ATRIAL ARRHYTHMOGENESIS DURING MYOCARDIAL INFARCTION

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A thesis submitted to the University of Adelaide in fulfilment of the requirements of the degree of

Doctor of Physiology

June 2014

To my children Ali & Rami

and my mum Jamilah

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Abstracts

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in the clinical practice. However, the underlying mechanism or pathophysiology is not fully understood despite our extensive research on AF. Furthermore, AF is commonly complicated by myocardial infarction (MI) with an incidence rate as high as 22%. Atrial fibrillation is also associated with poor short and long-term outcome after acute myocardial infarction. Although the association between myocardial infarction and AF is well established, our knowledge of the underlying mechanism by which MI leads to AF remains incomplete. This thesis focused on the pathophysiology of AF during MI in the clinical and bench-side setting. It also examined the prognostic value of AF post MI.

Chapter 2 is a systematic review and meta-analysis showing us the trend in AF incidence and prognosis over the last three decades with our advancement in both intervention and pharmacological therapy. The study reveals a significant declining in AF incidence post MI; however, mortality remains higher compared to non-AF even during the interventional era (2000s). This may be attributed to the fact that AF patients are older with more comorbidities and had less invasive procedures compared to non-AF patients but clearly more work is required in this area.

Chapter 3 focused on the mechanism of AF during the acute phase (60 minutes) of myocardial infarction. This was ovine model of myocardial infarction which was induced by percutaneous approach via the right femoral artery using angioplasty technique to induce infarct. The study involved 36 sheep divided into 3 groups; the first group included 12 animals with proximal left circumflex occlusion (LCX) to induce myocardial infarction with left atrial infarction or ischaemia. The second group included 12 animals with proximal occlusion of the left anterior descending artery (LAD) to induce myocardial infarction without left atrial ischaemia or infarction, and the third group included 12 sham animals which underwent the same procedure without induction of myocardial infarction. This model was unique as both LAD and LCX supply almost equivalent myocardium but the LCX only supplies the left atrium. The study found that occlusion of the LCX (MI with LA ischaemia) resulted in significant conduction slowing, greater

inhomogeneity in conduction and more AF inducibility and duration compared to LAD group or controls. On the other hand, occlusion of LAD resulted in only moderate conduction slowing with a slight inhomogeneity in conduction compared to controls. The study concludes that atrial ischaemia is the dominant substrate for AF after MI. However, there is additional contribution to this substrate due to raised intra-atrial pressure with diastolic dysfunction which is associated with left ventricular infarction.

Chapter 4 examined the role of atrial branches (left atrial ischaemia) disease on AF genesis during acute myocardial infarction in humans. This is a case-control study in which cases and controls were selected from a pool of 2460 patients who presented with AMI between 2005 and 2009. A total of 42 patients with left atrial branches disease (proximal lesion in right coronary artery or left circumflex artery) were matched with 42 control patients (MI patients with lesion distal to the left atrial branches). Both groups were also matched for left ventricular ejection fraction, age and sex. The study concluded that coronary artery disease affecting the atrial branches was an independent predictor for the development of atrial fibrillation after MI.

Chapter 5 focused on characterisation of left atrial remodeling of patients with coronary artery disease affecting the left atrial branches (atrial ischaemia) after AMI. In this case-control study, 26 consecutive patients with acute myocardial infarction and coronary artery lesion affecting the left atrial branches were matched with another 26 patients with MI without LA branches disease according to age, sex, body mass index and left ventricular ejection fraction. The study highlighted the importance of left atrial branches disease or atrial ischaemia results in left atrial structural remodeling characterised by atrial enlargement and this was independent of end diastolic pressure load (1), age, sex or left ventricular ejection fraction. It provides further evidence for the importance of atrial ischemia to the development of the substrate for AF.

Chapter 6 looked at the association between new onset AF and post MI ventricular fibrillation and the long-term outcome. From a prospectively collected cohort of 3200 patients with MI, 96 patients with new onset AF were matched 1:3 with 288 patients with no AF on the basis of left ventricular ejection fraction. The incidence of VF arrest during admission and long-term mortality was significantly higher in AF patients independent of LVEF.

In summary, AF post MI remains a poor prognostic indicator despite our advancement in intervention and pharmacotherapy. Although AF patients are usually older with multiple comorbidities, AF remains an independent predictor of poor outcome after MI. This is probably related to the total ischaemic burden (involvement of left atrium) and rapid ventricular rate in already compromised ischaemic myocardium. The mechanisms of AF during MI are a combination of atrial ischaemia or infarction, atrial stretch due to raised end diastolic pressure with diastolic dysfunction during MI. In addition, there may be neurohumoral and autonomic factors that play an additive role in the pathophysiology of AF in patients with MI. Finally, the management of AF post MI is suboptimal with lack of evidence-based medicine. Further studies require determining the optimal antiarrhythmic as well as the best anticoagulation regime, especially in those who require dual antiplatelet therapy.

Declaration

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

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Muayad Alasady

Acknowledgements

I am very grateful for my primary supervisor Professor Prashanthan Sanders for his mentorship and support over the years. He was an inspirational personality not just in research and clinical work but also in friendship. I would also like to thank my friend and mentor Professor Walter Abhayaratna who gave a lot of time and he has significantly contributed to the completion of this thesis. I am also thankful for my other co-supervisors, Associate Professor David Saint, Dr Anthony Brooks and Dr Matthew Worthley, for their encouragement and support over the years. I am also very grateful to Dr Nicholas Shipp who helped me to complete this thesis. I am very thankful for the scholarship I received during my candidature from the National Health and Medical Research Council, University of Adelaide Medtronic (Earl Bakken Electrophysiology Scholarship). I also thank Dr Glenn Young and Dr Kurt Roberts-Thomson for their role in my clinical training. I enjoyed working with co fellows: Drs Han Lim, Darryl Leong and Dennis Lau. I would like to thank my two friends Dr Rajiv Mahajan and Dr Rajeev Pathak for their support and advice over the years. I also would like to thank Dr Derek Chew for his help and guidance during my candidature.

My beloved two children Ali and Rami, thank you for being in my life. Finally, I would like to thank my mum and dad for their unlimited love and support throughout my life.

Publications and Communications to Learned Societies

Chapter 1:

1. **Manuscript**: Lau DH, Alasady M, Brooks AAG, Sanders P. New-onset atrial fibrillation and acute coronary syndrome. **Expert Reviews: Cardiovascular Therapeutics 2010; 8: 941-948.**

Chapter 2:

1. **Manuscript**: Muayad Alasady, MBChB;[1] Walter P. Abhayaratna MBBS, PhD;[2,3] Rajeev Pathak, MBBS;[1] Nicholas Chia;[1] Abhinav Mehta, MActSt;[2] Rajiv Mahajan, MD;[1] Han S. Lim; MBBS, PhD;[1] Dennis H. Lau, MBBS, PhD;[1] Stephen J. Nicholls, MBBS, PhD;[1] Matthew I. Worthley, MBBS, PhD;[1] Anthony G. Brooks, PhD;[1] Prashanthan Sanders, MBBS, PhD.[1] **Impact of Coronary Artery Intervention on the Incidence and Prognosis of Atrial Fibrillation after Acute Myocardial Infarction: A Systematic Review. Submitted to J Am Coll Cardiol 2014.**
2. **Presentation**: Presented at the Heart Rhythm Society 34th Annual scientific Meeting, May 2013, Denver, United States of America. *Heart Rhythm 2013:10: S307.*
3. **Presentation**: Presented at the Cardiac Society of Australia and New Zealand 60th Annual Scientific Meeting, August2013, Gold Coast, Australia and published in abstract form (**Heart, Lung and Circulation 2012;21:S126-S127**).

Chapter 3:

1. **Manuscript**: Muayad Alasady, MBChB;[1] Nicholas J. Shipp, PhD; [1] Anthony G. Brooks, [1] PhD; Han S. Lim, MBBS, PhD;[1] Dennis H. Lau, MBBS, PhD;[1] David Barlow;[1] Pawel Kuklik, PhD;[1] Matthew I. Worthley, MBBS, PhD;[1] Kurt C. Roberts-Thomson, MBBS, PhD;[1] David A. Saint, PhD;[1] Walter Abhayaratna, MBBS, PhD;[2] Prashanthan Sanders, MBBS, PhD.[1] **Myocardial Infarction and Atrial Fibrillation: Importance of Atrial Ischemia. Circulation: Arrhythmia and Electrophysiology. 2013; 6:738-745.**

2. **Presentation**: Presented at the Heart Rhythm Society 31th Annual scientific Meeting, May 2010, United States of America. Heart Rhythm 2010: 7: S420.
3. **Presentation**: Presented at the Cardiac Society of Australia and New Zealand 58th Annual Scientific Meeting, August 2010, Adelaide, Australia and published in abstract form (**Heart, Lung and Circulation 2010;19:S2**)
4. **Presentation**: Presented at the European Cardiac Society Congress, August 2010, Paris, France. European Heart Journal 2010: 31: S1041.
5. **Presentation**: Presented at the 3rd Asia Pacific Heart Rhythm Society Scientific session, October 2010, JeJu Island, South Korea. J Arrythmia 2010: 26: 1.

Chapter 4:

1. **Manuscript**: Alasady M, Abhayaratna WP, Leong DP, Lim HS, Abed HS, Brooks AG, Mattchoss S, Roberts-Thomson KC, Worthley MI, Chew DP, Sanders P**. Coronary artery disease affecting the atrial branches is an independent determinant of atrial fibrillation after myocardial infarction. Heart Rhythm 2011 July, 8 (7):955-960.**
2. **Presentation**: Presented at the Heart Rhythm Society 28th Annual scientific Meeting, May 2010, United States of America. Heart Rhythm 2010: 7: S59.
3. **Presentation**: Presented at the Cardiac Society of Australia and New Zealand 58th Annual Scientific Meeting, August 2010, Adelaide, Australia and published in abstract form. **(Heart, Lung and Circulation 2010; 2: S98)**
4. **Presentation**: Presented at the European Cardiac Society Congress, August 2011, Paris, France. European Heart Journal 2010: 31: S113.

Chapter 5:

1. **Manuscript**: Alasady M, Leong DP, Lim HS, Roberts-Thomson KC, Brooks AG, Worthley MI, Chew DP, Sanders P, Abhayaratna WP. **Left atrial structural remodeling as a consequence of myocardial infarction: relationship to adverse cardiovascular outcome. Submitted to American Journal of Cardiology (2014)**
2. **Presentation**: Presented at the Heart Rhythm Society 28th Annual scientific Meeting, May 2012, Denver, United States of America. Heart Rhythm 2010: 7: S217.

3. **Presentation**: Presented at the Cardiac Society of Australia and New Zealand 58th Annual Scientific Meeting, August 2010, Adelaide, Australia and published in abstract form (**Heart, Lung and Circulation 2010; 19:S188)**
4. **Presentation**: Presented at the European Cardiac Society Congress, August 2010, Stockholm, Sweden. European Heart Journal 2010: 31: S739-740.

Chapter 6:

1. **Manuscript**: Muayad Alasady, MBBS; Derek Chew, MBBS, MPH; Rajeev Pathak, MD; Rajiv Mahajan, MD; Anthony G. Brooks, PhD; Han S. Lim, MBBS, PhD; Dennis H. Lau, Kurt C. Roberts-Thomson, MBBS, PhD; Stephen J. Nicholls, MBBS, PhD; Matthew I. Worthley, MBBS, PhD; Walter Abhayaratna, MBBS, PhD; Prashanthan Sanders, MBBS, PhD. **New Onset Atrial Fibrillation is associated with Ventricular Fibrillation and Poor Long Term Outcomes after Myocardial Infarction. Submitted to Heart Rhythm Journal 214.**
2. **Presentation**: Presented at the Heart Rhythm Society 29th Annual scientific Meeting, May 2011, Boston, United States of America. Heart Rhythm 2011: 8: S138.
3. **Presentation**: Presented at the Cardiac Society of Australia and New Zealand 58th Annual Scientific Meeting, August 2010, Adelaide, Australia and published in abstract form (**Heart, Lung and Circulation 2010;19:S97-S98).**

Prizes and Award during Candidature

1. Ralph Reader Prize (Young Investigator Award-Finalist) at the Cardiac Society of Australian and New Zealand 58th Annual Scientific Meeting 2010.
2. Best Paper Award Prize (3rd prize) at the 3rd Asia Pacific Heart Rhythm Scientific Meeting 2010.
3. Nimmo Prize , Royal Adelaide Hospital 2010.
4. National Health and Medical Council Postgraduate Scholarship 2009-2011.
5. National Heart Foundation Travel Grant 2010
6. Highest scoring abstract at the Annual Scientific Sessions of the Heart Rhythm Society 2010.
7. Dawes Scholarship, Royal Adelaide Hospital; 2008-2010
8. Earl Bakken Electrophysiology Scholarship from the University of Adelaide; 2008-2009.
9. Divisional Scholarship, University of Adelaide; 2008-2009.

Chapter 1

1.1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice. In the Framingham Heart Study (2,3), the prevalence of AF was 1-2 % in an unselected adult population. With the ageing population, the prevalence of this arrhythmia will increase to more than 5% in patients over 65 years of age.(2,4) In addition, the community based age-adjusted AF incidence was significantly increased during 1980-2000. Such an increase in age-adjusted incidence suggested a relatively conservative estimate of a 3-fold increase in AF incidence over the next 50 years in the United States.(5) This change in AF incidence is multifactorial. Traditional risk factors such as systemic hypertension, diabetes mellitus, myocardial infarction and valvular heart disease are well established to predispose to AF. (6)In addition, increasingly it is recognised that there may also be previously unrecognised risk factors such as obesity and sleep apnoea that may account for the burgeoning incidence of this epidemic.(7,8) Indeed, the burden of disease is likely to increase further. The financial burden associated with the management of AF is estimated at $1.25 billion Australian dollars per annum and is expected to continue to increase to more than 12% over the next two decades.(5,9-12) Patients with AF usually have other cardiovascular comorbidities and are at increased risk of cardiovascular and cerebrovascular events and mortality compared to patients with no AF.(13) Hospitalisations and deaths associated with AF have risen steadily in United States since early 1980.(5,14,15)The number of hospitalisations for AF as primary diagnosis exceed 460 000 each year, and AF contributes to more than 80 000 annual deaths.(10,16) Atrial fibrillation is associated with increased mortality and morbidity in both genders and across a different range of ages.(13,17) In the Framingham Heart Study, AF was associated with 1.5 to 1.9-fold mortality risk after adjustment for other cardiovascular conditions with which AF was related.(6,13)

Although AF is a common arrhythmia and associated with significant mortality and morbidity, our current management of AF is limited by the incomplete understanding of the mechanisms of this arrhythmia.

1.1.1 Management of Atrial fibrillation

Atrial fibrillation is not a benign arrhythmia and can cause disabling symptoms ranging from palpitation, chest pain and decreased exercise tolerance to haemodynamic instability in some patients. In addition, AF might also manifest as stroke or heart failure. However, the majority of patients with AF are asymptomatic and diagnosed incidentally during routine medical check-up.

The mainstay of managing AF is anticoagulation and rhythm/rate control and is determined clinically based on multiple factors such as patient symptoms, age and underlying structural heart disease.

Atrial fibrillation is a common cause of cardiac thromboembolism especially in the elderly population. The risk of stroke secondary to AF increases from 1.5% per year between the ages of 50-59 years to 24% per year in patients over the age of 80 years.(18,19) Anticoagulation with warfarin reduces the risk of stroke by approximately 70%. While warfarin is an effective drug in prevention of stroke in patients with AF, its narrow therapeutic window, need for continuous INR monitoring, food and drug interaction, risk of bleeding and patients and physician resistance has resulted in under-utilisation of warfarin in patients who might benefit from such therapy.

Several newer anticoagulants have recently been introduced. Dabigatran, a direct thrombin inhibitor, is approved for use in many countries and was demonstrated in a large prospective randomised study to be non-inferior to warfarin in protecting against embolic events.(20,21) Rivaroxaban, a factor Xa inhibitor, was not inferior to warfarin as shown in the ROCKET AF trial.(22) Recently apixaban, another factor Xa inhibitor, when compared to warfarin demonstrated non-inferiority to embolic events but prevented hospitalisation and improved mortality.(23,24) While cost remains a concern in using thrombin and factor Xa inhibitors in the short-term, these drugs hold big promise in stroke prevention in patients with AF in the medium to long-term.

Finally, left atrial appendage closure device has been developed as adjunct and as alternative to pharmacotherapy in patients with atrial fibrillation and contra-indication to warfarin therapy.(25,26)

In general, the main goal in AF management is to maintain sinus rate (rhythm control) or to control patient ventricular rate response (sinus control vs rate control). Although some studies have not shown survival benefit for rhythm control over rate control strategy (27-30), such benefit might be offset by the adverse side effect of the anti-arrhythmic drugs (AAD) used in these studies. However, rapid restoration of sinus rhythm is important in patients with haemodynamic instability or in certain circumstances such as patients with hypertrophic obstructive cardiomyopathy or during the acute phase of acute myocardial infarction. Restoration of sinus rhythm can be achieved electrically by DC cardioversion or chemically by AAD. The rate control strategy can be obtained with various anti-arrhythmic drugs such as β-blocker or calcium channel blocker. The main risk of cardioversion is systemic embolisation; therefore patients with AF should be fully anticoagulated with warfarin with target INR 2-3 for 4-6 weeks prior to cardioversion if AF duration was more than 48 hour(31). However, cardioversion can be performed in patients with AF lasting more than 48 hours if the transoesophageal echocardiography (TOE) rules out left atrial thrombus. (32)The choice between AAD for rate or rhythm control depends on various factors, in particular underlying structural heart disease, type of AF and possible side effects. New anti-arrhythmic drugs such as vernakalant may offer an alternative choice to the old AAD such as amiodarone and Class I drugs. Catheter ablation for AF is a relatively new therapy that evolved over the last decade. This can be performed by transeptal puncture and isolation of the pulmonary vein using either radiofrequency energy or cryotherapy.(33,34) Additional procedures of substrate modifications such roofline and mitral isthmus can be performed depending on the type of AF. Patients with persistent or chronic AF may require a stepwise approach which includes PVI, roofline, mitral isthmus, CS isolation and targeting CFAE (continuous fractionation electrograms).(35) There is still a debate on the extent of ablation between electrophysiologists which explained the differences in technique and success rate among different centres across the world. These differences attributed to the gap in our knowledge in understanding the mechanisms of AF.

1.2 Mechanisms of Atrial Fibrillation

Atrial fibrillation is the most common cardiac arrhythmia encountered in clinical practice. However, the mechanism of AF is still poorly understood and its therapy still suboptimal. Several theories have been suggested for the mechanisms of atrial fibrillation over the years and include:

(i) Multiple wavelets hypothesis

(ii) Focal electrical discharges

(iii) Localised re-entrant activity with fibrillatory conduction

(iv) Rotors with fibrillatory conduction

1.2.1 Multiple Wavelets Hypothesis

In late 1950, Gordon Moe used a computer model for AF to demonstrate that a grossly irregular wavefront becomes fractionated as it divides around islets or strands of refractory tissue and each of the daughter wavelets are then considered independent offspring.(36,37) This hypothesis was subsequently confirmed by Allessie et al. during mapping of acetylcholine induced AF.(38) In this study of canine model, the investigators estimated that 4 to 6 wavelets required to maintain AF in the canine atrium. Further studies using anti-arrhythmic drugs and intra-operative mapping have also provided another supportive evidence for such critical number of wavelets.(39-41) In addition, Konings and co-workers performed high-density epicardial mapping during pace induced AF in patients undergoing surgical interventional for Wolff-Parkinson-White syndrome. They demonstrated different types of AF characterised by different number and dimension of re-entrant circuits depending on slowing in conduction due to arcs of conduction block.(42)

In the clinical setting, MAZE surgical procedure used similar concept by creating multiple lines to divide the atria into small compartments that are too small to sustain AF.(43) Similarly, percutaneous catheter ablation for AF has adopted a similar but less invasive technique.

1.2.2 Focal Electrical Discharges

The finding of AF initiation spontaneously by ectopy from the pulmonary vein region(44) has changed our focus from preventing this arrhythmia's ability to sustain itself to preventing the arrhythmia from initiation. However, atrial ectopy could originate from a number of other sites and initiate atrial fibrillation. These sites have included the vein/ligament of Marshall,(45) the coronary sinus,(46,47) the crista terminalis(48) and the superior vena cava.(49) However, pulmonary veins are the major source of ectopy (94%) that initiates AF.(44) Hence, pulmonary vein isolation is one of the most important targets for radiofrequency ablation for AF.

The presence of sleeves of atrial tissue inside the pulmonary veins has been well recognised.(50) It plays an important role not only in generation of ectopy but also initiation of atrial tachycardia(51,52) and atrial fibrillation.(44,47) It is also important to mention that the interaction between the pulmonary veins and the left atrium play a significant role in generation of ectopy that triggers atrial fibrillation. The pulmonary veins could be electrically isolated from the left atrium by eliminating pulmonary venous conduction.(53) These observations have led to the conclusion that the pulmonary veins are not electrically connected circumferentially to the left atrium but rather at isolated points at the ostium of the vein.

1.2.3 Localised Re-entry with Fibrillatory Conduction

The shortening of the effective refractory period of the atrial myocyte and the slowing of conduction velocity - features of electrical remodeling - are important in stabilising the arrhythmia by decreasing the circuit size and promoting re-entry. The requirements for re-entry can be summarised as:(54)

i) Unidirectional conduction block in one of the progating pathways.

ii) A core of non-excitable tissue (functional, anatomical or mixed) around which a wavefront propagates, and

iii) An excitable gap or tissue maintained ahead of the wavefront.

The area of the pulmonary veins and posterior left atrium form a zone for localised re-entry. The myocardial sleeves or the myocardial tissue that extend from the LA into the pulmonary vein became an area of interest to cardiologists and pathologists(55-58) since the important work by Haissaguerre and co-worker in 1997 and 1998 demonstrated that, in most patients with AF, the ectopic beats originate in the pulmonary vein areas, in particular the superior one. The sleeves extend into the PVs, covering them for a variable distance but there appears to be significantly greater extension in the upper veins than the lower or inferior one, probably responsible for the clinical observation that a greater number of ectopic beats originate from these veins.(59) Steiner at el(58) found that the myocardial sleeves are developed in 89% of the PVs and their length is 4-48 mm, mostly 10-13 mm. Their mean thickness is 1.1 mm but may be up to 5 mm, they are thickest at the veno-atrial junction, thinning out peripherally. Although, there was no obvious difference in the pattern of the sleeves between AF and non-AF, Steiner found in his extensive pathological analysis of 100 heart subjects with and without AF that scarring and deposition of amyloidosis on the myocardial sleeves of the pulmonary veins were universal features in the elderly population and likely substrate for triggering and sustaining this arrhythmia.

The orientation or the arrangement of the myocardial fibres in the pulmonary veins is complex with abrupt change in direction and short fibres arrange in mixed direction. These fibre orientations are consisting with an area of slow conduction and fractionated electrograms (60,61) In the clinical setting, decremental conduction from the pulmonary veins to the left atrium with heterogeneity in ERP was also observed.(62,63)These electrophysiological properties enhance re-entry and may predispose or increase the risk of AF and atrial tachyarrhythmia.

The posterior left atrium (PLA) is another area that plays a significant role in the initiation and maintenance of atrial fibrillation. Recent studies have shown the crucial and dynamic interplay between the posterior left atrium musculature and the pulmonary veins.(64-66) Todd et al had successfully terminated AF by surgically isolating the PLA en bloc. (64) Further post-operative electrophysiological study demonstrated sustained AF in isolated PLA but not in the remaining part of the atrium. In addition, Roberts-Thomson and colleagues found a line of functional conduction delay and block in PLA running vertically between the pulmonary veins which probably promotes re-entry and susceptibility to arrhythmias. (65) This line of functional block was also described previously by Markides et al.(66) It was most marked in patients with structural heart disease, in particular conditions with greater atrial enlargement (patients with severe mitral regurgitation or severe left ventricular dysfunction). Conduction in this area revealed greater anisotropy with propagation wave parallel to line, but significant slowing in conduction velocity when wave fronts propagated perpendicular to the line. Hence, wave fronts propagation undertook a circuitous course around the region of block with greater susceptibility for re-entry and atrial fibrillation. Finally, complex fractionation electrograms have been mapped to different sites of LA during AF ablation. The significance of these signals in AF pathophysiology is still debated. However, Roberts-Thomson and colleagues observed that the fractionated signals were distributed to the line of slow conduction in PLA. More recently, Atienza el al found that in patients with paroxysmal AF, fractionated electrogram at the PLA is intermittent and proceeded by inter-beat interval shortening. They suggested in this context, a fractionation is a reflection of fibrillatory conduction consequence of the dynamic interaction between drifting high frequency re-entrant sources originating at the pulmonary veins-left atrium junction (PV-LAJ) and the atrial anatomy.(67) Hence, CFAE should not be recommended as a stand-alone strategy in curing patients with paroxysmal AF.

1.2.4 Rotors with Fibrillatory Conduction

A rotor has been defined as stably rotating pattern of reaction and diffusion that surrounds a pivot point, also known as phase singularity. A curved wavefront radiates from the rotor into the surrounding tissue.(68) Initially Allessie el al demonstrated in animal model of isolated

rabbit atrial muscle a sustained rotating activity as early as 1973.(69) However, rotors were not identified as a possible mechanism of atrial fibrillation until much later. Schuessler et al demonstrated in isolated canine right atrial preparation that AF can be maintained by a single re-entrant circuit.(70) During acetylcholine induced AF, the number of re-entrant circuits significantly increased in dose dependent manner to begin before converting to a single, relatively stable, high frequency re-entrant circuit that resulted in fibrillatory conduction. Afterward, Skanes and colleagues also demonstrated stable high frequency sources in active AF using Langendorff-perfused isolated sheep heart in the presence of acetylcholine.(71) The presence of narrow-banded spectra with dominant frequencies suggested that the process involved with AF is not random and chaotic as previously suggested by multiple wavelets theory but it has evidence of periodicity. This was demonstrated in canine model of chronic AF by Morillo et al 1998 when they found activation intervals were not randomly distributed throughout the atria but rather well organised dispersion of cycle lengths was apparent during sustain AF, with the shortest cycle length localised at the PV-LA junction, followed by the LA free wall, LA appendage, RA free wall then RA appendage. In another study, Mandapati and co-workers used isolated sheep heart to demonstrate that AF was driven by micro re-entrant sources in the left atrium.(72) Using the optical and isochronal maps, it was determined that these highest frequency sources were a vortex rotating clockwise for the entire episode of AF. The frequency of the rotor was the highest frequency of all recorded sites which suggested that it was the mother rotor that was driving AF. These rotors tend to anchor to the site with the anatomical heterogeneity such as pulmonary vein ostia or posterior left atrium in patients with paroxysmal AF.(73-75) However, in patients with persistent AF, these rotors were found in other LA locations.(73,76,77) The waves travelling or radiating from the relatively stable rotors in LA undergo complex, spatially distributed conduction block patterns as they travel toward the RA, manifesting as fibrillatory conduction and resulting in left-to-right frequency gradients.(78,79)

The clinical relevance of these rotors can be seen from the effect of catheter ablation. In retrospective analysis by Sanders et al, targeting areas with high dominant frequencies resulted in prolongation of AF cycle lengths and AF (80) termination. Recently published data has shown

that PV isolation with RF ablation targeting areas of high frequency electrograms was associated with long-term sinus rhythm maintenance.(81)

1.2.5 Summary

The mechanism of AF is still not fully understood with support still existing for multiple wavelets, mother rotor and focal sources. However, good progress has been made with the advancement in our technologies and development of different animal models to study AF. It is likely that there is not one single mechanism for AF but different ones with substrate-specific mechanism.

1.3 Tachycardia Related Atrial Remodeling

Atrial fibrillation is a progressive disease with data from the epidemiological studies suggesting that the transition from paroxysmal AF to chronic occurred more often in patients with longer episode of the arrhythmia and those with underlying cardiovascular disease.(2) The development of atrial fibrillation seemed to beget more AF. It has been found that atria remodel secondary to the atrial arrhythmia. There are different types of atrial remodeling such as electrical, mechanical, structural, cellular and endocardial remodeling.

