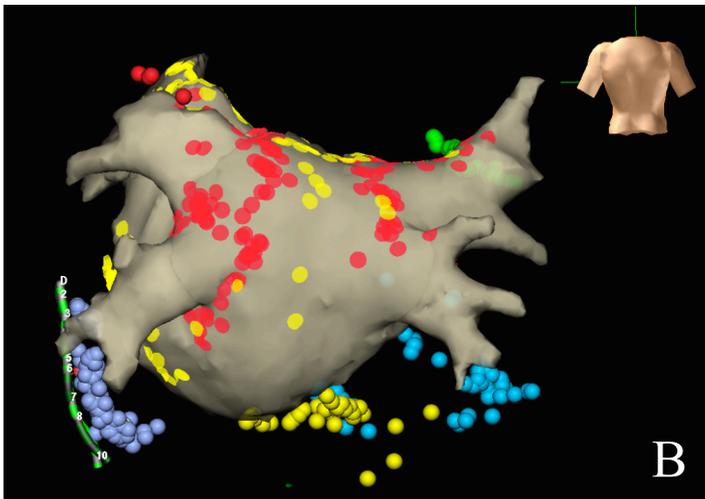
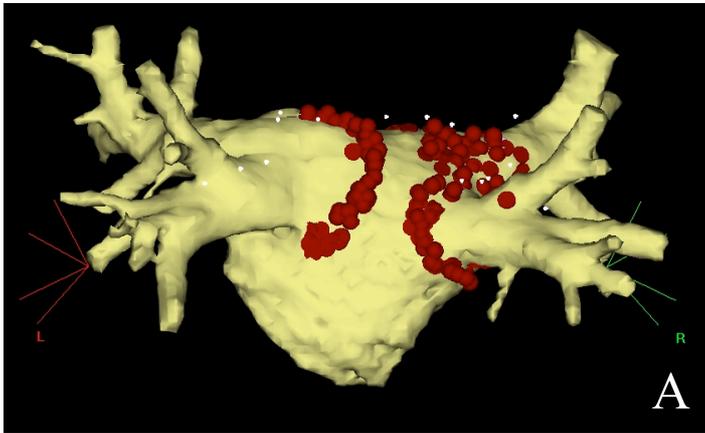


Figure 6.1. CARTO (Biosense Webster) map of CPVI in a patient with paroxysmal AF (A). NavX (Endocardial Solutions) image demonstrating extensive ablation in a patient with persistent AF (B).