1.3.1 Atrial Electrical Remodeling

1.3.1.1 Atrial refractoriness

The concept that “atrial fibrillation begets atrial fibrillation” was the result of the novel work of Wiffjels and co-workers. (82) In chronically instrumental goat model of AF, he found that there was a relationship between AF duration and sustainability. Wiffjels observed that in the normal goat, atrial fibrillation was lasting for a few seconds after induction. However, when AF was maintained for longer duration, the fibrillatory interval shortened and atrial fibrillation became more sustained on cessation of the fibrillation stimulus. These investigators observed shortening of atrial effective refractory period (AERP) with loss of normal atrial adaptation with less shortening at higher rate of atrial pacing. This finding was also confirmed by Morillo et al using canine model with rapid atrial pacing.(83) While none of the animals sustained AF for

more than 15 minutes at the baseline, half of the animals had easily inducible sustained AF after 6 weeks of rapid atrial pacing. Other investigators had also shown the importance of AERP heterogeneity with loss of normal rate adaptation of refractoriness which promotes re-entry and atrial fibrillation.(82,84,85)

These changes in atrial ERP have also been observed in multiple studies.(86-90) Franz and co-workers found significant shorter monophasic action potential duration in the right atrium following cardioversion of atrial fibrillation or flutter compared to control group.(91) Other investigators also found a significant shortening of AERP following cardioversion in patients with lone AF.(88) In addition, Attuel et al found maladaptation of ERP with significant increased insusceptibility to AF.(92) Boutjdir et al observed dispersion and maladaptation of cellular ERP in humans' right atrial tissue. Other researchers have also shown similar findings.(93) Finally, it has been accepted that the abbreviation of atrial effective refractory period and its spatial dispersion heterogeneity promotes AF re-initiation and provides a substrate for multiple wavelets re-entry which enhance AF to sustain itself.(94,95)

1.3.1.2 Fibrillatory Intervals

The fibrillatory waves were found to reflect the atrial cycle length and effective refractory period.(96) They are also good indicators of the average rate of AF.(96) In addition, as with atrial refractoriness, an increase in the dispersion of fibrillatory intervals has been reported.(97,98) The fibrillatory intervals found to be shorter and more disorganised in patients with persistent or chronic AF compared to those with paroxysmal one.(99,100) Cuppuci and co-workers also demonstrated the dynamic nature of fibrillatory intervals with prolongation seen prior to termination and shortening seen prior to persistence.(101)

1.3.1.3 Atrial Conduction

Conduction velocity plays an important role in the development of atrial fibrillation. Wijffels et al demonstrated that changes in the refractoriness is usually stabilised after a few days from AF induction, however, the slowing in conduction velocity occurs a few weeks post AF induction.(82) This observation explained why AF was more sustained after a few weeks of

repeated induction. Other investigators have also shown the slowing in conduction velocity following stabilisation of ERP.(102,103)

High density mapping is required for measurement of conduction velocity in humans which has limited its used in humans. However, various surrogate markers such as P wave duration, the presence of fractionated electrograms or double potential, conduction time, and conduction delay zones have been used to study the impact of AF on conduction velocity. P wave duration is a reliable and non-invasive marker for conduction delay and its prolongation has been associated with the development of AF,(104) the development of the arrhythmia after coronary artery bypass surgery,(105) and transition of paroxysmal AF to chronic AF.(106) Cosio et al found that patients with chronic AF following cardioversion showed prolonged P wave, longer conduction time and fragmented atrial electrograms.(107) In addition, similar changes in conduction properties were also seen using 3-D electro-anatomical mapping system capable of determining wavefront propagation velocity in human AF.(108)

1.3.1.4 Sinus Node Function

Sinus node dysfunction is commonly associated with atrial tachyarrhythmia and can lead to syncope after AF termination, a condition named sick sinus syndrome or tachycardia-bradycardia syndrome.(109,110) In canine model of electrical induced AF, Elvan demonstrated prolongation of sinus node recovery time, corrected sinus node recovery time, and the intrinsic cycle length with 2 to 6 weeks of atrial fibrillation.(102) However, significant sinus node recovery was observed one week post AF termination. These findings were further confirmed by other investigators who showed that sinus node dysfunction due to atrial tachycardia remodeling was fully recovered 4 weeks after termination of the tachycardia.(111)It is worth mentioning that atrial pacing induced sinus node dysfunction was also observed in the structurally normal heart and resulted in sinus node remodeling characterised by prolongation of the sinus node recovery time, sino-atrial conduction time and sinus cycle length.(112)

In clinical setting, it has been observed that sinus node dysfunction was found in patients undergoing cardioversion for chronic AF with sinus node recovery time was significantly longer in AF patients compared to control.(88,113,114) In these studies sinus node reverse remodeling

was also observed but it took more than 24 hours after restoration of sinus rhythm. This phenomenon of sinus node remodeling has also been observed with other atrial tachyarrhythmia such as atrial flutter.(115,116)

The mechanism by which sinus node remodeling occurs with atrial tachyarrhythmia is still poorly understood. Perhaps an increase in the time window due to sinus bradycardia with dispersion of refractoriness facilitate the condition for the development of atrial fibrillation.(117)

1.3.2 Atrial Ionic Remodeling

The changes in the electrical properties of the atria during AF, in particular shortening of ERP, decrease in ERP adaptation to rate as well as slowing in atrial conduction velocity perhaps reflect the underlying ionic remodeling of the atrial myocyte. The main ionic changes will be discussed below.

1.3.2.1 Calcium

Rapid atrial rate with AF significantly increases Ca+2 overload. The atrial myocytes respond by reduction of Ca+ 2 influx via down regulation of *I*Ca*L* to prevent cytotoxicity with calcium overload.(118) In addition, there is upregulation of the NCX exchanger to remove calcium from the cell. This results in a loss of cellular calcium and decreased action potential duration (APD) and wave length, which favours AF perpetuation. Rapid atrial pacing in canine model at 400 beats per minute resulted in progressive decreases of calcium dependent transient outward current (ITO) and the L-type calcium current (ICaL) density by approximately 70% after 6 weeks of tachycardia.(119)These results have also been observed in humans with atrial fibrillation.(120-122)Initially shortening in APD results from functional inactivation of ICaL. However, sustained AF causes persistent decreases in ICaL , mainly through down regulation of ICaL pore-forming α-subunit mRNA(123), and to less degree via post-transcriptional mechanisms such as protein dephosphorylation and breakdown.(124,125) Additional subunits of Lca+2 alpha2/ delta 1 and beta 1b, have also been found to be reduced in patients with chronic AF also contributing to the reduction in Ica amplitude.(126) In addition to a decrease in

IcaL, there is alteration in intracellular Ca+2 handling, which contributes to loss of APD rate dependence and favours re-entry and AF.(127)

The role of calcium handling in atrial remodeling has also been studied in humans. Short-term episode of AF (less than 15 minutes) was found to be associated with shortening of AERP and promotion of AF induction, such effect can be prevented by calcium antagonist verapamil (IcaL).(128,129) However, verapamil reduces the refractory period abbreviation caused by 24 hours atrial pacing but it has minimal impact on concomitant tachycardia induced promotion of atrial fibrillation. In fact, verapamil(130) or diltiazem(131) has no influence on atrial remodeling induced by longer duration of AF. Interestingly, a selective T-type calcium blocker called mibefradil significantly modified the atrial remodeling, suggesting a role for the T-type calcium channel in the atrial remodeling associated with persistent or chronic AF.(132) Moreover, susceptibility to spontaneous diastolic sarcoplasmic reticulum (SR) calcium release through ryanodine receptor channels might contribute to AF arrhythmogenesis by promoting both trigger as well as re-entry.(133)

1.3.2.2 Potassium

Earlier study on variety of potassium channels following atrial pacing in canine model have shown no alteration in expression or density in these channels, the inward rectifiers (IK1), ultrarapid (IKUR.D), rapid (Ikr), and slow (Iks) delayed rectifiers.(119) However, recent studies have shown some of these channels play a role in AF arrhythmogenesis. The resting membrane potential of myocyte is set by K+ conductance with the inward rectifiers K+ current primarily account for it, and becomes more negative during AF(134-136). The Ik1 is formed by Kir2-family subunits, especially Kir2.1. AF has been found to increase the expression levels of Kir2.1 mRNA (134,137) and protein (137) which enlarges Ik1.

The inward rectifier K+ channel (Ik1) and KAch act to maintain the action potential plateau. Recent studies have found KAch or its mRNA or protein expressions reduced in chronic AF, however, one study showed the opposite.(120,122,138)

1.3.2.3 Sodium

The role of sodium channels in AF pathogenesis is more limited compared with calcium and potassium. There have been conflicting results on the role of sodium channels on AF genesis,(123,139-141) while preclinical studies have suggested iNa or mRNA and protein expression levels remain unchanged or decreased, clinical studies have shown unchanged or increased iNa.(120,122) Schotten and co-workers demonstrated a significant up-regulation of the sodium-calcium exchanger (67%) in myocyte of patients with chronic atrial fibrillation at the time of mitral valve surgery. Jayachandran et al evaluated the effect of cariporide, a sodium-hydrogen exchange-inhibitor, on acute (5 hours) rapid atrial pacing induced atrial electrical remodeling.(142) They found that cariporide prevented rate related shortening of atrial refractoriness with blunting of the contractile dysfunction in the short-term, suggesting that cariporide may play a role in atrial remodeling to atrial arrhythmia. However, blockade of sodium-hydrogen exchanger did not prevent the long-term tachycardia related atrial remodeling in canine model.(143) Although it may appear it has a role in preventing contractile dysfunction, no effect was seen in electrical atrial remodeling in goat model.(144,145)

1.3.2.4 Renin Angiotensin System (RAAS)

Antagonism of the renin angiotensin system (RAAS) may reduce both the occurrence and relapse of AF. In the TRACE study(146), 1,749 patients with left ventricular dysfunction after myocardial infarction were randomised to either trandolapril or placebo. Of the 1,577 in sinus rhythm at the start of the study, a total of 64 developed AF during a mean follow-up of three years. Out of these 64 patients, 5.3% were in the placebo group compared with 2.8 % in the trandolapril group($P<0.05$).The result was even higher in the SOLVD study(147), when the risk of developing new AF was reduced by 78% with enalapril. Although the mechanism by which RAAS blockers reduced the incidence of AF is complex and not fully understood, there is clear evidence for RAAS activation during atrial fibrillation.(148,149) It is beyond any dispute that ACE inhibitors or AT II receptor blockers have implications on atrial structural and electrical remodeling; it is still unclear such beneficial effect on AF with heart failure is due to their actual

direct action of the arrhythmogenic substrate in the atrial or due to the positive effect on LV remodeling and haemodynamics.

1.3.3 Atrial Structural Remodeling

The atrial structural remodeling is a slower process than the electrical remodeling which usually takes a few hours to conclude. It is consisting of morphological changes to the atrial myocardial architecture and atrial ultrastructural.(150) These structural abnormalities with changes in cellular adhesion or coupling due to interstitial fibrosis lead to inhomogeneity in conduction that can result in local conduction block and re-entry.(151) The atrial structural changes with the relevant studies are discussed below.

1.3.3.1 Atrial Myocyte Degeneration, De-differentiation or Apoptosis

Many studies have described the presence of atrial myocardial tissues degeneration in patients with atrial tachyarrhythmia or atrial fibrillation.(152-154) The following degenerative changes were observed in atrial cardiomyocytes of patients with atrial fibrillation:

(i) Cellular hypertrophy.
(ii) Change in mitochondrial size and shape.
(iii) Disruption of the sarcoplasmic reticulum.
(iv) Widening of the intercalated discs.
(v) Peri-nuclear glycoprotein accumulation.
(vi) Central loss of sarcomeres myolysis
(vii) Increase in the extracellular space with fibrosis

No signs of irreversible changes that lead to cell death (apoptosis) or abnormalities in apoptotic marker such as proliferating nuclear antigen, P53, bcl-2 and TUNEL reactivity were found in chronic lone atrial fibrillation or experimental AF model. (150,155,156) However, signs of apoptic changes were seen only in one human study of patients with AF and dilated left atrium secondary to valvular heart disease or coronary artery disease. (153)

1.3.3.2 Cell-To-Cell Connections (Gap Junction)

Gap junctions are cluster of connexin family forming direct cytoplasmic continuity between cells to provide cell to cell pathway (electrical coupling). Gap junction plays an important role in rapid and homogenous propagation of the wavefront in the heart.(102,157-159) Therefore, alteration in gap junction distributions or channels could lead to change in conduction velocity and anisotropy resulting in re-entry.(160,161)The atrial myocyte express three different isoforms of gap junction channel proteins or connexin: connexin 40, connexin 43, and connexin 45. There are significant heterogeneity in the quantity and distribution of the connexin across cardiac chambers and species.(162,163) Such heterogeneity likely explained the conflicting results we have seen up to this date regarding the role of connexin in atrial remodeling. Elvan et al found in canine model that AF increases connexin 43 expression,(102) while another study in goat found that connexin 43 is unchanged, but the distribution of another connexin isoform, connexin 40, was altered.(158) In addition, the relation of gap junctional changes to stabilisation of AF was also studied in another goat model of AF.(157) While the homogenous distribution of connexin 40 was maintained during sinus rhythm, a significant heterogeneity was found after 2 weeks of AF, by the time intracellular ca+2 is deposited and just before AF became more sustained.(164) These animal data suggest that the heterogeneity of connexin distribution, rather than the up or down regulation, may play an important role in the susceptibility to AF. In contrast to these animal studies, Kostin and colleagues found in humans with chronic atrial fibrillation that reduced level of connexin 43 associated with lateralisation of the distribution of this protein, suggesting that there are inter-species variation in these proteins.(154)

1.3.4 Atrial Interstitial Fibrosis

Atrial fibrosis is a hallmark of atrial structural remodeling in patients with AF and underlying structural heart disease such as hypertension, congestive cardiac failure, valvular heart disease or coronary artery disease. It is the result of an accumulation of collagen to replace degenerative myocytes. Interstitial fibrosis disrupts and interferes with intercellular coupling; therefore it slows the conduction velocity and increases the heterogeneity of conduction

resulting in a substrate for arrhythmia or atrial fibrillation. In animal model of pace-induced AF, electrophysiological remodeling was fully reversible after cessation of pacing, while structural remodeling regressed slowly and partially.(165) Interstitial fibrosis has been found in patients with lone AF(166) as well as patients with underlying structural heart disease such as valvular heart disease or cardiomyopathy.(167,168) Oakes et al found that the extracellular matrix volume and composition was correlated with AF persistence.(169)

The precise mechanisms of atrial fibrosis and whether there are any differences between atria and ventricles in susceptibility to fibrosis remain unclear. There are three interrelated pathways involved in atrial fibrosis - the renin angiotensin system (RAAS), transforming growth factor-B1 and the oxidative stress pathways. These pathways are activated during different cardiovascular disease conditions and work together to promote fibrosis and AF.(170) In transgenic mice with cardiac restricted angiotensin converting enzyme (ACE), Xiao et al found increased angiotensin II production with significant atrial dilation with fibrosis and AF.(171) In addition, in animal model of ventricular pace-induced heart failure, Li and co-workers found increased level of angiotensin II.(172) Mitogen activated protein kinase are important downstream mediators of angiotensin II effects on atrial tissue structure(173) and change the cellular electrical coupling (gap junctions) in a way that enhance AF genesis.(174) Treatment with angiotensin converting enzyme blockers or angiotensin II receptor blockers has been found to reduce atrial fibrosis and AF in rapid paced canine atria. In addition, transforming growth factor-B1 (TGF-B1) is the primary downstream mediator of angiotensin effects.(175)Usage of angiotensin II receptor blockers inhibits TGF-B1 up-regulation.(176) In addition, targeted cardiac over-expression of TGF-B1 results in selective atrial fibrosis, conduction heterogeneity and increased propensity for AF.(177,178)

1.3.5 Atrial Mechanical Remodeling

Tachycardia induced cardiomyopathy (TIC) is a recognised complication of AF. Similarly, AF also impairs the left atrial mechanical function which is also known as atrial mechanical remodeling. Loss of atrial kick or contraction is not only effected the ventricular filling during diastole but also lead to stagnation of red blood cells with the potential risk of thrombosis and stroke.

Rapid atrial pacing both in human and animals studies resulted in significant reduction of left atrial mechanical function and left atrial appendage empty velocity. (179-182) Such findings were also seen in human studies after short atrial pacing or post cardioversion.(90,183)Logan et al found in early 1960s that atrial fibrillation was associated with loss of A wave with loss of atrial contraction. Later on, other researchers pointed out the close relationship between the degree of atrial dysfunction or remodeling and the duration of atrial fibrillation.(184-187) Sanders and colleagues found that there was reservation of atrial mechanical function after short duration of atrial tachyarrhythmia with appropriate response to the administration of calcium or isoprenaline.(185,188) In contrast, the response to isoprenaline infusion was weakening in those with longer duration of arrhythmia. Our knowledge on the mechanisms of atrial tachycardia induced cardiomyopathy is not fully understood. There are many possible cellular mechanisms that probably explain the tachycardia mediated atrial myopathy such as intracellular calcium overload(179,180), impaired cellular calcium handling(189), alteration in L-type calcium channels(190), hibernation of atrial myocyte (191), and myolysis (192). The atrial mechanical remodeling is not related to the mode of cardioversion whether it's spontaneous, pharmacological or electrically mediated.(181,193-198) It is easier to cardiovert patients with short duration of atrial fibrillation than those with longer episodes. The atrial structural changes occurring during sustained atrial fibrillation may also account for atrial mechanical dysfunction with less chance of successful cardioversion.(185)

1.3.6 Time Course of Atrial Remodeling

Atrial fibrillation is a progressive disease which has the ability to sustain itself with time. The fact that AF itself produces functional and structural changes has provided explanation to the progressive nature of this disease. The atrial electrical remodeling or the shortening of atrial refractory period occurs within a few days of atrial fibrillation.(82,83) Morillo and colleagues found in canine model of atrial pacing at 400/minute that the atrial refractory period was reduced by 15%. The reduction in AERP resulted in AF stability. However, domestication of atrial fibrillation must rely on a second factor since the persistence of AF continues to increase after electrical modelling has completed. Atrial fibrillation induced structural remodeling in

different time domains.(82) The atrial structural changes occur weeks to months after the onset of atrial fibrillation. Furthermore, atrial structural remodeling also results from the underlying cardiovascular disease. Therefore, structural change associated with AF occurs as a result of both AF and the underlying cardiovascular disease. Although the role of the atrial structural remodeling in progression of AF is still unclear, the associated interstitial fibrosis causes intra-atrial conduction delay with increased susceptibility to AF. It is worth mentioning that the reverse electrical remodeling occurs within a few days after restoration of sinus rhythm while the recovery of the mechanical and structural remodeling needed a longer period of time.(82,86,182,184,193,199,200) Understanding the mechanisms and the time course of atrial remodeling will guide us to new strategies to prevent and terminate atrial fibrillation.

1.4 Inflammation and Atrial Fibrillation

Many studies have reported association between inflammatory markers such as the circulating level of cytokines, C-reactive protein, complement, and the activation state of leukocytes and AF. However, it is still unclear whether inflammation is an epiphenomenon or causally related to AF initiation and perpetuation.(201) One of the mechanistic links between AF and inflammation is atrial fibrosis. Animals studies found increased deposition and turnover within atrial myocytes after challenge with inflammatory markers such as C-reactive protein, cytokines and complement.(202)Metalloproteinase (MMP) is key mediator in extracellular matrix turnover. The MMPs is regulated by myeloperoxidase which generates reactive oxygen species which in turn activates MMPs. Rudolph et al found higher plasma concentrations of myeloperoxidase and a larger myeloperoxidase burden in atrial tissue in patients with AF compared to individuals with no AF.(203) In addition, Frustaci et al demonstrated the presence of inflammatory cells and termination of AF with treatment with corticosteroids.(166) Dernellis et al also demonstrated the role of methylprednisolone in reducing C-reactive protein resulting in reducing the recurrence and progression of paroxysmal AF to persistent AF.(204) The role of corticosteroids in suppressing inflammation and prevention of AF has also been demonstrated in many other studies.(205,206)

1.5 Mechano-Electric Feedback and Atrial Fibrillation

Numerous bench-side as well as clinical studies showed an increased vulnerability to atrial fibrillation by atrial stretch and dilation. The relationship between AF and atrial stretch is rather complex with AF is a known cause of atrial dilation as well as a consequence of it. Atrial stretch and dilation presents in a wide spectrum of clinical conditions that are associated with atrial fibrillation such as heart failure, myocardial infarction and valvular heart disease. However, the mechanisms by which atrial stretch and dilation results in AF are not fully understood. The role of atrial stretch in the substrate for AF has been determined in various animal and human studies.

1.5.1 Acute Atrial Stretch and Atrial Fibrillation

1.5.1.1 Animal Studies

The effect of acute atrial stretch on atrial refractory period has revealed divergent results. In canine model of simultaneous atrioventricular pacing, acute stretch due to raised atrial pressure resulted in an increase in atrial refractoriness in both left and right atrium.(207) However, abbreviation of atrial refractoriness was seen in another model.(208) In contrast, Wijffels and colleagues also evaluated acute atrial stretch by volume overload with sudden infusion of 0.5-1 litre of haemocoel which resulted in no significant change in atrial effective refractory period. However, Sideris et al found in canine model of acute volume overload that acute stretch resulted in AERP prolongation.(209) There are many possible reasons for these conflicting results such as differences in species, variety of experimental conditions which could lead to different duration and intensity of stretch. In addition, the neurohumoral may also play a role in these conflicting results.

However, the data was more consistent in isolated heart preparation which demonstrated a reduction in atrial refractory period. Allessie and co-workers demonstrated abbreviation of refractoriness associated with increased atrial pressure (atrial dilation) in Langendorff-perfused rabbit heart.(210) In this model, the right and left atrial pressure was increased over a wide range of values by ligating the pulmonary vein as well as the caval vein with varying exit of fluid

perfused through the pulmonary artery. While there was no change in atrial refractoriness at low pressure (less than 7-8 cm H2O), there was a significant reduction in AERP when the pressure increased above a certain value. Similar finding was also demonstrated in isolated Langendorff-perfused guinea pig heart study, where acute atrial stretch was produced by intra-atrial balloon catheter.(211) In this model, the left atrial monophasic action potential (MAPd50) was significantly decreased due to a decrease in the duration of the plateau phase but there was an increase in the MAPd90 due to the presence of early after depolarisation.

The effect of acute atrial stretch on conduction velocity was also assessed in few studies. Early studies revealed prolongation of intra-atrial conduction associated with volume overload.(208,212) More recently, Chorro et al used high density map to measure the atrial conduction velocity during acute atrial stretch.(213) They found a significant reduction in atrial conduction and increase in conduction heterogeneity which potentially creates a substrate for re-entrant and AF. In addition, Ejisbouts et al demonstrated slowing in conduction velocity, increased intra-atrial conduction delay and promotion of the spatial heterogeneity in conduction.(214)

1.5.1.2 Clinical studies

The impact of acute atrial stretch studies in human beings has also shown heterogenous results. The difference in experimental models, pacing protocol with different degrees of atrial stretch might explain such divergent results, however. Calkin and colleagues found that simultaneous atrioventricular (AV) pacing produced no significant change in atrial refractory period at a drive cycle length of 400 ms in patients with no documented structural heart disease and there was no increase in frequency of AF induction.(215) Nevertheless, the same group demonstrated significant reduction of AERP by using a different pacing protocol with atrioventricular interval of 0 ms which might result in more acute rise in atrial pressure (acute atrial stretch).(216) However, Klein and co-workers found that an increase in atrial ERP during pacing at cycle length of 400 ms occurring when the AV interval was decreased from 160 to 0 ms.(217) In addition, Chen and colleague observed in patients without structural heart disease,

a heterogenous increase in AERP associated with an elevation in the atrial pressure as a result of simultaneous AV pacing.(218)

While pacing protocol and experimental model might explain in part such divergent results, other factors such as autonomic nervous system and renin angiotensin system may have contributed to such findings. Tse et al observed shortening of atrial refractoriness with acute atrial stretch which was enhanced by autonomic blockade and weakening by calcium channel blockade.(219)

The importance of atrial stretch is not only laying in creating the substrate for AF but also in triggers and initiation of this arrhythmia. Recent studies in patients with paroxysmal AF found that AF trigger originated more frequently in the superior dilated veins.(220,221) These clinical studies suggested the hypothesis that AF might start by stretch activated source in the pulmonary vein regions.(222)

1.5.2 Chronic Stretch and Atrial Remodeling

Conditions associated with chronic stretch such as heart failure and mitral regurgitation predispose patients to AF. The studies on the role of chronic atrial stretch demonstrated more consistent results than the one on acute atrial stretch.

1.5.2.1 Animal studies

The effect of chronic atrial stretch on the substrate for atrial fibrillation has been studied in several animal models. The first animal model of chronic atrial stretch was described by Boyden and colleagues in 1981.(223) In this canine model, partial occlusion of the pulmonary artery with excision of the tricuspid valve resulted in right atrial dilation with structural remodeling at 2, 20 and 30 weeks. The dogs were vulnerable to AF but no change observed in their action potential. Further histopathological exam revealed fibres hypertrophy with interstitial fibrosis. Another study by the same author also evaluated the effect of chronic stretch on the atria in spontaneously occurring feline cardiomyopathy.(224) Boyden also confirmed the presence of

marked atrial remodeling such as interstitial fibrosis, cellular hypertrophy and degeneration, and thickened basement membranes.

With more advanced mapping techniques investigators have extended these findings to study the electrophysiological properties of the atria. In canine model of mitral regurgitation, Verheule et al found that the left atrium became dilated after the first minutes of MR, thereafter increased gradually to more than 129% of the baseline width during the first weeks of MR.(225) Histological exam showed an area of inflammatory infiltrates with slight interstitial fibrosis, however, there was no significant change in the distribution of gap junction proteins (CX 40 and CX43) and the size of myocyte did not increase significantly.(225,226) Although the AERP was homogenously increased and there was no change in overall conduction velocity, further optical mapping revealed marked heterogeneity in conduction in the left atrium during pacing at shorter cycle length with extra stimuli.(227)The authors concluded that the atrial structural remodeling resulted in heterogeneity in conduction with increased propensity to AF. Similarly, Li el al found in canine model of heart failure induced by rapid ventricular pacing, increase in ERP, conduction heterogeneity and interstitial fibrosis.(228)In addition, Neuberger and co-workers found in another model of chronic stretch in goat due to complete AV block that AERP was unchanged but there was conduction slowing and increased AF duration without interstitial fibrosis.(229) However, Kistler et al found increased interstitial fibrosis with significant conduction abnormalities in ovine mode of hypertension but there was no change in AERP.(230)

1.5.2.2 Clinical studies

The relationship between chronic atrial dilation or stretch has been evaluated in few clinical studies. Chen and colleagues found longer AERP in patients with atrial dilation and no prior history of atrial fibrillation compared to control patients with normal atrial size.(231) Many investigators have found significant electro-anatomical remodeling in patients with chronic atrial stretch that associated with known clinical condition such as congestive cardiac failure, mitral stenosis and atrial septal defect. In patients with heart failure Sanders and colleagues found significant AERP prolongation, conduction slowing and increased propensity for AF.(232)

Similar abnormalities were reported by Roberts-Thomson in patients with atrial septal defect and chronic left atrial stretch.(233) In addition, John et al found that the electro-anatomical changes that occurred due to chronic atrial stretch in patients with mitral stenosis was reversed after mitral commissurotomy.(234) Earlier on, Sparks et al also found significant increase in the atrial size , AERP, sinus node recovery and undergoing asynchronous (VVI) ventricular pacing for 3 months.(235) Interestingly, all the aforementioned changes reverse after correction of the AV dysynchrony by DDD mode pacing.

1.5.3 Is Atrial Fibrillation a Consequence or a Cause of Atrial Dilation?

The relationship between AF and atrial size has been very well known for more than 50 years. While atrial dilation predispose to AF, atrial dilation is also a consequence of AF. Fraser et al and others found that strong correlation between atrial enlargement and the incidence of AF in patients with mitral valve disease.(236) Later on, Henry and co-workers found the incidence of AF significantly increased (54%) in patients with valvular heart disease and left atrial dimension more than 40 mm, however, AF incidence was rare (3%) when the LA diameter was less than 40 mm.(237)In addition, this relationship was further confirmed by large prospective clinical trials which established left atrial dilation as an independent risk factor for development of atrial fibrillation.(238-240) Furthermore, Grigioni et al showed the left atrial size was (apart from age) the only predictive parameter for the occurrence of AF in patients with mitral regurgitation. The severity of mitral regurgitation as well as left ventricular ejection fraction were not independent predictors of AF.(241) One can conclude according to these data that atrial dilation may be a cause of AF, therefore, intervention that maintains left atrial size may play an important role in prevention of AF.(240)

On the other side, many studies have also implied that atrial dilation is also a consequence of AF. Phillips el at reported many patients with AF a cause of reversible cardiac failure and dilation.(242) Later on, Keren et al found that patients with mitral stenosis and sinus rhythm had dilated left atrium but normal right atrium size.(243) However, bi-atrial dilation was found in patients with AF mitral stenosis as well as patients with lone AF. Likewise, Sanfilippo and colleagues showed in small but prospective echocardiographic study that AF patients with

normal atrial size at baseline developed significant bi-atrial dilation 20.6 months during follow up.(244) In addition, data from the Stroke Prevention in Atrial Fibrillation (SPAF) trials estimated that the independent contribution of AF (>1 year) to the increase in LA diameter is around 2.5 mm.(245)

These studies suggested that atrial enlargement and AF are mutually dependent. However, none of the above-mentioned studies have established a causal relationship between AF and atrial dilation. Nevertheless, both could be surrogates for the same underlying condition.

1.5.4 Mechanistic Link between Atrial Stretch and Atrial Fibrillation

The electrophysiological findings from acute stretch such as shortening of the action potential, a decrease in the resting diastolic potential, the occurrence of early after depolarisation and generation of ectopic beats were described by Franz el al.(246) These changes mediated via stretch-activated channels which might provoke stretch induced arrhythmia through occurrence of ectopy or change in excitability gap or refractoriness. The stretch activated ion channel may play a significant role in induction of AF as the blockade of this channel by gadolinium or tarantula has been shown to reduce the vulnerability to AF.(247,248) In addition, streptomyocin, another inhibitor of stretch activated channels, has also shown to decrease after depolarisation and reduced AERP shortening.(249) Calcium channel blockers have also been shown to reduce stretch, thus calcium loading may also be another potential underlying cellular mechanisms.(219,250) The autonomic nervous system has also been implicated in stretch induced AF, blockade of the autonomic nervous system facilitate AF with increased ERP inhomogeneity.(219) Furthermore , the electrical and structural remodeling that occur due to acute atrial stretch such as ERP shortening, slowing in conduction and increase LA size may promote re-entrant and AF.(113,210,211,214,218,250)

Chronic atrial stretch may induce a different sort of mechano-electric feedback. Chronic stretch has been shown to activate various intra-cellular signal pathways such as calcium/calmodulin dependent pathway, mitogen-activated protein kinase pathway, the janus kinase/signal transducer and activators of transcription pathway.(251) Chronic stretch also promotes local

secretion of angiotensin II and other growth factors cause activation of second messengers system.(252) The activation of these pathways lead to promotion of cellular hypertrophy, fibroblast proliferation and activation of matrix protein kinase resulting in tissue fibrosis.(253)

1.5.5 Summary

Although atrial stretch and dilation is strongly associated with AF, the data on acute stretch and electrical remodeling is still conflicting. In addition, the mechanism by which stretch leads to AF is still incomplete. Further study is required to fill the gap in our knowledge to understand the mechanistic link between AF and atrial stretch for better prevention and treatment of AF.

1.6 Autonomic Modulation in Atrial Fibrillation

The intrinsic cardiac autonomic nervous system has been implicated in initiation and perpetuation of AF.(254-256) Po et al demonstrated in animal model that direct application of acetylcholine into the atrial and pulmonary veins preparations resulted in heterogenous shortening of the action potential, in particular inside the pulmonary vein leading to PV tachycardia.(257) These data are in agreement with optical mapping studies showing periodic high frequency re-entrant activity during cholinergic induced AF, in particular at the PV-LA junction area.(71,72)

Direct stimulation of the vagus nerve is a method used for AF induction and maintenance for long time in animal model.(36,258) Studies have shown direct stimulation to the ganglionic plexus in the atria leading to shortening of the AERP and increased electrograms fractionation, induced PV ectopy and initiated AF.(254,259,260) However, the mechanism by which the autonomic nervous system contributing to the maintenance of clinical AF is not fully understood. In addition, AF itself have heterogenous change on the sympathetic innervation of the atria.(261) In canine model of rapid atrial pacing, Jayandran and colleagues performed positron emission tomography of the atria identifying the sympathetic nerve endings or terminals. They found an increase in the sympathetic innervation of the atria and increased heterogeneity of the sympathetic innervation.(261) The author suggested that the

heterogeneity of autonomic innervation may promote heterogeneity of AERP and maintaining AF.

1.7 Complex Fractionated Atrial Electrograms

Complex fractionated atrial electrograms (CFAE) may play a role in sustaining AF via a variety of mechanism that promote re-entry. Therefore, targeting areas of CFAE has been integrated into various catheter ablation protocols that are used to treat AF.

The definition of CFAE varies between different clinical studies but the most widely used definitions are summarised as follows

i. Continuous electrical activity or electrograms with FF interval <100 ms;(262)
ii. Fractionated atrial electrograms with a cycle length ≤ 120ms or ≥ 2 deflections or perturbations of the baseline with continuous deflection of a prolonged activation complex;(263)
iii. Fractionated potentials with ≥ 3 deflections or continuous activity;(264)
iv. Electrograms with a cycle length ≤ 120 ms or shorter in the coronary sinus or displayed continuous electric activity.(265)

1.7.1 Mechanism of CFAE

There are a few mechanisms possible underlying the appearance of CFAE. This area of high fractionated electrograms could represent an area of slow and anisotropic conduction. Gardner el found in canine model of healed infarct heart that CFAE was correlated with area of fibrosis resulting in reduced cell to cell conductions thereby slowing conduction.(266) Similarly, Spach and colleagues made identical observations in human atria.(267) In addition, Roberts-Thomson found that the area of fractionated electrograms occurred almost exclusively along the line of conduction block on the posterior left atrium.(268) However, CFAE may represent pivoting points causing turning around of propagating wave fronts as shown in patients undergoing surgery for Wolf-Parkinson-White.(269) Furthermore, Kalifa and co-workers used isolated sheep heart to demonstrate that the most fractionated signals were found at the border zone

where the greatest variability in wave front propagation were observed.(270) Finally, CFAE could be vagally mediated as demonstrated by Lin et al canine model where increasing acetylcholine led to increase in electrograms fractionation.(271)

1.7.2 Mapping and Targeting CFAEs

Targeting CFAE during AF ablation has yielded various degrees of success. Nademanee et al had the best experience with success rate of 81%; at longer term follow up of more than two years with a mean procedure rate of 1.68 per patient. These CFAEs are frequently seen on the pulmonary vein areas, inter-atrial septum, anterior left atrium, left atrial roof, mitral annulus, base of left atrial appendage and proximal coronary sinus.(263,272) Others laboratories did not experience the same success rate Nademanee's group enjoy even as hybrid procedure with isolation of the pulmonary veins.(265,272,273) Even though there is no clear explanation for such discrepancy, different ablation and mapping techniques, choice of the radiofrequency power might influence eventual outcome.

1.8 Clinical Substrate for AF

There are many risk factors for AF such as age, hypertension, valvular heart disease, heart failure, male gender, diabetes mellitus and myocardial infarction. Furthermore, recent studies have also shown obesity and obstructive sleep apnoea as a significant risk factor for development of AF.

1.8.1 Hypertension

Hypertension is one of the main risks for AF. The risk of AF development is 1.4 to 1.5-fold higher in patients with hypertension compared to the general population.(274) The mechanism by hypertension predisposed to AF is multifactorial via diastolic dysfunction, left ventricular hypertrophy and left atrial stretch. In ovine model of hypertension (one kidney one clamp model), Lau et al studies the short and long-term impact of hypertension on left atrial remodeling and AF inducibility. Hypertension was induced by surgically clamping the renal artery. Progressive left atrial remodeling such as dilation/dysfunction, interstitial fibrosis, slow

in conduction and increase in conduction heterogeneity index was observed within 4 weeks in hypertensive animals compared to controls. (275) In another ovine model of long standing hypertension Kistler et al also demonstrated significant electrical and structural atrial remodelling that explain the increased in susceptibility to AF in patients with longstanding hypertension.(276)

Hypertension is associated with increased risk of stroke, cardiovascular mortality and hospitalisations in patients with atrial fibrillation.(277)

1.8.2 Age

Age is considered one of the strongest predictors of AF. The risk of AF increases from 2.3% in patients older than 40 years to 5.9% in those older than 65 years. Ageing is associated with structural and electrophysiological changes that increased the risk of AF development.(278-284). Increased atrial interstitial fibrosis with area of low atrial voltage is the main feature of the ageing process.(278,279) In addition, age also caused left atrial remodeling such as prolongation in ERP, slowing in conduction velocity and anisotropy with increased electrograms fractionation.(280-282,285)

1.8.3 Obesity and Obstructive Sleep Apnoea

Obstructive sleep apnoea and obesity are growing problems among the population in western countries and both are strongly associated with the development of atrial fibrillation.(286,287) There are many pathophysiological factors in patients with obstructive sleep apnoea (OSA) that contributors may contribute to development of AF. These factors include swinging hypertension, increased intrathoracic pressure leading to left atrial stretch which may lead to AF(288), autonomic changes, hypoxia and oxidative stress with inflammation.(289,290) All of these factors have been variably implicated as causes for left atrial remodeling by causing tissue fibrosis, a potential risk for AF development. Abed et al observed in an ovine model of obesity a direct impact on the atrial myocardium that manifest with increased fibrosis, decreased ERP and prolonged conduction times.(291) Dimitri et al found that OSA is associated with significant left atrial changes characterised by left atrial dilation, low voltage, widespread

conduction abnormalities and long sinus node recovery.(292) The presence of OSA is a well-recognised factor for AF recurrence after catheter ablation for AF.(293)

Body mass index is a strong predictor of AF development and is also associated with high recurrence rate after AF ablation.(291,294,295)

1.8.4 Valvular Heart Disease

Mitral valve disease, whether it is regurgitation or stenosis, is a well-recognised risk factor for AF.(296,297) The annual risk of AF development in patients with mitral stenosis is about 5% and is associated with significant increase in patient morbidity and mortality.(298,299) In canine model of AF, Verheule et al demonstrated left atrial enlargement with increase in atrial ERP, increase in conduction heterogeneity with increased in fibrosis/inflammation which promotes AF genesis.(225)

In patients with mitral stenosis undergoing commissurotomy, Fan and colleagues found a significant shortening in ERP, sinus node remodeling without changes in conduction velocity. (365) On the other hand, John et al observed left atrial enlargement, lower atrial voltage with scarring and site specific conduction abnormalities in patients with mitral stenosis. (300) Left atrial remodeling in patients with mitral stenosis is associated with AF development.

1.8.5 Congestive Heart Failure

In Framingham study heart failure was one the strongest predictors of AF development with a relative risk of up to 5.9.(296) The prevalence of AF increased with severity of heart failure with <10% in those with New York Heart Association (NYHA) functional class I to 50% in those with NYHA class IV heart failure.(301) The causal relationship between AF and heart failure is complex and compound interaction between the two conditions is often associated with detrimental consequences as compared to each condition alone.(302-304). In CHARM study (Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity program), which enrolled patients with chronic heart failure, AF was associated with increased risk of

worse cardiovascular outcome, even those with heart failure and preserved left ventricular function.(305)

In canine model of chronic heart failure that was induced by rapid ventricular pacing, Li et al found AF was sustained by interstitial fibrosis and conduction heterogeneity without change in conduction velocity or atrial ERP.(228) Using Pirfenidone, anti-fibrotic agent, AF vulnerability was significantly attenuated or reduced.(306)

Sanders el al describes in detail the atrial changes in humans with ischaemic and non-ischaemic cardiomyopathy. They found significant atrial remodeling such as increase in atrial ERP, slowing in conduction velocity and sinus node dysfunction. In addition, there was a structural abnormality as described by area of low voltage and scar using an electro-anatomical mapping system.(232) The syndrome or clinical entity of congestive heart failure represents a heterogenous group where the different underlying cause pathology resulted in different prognostic value.(307) Hence our understanding of the pathophysiological mechanisms of AF in heart failure remains incomplete.

1.8.6 Diabetes Mellitus

Diabetes mellitus is a well-recognised risk for development of AF and odds ratio of up to 2.1. (296,308,309) A few studies had examined the association between these two conditions in animals models. Kato and colleagues assessed the electrophysiological properties in Langendorff-perfused hearts from a genetically non overweight diabetic rat model. They found increased interstitial fibrosis with intra-atrial conduction disturbance without change in atrial ERP leading to increase in atrial arrhythmogenesis as compared to control groups. (310) In another study Otake el al used Langendorff of streptozotocin-induced diabetic rat to demonstrate the role of neutrally mediated remodeling in promotion of AF genesis. There was shortening in ERP with increase in heterogeneity and increased AF incidence following sympathetic nerve stimulation. (311) Our knowledge on mechanistic link between diabetes and AF is limited and further work is needed to understand such link.

1.8.7 Sinus Node Disease

Sinus node disease is usually associated with AF and the relationship has been well established. The clinical spectrum of sinus node disease such as sinus arrest, persistent sinus bradycardia or tachy-brady syndrome is well associated with AF. (328,369)Study on patients with sinus node disease requiring implantation of permanent pacemaker showed increased incidence of AF from 1% at one year and 28% at 10 years.(370) Initial studies on patients with sick sinus syndrome had shown abnormalities in sinus node function such as sinus node automaticity, sino-atrial conduction time and sinus node recovery time under premature atrial stimulations and various pharmacological stress.(371-375) Subsequent studies on patients with sick sinus syndrome revealed unchanged or increase in ERP with unchanged or greater dispersion of refractoriness.(135,376-378) Furthermore, various abnormalities in conductions had been described as well. These changes include slowing in atrial conduction tissue as evidenced by prolongation of the P wave duration on cardiac electrocardiograms, increased conduction time and presence of greater number/duration of double potentials.(377-379) Sanders and co-researchers undertook right atrial high density electro-anatomical map in patients with sinus node disease which demonstrated extensive structural abnormalities as manifested by area of low voltage and scarring. (377) The prevalence of high fractionated electrograms was more abundant in the high right atrium area suggesting more diffuse disease process.(377,380) These areas of high fractionated electrograms were found to predict development of AF.(381)

1.9 AF and AMI

AF is also a common arrhythmia during acute coronary syndromes. It carries worse short and long-term outcomes in this setting. It is associated with increased risk of death during hospitalisation and follow-up. A combination of rapid ventricular response with reduced ventricular diastolic filling and increased oxygen demand during AF, further compromise the patient's haemodynamics, impair coronary circulation and adversely affect the patient's outcome. AF and congestive heart failure (CHF) are commonly encountered together, particularly in the presence of ischaemic heart disease. The shared mechanisms between AF

and CHF include myocardial fibrosis and dysregulation of intracellular calcium and neuro-endocrine function.(232,312,313) AF is an ominous arrhythmia in ischaemic cardiomyopathy(314).Previous primary and secondary prevention studies of implantable cardioverter defibrillators (ICD) found that AF patients not only received more inappropriate shocks but also more appropriate shocks.(315-317) Patients with AF during acute myocardial infarction (AMI) are usually a sicker and older population than patients without AF, therefore, AF may be in part a surrogate marker of the overall poor clinical status of such a population.

Despite its significance and common occurrence during AMI, there have been no studies or clear guidelines for AF in AMI addressing the relevant management issues in this setting. In addition, the underlying mechanism of AF during AMI is still uncertain.

1.9.1 Epidemiology of ischaemic atrial fibrillation

Atrial fibrillation is a common complication of myocardial infarction. Its incidence rate ranges between 6-22% (318-324). The variation in the incidence rate is probably related to different population demographics, different therapeutic modalities used across different studies as well as different definitions used for AF (early vs late). AF frequently complicates AMI in the elderly. For instance Rathore et al found that in a pooled analysis of 106,780 elderly patients (>65 years) from the cooperative cardiovascular project dataset of 234,769 Medicare patients hospitalised for acute MI, the incidence of new onset AF was 22.1%. However, in the GUSTO I trial(320) 10.5% of the 41,021 patients developed AF during hospitalisation. In the GUSTO-3 trial(320,321) which compared reteplase versus alteplase for the treatment of acute MI within 6 hours of symptom onset, the incidence of new AF was 6.5% (906 out of 13,858 patients). This result was similar to the data from GISSI-3.(325)

As mentioned previously, many studies have investigated the overall incidence of AF complicating AMI. However few observed outcomes over time in the proportion of AMI patients developing AF. As part of a secondary analysis of the SPRINT trial,(318) a total of 2866 consecutive patients with AMI from coronary care units throughout Israel from 1992 to 1996 (thrombolytic era) were compared to 5803 AMI patients admitted to coronary care units

between 1981 and 1983 (pre-thrombolytic era). The incidence of AF between these two groups was similar (8.9% versus 9.9%). Interestingly, there was a decline in the occurrence of AF during the three periods surveyed in the thrombolytic era. The incidence of paroxysmal AF declined from 10.2% in 1992 to 8.9% in 1994 and to 7.4% in 1996. After adjustment for other potential cofounders, the odds of developing AF were 19% ($P<0.05$) lower in 1996 compared with 1992. Similarly, Goldberg et al (323) found in a community-wide study of 2596 patients that there was significant decline in the incidence of AF in patients with AMI hospitalised in 1997 compared with those hospitalised in 1990 ($P<005$). Such findings by the same group(326) were not apparent in Worcester Heart Attack Study between 1975-1984. A significant decline in the incidence of AF have also been seen in relatively small groups of patients with AMI who received thrombolytic therapy.(327) These findings indicate that despite an increasingly older population with higher prevalence of co-morbidities, the risk of development of AF in the setting of AMI has declined. Although there is no clear reason for this decline, the use of early revascularisation therapy combined with new pharmaceutical therapy may have favourably affected both the incidence and survival associated with AF via different mechanisms. Despite these declines in incidence rates, AF remains a common complication in both patients with ST segment elevation MI or non-ST segment elevation MI with an overall incidence of 7.5%.(328)

Over the past decade, the widespread usage of angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers and beta blockers has been associated with a reduction of AF incidence in MI. The OPTIMAAL trial conducted between 1999 and 2002 compared the ACE-inhibitor captopril to the angiotensin II receptor blocker in patients with AMI and congestive cardiac failure or impaired left ventricular function. Of the 4822 patients without AF at baseline, 96 (2.0%) developed AF during the first three months which subsequently increased to 7.2% during the entire follow-up period of 3 years.(329) In the TRACE trial where the ACE inhibitor trandolapril was compared to placebo, the incidence of new AF during 2-4 years follow-up was 5.3% in placebo vs 2.5% in Trandolapril ($P<0.005$).(146) In the DIAMOND-AMI study, incidence was similar; 2% developed new-onset AF.(330) The effect of the beta-blocker carvedilol on ischaemic AF had been demonstrated in the CAPRICORN trial, where the incidence of AF reduced from 5.4% to 2.3%($P<0.05$).(331)

In summary, the incidence of AF complicating AMI ranges between 2-22%. The variation in reported incidence of AF following AMI probably relates to heterogeneity in study population demographics as well as using different definitions of AF (early versus late). The widespread use of early revascularisation therapy, whether PCI or thrombolysis has led to a decline in the incidence of AF during AMI. Finally, modern pharmacotherapy may also have played a role in changing the epidemiology of ischaemic AF. Nonetheless, one would expect AF to remain a common problem in the setting of AMI as the population ages with multiple co-morbidities.

1.9.2 Prognostic significance and clinical predictors of atrial fibrillation after AMI

The prognostic significance of AF during acute coronary syndromes has been extensively studied.(146,318-321,324,325,327-329,332) Most studies have shown that AF carries worse short and long-term outcomes. For instance, in GUSTO 1,(320) death, stroke, heart failure, re-infarction, cardiogenic shock, ventricular fibrillation and asystole occurred more frequently in patients with AF than without AF. The 30-day mortality rate was higher in patients with than without atrial fibrillation even after adjustment for baseline differences (OR 1.3. 95%CI 1.2-1.4). This was found in patients who developed the arrhythmia during admission but not in those with arrhythmia at trial entry. The trial did not differentiate between patients with paroxysmal or persistent AF. The mortality rate remained significant between the two groups (AMI with AF vs AMI with no AF) after 12 months of follow-up ($P<0.05$). These results were further replicated in GUSTO-III.(321) In addition, independent predictors of new AF were found to include age, systolic blood pressure, Killip class, worsening heart failure, hypotension, third degree heart block, ventricular fibrillation and prior bypass surgery. It was unclear from this study why the use of class I antiarrhythmic agents, sotalol, and digitalis in the 2 weeks before enrolment also independently predicted AF.

Eldar et al(318) compared the outcome of paroxysmal AF in the thrombolytic era with that in the prethrombolytic era and found that patients with AF complicating AMI had favourable prognosis in the thrombolytic era. As previously mentioned, modern therapy, whether pharmacological or invasive has improved the overall prognosis of patients with AMI. However,

patients with AF have a worse prognosis when compared with patients without this arrhythmia. This is consistent with the TRACE(146) study group report which found an adverse prognosis of AF after adjustment for baseline characteristics and left ventricular function at recruitment. The OPTIMAAL study evaluated patients with AF, AMI and left ventricular dysfunction (LVEF<40%). Patients with AF had significantly higher total mortality (OR 3.83, 95% CI 1.97-7.43), cardiovascular death, stroke and all-cause hospitalisation.

AF adversely affects outcome independent of the patient age.(319) Age is also of the strongest predictors of new AF. Other predictors include male gender, history of angina, higher Killip's class, higher diastolic blood pressure, and higher heart rate during randomisation.

In a pooled database of 120,566 patients with ST-segment elevation MI (STEMI) and non ST-segment elevation MI enrolled in 10 clinical trials, Lopes et al,(328) found that AF was associated with poorer outcomes in both STEMI and NSTEMI than those without AF. AF had a large impact on short-term mortality risk following NSTEMI compared to patients with NSTEMI with no AF (P<0.001). AF with NSTEMI was also associated with increased risk of stroke compared to patients with NSTEMI and no AF (P<0.001).

After ACS, AF was also associated with increased hospital complications such as heart failure, acute mitral regurgitation, hypotension and cardiogenic shock. These results were consistent across the 10 trials included in this meta-analysis,(328) despite heterogeneous populations, subject ages, and prior risks factors. The prognostic significance of atrial fibrillation in patients with AMI treated with percutaneous coronary intervention (PCI) was evaluated by Kinjo et al. The main finding of this study was that the unadjusted in-hospital mortality rate was significantly higher in patients with AF than in those without AF. However, after adjustment for demographic characteristics and clinical factors, AF was not associated with increase in in-hospital mortality. Numerous confounders accounted for this result, including age, gender, diabetes mellitus, hypertension, previous MI, cerebrovascular disease, systolic blood pressure <100 mmHg, tachycardia, Killip class, multivessel disease and final TMI flow grade. This finding was similar whether AF presented during admission or developed during hospitalisation. This might be a reflection of the favourable impact of PCI on AF patients. Other in-hospital events

such as cardiogenic shock, congestive heart failure, ventricular tachycardia and fibrillation were significantly higher in AF patients. The adverse outcome in this study probably was not a function of AF per se but the company it keeps. In keeping with other studies, one year mortality was higher in AF patients regardless of other confounders. These results were consistent with another study by Asanin et al,(333) who found that heart failure mostly preceded the occurrence of new onset AF after AMI, but only late AF was independently related to long-term mortality. Such a result was related more to the duration and recurrence of atrial fibrillation which exceeded 22% rather than the first transient episode of AF during the acute phase of myocardial infarction.(333,334) In this study of patients with AF, 56% were found to have AF of >7 h duration. Characteristics such as age, previous MI, longer time to treatment and less frequent use of thrombolysis seemed to prolong AF. Furthermore, left atrial enlargement was found in these patients and it was correlated with previous MI, congestive heart failure and lower ejection fraction. Since left atrial dimension affects sinus rhythm, it appears that patients with left atrial enlargement are more likely to develop longer AF durations.

In summary, AF is an independent predictor of increased morbidity and mortality. In some studies, however, AF seemed to represent a surrogate marker of worse outcome.

1.9.3 AF and left ventricular dysfunction with acute myocardial infarction

AF and congestive heart failure (CHF) are commonly encountered together with a complex relationship which is more evident in the presence of ischaemic heart disease. AF and CHF share similar drug therapies and common mechanisms including myocardial fibrosis and impaired intracellular calcium regulation and neuroendocrine dysfunction.(232,312,313) It was found that post infarction HF was mostly followed by AF, and that HF was the most important predictor of AF. In the GUSTO-I trial,(320) patients with AF had larger infarction, more extensive coronary artery disease, poorer perfusion, and lower ejection fraction than those with normal sinus rhythm. Pedersen et al,(146) reported that 50% of patients with AF had left ventricular ejection fraction ≤35% compared with 30% of those without AF. Similar findings were found by Asanin et al.(335)

AF is also an ominous arrhythmia in heart failure disease patients with ischaemic heart disease. Pedersen et al,(314,336) analysed data of 6676 patients with AMI admitted to 27 centres in Denmark from 1990 to 1992 and screened for inclusion into Trandolapril Cardiac Evaluation (TRACE) study. In brief, patients with AMI, clinical data included presence of AF/flutter by ECG and complication during hospitalisation were prospectively collected. Left ventricular systolic function was determined by wall motion index by echocardiography. The relationship between AF/atrial flutter and mode of death were analysed over 4 years of follow-up. There was an excess mortality found in patients with AF/flutter following myocardial infarction. This was due to an increase in both sudden cardiac death (SCD) and non-sudden cardiac death (non-SCD). During follow-up, 1659 patients (34%) died, (50% with AF/AFL and 30% without, P< 0.0001). SCD occurred in 536, non-SCD occurred in 725 and 398 died of non-cardiovascular causes. The adjusted risk ratio of AF/AFL for total mortality was 1.33 (95% CI: 1.19-1.49; p<0.0001) and the risk ratio for SCD was 1.31(95% CI: 1.07-1.60; p<0.009). The adjusted risk ratio of AF/AFL for non-SCD was 1.43(95% CI: 1.21-1.70; P<0.0001). Previous studies on implantable cardioverter defibrillator (ICD) studies found that in both primary and secondary prevention of life threatening ventricular arrhythmia, AF patients not only received more inappropriate shock but also more often appropriate shocks.(315-317) In fact, AF begets ventricular tachyarrhythmia in ICD patients. In this population with ischaemia, the occurrence of ventricular tachycardia or fibrillation is facilitated by ischaemia via high ventricular rates and the irregular RR interval during AF. As a consequence, a short-long-short RR sequence occurs; a re-entrant ventricular arrhythmia may be initiated and maintained in a ventricular scar tissue from old myocardial infarction.