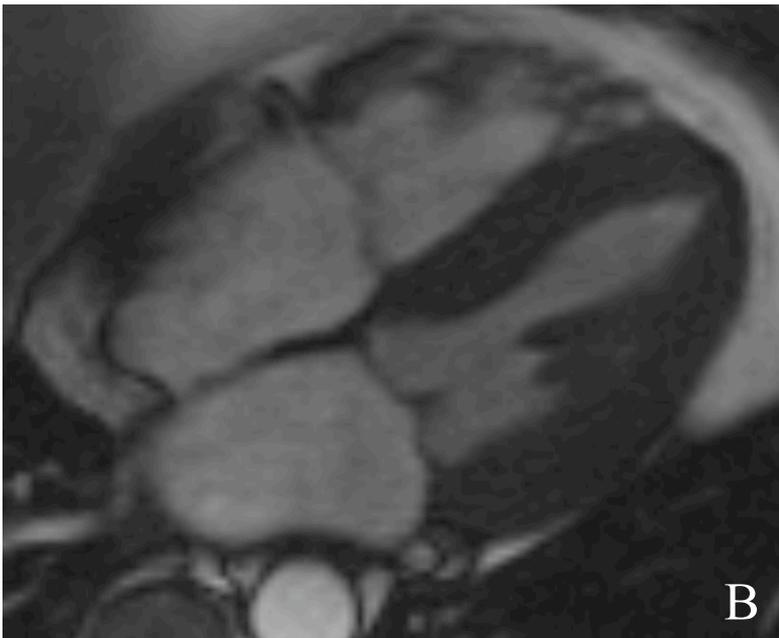
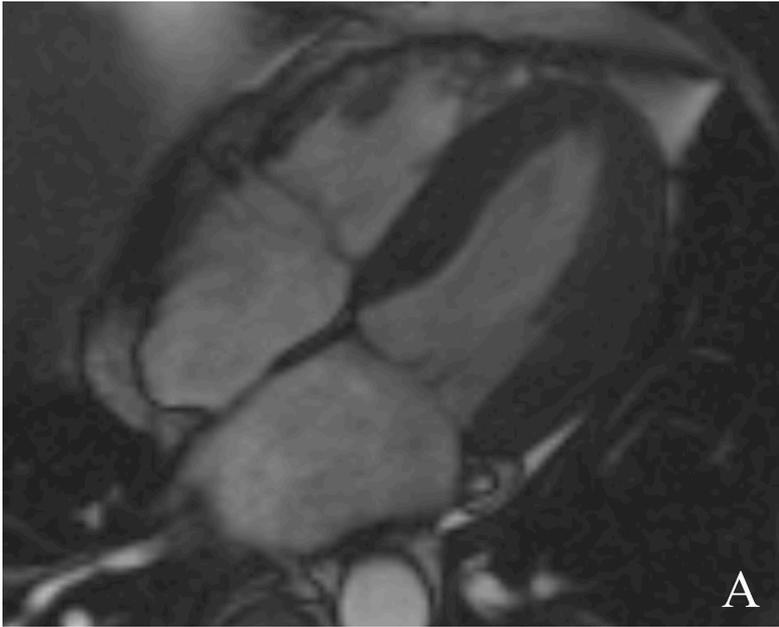


Figure 6.3. Horizontal long axis cardiac magnetic resonance image of the heart, at end-systole, in the same patient, pre (A) and 12 months post-ablation (B). There was a reduction in left atrial size post-ablation.

CHAPTER 7

DISCUSSION

Atrial fibrillation is the most common arrhythmia with a significant burden of morbidity and mortality. In addition to the well-recognised complications of stroke, heart failure and increased mortality, patients with atrial fibrillation can suffer from disabling symptoms adversely affecting their quality of life. The ageing Australian population represents a major challenge in optimally managing such patients.

Radiofrequency catheter ablation is a potentially curative therapy for select patients with AF. Over the last decade, radiofrequency catheter ablation of AF has evolved from a largely experimental procedure to one that is widely performed worldwide. Although AF ablation has been shown to be more efficacious in maintaining sinus rhythm at medium-term follow-up and is associated with reduced symptoms and improved quality of life, the effects of ablation on cardiac structure and function and moreover, its implications for long-term stroke risk, heart failure and mortality have not been established. In order to investigate these, an accurate, reproducible, high-resolution, non-invasive imaging modality is required. Cardiac magnetic resonance imaging has emerged as the “gold standard” non-invasive imaging modality for assessment of cardiac chamber volume and function.

The studies presented in this thesis evaluated patients with AF using cardiac magnetic resonance imaging. In Chapter 3, the accuracy of the biplane area-length method, which is commonly used for measuring LA volume, was compared with the “gold standard” volumetric method of determining volumes using CMR. In Chapter 4, patients with “lone” AF, who by definition have no structural heart disease using conventional

imaging modalities, were studied using the more sensitive CMR and compared with healthy controls. In Chapter 5, the clinical and imaging predictors of recurrent AF following radiofrequency catheter ablation were studied. Finally, in Chapter 6, the medium to long-term effects of AF ablation on cardiac structure and function were assessed.