1.9.4 Management of atrial fibrillation during myocardial infarction

The occurrence of new AF during ACS represents high risk patients in which required rapid intervention. It affects the short-term outcome and also has implications for the long-term patient outcome as well. Our current therapy is limited by lack or inconsistency of data according to evidence-based medicine. There is only one study (The GUSTO-III experience)(337) which was conducted as prospective substudy of GUSTO-III. The aims of the study were to

evaluate the effect of different early therapeutic interventions for AF on the 30 day and one year mortality, including the use of drugs or cardioversion. Of 1138 study patients, 317(28%) received antiarrhythmic agents (AAD), including class I AAD (12%), sotalol(5)% and amiodarone (15%); electrocardioversion was attempted in 116(10%). Sinus rhythm was restored in 72% with class I AAD, 67% of those treated with sotalol, 79% of those receiving amiodarone, and 67% of those having electrical cardioversion. There was no difference among the treatment groups in the incidence of sinus rhythm at the time of discharge or before death. There was a trend towards lower mortality associated with the use of class I AAD and sotalol in managing patients with AF during AMI. In contrast, there was no association between the use of amiodarone or electrical cardioversion and 30 day or one year mortality. The investigators argued against comparing this result with the negative finding in CAST(338,339) (cardiac arrhythmia suppression trail), SWORD trial(340) (survival with oral d-sotalol trials), which investigated the use of class I AAD or sotalol in preventing ventricular arrhythmia. What they have shown was a potential benefit of this therapy in the short-term management of patients with AF during AMI, whilst no further benefit was observed after hospital discharge.

Restoration of sinus rhythm is probably the preferable strategy in the acute setting especially in haemodynamically compromised patients, with special attention to the patient blood pressure, and electrolytes. However, rate control is another acceptable alternative strategy with the use of β-blockers or digoxin. There is no available study or data comparing the prognostic significance of 'rhythm vs. rate control' strategy in the setting of AF complicating AMI. In addition to that, the data on anticoagulation is also limited but there is convincing evidence supporting that AF complicating AMI increases the risk of stroke during hospitalisation or follow-up.(320,341,342) The ACC/AHA/ESC 2006 guidelines (343) recommended the administration of unfractionated heparin in patients with AF and AMI, during the acute phase, aiming at a 1.5-2-fold increase in APTT (class 1, level C). Long-term anticoagulation is more problematic especially after PCI with or without AMI. The general consensus would be triple therapy (warfarin, aspirin and clopidogrel) for six weeks followed by OAC (INR 2.0-3.0) in combination with clopidogrel for 9-12 months. In a prospectively collective cohort study, Fenestrand et al,(344) used data from the register of information and knowledge about

Swedish heart intensive care admission (RIKS-HIA), a total of 6182 patients between 1995-2002 were studied. They investigated the prescription of oral anticoagulation (OAC) in patients discharged alive with AF after AMI and the influence of (OAC) treatment on 1-year mortality. The prescription of OAC was only in (30%) of AMI patients with AF, despite the fact that OAC was associated with a 29% relative and 7% absolute reduction in 1-year mortality after adjustment for confounding variables. This result was mainly caused by a reduction in fatal stroke. Patients undergoing PCI represent a high-risk population due to presence of ACS, age and comorbidities. A recent study by Ruiz-Nodar et al,(345) reported reduction in mortality and major adverse event (MACE) in patients with AF undergoing PCI. A total of 426 patients with AF undergoing PCI and stenting between 2002 and 2006 were studied. Of these drugs prescribed at discharge, aspirin and clopidogrel were used in 174 patients (40.8%) whereas more than 213 patients (50%) were discharge on triple therapy (aspirin, clopidogrel and warfarin). The incidence of adverse events was high (36.6%), with major bleeding in 12.3%, thrombo-embolic events in 4.2%, and MACE in 32.3%. All-cause mortality was high (22.6%). Among the patients treated with coumarins, there was a non-significant increase in major bleeding (14.9% vs.9.0%, P=0.19), but the beneficial effect of coumarins was confirmed by multiple regression analysis, where age and non-treatment with coumarins were the only independent predictors of MACE (log-rank test P=0.02) as well as a lower all-cause mortality (log-rank test P=0.02). The combination of coumarins plus aspirin after PCI is less effective than ticlopidine and aspirin in preventing stent thrombosis (346-348). Meanwhile, oral anticoagulation is superior to dual antiplatelet therapy with aspirin and clopidogrel in patients with AF to minimise risk of stroke (349). This might explain the reason behind triple therapy in patients with AF post PCI intervention. However, such a combination might increase the risk of bleeding.(350-352) In addition, the selection of therapy is usually challenged by several variables which influence the patient's outcome. The use of inotropic agents or development of valvular incompetence may further complicate our management.

1.9.5 Prevention of atrial fibrillation in the setting of AMI.

In the post-infarction setting, the initial success with restoration of sinus is good,(337,353) but the risk of AF recurrence is high (22.5%).(333) In addition to that, AF recurrence is not only associated with left ventricular dysfunction or congestive heart failure and advanced age, but also independently predicts in-hospital as well as long-term mortality. This explains why prevention of such an arrhythmia is important in high risk population with poor clinical condition.

The new therapeutic modality of AMI in terms of early reperfusion with PCI or thrombolysis and anticoagulation has reduced the likelihood of new incidence of AF and recurrence. In addition to that, the widespread use different drugs in ischaemic heart disease such as β-blockers, ACE inhibitor and AT II inhibitors have contributed to the reduction in developing AF. These drugs may act by modulation the ischaemic substrate on the ventricle or directly on the atria.

Antagonism of the renin angiotensin system (RAAS) has shown to reduce both the occurrence and relapse of AF. In the TRACE study,(146) 1,749 patients with left ventricular dysfunction after myocardial infarction were randomised to either trandolapril or placebo. Of the 1,577 in sinus rhythm at the start of the study, a total of 64 developed AF during a mean follow-up of three years. Out of these 64 patients, 5.3% were in the placebo group compared with 2.8 % in the trandolapril group($P<0.05$).The result was even higher in the SOLVD study,(147) when the risk of developing new AF was reduced by 78% with enalapril. The RAAS effect is very obvious in patients with heart failure and AF but such an effect was lacking in patients with AF and preserved left ventricular function. A recent meta-analysis included 11 randomised controlled trials of ACE inhibitors or ARBs for their efficacy in preventing AF.(354) The trial had included patients with MI, hypertension, or following cardioversion. The trials enrolled patients with MI revealed only significant relative reduction in the onset of AF, in the presence of left ventricular dysfunction. In addition to that, all the trials enrolled patients with heart failure showed significant reductions in AF, with a relative risk reduction (RRR) of 44%. However, in the post hoc analysis of the effect of ramipril on the incidence of AF in the HOPE study(355) (Heart Outcomes Prevention Evaluation) where patients with left ventricular ejection fraction <40 %

were excluded, ramipril did not affect the incidence rate of this arrhythmia. It is worth mentioning, this study was underpowered as the incidence rate of AF was low at 2.1%. Although it is beyond any dispute that ACE inhibitors or AT II receptor blockers have implications on atrial structural and electrical remodeling, it is still unclear such beneficial effect on AF with heart failure is due to their actual direct action of the arrhythmogenic substrate in the atria or due to the positive effect on LV remodeling and haemodynamics. Despite the fact, these were secondary analysis but the results are important as the reduction of new AF occurrence was associated with neutral or decreased mortality.

With class III AAD, amiodarone and dofetilide, the incidence of AF has been reduced by 51-70%(356,357). Such reduction with dofetilide was not significant in post-AMI patients with heart failure.

Finally, the beneficial role of carvedilol in prevention of AF in the context of AMI has been shown in two clinical trials. In the Carvedilol Post-Infarct Survival Control in the Left Ventricular Dysfunction (358)(CAPRICORN), a 59% risk reduction in the development of AF/AFL was seen in carvedilol versus placebo P<0.0003). Similarly, in COPERNICUS (Carvedilol Prospective Randomised Cumulative Survival), AF was reported more in placebo compared with carvedilol.
In summary, most of the new therapeutic modalities of AMI might have a positive impact on the incidence as well as prognostic significant of AF with AMI, either directly or via improving the outcomes of coronary artery disease by modulating the electrical or structural remodeling and the neurohumoral response.

1.9.6 Pathophysiology of atrial fibrillation during acute myocardial infarction

The mechanism underlying the genesis of AF during AMI is rather complex and multifactorial in aetiology. There are many causes for this arrhythmia in the setting of AMI. Atrial ischaemia is probably the main reason for AF occurring very early during the course of AMI. However, heart failure or left ventricular dysfunction is associated more with AF that occurs late during the infarct course. Other factors involved included pericarditis, valvular heart disease and drugs (especially inotropes). Hod et al,(359) studied the incidence of AF in the first hours of an

evolving MI. Out of 214 patients with AMI, only 7 (3%) developed within three hours of the onset of chest pain. In all cases of early AF, there were occlusions in both left circumflex proximal to the origin of the left atrial circumflex branch and right coronary artery and left circumflex proximal to the origin of the atrioventricular nodal artery. In another study by Kyriakidis et al,(360) found that in all patients with atrial tachyarrhythmia (12 out of 266) who subsequently underwent coronary angiography, the origin of the sinus node artery started just after an occluded right coronary or left circumflex artery or was involved in the occlusion. In agreement with the previous study, all patients had inferior AMI as well. In contrast, to the previous finding, Tjandrawidaja et al reported that compromised SA nodal or LCA arteries were associated with the development of early atrial tachyarrhythmia but not early VA block. Compared to patients without compromise, patients with a compromised atrial branch (at least one) sustained a higher incidence of both early arrhythmia (12.6% vs 4.3%; P=0.002). In contrast, a compromised AV nodal branch, which supplies the AV nodal predominantly, was associated with higher AV block (first degree: 6.8% vs 2.4%; P=0.037; second or third degree: 5.3% vs 1.2%; P=0.014). This result was consistent with James et al's,(361) post-mortem study from the prethrombolytic era in which infarction of the SA node was found in all 11 cases with AMI who developed atrial tachyarrhythmia. Atrial infarction whether it is on the right or left atrium has an important role in triggering and maintaining atrial tachyarrhythmia during acute myocardial infarction. In addition to that, the role of myocardial ischaemia in the genesis of atrial fibrillation was also demonstrated in animal models. These studies were limited as it was in vitro and lack the real interaction between ischaemia and the neurohumoral effect, namely the renin angiotensin and the autonomic nervous system. In a canine study,(362) Sinno and colleagues evaluated the role of atrial ischaemia in the promotion of AF. They induced atrial ischaemia by occlusion of a right atrial coronary artery branch. They observed that atrial ischaemia promoted the development of AF. These findings suggest that atrial ischaemia induces substrate that supports AF maintenance, and may be relevant to AF mechanism in association with coronary artery disease. The role of ischaemia in AF genesis has also been demonstrated in many human studies. For instance, Budeus et at,(363) examined the incidence of atrial late potential in patients with proximal stenosis of the right coronary artery. They also

investigated the anti-ischaemic effect of successful PCI of the right coronary artery. In that study, the stenosis of RCA was associated with atrial late potentials and successful PCI of the RCA eliminates pre-existent atrial late potentials and may reduce the risk of AF. Recent data has also shown induction of AF during balloon angioplasty of the right coronary artery and termination of AF after angioplasty perfusion of the occluded atrial branches.(364) In fact, transient ischaemia for less than even one minute will be long enough to cause mechanical as well as haemodynamic changes in both atria and ventricles. The left atrial tissue is more sensitive to hypoperfusion and ischaemia than the ventricular one, and haemodynamic as well as electrical changes will occur in response to such an insult. Left atrial response to myocardial ischaemia relies on location of the coronary artery lesions.(365,366) Left atrium maximal +dp/dt and contractility increase significantly in patients with left anterior descending artery lesions while patients with proximal left circumflex artery lesions had shown reduction on both LA maximal +dp/dt and contractility. A different pathological mechanism lies behind this disparity of response. Left atrial ischaemia is probably the most likely explanation for such a response as the left atrium receives its blood supply from the circumflex and right coronary artery.(367-370) Nevertheless, raised end diastolic pressures (left atrial stretch) may be the explanation for AF with left anterior descending artery occlusion. In addition, Ozmen et al,(371) have also demonstrated the effect of angioplasty balloon-induced ischaemia on atrial conduction abnormalities as estimated by P wave maximum and dispersion. The study enrolled 67 patients with single vessel disease (left anterior descending artery (LAD) in 28 patients, right coronary artery (RCA) in 22 patients, and left circumflex (LCX) artery in 17 patients. The P wave value at the baseline was not different among the three groups (LAD, LCX, and RCA). However, P dispersion and maximum was significantly higher in all three groups during the balloon occlusion compared to baseline ($P < 0.05$). This indicates that atrial ischaemia is not the only culprit factor of AF genesis during AMI, but it is rather interactive with autonomic factors, atrial stretch, and neuroendocrine response to initiate and sustain AF during AMI. At the ventricular level, many studies using various kinds of myocardial stretch, have been shown to induce ventricular arrhythmias due to the occurrence of transient depolarisations and shortening of the membrane action potential and refractory period.(91,372-376) However, few studies have

been performed to assess the actual role of mechano-electrical feedback in atrial tissue in humans. The onset of atrial tachyarrhythmia or fibrillation during myocardial infarction, thought to be related to elevated end-diastolic pressure, resulted in elevation of left atrial pressure which stretch atrial wall. Nevertheless, up to our knowledge, there is no study in humans which evaluated such a relationship. Moreover, there have been conflicting results on the effect of mechanical feedback on the electrical properties of the atrium. On many studies, the effect of atrial pressure on atrial refractoriness was assessed by varying the atrial-ventricular (AV) interval during sequential AV pacing. While Calkins et al found either a shortening or no change on atrial ERP, Zipes reported a prolongation of atrial ERP.(207,215-217) In contrast to human studies, the results were more consistent in animal model (210,211). These studies have shown that the mechano-electrical feedback is produced by activation of stretch activated channels, which can affect both the inward and outward ionic currents and lead to shortening of action potential duration, increasing automaticity and trigger activity(210,377,378). These electricals remodeling affect the pulmonary veins and would result in increased arrhythmogenic activity of the pulmonary veins and further induce ectopic firing from pulmonary veins that may contribute to the genesis of AF.

Finally, the renin-angiotensin system might play some role in AF genesis and sustainability as well, in particular, AT II which promotes atrial fibrosis and mitogen activated protein kinase(172). This might explain the reduction in incidence rate of late onset AF with the use of ACE inhibitor or ATII receptors blockers, especially in the context of heart failure as previously stated. These agents also reduce left atrial filling pressures and ventricular wall stress which in turn decrease left atrial dimensions.

In summary, atrial ischaemia and acute atrial stretch interact with other modulators to generate AF during AMI.

Chapter 2

Impact of Coronary Artery Intervention on the Incidence and Prognosis of Atrial Fibrillation after Acute Myocardial infarction: A Systematic Review

2.1 Introduction

Atrial fibrillation (AF) commonly complicates acute myocardial infarction (AMI) with incidence rate of 6-21% of cases.(318,320,325,333,379) In this setting, AF is associated with increased risk of adverse out-come during hospitalisation and long-term follow up. This adverse prognostic implication is particularly high in patients with MI and depressed left ventricular dysfunction.(380)

Over the last 3 decades, there have been many medical and interventional modalities that have revolutionised the management of acute myocardial infarction. In particular, advancement in thrombolysis and percutaneous coronary intervention (PCI) has made it possible to treat patients with AMI successfully with reduced mortality and morbidity.(381) The Heart Institute of Japan Acute Myocardial Infarction registry revealed that AMI patients in the era of acute revascularisation have favourable long term prognosis.(382) In addition, investigators from GRACE (the Global Registry of Acute Coronary Events) also found an increase in use of established medical interventions including angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), B-blocker and statin which has also been associated by significant decreases in the rate in-hospital death, cardiogenic shock, and new MI among patients with non-ST-segment elevation myocardial infarction (non-STEMI).(383)

While there is established evidence on the favourable outcome in AMI patients treated during the interventional era (1990s-2000s), whether such intervention has had any impact on AF incidence and prognosis after AMI during the last 3 decades remains unknown.

2.2 Methods

Using the key words “Myocardial Infarction” and “Atrial Fibrillation” and “Incidence” or “Prognosis”, Pub Med, Scopus and Medline were searched for prospective cohort and case control studies that conducted between 1980 and December 2010 (Figure 1). In addition, this search was supplemented by hand-searching of bibliographies of published studies. Studies with new onset AF after MI were included in this meta-analysis. Studies which did not differentiate between new onset AF and pre-existing one were excluded from the study. AF and myocardial infarction definition was used according to the definition during this time. Individual case report, editorial, and literatures review were excluded from the study. Studies in language other than English were also excluded from the study. The studies which had enough data such as standard deviation and confidence intervals were included in the results of each end point (AF incidence, patients’ age and overall long term mortality) (Figure 1).The resultant citations were reviewed independently by 2 researchers.

2.3 Statistical Analysis

Overall analyses evaluated both Fixed Effect Model (FEM) and Random Effect Model (REM) to assess effect size magnitude. Fixed effect result was presented for homogenous data across the studies and REM used for heterogeneous studies. Mean differences were calculated for continuous variables and risk ratio for dichotomous variables. For each mean and risk difference, 95 % confidence intervals were evaluated. Homogeneity was assessed using I^2 statistic.

2.4 Results

Out of 472 studies, only 49 studies met the inclusion criteria including 9, 25 and 15 studies represented each progressive decade of the analysis (figure 1).

The overall incidence of new-onset AF post AMI was 10.8% for the entire period (7.8 -18%; figure 2). The incidence rate of new onset AF declined over the 3 decades [p<0.001, 95%CI (0.086-1.0)] figure 2; being 13.7% in the 1980's, 10.5% in the 1990's and 9.6% in the 2000's.

New onset AF post MI remains a significant risk for all cause and cardiovascular mortality throughout the last three decades [pooled RR 2.5, 95% CI (2.04-2.89)] (figure 3); and the strength of association has not changed over time (p=0.42) (figure 3).

Although AF patients were older than non-AF patients over the entire period of the studies, there was no difference in patients' age when comparing AF patients over the last three decades (figure 4).

2.5 Discussion

This meta-analysis highlighted important findings that the incidence of new-onset AF after MI has declined over the last three decades. However, the prognostic impact of AF after MI has remained unchanged.

Although AF in the community continues to increase in frequency,(5,384) the incidence rate of AF after myocardial infarction is declining. In the current study, there was a significant reduction in AF incidence when comparing the pre-thrombolytic era (1980s) against thrombolytic (1990s) or percutaneous coronary interventional (PCI) era figure. The reduction in AF incidence rate post MI is probably a reflection of our advancement in all aspects of cardiology; pharmacotherapy and intervention therapy.

There are several mechanisms by which MI can result in the substrate for AF. These include atrial ischaemia or infarction, inflammation, electrolyte imbalance, haemodynamic instability due to left ventricular dysfunction, atrial stretch and neurohumoral activation.(385-388)

The extensive usage of beta-blocker, renin-angiotensin blocker drug, statin and other upstream therapies may have had a beneficial effect on the incidence of AF after MI by modifying the underlying etiological factors for AF.(331) Several studies have shown the early introduction of beta-blockers after MI will limit the extent of myocardial injury and improve survival.(331,389)

In the Carvedilol Post-Infarct Survival Control In the Left Ventricular Dysfunction study (CAPRICORN),(358) a 59% risk reduction in the development of AF/AFL was seen in carvedilol group versus placebo P<0.0003). Similarly, in COPERNICUS (Carvedilol Prospective Randomised Cumulative Survival), AF was reported more in placebo compared with carvedilol group.(390)The mechanisms for the favourable effects of β-blockers include blocking myocardial sympathetic activation, reducing the heart rate and the blood pressure and changing the natural history of myocardial tissue remodeling. Recent studies have shown that B-blockers also reduced the incidence of arrhythmias after AMI.(391) Antagonism of the renin angiotensin system (RAAS) may reduce the occurrence and relapse of AF after MI.(146,329,392,393) In the TRACE study,(146) 1,749 patients with left ventricular dysfunction after myocardial infarction were randomised to either trandolapril or placebo. Of the 1,577 in sinus rhythm at the start of the study, a total of 64 patients developed AF during a mean follow-up of three years. Out of these 64 patients, 5.3% were in the placebo group compared with 2.8 % in the trandolapril group (P<00.05). The RAAS effect is very obvious in patients with heart failure and AF but such an effect was lacking in patients with AF and preserved left ventricular function.(354) Statin therapy has also been implicated in the declining of AF incidence after coronary artery disease.(394) Statin possesses many properties, which might contribute to its effect on AF incidence after MI such as anti-inflammatory, anti-sympathetic and direct antiarrhythmic through cell membrane ion channels stabilisation.(395-397)

Atrial ischaemia or infarction has been reported to result in electrical and structural remodeling of the atria; both established precursors for development of AF.(1,362) Indeed we have recently observed that atrial branch artery disease was more frequently associated with the development of AF after acute coronary syndrome.(385) Early reperfusion with thrombolytic therapy and primary percutaneous coronary intervention may reduce the atrial insult and account in part for this declining in AF incidence. It also has been shown to reduce P wave dispersion and duration indicating reduced conduction abnormalities.(398)The decline in the incidence of AF after MI has previously been reported with the advent of thrombolytic therapy.(327) To our knowledge, there has been no study that measures the impact of primary PCI on the incidence of AF after AMI. Primary PCI is superior to thrombolytic in terms of

perfusion rates, reducing the risk of recurrent ischaemia and infraction and improving the prognosis in patients with ST-segment elevation myocardial infarction.(399-401)Therefore, PCI may additionally contribute to this declining in AF incidence post AMI but further study is required to assess such finding.

The other important finding in this study is that despite the declining in AF incidence after MI, its adverse prognostic impact has not changed over time. In fact, the risk of death in patients with AF post MI in our study was more than 2.5 folds higher than patients with MI and no AF throughout the last three decades until 2010.

Although previous studies have confirmed the unfavourable outcome of new- onset AF patients post MI, whether AF is independently predictor of such outcome remains conflicting.(325,402-406) Studies in pre-thrombolytic era revealed that AF is not associated with poor short or long term outcome after adjusting to other clinical variables,(332,403) however, many studies in reperfusion era (thrombolytic or PCI) shown that AF is independently predictive of worse short and long term prognostic outcome. (320,321,325,328,406) Our study provides further insight to the adverse prognostic significance of AF throughout the last three decades. The conflicting results in prognosis of new onset AF after MI between studies in pre-thrombolytic and thrombolytic era may be related to the fact that more serious clinical variables, such as poor LVEF and re-infarction, were associated with new onset AF in pre-thrombolytic era compared to interventional era. These are powerful clinical variable which might conceal the impact of AF as independent predictive of poor outcome.(320,325,332,337,403,406)

2.6 Conclusion

The incidence of AF post MI is declining due to early and aggressive reperfusion therapy; however, its poor prognostic significance has not changed. It highlights the importance for aggressive management of patients who develop AF after AMI.

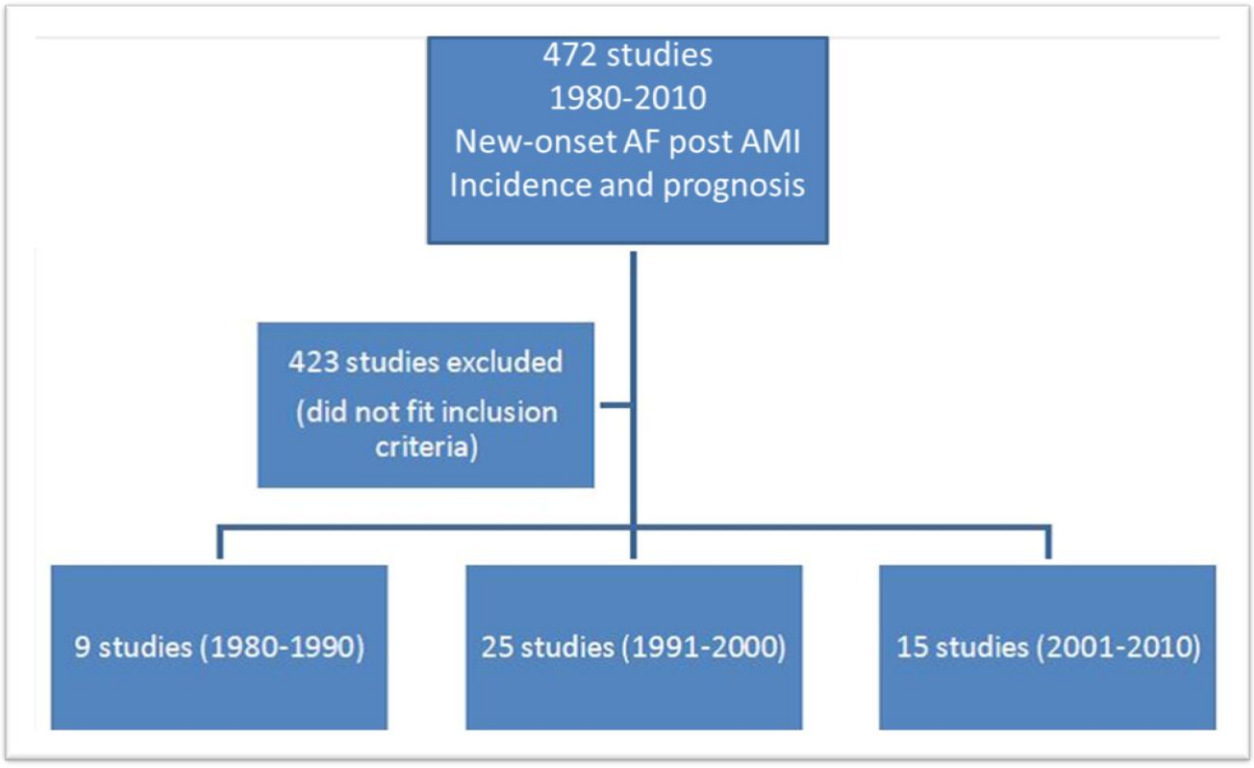


Figure 1. Study design. Studies with only new onset AF after acute myocardial infarction and in English language were included this meta-analysis. Case report, literature review and studies were also excluded from meta-analysis.

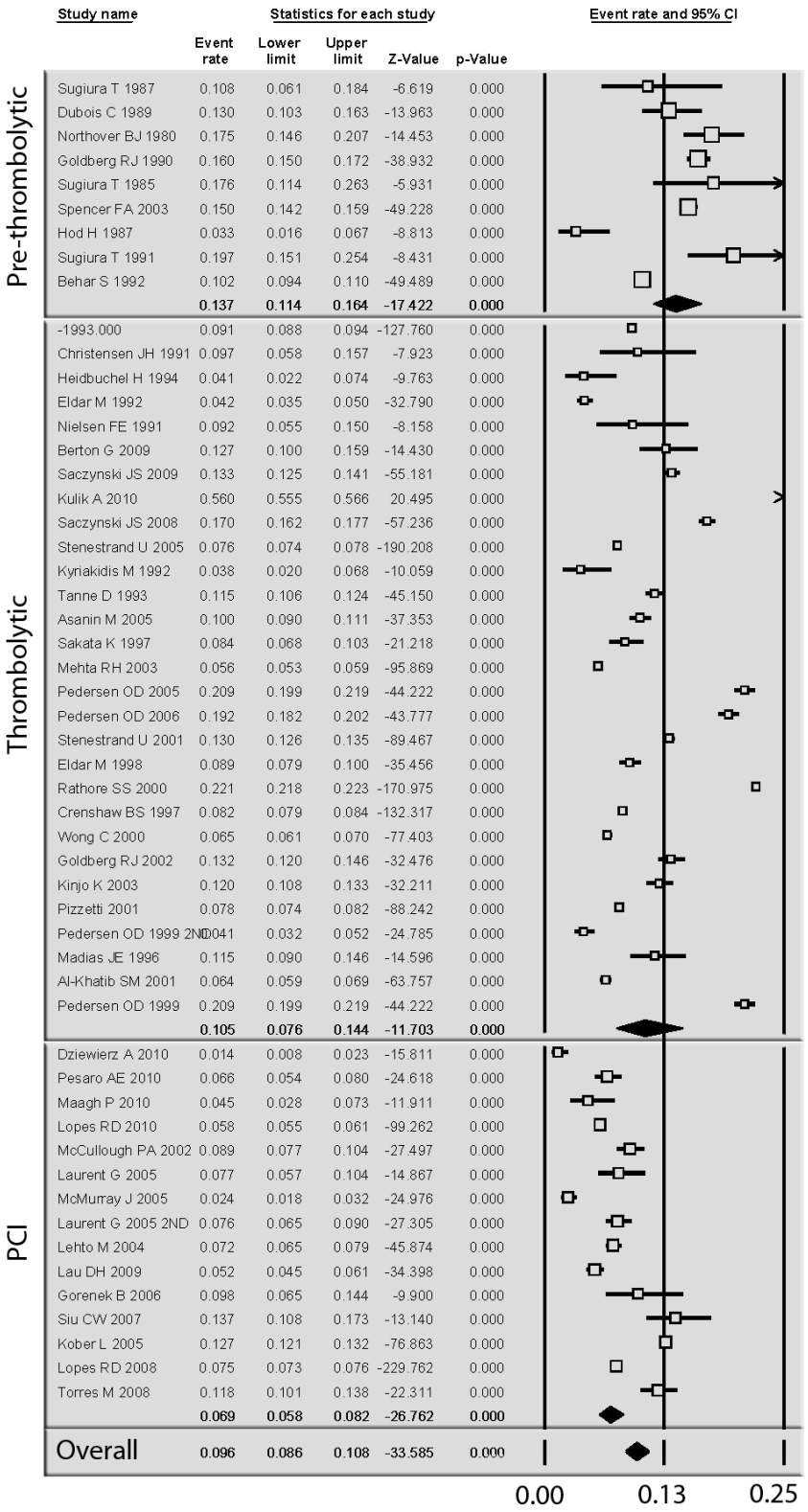


Figure 2**.** AF incidence after MI. Declining incidence of AF after MI over the past three decades {P<0.001, 95% CI (0.086-1.00)}.

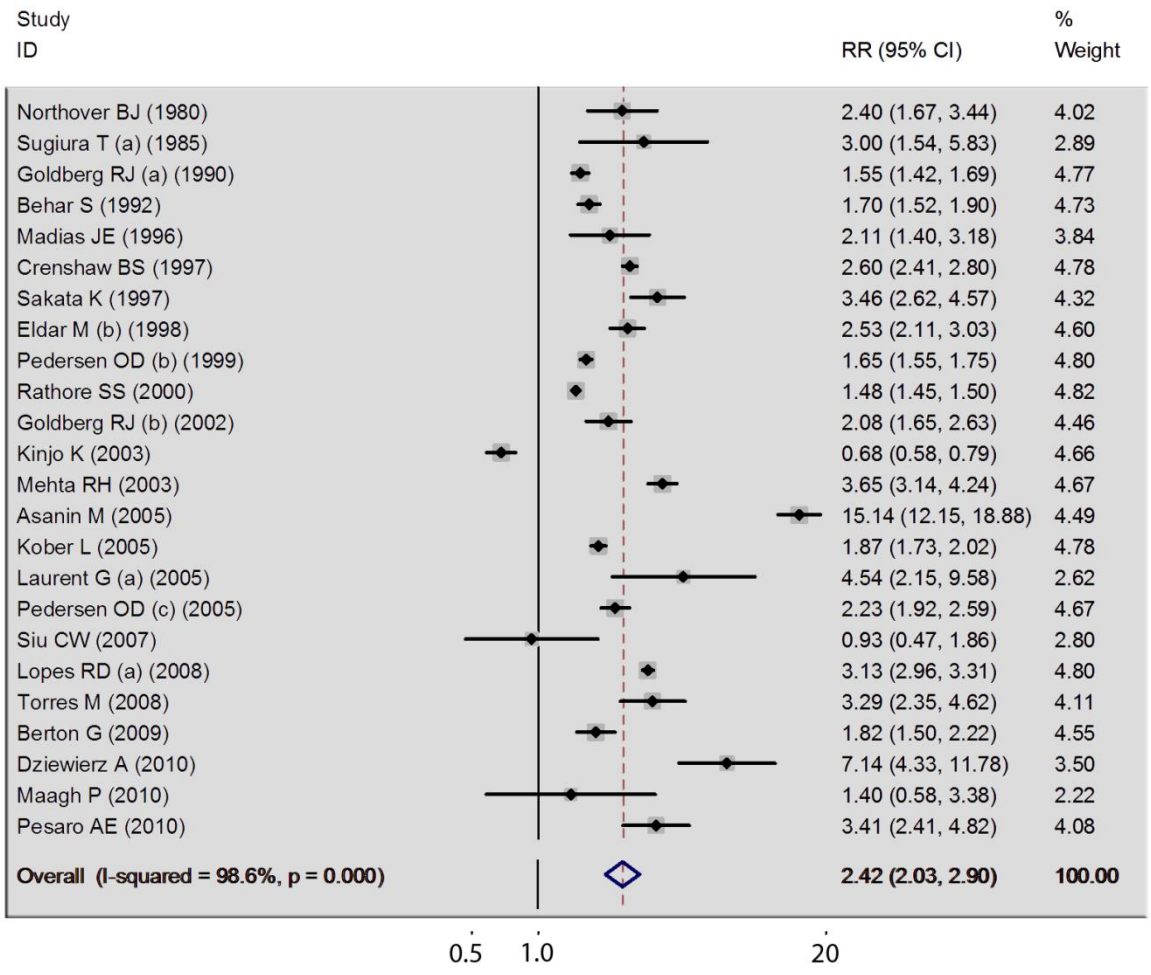


Figure 3**.** AF and mortality post MI. AF post MI remains a significant risk factor for all cause and cardiovascular mortality (pooled RR 2.5, CI 95% 2.04 -2.89). However, the Strength of association between AF post MI and death has not changed over time (p 0.5). The studies with sufficient data (standard deviation and confidence intervals) for statistical analysis were included in figure.

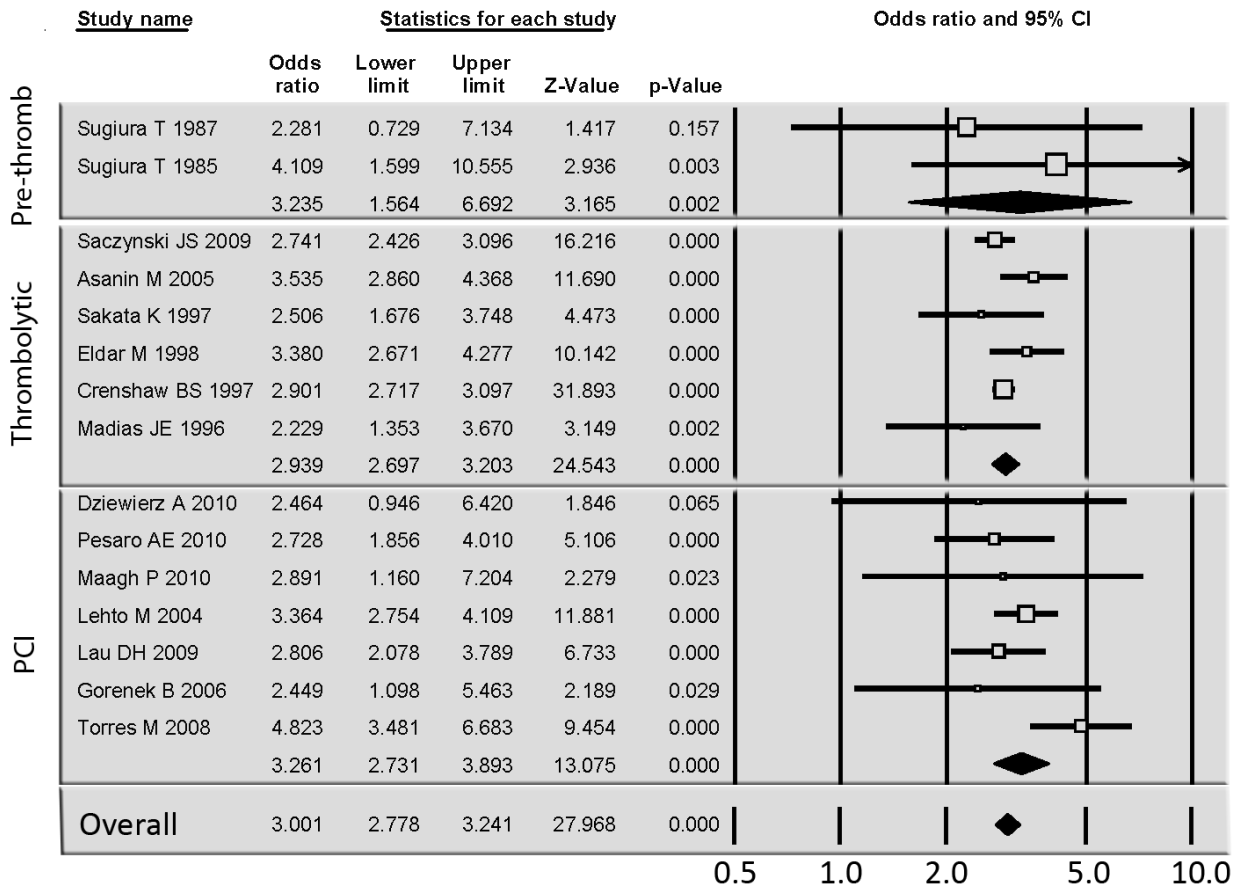


Figure 4**.** Age difference between AF and non AF patient post MI**.** AF patients were older compared to non AF patient throughout the three era (mean ± SD, 71 ±1 vs 67± 4, p=0.005).

A fewer studies was analysed in this figure due to insufficient data in the original studied.

Chapter 3

Myocardial Infarction and Atrial Fibrillation: Importance of Atrial Ischaemia

3.1 Introduction

Atrial fibrillation (AF) remains a common problem in the setting of myocardial infarction (MI) despite the increasing use of early reperfusion strategies.(318,320,321,342,407) When AF occurs after MI, it tends to recur in more than 20% during late follow up.(333,342) Although the prognostic significance of AF after MI is well established,(146,318,320,325,407) the mechanism for this heightened risk of AF is not fully understood. The relative contribution of atrial ischaemia, ventricular dysfunction, haemodynamic changes and neurohumoral abnormalities to the development of AF after MI has not been evaluated.

The role for atrial ischaemia or infarction in the pathogenesis of AF after MI has been suggested.(362) Atrial infarction has been observed in 17% of MI patients in a large post-mortem study.(408) The increased risk of atrial tachyarrhythmia in patients with atrial infarction has previously been described.(361,409) In a post-mortem series, James et al demonstrated that atrial infarction was present in all MI cases that developed atrial tachyarrhythmia. The human left atrium gets its blood supply from the sino-atrial branch which arises from the right coronary artery in 50-60% of the cases or the left circumflex artery in 40-50% of the cases.(368) In addition, there are LA branches which arise from the proximal part of the left circumflex artery. Coronary artery disease involving the atrial branches is associated with higher incidence of new onset AF after MI.(359-361,385)

In sheep, the circumflex coronary artery (LCX) is the dominant coronary arterial supply to the atria. In contrast, while the left anterior descending (LAD) supplies an equivalent extent of the ventricular myocardium it does not have a major contribution to the atria.(410) This anatomic difference in blood supply provides a unique model to evaluate the role of atrial ischaemia or

infarction. Therefore in the current study, we induced acute MI in an ovine model to understand the mechanism by which MI results in the substrate for AF. In particular, by evaluating the differences in LCX and LAD infarction, we aimed to determine the contribution of atrial ischaemia/infarction in creating the substrate for AF while controlling for other perpetuators associated with MI such as atrial stretch, haemodynamic change and neurohumoral activation.

3.2 Methods

Forty-four Merino-Cross Wethers with a weight of 56±8 kg were studied (figure 1). Following acclimatisation, animals were allocated to either MI (equally with LAD and LCX occlusion) or control (Sham operated) group. All procedures were conducted in accordance with the guidelines outlined in the "Position of the American Heart Association on Research Animal Use" adopted on November 11, 1984 by the American Heart Association. Approval for the performance of the study was provided by the Animal Ethics Committees of the University of Adelaide and SA Pathology, Australia.

3.2.1 Study Protocol

All procedures were performed under general anaesthesia. Sodium thiopental (15-20mg/kg) was used for induction to facilitate endotracheal intubation and isoflurane (2-4%) in 100% oxygen was used for maintenance. Invasive blood pressure, heart rate, LA pressure (LAP), end-tidal CO_2, oxygen saturation and temperature were continuously monitored throughout the study protocol.

3.2.2 Myocardial Infarction

MI was induced by first cannulating the left coronary system using a 7F guiding sheath (AL1; Boston Scientific, USA) and then inflating of a percutaneous coronary angioplasty balloon (Voyager NC, Abbott group). In each case the procedure was performed percutaneously through the femoral artery. The angioplasty balloon was sized and inflated to achieve a total occlusion of either the left anterior descending artery (LAD) or left circumflex artery (LCX)

vessels. Eleven animals developed early fatal arrhythmia without completion of the study duration that precluded collection of electrophysiological data; these animals were excluded. The remaining animals were equally divided into those undergoing occlusion of the proximal LCX (n=11; to induce left atrial ischaemia/infarction in addition to left ventricular infarction) and occlusion of the proximal LAD (n=11; left ventricular infarction with no atrial ischaemia/infarction). The angioplasty balloon was kept inflated for 45 minutes and acute ischaemia was confirmed on surface ECG with ST-segment elevation. A further 11 animals served as sham-operated controls undergoing the identical protocol without MI induction.

The left ventricular ejection fraction was assessed using transthoracic echocardiography at the baseline and 30 minutes following balloon inflation. The presence of infarction was identified by staining with TTC (2, 3. 5 Triphenyl tetrazolium chloride) as previously described.(411-413)

3.2.3 Electrophysiology study

Open chest electrophysiological studies were performed via a midline thoracotomy. Using a limited pericardiotomy, a custom designed 64-electrode epicardial plaque with 5mm inter-electrode distance, was applied to the LA. Surface-ECG and overlapping bipolar electrograms were continuously monitored and stored for off-line analysis using a computerised recording system (LabSystem Pro, Bard Electrophysiology, Lowell, MA, USA). Electrograms were filtered from 30-500Hz, and measured with computer-assisted callipers at a sweep speed of 200mm/s. Electrophysiological evaluation was performed at 15 minute intervals until the termination of the procedure. The following parameters were determined at each time point.

3.2.3.1 Atrial refractoriness

Left atrial ERP was measured by pacing from one pre-specified corner of the plaque at twice the diastolic threshold at two cycle lengths (CL; 400 and 250ms). A single extrastimulus (S2) was introduced after 8 basic stimuli (S1) starting with a coupling interval of 300-ms and reducing in 10-ms decrements until loss of capture. Atrial ERP was defined as the longest S1-S2 interval not resulting in a propagated response. The ERP was measured three times at each CL at each time

point, and if the maximum and the minimum amounts differed by >10 ms, two additional measurements were taken and the total averaged.

3.2.3.2 Atrial conduction

Conduction was assessed during stable S1 pacing at cycle lengths of 400 and 250ms. Activation maps were created using semi-automated custom made software, as previously described.(414,415) Each annotation was manually verified with the local activation time annotated to the peak of the largest amplitude deflection on bipolar electrograms. Local conduction velocity was calculated from the local vectors within each triangle of electrodes as previously described.(414,415) A mean conduction velocity can then be derived for each activation map.

Conduction heterogeneity was assessed using established phase mapping technique during S1 pacing.(416) In brief, the largest activation time difference between every four adjacent electrodes was first determined and divided by inter-electrode distances. The largest value at each site was then used to create a phase map, with values also displayed as a histogram. Absolute conduction phase delay was calculated by subtracting the 5^{th} from the 95^{th} percentile of the phase-difference distribution (P_{5-95}). The conduction heterogeneity index (CHI) was then calculated by dividing the absolute phase delay by the median (P_{50}). The CHI is used to evaluate the heterogeneity in conduction in the atrial tissue.

3.2.3.3 AF vulnerability

The inducibility and duration of AF was evaluated using extra stimuli program during atrial ERP testing at cycles lengths of 400 and 250 ms. Induced AF episodes were carefully documented with percentage of inducibility taken as the number of AF episodes over the total number of S1-S2 drive trains delivered. AF was defined as a rapid irregular atrial rhythm of ≥2s. Mean duration of AF episodes were derived from the average of all induced AF episodes in in each group. Sustained AF was defined as arrhythmia of >10 minutes duration. If AF was sustained, no further data was collected.

3.3 Statistical analysis

All continuous variables are reported as mean±SD and assessed for normality utilizing the Shapiro-Wilk test. To compare changes in the outcome measures between the three treatments groups a linear mixed effects model was fitted to the data. In the model, treatment group, time and the interaction between treatment group and time were fitted as fixed effects while animal was fitted as a random effect. Kruskal-Wallis test was used to compare AF duration between the groups. Negative binomial regression was used to compare AF incidence between the groups. Statistical significance was established at $P<0.05$.

3.4 Results

Eleven animals were excluded from the analysis due to fatal arrhythmias before completion of the study protocol. A total of 33 animals were studied in the following groups: LCX occlusion (n=11; ventricular and atrial ischaemia/infarction); LAD occlusion (n=11; ventricular infarction alone); and CTL (n-11; sham operated; Figure 1). TTC staining demonstrated that the LCX and not the LAD group or the controls had atrial infarction (LCX 11 vs. LAD 0 vs. CTL 0; $p<0.05$).

3.4.1 Haemodynamic and heart rate changes

Figure 2 demonstrates the haemodynamic changes seen in each group. There was no significant difference between the groups in mean arterial blood pressure (MAP) over time. The LVEF was similar between the groups at baseline (LCX vs. LAD vs. CTL: 60±4 vs. 61±3 vs. 62±5%, p=ns). There was a significant reduction in LVEF in the MI groups 30 minutes post balloon inflation compared to CTL (LAD 37±2.7% [P=0.0002]; and LCX 36± 4% [P=0.0001]); however, there was no significant difference in LVEF between MI groups (P=0.2). In keeping with reduction of LVEF, there was significant increase in LAP in MI groups compared to CTL (LCX: $P<0.001$; and LAD: $P<0.001$; Figure 2A). Importantly, this increase in LAP demonstrated no difference between the LCX and LAD groups (P=0.2).

There was no difference in heart rate between the groups at baseline (P=0.6; Figure 2B). However, with MI, animals in both MI groups became more tachycardic compared to CTL at 30 minutes post balloon inflation (LCX vs. CTL [p= 0.02]; LAD vs. CTL [p=0.03]). There was no significant difference in heart rate between LCX and LAD over time (P=0.5).

3.4.2 Atrial electrical changes due to MI

3.4.2.1 Effective Refractory Period

The left atrial ERP shortened in both MI groups compared to CTL (P=0.004); however, there was no significant differences between the MI groups (P=0.6). The reduction in ERP was observed as early as 15 minutes but became statistically significant 30 minutes after MI (figure 3).

3.4.2.2 Conduction velocity

Figure 4 demonstrates representative examples of activation maps in each group. Activation contours drawn at equal time intervals highlight areas of isochronal crowding. This figure demonstrates that while there are some changes observed in the LAD group, the most marked impact on conduction was in the LCX group.

With MI there was a reduction in atrial conduction velocity (Figure 5). Left ventricular infarction alone, as observed in the LAD group, induced a modest but significant change in conduction compared to CTL (P=0.01). However, with additional atrial ischaemia as observed in the LCX group, there was marked and progressive slowing of conduction compared to LAD (P<0.001) or CTL (P<0.001).

There was also evidence of significant increase in conduction heterogeneity as reflected by the absolute range of conduction phase delay (p5-95, expressing the total range in maximal differences in activation time) and the CHI (to express the heterogeneity of conduction, overall mean P5-95/P50) (Figures 6). The absolute range of conduction phase delay was increased in the LCX group compared to LAD (P<0.001) or CTL (P<0.001; Figure 6A). The CHI was markedly increased in the LCX group compared to LAD (P<0.0001) or CTL (P<0.001; Figure 6B). There

were no differences in these parameters of conduction heterogeneity over time in the LAD and CTL groups.

3.4.3 AF vulnerability

Figure 7A demonstrates the number of AF events in each of the groups. The AF incidence rate ratio (IRR) was significantly higher in LCX compared to LAD (LCX vs. LAD, IRR 6 [2-18], P=0.001) or CTL group (LCX vs. CTL, IRR 12 [3.26-44.14], P<0.001). In contrast, there was no significant differences in IRR between the LAD and CTL groups (IRR 2 [0.47-8.5], P=0.4). In addition, when AF developed it persisted for a significantly longer duration in LCX group compared LAD or CTL groups (p<0.05; Figure 7B). Three (27%) in LCX groups developed sustained AF while this was not observed in the other groups.

3.5 Discussion

This study provides new information on the relative contribution of atrial ischaemia/infarction to the development of the substrate for AF associated with MI. Using the ovine coronary circulation, that has differential blood supply to the atria (supplied by the LCX) but equal supply to the ventricle from the LAD and LCX, it demonstrates that:

1. Atrial ischaemia is the important determinant for the development of the AF substrate during MI. This is characterised by slowed and heterogeneous conduction. These abnormalities were independent of left ventricular function or the haemodynamic changes that occur during the acute phase of MI. As a result of these abnormalities, not only was AF more frequently induced but more frequently became sustained.
2. Acute MI, independent of atrial ischaemia, results in significant haemodynamic changes and atrial stretch. These factors were associated with the abbreviation of ERP but only modest change in the conduction properties of the atria.

Although the incidence of AF and its prognosis after MI has been extensively studied,(146,318,320,325,379,407) data on AF pathophysiology after MI is limited.(362) To our

knowledge, no prior study has evaluated the relative influence of factors associated with acute MI that contribute to the AF substrate.

3.5.1 Ventricular Infarction, atrial stretch and the haemodynamic changes

Ventricular infarction in both LCX and LAD groups resulted in comparable moderate LV dysfunction with similar changes in heart rate and blood pressure with early and persistent rise in LA pressure. As such, the electromechanical response to ventricular infarction would be of a similar intensity in both groups. This was associated with equivalent significant reduction in ERP in both MI groups. In addition, the acute LA stretch resulted in a modest slowing in conduction velocity (with proximal LAD occlusion). These findings are consistent with previous animal studies showing that electromechanical feedback is produced by activation of stretch activated channels, which can effect both inward and outward ionic currents and lead to shortening action potential duration, increased automaticity and trigger activity.(210,377,378) Shortening of the action potential and/or ERP has also been demonstrated in the ventricles.(91,372,417) However, other studies in human or dogs have provided conflicting results on the effect of acute pressure or volume load on atrial refractoriness, attributed as the means of causing stretch or the degree of stretch.(215,216) The acute LA stretch with associated neurohumoral changes resulted in abbreviation of atrial ERP and may partially explain the increased inducibility of AF observed with ventricular infarction alone.

3.5.2 Atrial Ischaemia or infarction

LA ischaemia/infarction due to occlusion of proximal LCX artery resulted in profound slowing in conduction velocity with increased areas of isochronal crowding and marked increased in heterogeneity in conduction, all established pre-requisites for the development of re-entry and AF.(362) Sinno and Nattel have previously observed similar findings when targeting isolated atrial branches. (362)While clinically isolated atrial branch occlusion is rare, the findings of the current study, mimicking the clinical scenario, confirm the importance of atrial ischaemia in the development of the AF substrate. AF after MI tends to recur in more than 22% of the cases during late follow up.(333,342) While left ventricular dysfunction is strongly associated with

development of AF recurrence after MI,(333) some studies have shown AF recurrence post MI was independent of LV dysfunction.(342) Furthermore, patients post MI with atrial structural abnormalities such as enlarged LA, have increased propensity for AF recurrence. In a canine model of chronic (>7 days) coronary artery occlusion, Nishida K et al, found that stable re-entrant sources at the border of atria infarcted area was associated with significant peri-infarct fibrosis.(418) Atrial fibrosis is likely an important factor in stabilizing re-entry and promoting AF. Acute atrial ischaemia together with LA stretch synergistically interacts resulting in significant slowing in conduction velocity and marked increase in conduction heterogeneity as observed in LCX group. These electrophysiological changes are consistent with previous observations at the ventricular level.(419,420) In addition, the significant reduction in atrial ERP observed with AMI is consistent with observations by Jayachandran et al.(142) However, the reduction in ERP in the current study was equivalent and persistent in both LCX and LAD group suggesting that it was more likely due to LA stretch and the associated haemodynamic and neurohumoral changes associated with MI rather than due to atrial ischaemia per se.

3.5.3 Mechanisms of ischaemia related atrial changes

The major pathophysiological conditions resulting from acute MI are elevated extracellular potassium, acidosis and anoxia. These changes lead to reduction in membrane excitability, shortening of action potential duration (APD) and prolongation of recovery of excitability following an action potential.(421,422) It is difficult to determine the ionic mechanisms of the electrical changes, and the contribution of each pathophysiological condition to each electrical change. However, using an ionic-based theoretical model of cardiac ventricular cells exposed to the above pathological conditions (elevated [K]o, acidosis and anoxia), Shaw et al found that the depression of membrane excitability and delayed recovery of excitability caused by elevated $[K]_0$ with additional excitability depression by acidosis .(422) In addition, the major changes in action potential duration (shortening) can only be explained by anoxia-dependent opening of $I_{K\,(ATP)}$.

3.5.4 Clinical Implication

Atrial ischaemia or infarction with increased LA pressure plays an important role in LA electrical changes that promotes AF occurrence during the acute phase of MI. It is likely that such changes may be responsible for the late and significant recurrences of AF after MI. Recent clinical data has suggested the importance of atrial branch compromise in patients with coronary artery disease as an important determinant of developing AF.(385) Given the paroxysmal nature of AF after MI with usage of dual antiplatelet therapy in patients with coronary stenting, oral anticoagulation has been underutilised in this population.

The drug efficacy in treating AF may be related to the underlying mechanisms.(423) In experimental models, class III antiarrhythmic- drugs are more effective in AF associated with structural remodeling than in atria remodelled by sustained atrial tachycardia. Likewise beta-blockade and calcium channel blockers inhibit the arrhythmogenic consequences of acute atrial ischaemia, whereas Na^+ channel or K^+-channel blockers are ineffective.(424) In addition, other studies have also shown the favourable effect of early coronary reperfusion on AF incidence post MI which may in part be explained by reduced the total ischaemic burden at both the ventricular and atrial level.(385,425) Atrial ischaemia or infarction is rarely considered as a direct contributor to the development of AF after AMI. This study showed the direct relation between AF and atrial infarction. Moreover, the efficacy of different anti-arrhythmic drugs may be related to the underlying substrate with the potential therapeutic implications of AF mechanisms related to acute atrial infarction.

3.6 Study limitations

This study evaluated the changes in the atrial electrical changes during the initial 45 minutes of MI. The impact of neurohumoral factors have not been fully evaluated in this study. Finally, this is an ovine model with MI induced by balloon inflation in the coronary arteries; the pathogenesis of MI in humans is the result of plaque rupture and thrombosis which might imply a different cardiovascular response**.**

3.7 Conclusion

The pathophysiology of AF after MI is multifactorial but atrial ischaemia has dominant role in the development of the substrate for AF.