Left atrial volume is an important marker of cardiovascular outcomes both in the general population and in patients with AF. It is commonly calculated using the biplane area-length method. The accuracy and reproducibility of this method has not been clearly established. In chapter 3, the biplane area-length method was compared with the “gold standard” method for determining chamber volumes using CMR. The biplane method correlated closely with the “gold standard” volumetric method in healthy controls. However, in subjects with atrial fibrillation, there was only a moderate correlation between the biplane method and the volumetric method, suggesting that in subjects with LA dilatation, the biplane method is not an accurate and reproducible measure of LA volume.

“Lone” AF has traditionally been associated with a low risk of stroke and a favourable outcome. However, over long-term follow-up, a significant proportion of such patients progress to paroxysmal and persistent forms of AF. Although by definition, patients with “lone” AF have no structural heart abnormalities on echocardiography, there may be subtle abnormalities detectable only by more sensitive imaging modalities. In Chapter 4, subjects with “lone” AF were studied using a comprehensive CMR protocol and compared with healthy control subjects. Although, there were no differences in left

and right atrial volumes between the two groups, subjects with “lone” AF had significantly lower left and right atrial ejection fractions, consistent with atrial mechanical dysfunction. Furthermore, subjects with “lone” AF had elevated left and right ventricular EDVs and LV mass compared with controls. These findings indicate that despite the absence of structural or functional abnormalities on echocardiography, subjects with “lone” AF have demonstrable atrial functional and ventricular structural changes compared with healthy controls. These observations suggest the presence of an abnormal substrate in “lone” AF that may explain the disease progression observed in such patients.

Radiofrequency catheter ablation of AF is now widely used throughout the world. Although catheter ablation of AF can be highly successful in alleviating symptoms and improving quality of life, it is associated with a small, but clinically significant risk of adverse events. In addition, a sizeable proportion of patients develop recurrent AF and require repeat procedures with the inherent risk of adverse events. In the clinical setting, it would be highly desirable to be able to predict the chances of success following catheter ablation. In Chapter 5, patients undergoing catheter ablation were closely followed up for 12 months to detect recurrent atrial fibrillation, and their baseline clinical and CMR parameters were assessed to determine pre-procedural predictors of recurrence. On multivariate analysis, it was found that increased LA volume and female gender were the only independent predictors of recurrent AF at 12 months post-ablation.

The symptomatic benefits of RFCA of AF have been clearly demonstrated. However, the effects of catheter ablation on cardiac structure and function have not been well studied. In Chapter 6, patients undergoing AF ablation had CMR, with three-dimensional imaging of the LA, at baseline and 12 months post-ablation. There was a significant reduction in all chamber volumes following ablation, notably maximal left and right atrial volumes and left and right ventricular EDVs. There was also a significant reduction in LV mass post-ablation. However, there was a small, but statistically significant reduction in LA ejection fraction post-ablation. Right atrial and ventricular ejection fractions improved following ablation, but there was no significant change in LV systolic function. These results show a promising pattern of reverse remodelling in all the cardiac chambers post-ablation. This may explain the tendency for early arrhythmia recurrence to disappear by 3 months post-ablation, as the reverse remodelling may reduce the risk of atrial arrhythmias.

In summary, the studies in this thesis demonstrate that CMR is a valuable, accurate, non-invasive imaging modality, which is ideally suited for assessing patients with AF and for serial follow-up post-ablation. There are several avenues of further research that would extend the findings presented in this thesis. Left atrial scar imaging is now possible with modern CMR sequences in selected centres. Non-invasive assessment of LA scar has many potential applications, including assessment of various treatment strategies that could reduce progression of LA scarring in different disease states, and hence reduce the risk of developing AF. In addition, future studies are required to assess the impact of ablation related scarring on LA mechanical function and its association with thromboembolic risk. The ultimate question regarding AF ablation involves its

effects on hard clinical outcomes, particularly stroke, heart failure and mortality. The answers to these questions can only be determined through large, multicentre, randomised trials. In the meantime, CMR can provide an insight into the possible effects of AF ablation on long-term clinical outcomes through surrogate measures of cardiac structure and function. In future, CMR is likely to become an integral part of evaluating patients with AF and tailoring appropriate treatment strategies.

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