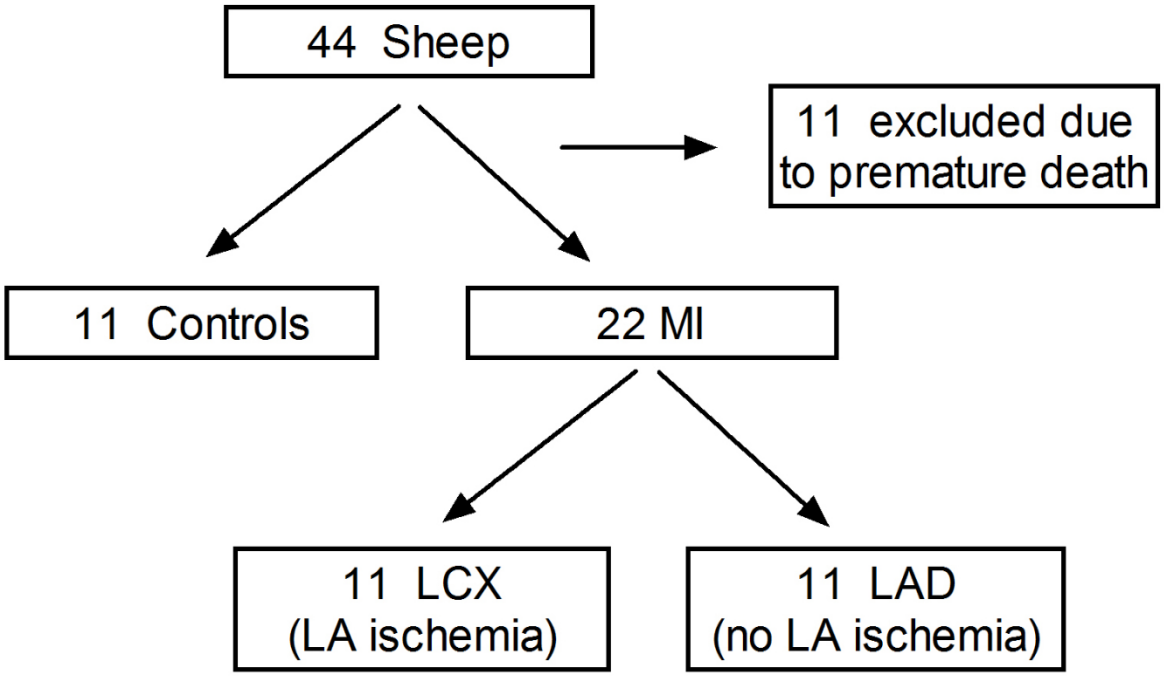
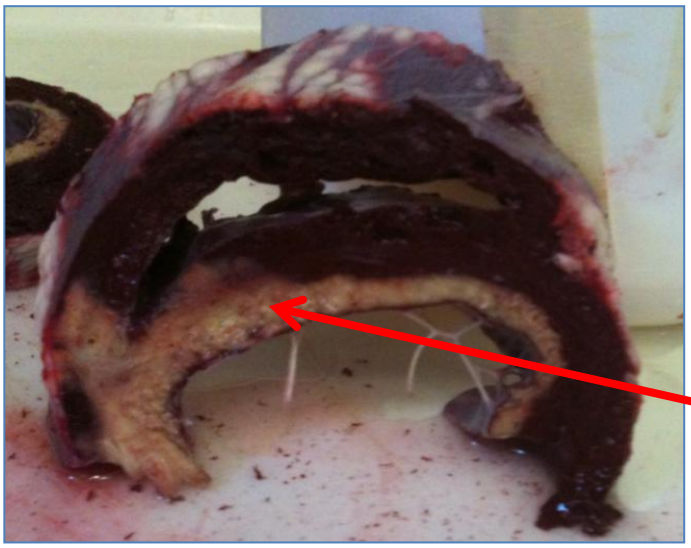


Figure 1**: (A)** Summary of the study design.



(**B)** Infarcted tissue (red arrow) in left anterior descending artery territory (LAD) highlighted using TTC staining.

Figure 2A. Haemodynamic changes over 45 minutes post infarct.

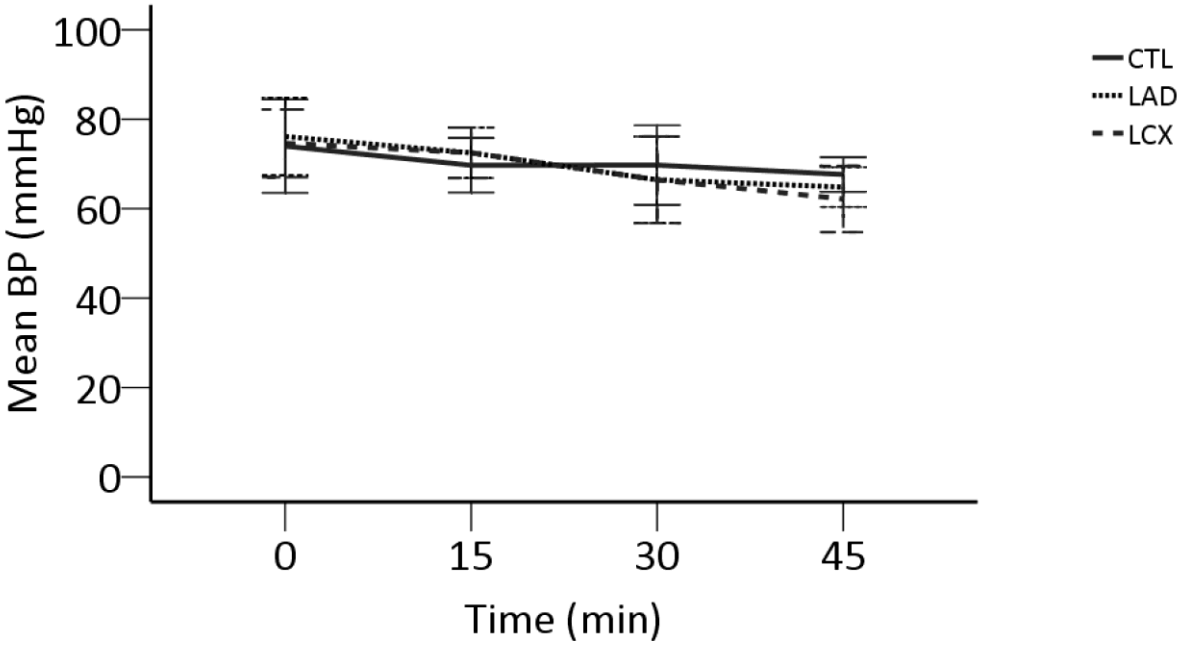


Figure 2**: (A)** Haemodynamic changes of the three groups (LCX, LAD and control) over 45 minutes. It showed no haemodynamic differences between the groups over time.

Figure 2B. Left atrial pressure changes

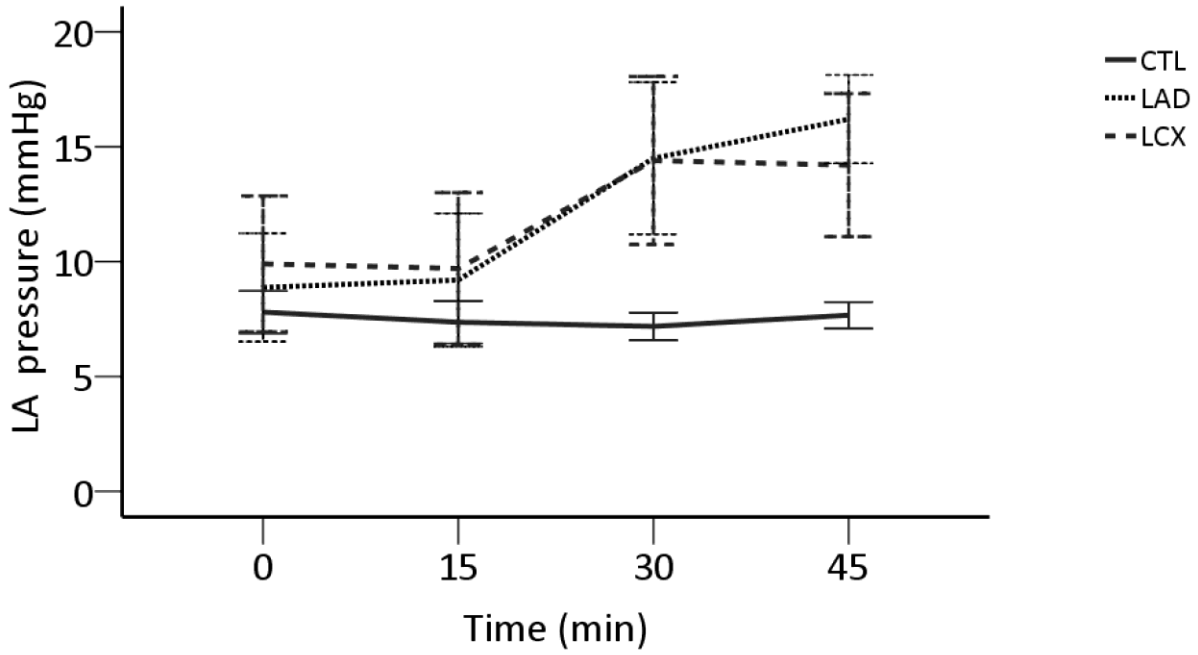


Figure 2B**.** Left atrial pressure (LAP) changes over time in the three groups (LCX, LAD and CTL). It shows a significant increase in LAP in MI group compared to CTL. Meanwhile, there was no diference in LAP between LCX and LAD

Figure 3. Changes in atrial effective refractory period over 45 minutes.

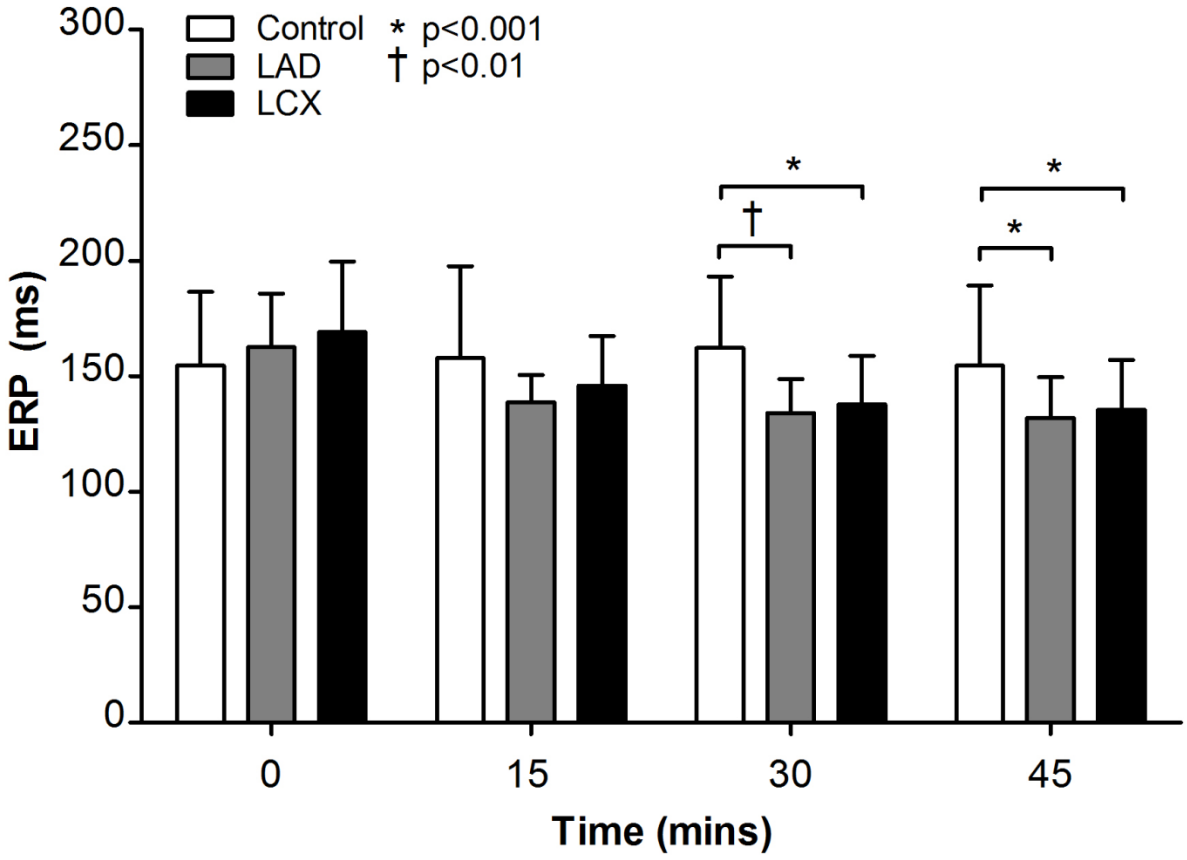


Figure 3**:** Changes in atrial ERP at cycle length 400 msc over 45 minutes after balloon inflation. There was a significant reduction ERP over time which started as early as 30 minutes and persisted in MI groups (LCX and LAD) compared to CTL (P=004). There was no significant difference between LCX and LAD groups.

Figure 4A**. Activation map in a CTL animal**

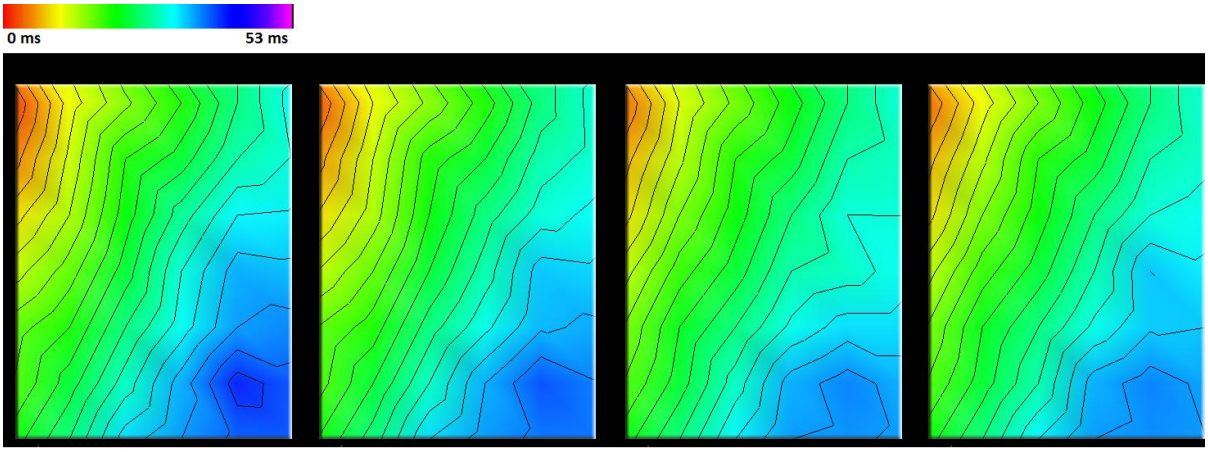


Figure 4B**. Activation map in a LAD occlusion animal (ventricular infarction alone)**

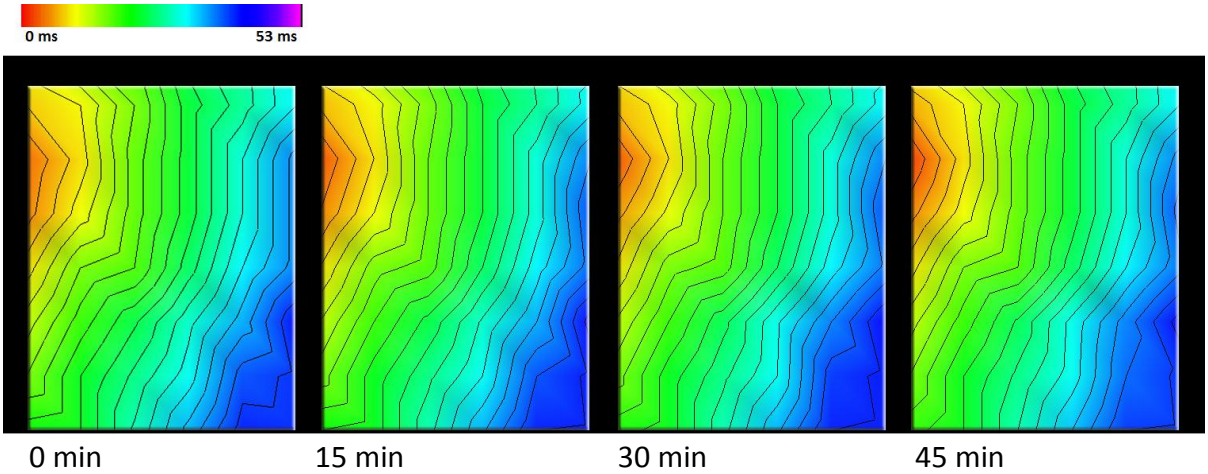


Figure 4C**. Activation map in a LCX occlusion animal (atrial and ventricular infarction)**

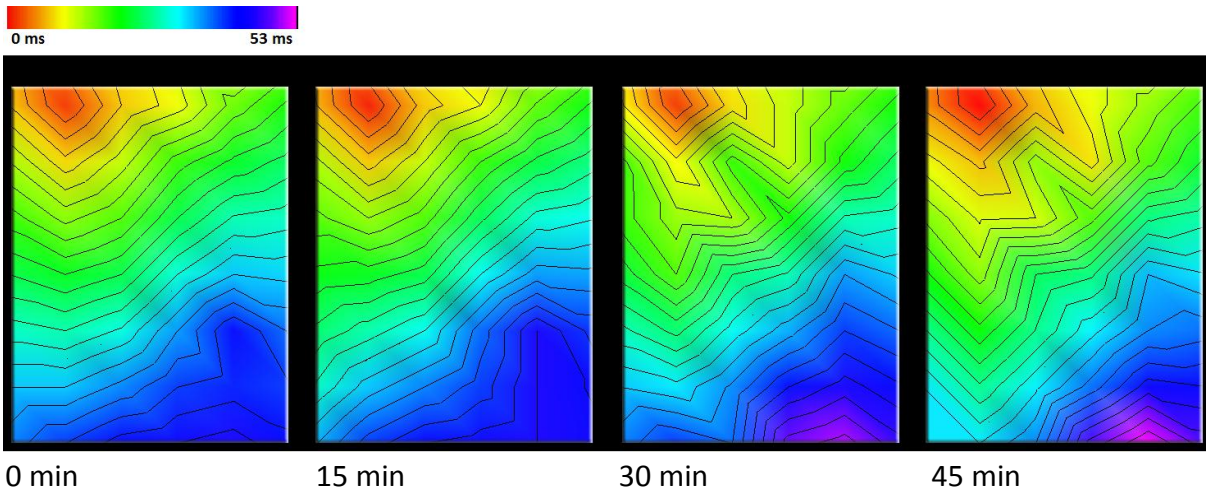


Figure 4: Representative activation maps from each group at 15 minutely intervals for the study duration at a CL of 400-ms. Each map has used fixed scale (0-53 ms) to facilitate comparison between the groups. **(A)** CTL group showing normal conduction with no isochronal crowding. **(B)** LAD group showing a slight reduction in CV but no significant isochronal crowding. **(C)** LCX group with atrial ischaemia showing slowing in conduction velocity, isochronal crowding with susceptability to re-entry.

Figure 5**.** Changes in conduction velocity

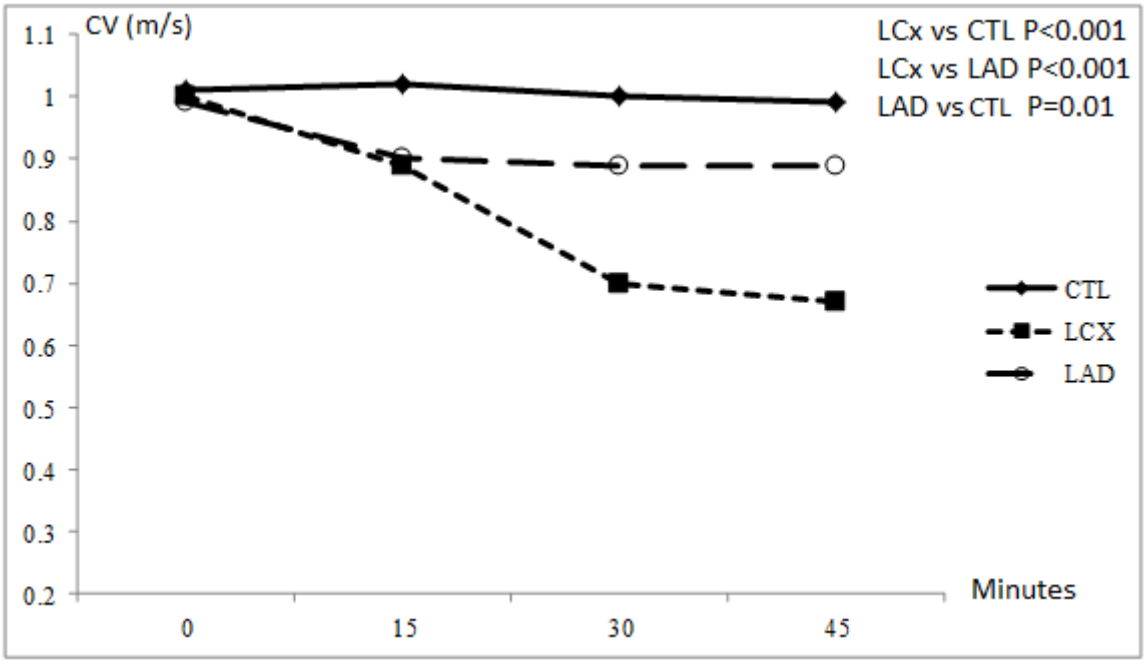


Figure 5: Conduction velocity with time in each of the groups. Demonstrated is the marked and progressive slowing in CV in LCX group compared to LAD or CTL. There was modest reduction in CV in LAD group compared to CTL.

Figure6A. Changes in absolute inhomogeneity of conduction

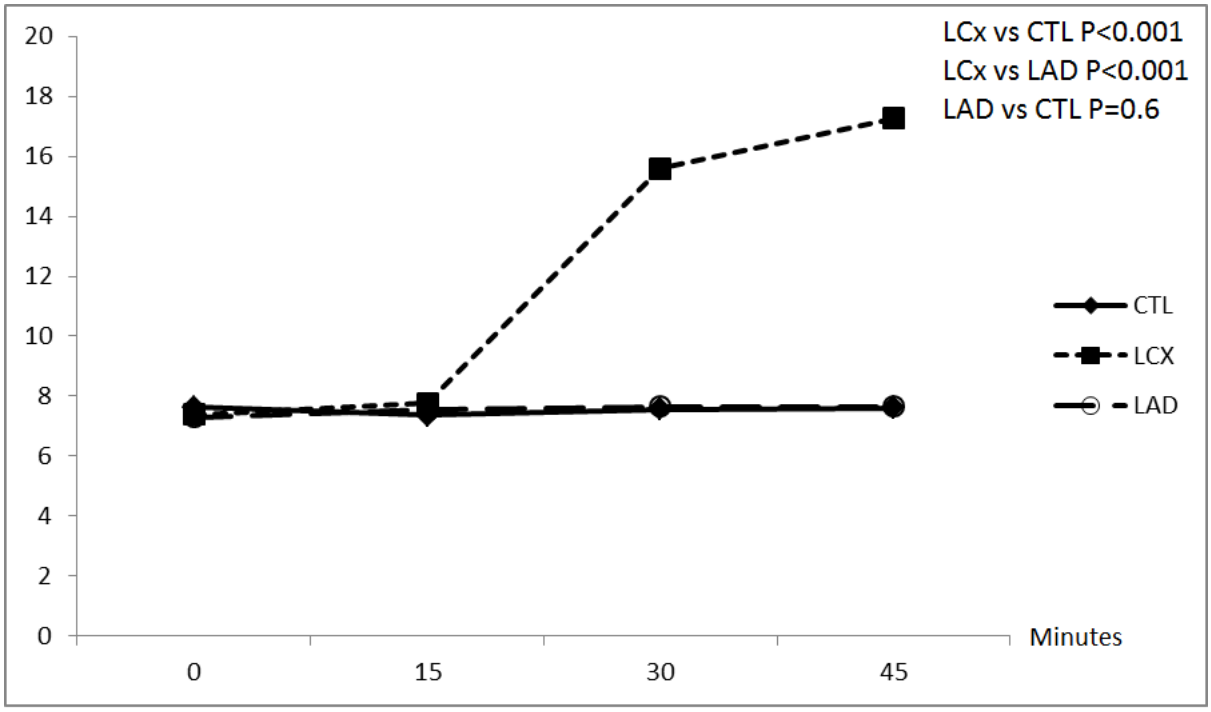
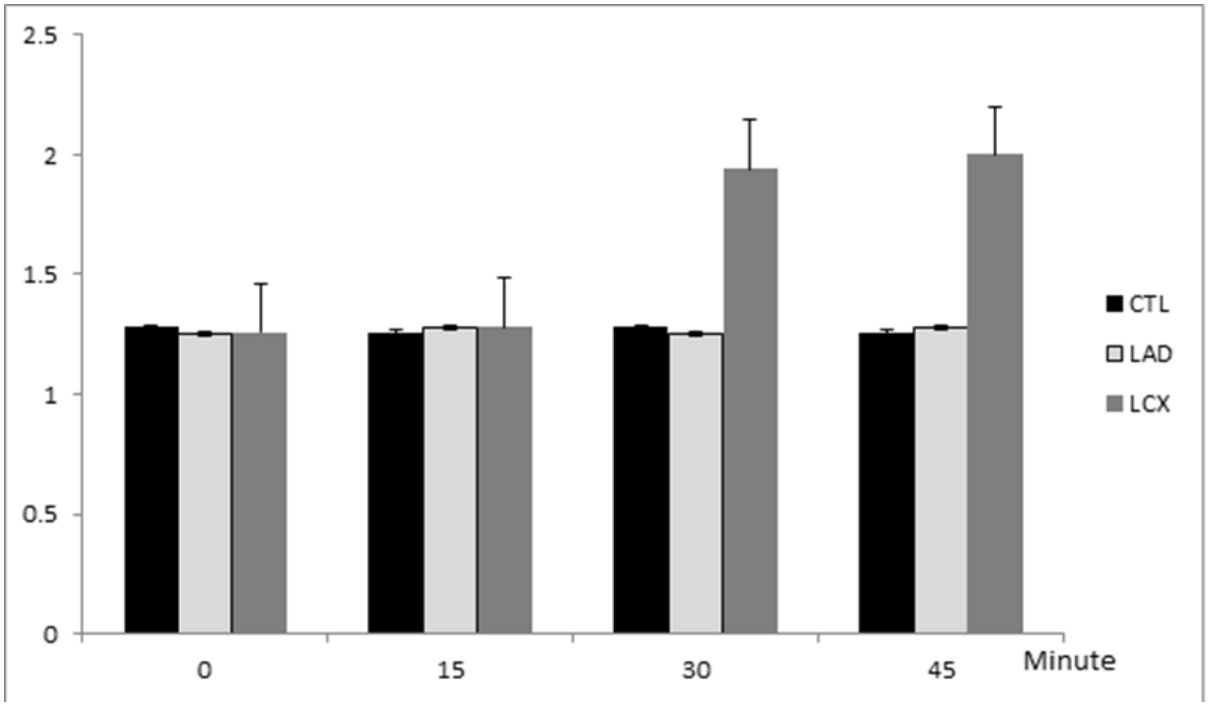


Figure 6: (A) Absolute inhomogeneity of conduction (P5-95). The LCX group demonstrates marked and progressive changes compared to LAD or CTL. This was evident 15 minutes after angioplasty balloon inflation in LCX.

Figure 6B. Change in conduction heterogeneity index (CHI)



(B) Conduction heterogeneity index (CHI) significantly increased over 45 minutes (15 minutely intervals) in LCX group compared to LAD or CTL. The result was evident 30 minutes post MI.

Figure 7A. AF inducibility.

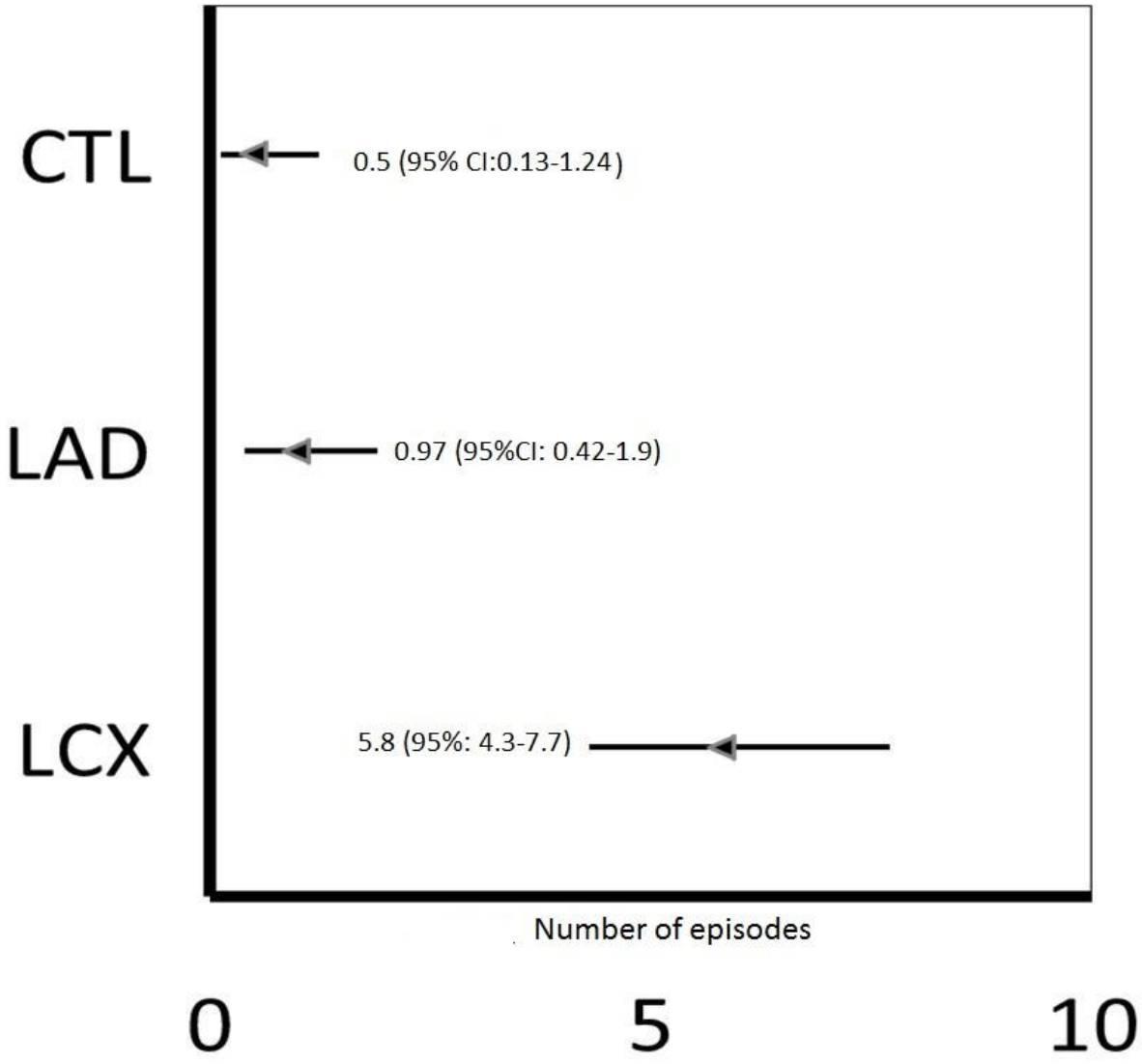
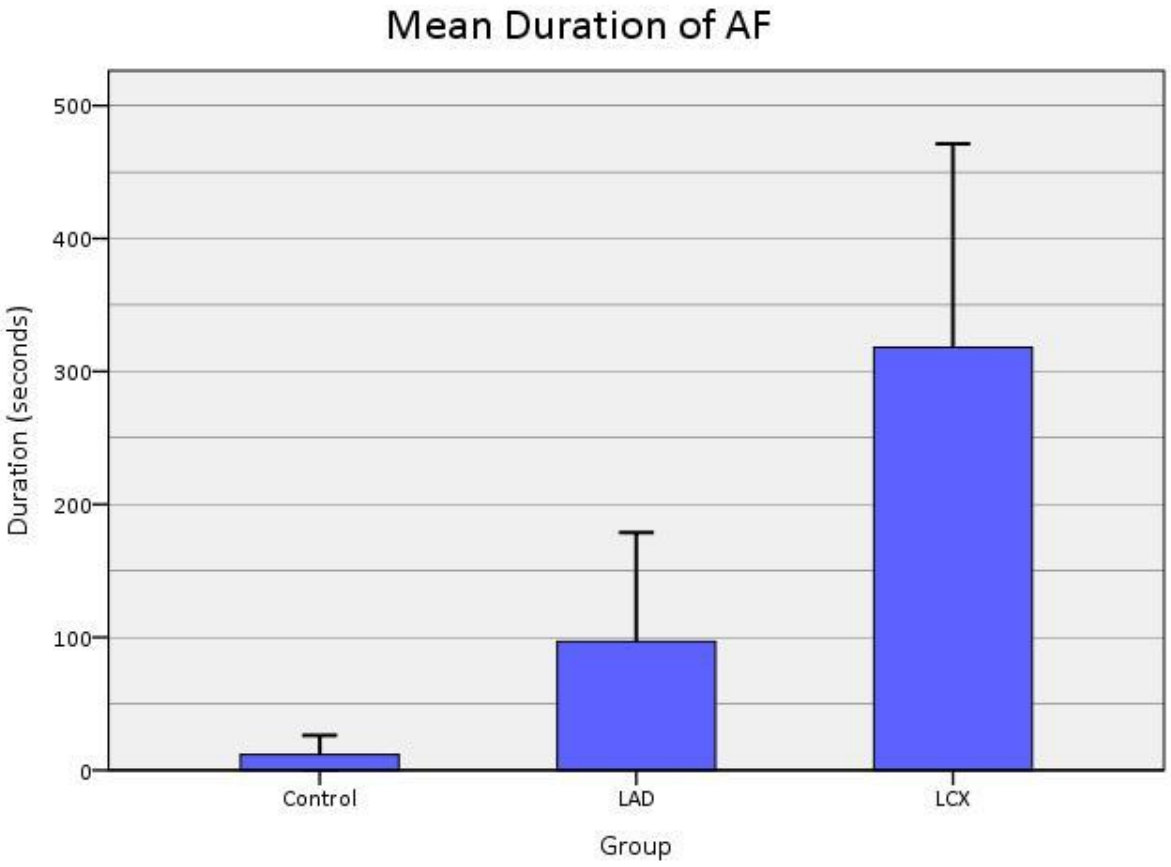


Figure 7: (A) Number of AF episodes in each group during ERP testing. This was significantly higher in LCX groups compared to LAD or CTL. There was no difference in AF inducibility between LAD and CTL.

Figure 7B. AF duration (seconds)



(B) Mean duration of all induced AF in each group (seconds). This was significantly longer in LCX compared with CTL or LAD.

Chapter 4

Coronary Artery Disease Affecting the Atrial Branches is an Independent Determinant of Atrial Fibrillation After Myocardial Infarction

4.1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the community with prevalence of more than 4% in patients aged over 65 years.(2,3,426) The incidence of new onset AF associated with acute coronary syndrome the incidence of AF is 6-22%, and its occurrence in this setting is associated with increased short- and long-term morbidity and mortality.(318-323,427) However, the underlying pathophysiology for AF in the acute setting of myocardial infarction (MI) has not been clearly delineated. Indeed, findings from published studies that have assessed the association between atrial ischaemia and the early occurrence of AF have been inconsistent.(359-361,428) However, these studies have not evaluated the potential role of a number of factors that may have promoted the development of AF during MI such as age, the presence of left ventricular (LV) dysfunction and left atrial (LA) enlargement. In cohort of consecutive patients with acute MI, we evaluated the characteristics associated with the development of new-onset AF.

4.2 Methods

4.2.1 Study Population

The study comprised 2460 consecutive patients who presented to the Flinders Medical Centre Cardiac Care Unit with acute MI between 2004 and 2009. All patients had a diagnosis of myocardial infarction which was validated according to the ESC/ACC 2003 definition.(429) The selection of the study population for this nested case-control study is illustrated in Figure 1. Patients were included in the study group if they had documented AF within the first 7 days after the MI. All patients were continuously monitored with telemetry in the coronary care unit for AF for at least 72 hours post-MI then by daily and clinically indicated 12-lead

electrocardiography (ECG). AF was diagnosed on surface 12-lead ECG and was defined by an irregular rhythm with absence of discrete P-waves and persisted for ≥30 seconds in accordance with the HRS guidelines.(34)_ Patients were excluded from the study if they did not have an assessment of coronary anatomy by angiography during the week after their MI or subsequent assessment of cardiac structure and function using echocardiography within one month post-MI; had history of preexisting AF; prior documentation of heart failure or reduced LV ejection fraction<50%; documentation of heart failure during the index admission; severe valvular heart disease; moderate-severe LV hypertrophy (defined as an LV mass adjusted for height of 143g/m^2 for men and >102g/m^2 in women);(430) recent coronary artery bypass graft (CABG); or pericarditis.

In total, 42 cases were identified as subjects who developed new-onset AF during the first week post-MI. The control group comprised 42 MI patients without AF who were matched to cases for age, sex, and LV ejection fraction identified from the same cohort of patients. The study protocol was approved by the institutional Clinical Research Ethics Committee.

4.2.2 Coronary angiography

Coronary angiograms were assessed by a single investigator blinded to the rest of the patients' clinical data. Evaluation of the coronary artery anatomy included a detailed assessment of coronary disease affecting branches that supply the left and right atria (Figures 2 and 3). Specifically, the following branches were evaluated: left circumflex atrial branch (arising from the left circumflex artery before the obtuse marginal branch); sinoatrial branch (arising from either the proximal portion of left circumflex artery or the right coronary artery); right atrial intermediate branch; and atrionodal branch which usually arises from the right coronary artery. Coronary flow in the infarct-related artery was graded according to methods employed in the Thrombolysis in Myocardial Infarction (TIMI) trial.(431) Coronary circulation to the atria was considered to be reduced if there was a critical coronary artery lesion proximal or at the level of the atrial branch that resulted in TIMI flow ≤ 2 just distal to the lesion (Figures 2 and 3). All patients (STEMI and NSTEMI) were loaded with clopidogrel and aspirin prior to percutanous

coronary intervention (PCI) then continued with dual antiplatelet therapy for a duration decided by the treating physician.

4.2.3 Echocardiography

All patients underwent transthoracic echocardiography (Vivid 7, GE Healthcare, Norway) within one month post-MI. LA volume was measured using standard apical 2- and 4 chamber views on the frame just prior to mitral valve opening and as specified by current American Society of Echocardiography guidelines.(432) LA volume was indexed to body surface area. Mitral inflow velocity was obtained in the apical 4-chamber view by placing a pulsed Doppler sample volume between the tips of the mitral leaflets. Mitral annular velocity was assessed during the early phase of diastole (e') using pulsed wave Doppler sampling of septal mitral annular motion from the 4-chamber view. LV ejection fraction was measured in apical 2-and 4 chamber views using Simpson's method of discs. LV diastolic filling pressure was estimated by the ratio of mitral inflow peak E velocity to e'.(433) All echocardiographic assessments were performed by experienced cardiac sonographers and reported by a single investigator blinded to the patient details.

4.2.4 Statistical Analysis

Continuous variables were reported as mean ± standard deviation when normally distributed. Categorical variables were compared using Fisher's exact test. Cases and controls were compared using conditional logistic regression model for the binary outcomes and paired t-test for the continuous outcomes. A p-value <0.05 was considered statistically significant. All calculations were performed using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA).

4.3 Results

Of the 2460 patients who were admitted with MI during the study period, 149 (6%) developed AF within the first week. After excluding patients with prior AF, severe valvular heart disease, LV hypertrophy, LV dysfunction, recent CABG or pericarditis; we identified 42 AF cases and 42 controls (MI but no AF) who were matched for age, gender, and LV ejection fraction and had

undergone both coronary angiography and echocardiography (Figure 1). There was no difference in baseline cardiovascular risk factors between the two groups (Table 1). Patients with new-onset AF had higher proportion of inferior MI (p=0.003) (Table 2).

4.3.1 Angiographic Findings

The prevalence of left circumflex artery disease or triple-vessel disease was not significantly different between the groups. However, left main stem (p=0.02) and right coronary artery disease (p<0.0001) was more frequently present in AF cases compared to controls. Controls were more likely to present with ST-segment elevation MI (p=0.03) and accordingly were more likely to undergo early revascularisation with primary angioplasty within 6 hours (p=0.004; Table 2). In addition, the time to PCI from symptom onset was shorter in controls compared to cases (2.8 ±0.7 vs. 3.95±1.6 hours; p=0.047). While all recruited MI patients presented with TIMI flow ≤ 2 prior to PCI, good coronary reperfusion was achieved in most patients with TIMI flow 3 observed in 97.3% of controls vs. 90.3% of cases (p=0.3). This result was comparable in both major coronary arteries as well as the atrial branches.

There was at least one significant atrial branch with reduced flow as evident by critical lesion proximal or at the level of the atrial branch itself in AF cases compared to controls (right coronary atrial branch 66.7% vs.19% [odds ratio (OR) 4.3, 95% CI: 1.7-11; p<0.0001]; and left circumflex atrial branch 43% vs. 17% [OR 6.5, 95% CI: 1.4-29]; p=0.009). Fifty percent of AF cases had reduced circulation to the SA nodal branch originating from the right coronary or left circumflex arteries compared to only 2.4% of controls (p<0.0001).

4.3.2 Echocardiographic Findings

LA volume index was enlarged in AF cases and normal in controls (40±11ml/m^2 vs. 26±7ml/m^2, respectively; p=0.001). The atrial structural remodeling was accompanied by the observation that LV diastolic filling pressure (E/e') was higher in AF cases compared to controls (17±8 vs.11±3, respectively; p=0.002). However, there was no significant difference in LV ejection fraction (49±13% vs. 51±15%, p=0.3) and LV end-diastolic diameter (4.8cm vs.4.6cm; p=0.6).

between the two groups.

4.3.3 Independent Determinants of Atrial Fibrillation

In multivariable analysis, right coronary atrial branch disease (OR 14.6, CI 3.30 - 64, p=0.0001) and left circumflex atrial branch disease (OR 7.2, CI 1.39 - 27, p=0.003) were predictors of new-onset AF during the first week post-MI after adjustment for LA volume index (p<0.0001) and E/e' (p=0.20).

4.4 Discussion

This case-contol study provides new information on the mechanisms of AF after myocardial infarction. It observes that coronary disease affecting the atrial branches is a predictor for the development of AF early after MI, independent of the measurable effects of age, gender, LV ejection fraction, LV filling pressure and LA size. Coronary artery disease affecting the atrial branches, possibly due to atrial ischaemia, was associated with promotion of AF genesis, regardless of whether it originated from the left or right coronary system. .

Previous studies provide conflicting results regarding the association between atrial ischaemia and the early occurrence of AF.(360,361) While some studies have reported that coronary disease affecting the sinoatrial branch is a prerequisite for development of AF during the acute phase of MI,(359,428) others have observed isolated occlusion of the left circumflex artery proximal to the origin of its LA circumflex branch with reduced circulation to the atrioventricular nodal branch.(360,361) In our study, we documented pathology affecting all atrial branches. Differences in methods of ascertainment of coronary disease status and identification of AF cases may account for differences in study findings. Whereas all coronary angiograms were performed within 48 hours in our study population, the timing in other studies varied between 1-28 days. Other studies have limited the duration of their observation for new-onset AF to the 3-12 hours post-MI onset, during which time the incidence of AF is very low. (359) However, a greater burden of AF has been observed with an extended observation post-MI, with a reported incidence as high as 21% during the first week after MI. Atrial

ischaemia or infarction has been reported to result in electrical and structural remodeling of the atria, both established precursors for the development of AF.(142,362) In animal models, ischaemia has been shown to uncouple gap junction as early as 10 minutes through multiple factors such as increase of diastolic cytoplasmic ($Ca^{2}+$), intracellular acidification and connexin dephosphorylation.(434,435) These effects creates a substrate for AF maintenance by the development of local conduction block that the promotion of reentry(362)

In this observational study, we are unable to adequately control for the effects of confounders that may have contributed to our finding that early reperfusion therapy, particularly with primary coronary angioplasty, has a favorable effect on prevention of AF post-MI. However, the favorable effect of early reperfusion therapy on preventing AF post-MI has been shown previously in patients treated with thrombolytic therapy.(327) In addition, despite an increasingly older population with higher prevalence of co-morbidities, there is community-based evidence that the incidence of AF in the setting of acute MI has declined with the contemporary use of early reperfusion therapy.(323)

Together with the angiographic data, our echocardiographic findings have provided novel insights as to the mechanisms underlying the development of AF after MI. Although LV ejection fraction was matched in both groups, LV filling pressure was higher in AF cases compared to controls. Previous studies have shown a linear relationship between LV end-diastolic filling pressure and LA pressure.(436,437) Left atrial stretch has been shown to trigger and form the substrate for arrhythmias.(210,211) However, our findings indicate that atrial branch disease remained a predictor of AF even after adjustment for E/e', suggesting that in these patients with coronary artery disease, atrial ischaemia may promote the formation of a substrate for AF that is independent of increased filling pressures. The effect of ischaemia on LA pump function had been previously shown by Stefanadis et al who found that LA contractility increases significantly in patients with left anterior descending artery disease but decreases in patients with proximal left circumflex artery disease.(365) However, the relative contribution of atrial ischaemia and increased LV filling pressure to the observed atrial remodeling in AF cases is unable to be determined by this study.

4.5 Study Limitations

We recognise that there is potential for selection bias in this study which includes only those patients who have had coronary angiography and echocardiography during the acute setting of their MI. The duration of continuous ECG monitoring was limited to 72 hours. Thereafter, patients had only daily and clinically indicated ECG recording. Consequently, it is possible that asymptomatic periods of AF may have been underreported. In addition, the presence of atrial ischaemia or infarction can be difficult to diagnose on surface ECG due to relatively small mass of the atrial wall. Hence, we were unable to objectively assess the presence of atrial ischaemia using surface ECG assessment of PR segment in this study. The onset of AF in the clinical setting is critically dependent on triggers, perpetuators and their interaction with the underlying substrate.(438) In this study, we have been able to observe clinical predictors for the frequent occurrence of AF in MI but have not evaluated the subsequent mechanisms or activation of the autonomic or humoral responses that may be attributed to MI.

4.6 Conclusion

Atrial ischaemia, as evident by coronary disease affecting the atrial branches, is an independent determinant of AF in the acute setting after MI.

Table 1**: Characteristics of Study Population according to AF Status**

	MI with AF (n=42)	**MI with no AF (n=42)**	**p-value**
Clinical			
Male sex, n (%)	28 (66.7)	28 (66.7)	1.0
Age, y (SD)	72 (9.5)	71 (10)	0.7
BSA, m^2 (SD)	1.94 (0.20)	1.90 (0.16)	0.3
Systemic hypertension, n (%)	26 (61.9)	27(64.0)	0.8
Diabetes mellitus, n (%)	10 (23.8)	16(38)	0.2
Statin, n (%)	18 (42.8)	24(57)	0.2
ACE inhibitor or ARB, n (%)	34 (81)	34(81)	1.0
β-blocker, n (%)	37 (88)	36(85.7)	0.4
Echocardiographic			
LV ejection fraction, % (SD)	49 (13)	51 (15)	0.3
E/e', (SD)	17 (8)	11 (3)	0.02
Mitral E/A, (SD)	1.4 (0.5)	0.9 (0.8)	0.04
LAV index, mL/m^2 (SD)	40 (11)	26 (7)	0.01
LV end-diastolic diameter, cm (SD)	4.74 (0.50)	4.69 (0.60)	0.6
LV posterior wall, cm (SD)	1.00 (0.15)	0.99 (0.19)	0.8
IV septal wall, cm (SD)	1.02 (0.24)	1.04 (0.25)	0.7

Table 2**: Patients Angiographic Characteristics according to AF Status**

	No AF (n=42)	**AF (n=42)**	**p-value**
ST-elevation myocardial infarction, n (%)	16 (38.1)	7 (16.7)	0.03
Non ST-segment elevation MI, n (%)	26 (61.9)	35 (83.3)	0.049
Inferior myocardial infarction, n (%)	14 (33)	36 (85.7)	0.003
Anterior myocardial infarction, n (%)	28 (66.6)	6 (14.3)	0.001
Primary angioplasty, n (%)	15 (35.7)	4 (9.5)	0.004
Percutaneous coronary angioplasty with stenting (PTCA+stenting)	36 (85.7)	31 (73.8)	0.3
Coronary artery bypass graft (CABG)	6 (14.2)	11 (26.1)	0.3
Left main stem disease, n (%)	3 (7.1)	11 (26.2)	0.02
Triple-vessel disease, n (%)	8 (19.0)	14 (33.3)	0.1
Right coronary artery disease, n (%)	9 (21.4)	30 (71.4)	<0.0001
Left circumflex disease, n (%)	17 (40.5)	25 (59.5)	0.08
Right atrial branch disease, n (%)	8 (19.0)	28 (66.7)	<0.0001
Left atrial branch disease, n (%)	7 (16.7)	18 (42.9)	0.009
Sinoatrial branch disease*, n (%)	21 (50)	1 (2.4)	<0.0001

* Branch from right coronary artery or left circumflex

Figure 1

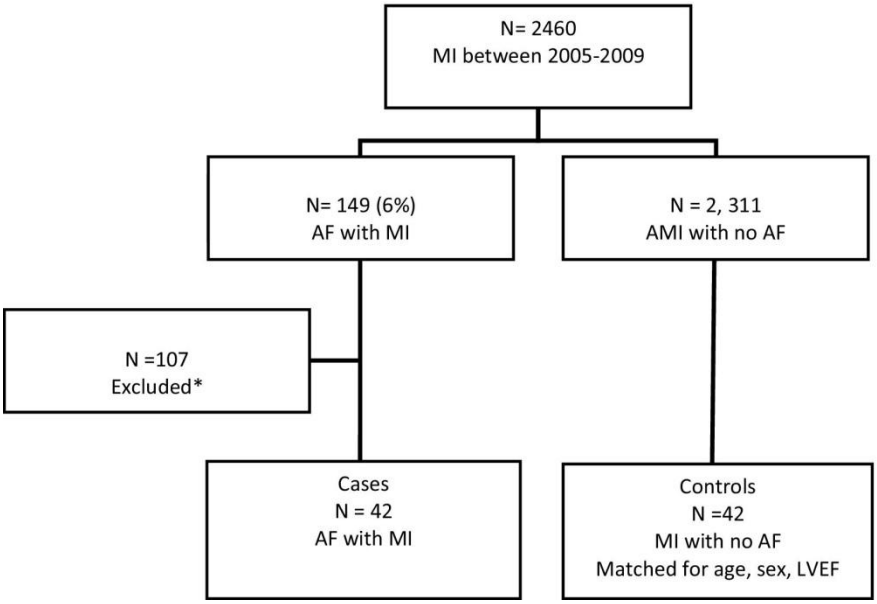
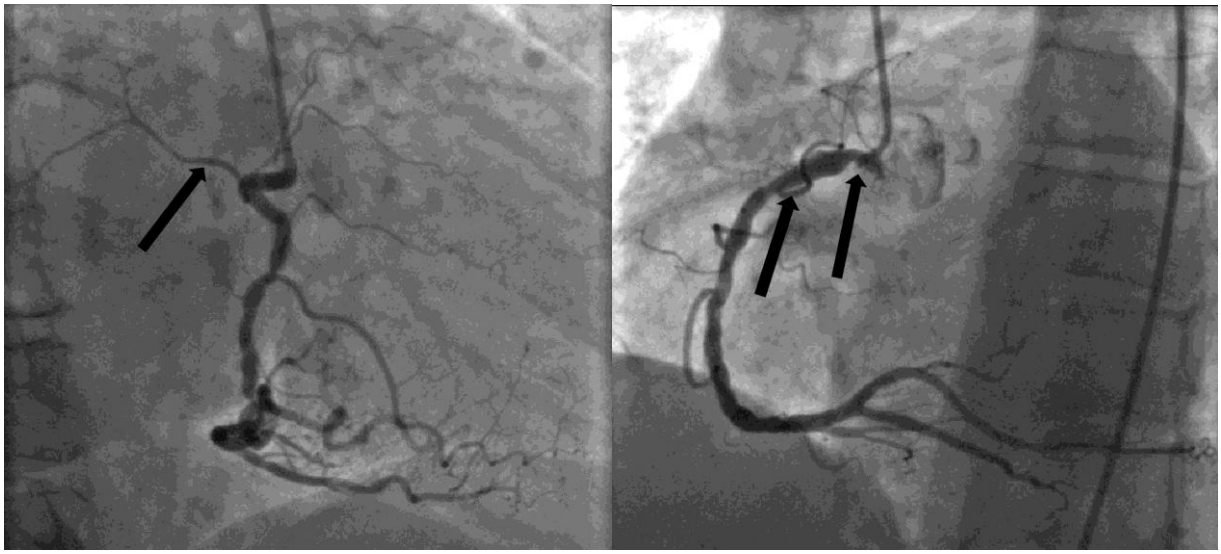


Figure 1. Study Design

Selection of study population. *Patients were excluded from the study if they did not have an assessment of coronary anatomy by angiography within 1 week after their MI or subsequent assessment of cardiac structure and function using echocardiography within one month post-MI; had history of preexisting AF; prior documentation of heart failure or reduced LV ejection fraction<50%; severe valvular heart disease; moderate-severe LV hypertrophy; recent coronary artery bypass graft (CABG); or pericarditis.

Figure 2

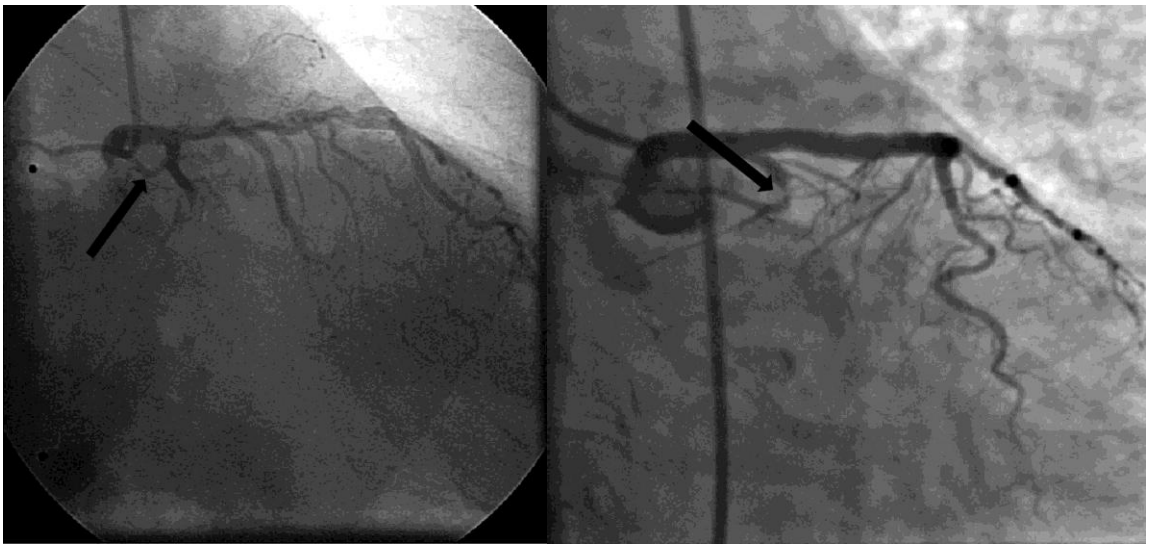


A B

Figure 2.

Left panel (A): Coronary angiography of a control patient with normal right coronary atrial branches (black arrows). *Right panel (B)*: Coronary angiography of a patient with proximal right coronary lesion and reduced circulation to right coronary atrial branches (black arrow).

Figure 3



(A) **(B)**

Figure 3. *Left panel (A)*: Coronary angiography of a control patient with left circumflex occlusion distal to intact sinoatrial branch (black arrow). *Right panel (B)*: coronary angiography of patient with total occlusion of the left circumflex proximal to compromise left circumflex atrial branch (black arrow).

30 min 45 min

Chapter 5

Atrial Remodeling as a Consequence of Myocardial Infarction: The Role of Atrial Branches Disease

5.1 Introduction

Left atrial volume (LAV) is a potent predictor of adverse cardiovascular outcomes in population-based studies as well as in patients with heart failure and acute myocardial infarction (AMI).(439-445) Left atrial volume has also been shown to predict risk of AF development in various structural heart diseases such as cardiomyopathy.(239,240,446,447) Furthermore, recent studies have shown that LA dilatation is commonly encountered in patient with acute myocardial infarction to an extent that exceeds the degree of heart failure or left ventricular dysfunction.(440,445,448) The aim of this study was to determine the contribution of left atrial arterial branch disease, a surrogate for left atrial ischaemia, in the mechanism of left atrial dilation post myocardial infarction.

5.2 Methods

5.2.1 Patient Population

In a case-control study of patients with acute myocardial infarction, 26 consecutive patients in whom the culprit lesion involved the left atrial blood supply were matched with 26 AMI controls presenting during the same period without LA branch disease according to age, sex, body mass index and left ventricular ejection fraction. All patients had a diagnosis of MI which was validated according to the ESC/ACC definition 2003.(429) Patients with a history of pre-existing atrial fibrillation, severe valvular heart disease, severe left ventricular hypertrophy, and moderate-severe left ventricular dysfunction (EF <40%) were excluded from the study to avoid confounding.

5.2.2 Angiographic Analysis

Patients' coronary angiography was thoroughly examined to identity the left atrial blood supply as shown in figure 1. The left atrial circumflex branch usually arose from the proximal portion of left circumflex artery before the obtuse marginal branch or from the sino-atrial branch which originates from the proximal portion of left circumflex artery or right coronary artery.(368) (361)Impaired left atrial blood supply was defined by critical coronary artery lesion (≥70%) proximal or at the level of the atrial branch with TIMI flow less than 2, distal to the lesion. The flow in the infarct- related artery (IRA) was graded as assessed in the TIMI (Thrombolysis in Myocardial Infarction) trial.(431) AF was diagnosed on surface 12-lead ECG and was defined by an irregular rhythm with absence of discrete P-waves and persisted for ≥30 seconds in accordance with the HRS guidelines.(32) All patients were continuously monitored with telemetry in coronary care unit for AF for at least 72 hours post-MI then by daily and clinically indicated 12-lead electrocardiography (ECG).

5.2.3 Echocardiographic Protocol

All patients underwent routine transthoracic echocardiography within one month post infarct in the left lateral recumbent position. Imaging was undertaken using a commercially available machine (Vivid 7; GE, Vingmed Norway) and all measurements were taken in accordance with the American Society of Echocardiography. Left ventricular ejection fraction was measured in apical 2-and 4 chamber views using Simpson's method. Left atrial volume was measured using standard apical 2- and 4 chamber views at end-systole by the modified Simpson's rule and was indexed to body surface area. Transmitral flow velocity was obtained by pulse-wave Doppler echocardiography at the tips of the mitral leaflets. Early diastolic septal mitral annular tissue velocity was measured by tissue Doppler imaging. All patients' medical records were reviewed for common medical co-morbidities as documented by the treating physician.

5.3 Statistical Analysis

Comparison of baseline characteristics and clinical variables between patients with and without diseased left atrial branch were performed using the two-sample t -test for continuous

variables and chi-square test for categorical variables. Cases and control were compared using conditional logistic regression model for binary outcomes and the paired t-test for continuous outcomes. P value less than 0.05 was considered statistically significant.

5.4 Results

There was no significant difference between the two groups in baseline characteristics and medical therapy (table 1).

5.4.1 Angiographic findings

All patients with impaired LA branch circulation presented with inferior or inferolateral MI with proximal lesion in the right coronary artery or left circumflex artery (table 2). However, patients in the controls group presented more frequently with anterior infarct (table 2). The sino-atrial branch was compromised in 80.7 % of the cases and the left circumflex atrial branch in 69.2%. No control patient exhibited disease affecting the LA blood supply.

5.4.2 Echocardiographic findings

The mean LAVi was greater in patients with compromised LA branch compared to control (42±8 vs 26±7; P<0.0001). The left ventricular filling pressure (E/e') was higher in patients with compromised LA arterial branches compared to controls (table 1). However, after adjustment for E/e', the association between compromised LA arterial branches and LAVi persisted

5.4.3 Cardiovascular outcome

There was a trend toward significant increase in major adverse cardiovascular outcome in patients with LA branch disease and enlarge LA size compared to controls. The composite of death (3), stroke (1), complete heart block (2), were significantly higher in patients with LA branch disease and enlarged LA volume compared to control (19 % vs. 3.8%, P=0.08). While all cases (patients with LA branch disease) developed AF, only 2 patients from the controls group developed AF within one week post MI (p<0.0001).

5.5 Discussion

Our findings highlight the importance of left atrial branches disease or atrial ischaemia in pathogenesis of left atrial structural remodeling in the setting of AMI. Coronary artery disease affecting the left atrial branches was associated with left atrial enlargement independent of elevated end diastolic pressure load (E/E'), LVEF or patients' age.

Although, left atrial dilatation occurs in the setting of heart failure whether due to systolic or diastolic dysfunction, left atrial ischaemia as evident by impaired left atrial circulation was also another important determinant in LA structural remodeling post-acute myocardial infarction (AMI) as shown in this study. The LAVi is well recognised marker of diastolic dysfunction which is mainly a reflection of elevated left ventricular filling pressure (E/E').(449) Consequently, left atrial pressure will be elevated during ventricular diastole in patients with diastolic dysfunction results in LA distension. However, such changes explained the chronic form of atrial stretch and dilatation. Our findings emphasised the incremental value of atrial branch disease or ischaemia in the acute form of LA remodeling during MI. Atrial fibrillation commonly complicates acute myocardial infarction with incidence rate as high as 20%.(320,321,342,450,451) Atrial fibrillation recurrence is also very high after its initial transient episode post AMI.(333,342) The underlying mechanism for such recurrence is beyond the acute haemodynamic changes that occur during AMI; a substrate is the most likely explanation for such high recurrence rate (approximately 34%). Siu et al found AF recurrence after its first transient episode post AMI was independent of left ventricular dysfunction.(342) More importantly, there was a five-fold increase in the risk of ischaemic stroke development which was simultaneously coinciding with occurrence of AF in majority of the cases (77%). The significant importance of LAVI post AMI in predicting worse outcomes in this subset patient is probably partly related to atrial branch disease or atrial ischaemia with propensity for AF development. In addition to the substrate with future AF recurrence and stroke, loss of atrial contraction or kick is also contributing to patient worse outcome during the acute phase of AMI by affecting end diastolic filling and consequently stroke volume. Abhayaratna et al found that LA reservoir function was predictor of first AF or flutter independent of LV ejection fraction or diastolic function. (452) In addition,

the relative high prevalence of severe LAVI (>50 ml/m2) in patients with coronary artery disease which considerably exceeded the prevalence of severe LVEF may be partly related to LA ischaemia or infarction.(448) In addition, our finding of greater AF incidence post MI in patients with coronary artery disease affecting the atrial circulation is consistent with other a few previous studies.(360,361)

5.6 Study Limitations

There is a potential for selection bias in this study which includes those patients who underwent coronary angiography and transthoracic echocardiography during the acute setting of their AMI. While this study demonstrates the link between LAV and compromise of LA arterial branches, it did not assess serum B-type natriuretic peptide (BNP) level which might add more value to the findings in assessment of HF, in particular diastolic HF. In addition, the lack of data on pulmonary veins pulse waves which also give good estimation on the degree of diastolic dysfunction.

5.7 Conclusion

Atrial ischaemia as evident coronary artery disease affecting the atrial branches plays significant role in LA structural remodeling during the early phase of myocardial infarction

Table 1

Patient Characteristics

	Diseased LA branches n=26	Normal LA branches n=26	P-value
Age, years	71 ±10	72± 9.5	0.7
Men, n (%)	16 (61)	16 (61)	1
BSA, m^2 (mean, SD)	1.75± 0.12	1.90± 0.16	0.2
Hypertension, n (%)	19(73)	17(65.3)	0.8
Diabetes mellitus, n (%)	9(34.6)	8(30.7)	0.7
ACE/AR blocker, n (%)	21 (81)	20 (77)	0.7
B-blocker, n (%)	23 (88)	24 (92)	0.65
Statin therapy, n (%)	16 (61)	12 (45)	0.4
LVEF, %	48 ± 15	51±17	0.5
LVEDD (mm)	49.5 ±0.2	47.5 ±0.3	0.3
IVS (cm)	1 ± 0.2	0.97 ± 0.3	0.7
PW thickness (cm)	1.1±0.2	1± 0.2	0.1
LA diameter (cm)	4.2± 0.5	3.6 ±0.4	<0.001
LAVI (ml/m^2,)	42 ±8	26 ± 7	<0.0001
E/A	1.4± 0.8	0.95 ± 0.3	0.03
E/E’	17 ± 7	10.5 ±3	<0.0001

Table 2

Angiography and myocardial infarction features

	Diseased LA branch n=26	Normal LA branch n=26	P value
Inferior or inferolateral MI, n (%)	26 (100)	7 (27)	<0.0001
Anterior MI, n (%)	0	19 (73)	
STEMI	4 (15)	9 (34)	0.2
NSTE-ACS	22	17	0.1
Primary coronary angioplasty	4	9	0.2
RCA disease	20 (77)	6 (23)	<0.0001
LCX artery disease	21 (80.7)	11 (42)	0.004
Left atrial circumflex, %	18(69.2)	-	-
Sino atrial artery, %	21(80.7)	-	-

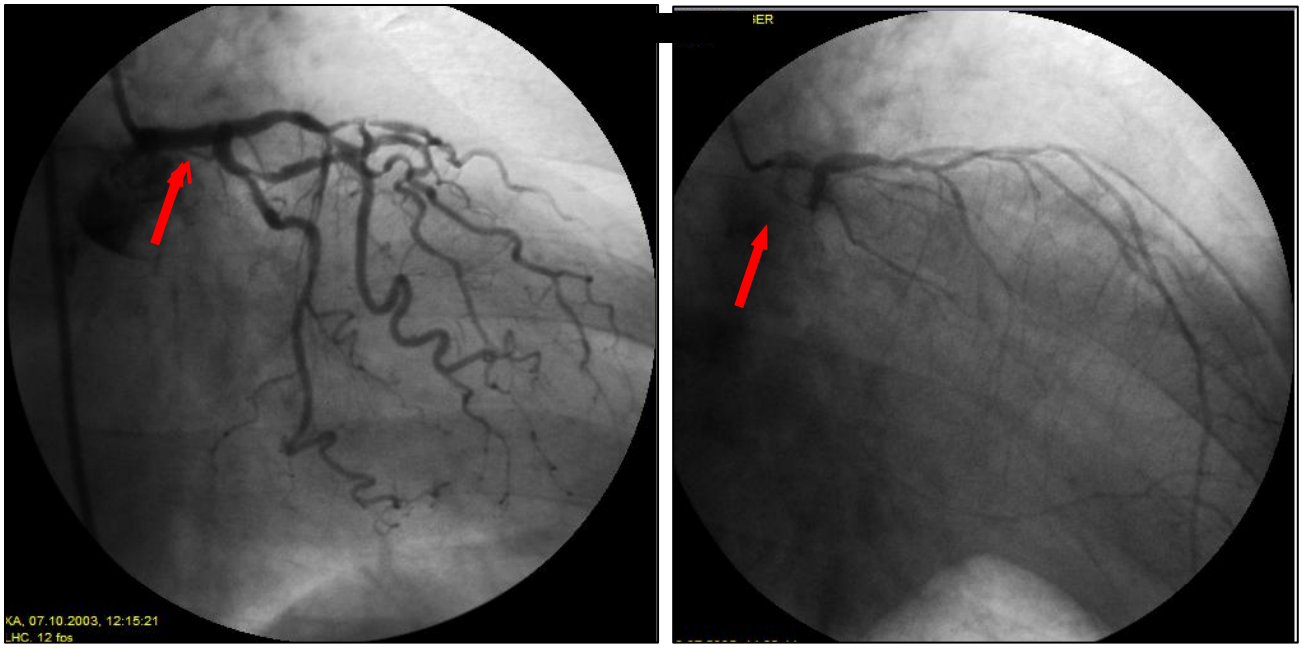


Figure1: Left-Coronary angiography of patient with normal sino-atrial branch arising from the proximal left circumflex artery (red arrow). Right- Coronary angiography of patient with proximal total occlusion of the left circumflex artery and absent sino-atrial branch (red arrow).

Chapter 6

Atrial Fibrillation Post Myocardial Infarction is Associated with Ventricular Fibrillation and Poor Long Term Outcomes

6.1 Introduction

Atrial fibrillation (AF) is a common complication of myocardial infarction (MI) with incidence of 6-22%(1,318-324,407). Despite the prognostic benefits of thrombolytic therapy and percutaneous coronary intervention that has been consistently demonstrated in studies during the reperfusion era, AF remains as an independent predictor of adverse short -and long-term outcomes.(320,321,325,328,406) These findings may be related to progressive circulatory failure. A combination of rapid ventricular response that results in reduced ventricular diastolic filling and increased oxygen demand during AF has the potential to compromise the patient's haemodynamics, impair coronary circulation and adversely affect prognosis. AF and congestive heart failure (CHF) are commonly encountered together, with a shared biological mechanism in the setting of ischaemic heart disease that includes the promotion of myocardial fibrosis and dysregulation of intracellular calcium and neuroendocrine function(232,312,313). However, it is also possible that the adverse prognostic effects of AF in the setting of acute MI may also be related to sudden cardiac arrhythmic death. Interestingly, primary and secondary prevention studies of implantable cardioverter defibrillators (ICD) have found that patients with AF not only require more appropriate device therapy but also receive more inappropriate ICD therapy.(315-317) However, there are no studies that have provided direct evidence to support the claim that AF "begets" ventricular fibrillation (VF), particularly in the setting of hospitalisation for acute MI. The aim of the current study was to determine the relationship between the development of new-onset AF and in-hospital VF and long-term mortality after MI.

6.2 Methods

6.2.1 Study population

This case-control study comprised of 3,200 patients who presented to the Flinders Medical Centre from 2003 to 2009 with diagnosis of acute MI that was validated according to the ESC/ACC 2003 definition.(429) Our institutional clinical research ethics committee approved the study protocol.

6.2.2 Study design

The study design and the selection criteria are illustrated in Figure 1. MI patients who developed AF within 5 days during admission were matched with a control group of patients with MI who did not develop AF over the first 5 days of their index admission; with a ratio of one case to three controls that were matched to the category of ejection fraction. Of the 3,200 patients with MI, 149 (4.6%) developed new inset AF. After exclusion of patients without a complete data set, 96 patients remained as study cases. The control group comprised of 288 patients with MI and no AF. Patients' baseline demographic characteristics, comorbidities, drugs and electrolyte were all collected in data base registry. All patients underwent 2D transthoracic echocardiography during admission (Vivid 7, GE Healthcare). LV ejection fraction was measured from apical two-and four-chamber views using the Simpson biplane method of discs.

All patients were admitted for coronary care unit for at least 72 hour monitoring with telemetry then by daily clinical assessment and 12 leads electrocardiography if clinically indicated. AF was diagnosed on surface 12-lead ECG and was defined in accordance with HRS guidelines as an irregular rhythm with absence of discrete P-waves that persisted for ≥30 seconds.(453) Ventricular fibrillation was defined as a sustained broad complex continuously variable waveform. Ventricular tachycardia was defined as a regular broad complex rhythm of at least three beats.

6.3 Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD). Differences in quantitative variables between the groups were tested using Student *t*-test. Categorical variables were compared between the groups using Chi-squared tests. Cases and controls were compared using the logistic log regression model for binary outcome. Kaplan-Meier survival curves and Cox proportional hazards analysis were used to evaluate differences in survival rates between study groups. P-value < 0.05 was considered statistically significant. All statistical analysis was performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

6.4 Results

Of the 3,200 patients with MI, 149 patients (4.6%) developed new-onset AF with incidence rate of 6.05% (Figure 1). Patients with new-onset AF post MI were older (73±9 vs. 65±14, P=0.001) and more frequently women (35% vs. 31%; P=0.02). There was no difference between the groups in EF (52%±12% vs. 48%±13%, p=0.4), cardiovascular risk factors or pharmacotherapy (Table 1).

6.4.1 Predictors in-hospital Ventricular fibrillation

The incidence of in-hospital VF was higher in patients with MI and new onset AF than control group (12.5% vs. 2%, p=0.03). On univariable analysis, predictors of VF included AF (OR 5.45, 95%CI: 1.16-18; P=0.008) and ST-segment elevation MI (P=0.03) (Figure 3). After adjustment for other factors, predictors of in-hospital VF included new-onset AF post MI (OR 2.6, 95% CI: 1.33-5; P=0.005) and ST-segment elevation MI (OR 4.6, 95% CI: 1.3-15.7; P=0.01) but not age (OR 0.99, 95% CI: 0.94-1.04; P=0.8) or sex (OR 1.2, 95 CI: 0.37-3.8; P=0.7).

6.4.2 Mortality

There was a trend towards increase in-hospital mortality for patients with MI and new onset AF compared to controls (7% vs. 4%, P=0.06). Long-term mortality rates were higher for patients with MI and new onset AF compared to controls (29% vs. 11.8%; P=0.005) (Figure 4).

6.5 Discussion

This study highlights the clinical importance of new-onset AF during hospitalisation with acute MI in predicting in-hospital VF and poor long-term outcome. This association was independent of LVEF.

An increased ventricular response rate with the onset of AF might directly precipitate VF in an already compromised substrate of ischaemic myocardium through an increase in oxygen demand resulting in even more ischaemia and consequently promoting ventricular susceptibility to arrhythmia.(454) The irregular-irregular rhythm of AF leads to short-long-short sequences that might facilitate ventricular tachyarrhythmia.(455) In addition, an irregular rhythm may increase ventricular stretch and induce pro-arrhythmia via electro-mechanical feedback. Atrial arrhythmia, particularly in context of ischaemia, may also alter autonomic tone resulting in an increase in sympathetic tone and decrease in parasympathetic tone with a consequent enhancement of myocardial susceptibility to ventricular arrhythmia.(456,457) Nevertheless, AF-VF association during MI may simply be an epiphenomenon due to a decrease in myocardial fibrillatory threshold during the acute phase of myocardial ischaemia.(458) Regardless of the mechanism, our findings are supported by studies showing that 10% of ventricular therapies in ICD recipients were immediately preceded by AF with a rapid ventricular response.(454,459)

AF and left ventricular dysfunction are commonly encountered together with a complex relationship which is more evident in the event of myocardial infarction or coronary artery disease. Most studies reported that the incidence of heart failure or LV dysfunction is significantly higher in AF patients compared to sinus rhythm with incidence as high as 65%.(318,320,460) Meanwhile, post infarct heart failure is commonly followed by AF and EF is the most important predictor of AF after MI.(321,460,461) Left ventricular ejection fraction is one of the most important determinants of patients prognosis post MI. However, this study showed new onset AF adversely affects MI patients independent of LVEF. New onset AF was

associated with increased in hospital VF and mortality independent of the patients EF. In addition, new onset AF was also associated with increased long term mortality compared to non AF patients. Others factors influence patients long term outcome are age and lack of b-blockers usage.

AF adversely influences the prognosis of patients with MI through a number of mechanisms including cerebral and systemic thromboembolism, tachycardia-induced cardiomyopathy, haemodynamic changes during the acute phase of MI and the toxic effects of drug therapy for AF. This study has demonstrated another mechanism by which AF may affect prognosis through an increased risk of VF post-MI. Although AF may be in part a surrogate marker of the overall poor clinical status in an older and more debilitated population, our study showed that the value of AF as a predictor of reduced long-term survival was independent of factors such as EF or age.

6.6 Study Limitation

We acknowledge inherent limitations of our case control study. However, we have minimised the effect of misclassification bias through the systemic collection of data including routine ECG-monitoring in the immediate post-MI period and ascertainment of vital status.

6.7 Conclusion

New-onset AF complicating hospitalisation for an acute MI is independently associated with increased risk of in-hospital VF and reduced long-term survival. Further studies are required to determine whether closer ECG monitoring and intensification of medical therapy will offer cost-efficient clinical benefits for patients with MI who develop new-onset AF during their admission.

Figure 1.

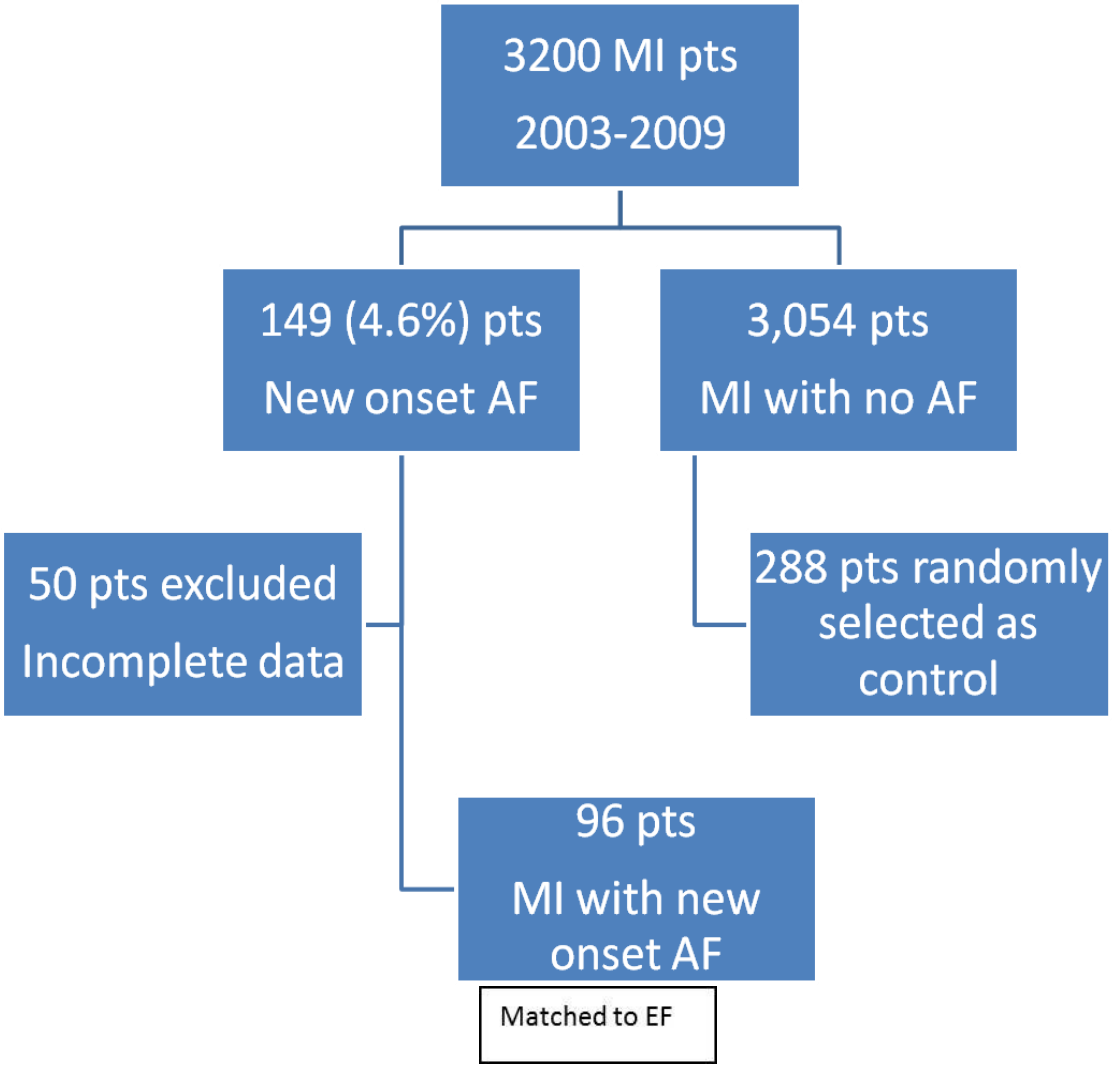


Figure 1: Study design

	MI with New-AF N=96 pts	MI with No-AF N=288 pts	P-value
Mean age	73±10	65±14	0.001
Male sex, n(%)	54 (65)	200 (69)	0.02
Hypertension, n(%)	56 (58)	168(58)	1
Diabetes Mellitus, n(%)	27 (28)	84 (29)	0.8
Hypercholesterolemia, n(%)	50 (52)	141 (49)	0.6
B-blocker, n (%)	83 (86)	213 (85)	0.8
ACE-I/ARB	76 (79)	201 (80)	0.9
STEMI, n(%)	11 (11)	81 (28)	0.001
LVEF	50±12	48±13	0.4

Table 1: Characteristics of the study population. STEMI (ST-segment elevation; ACEI (angiotensin converting enzyme inhibitor; ARB (angiotensin receptor blocker), LVEF (left ventricular ejection fraction).

Figure 2.

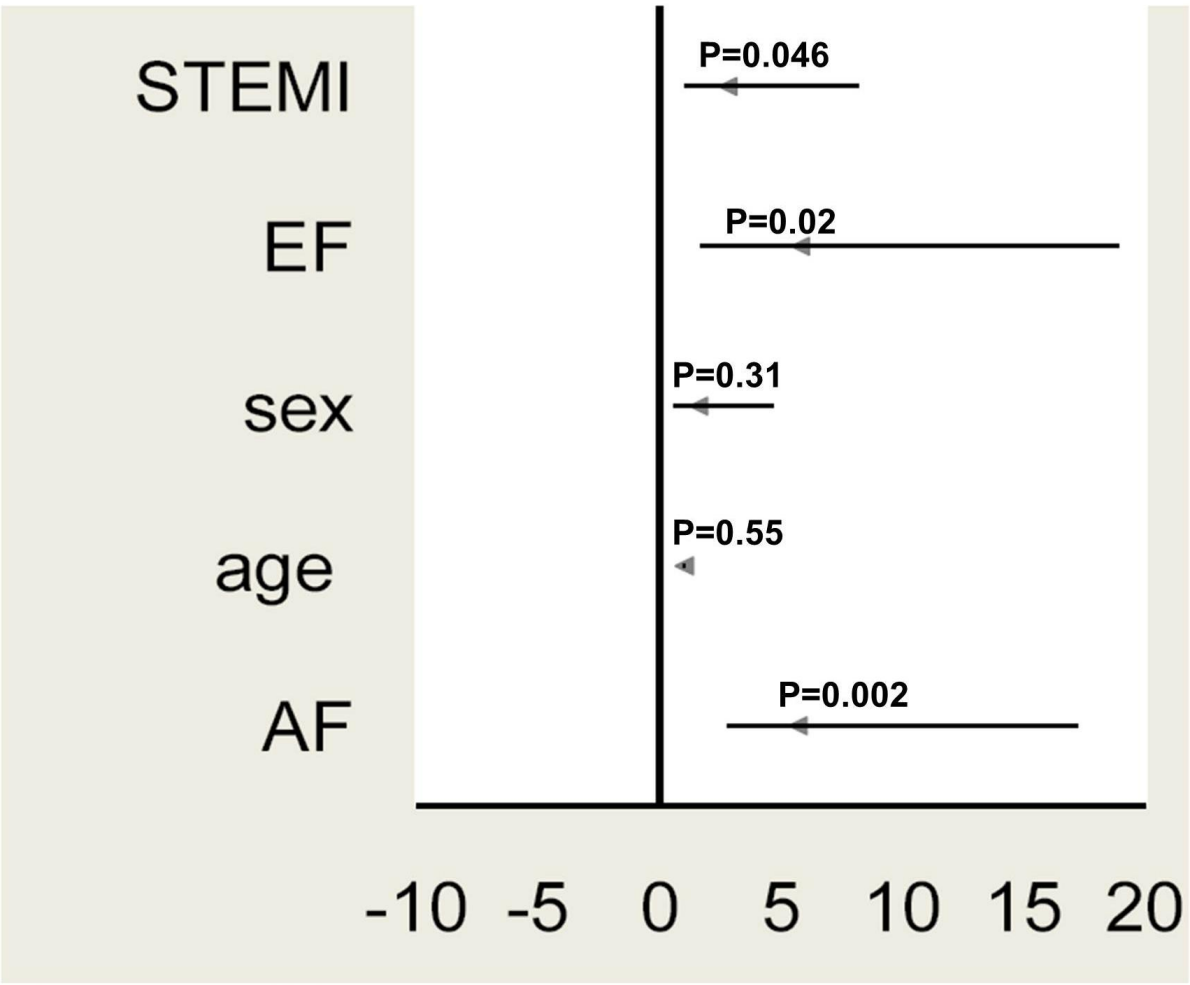


Figure 2: Forest Plot showing univariate predictors of in-hospital VF

Figure 3**.**

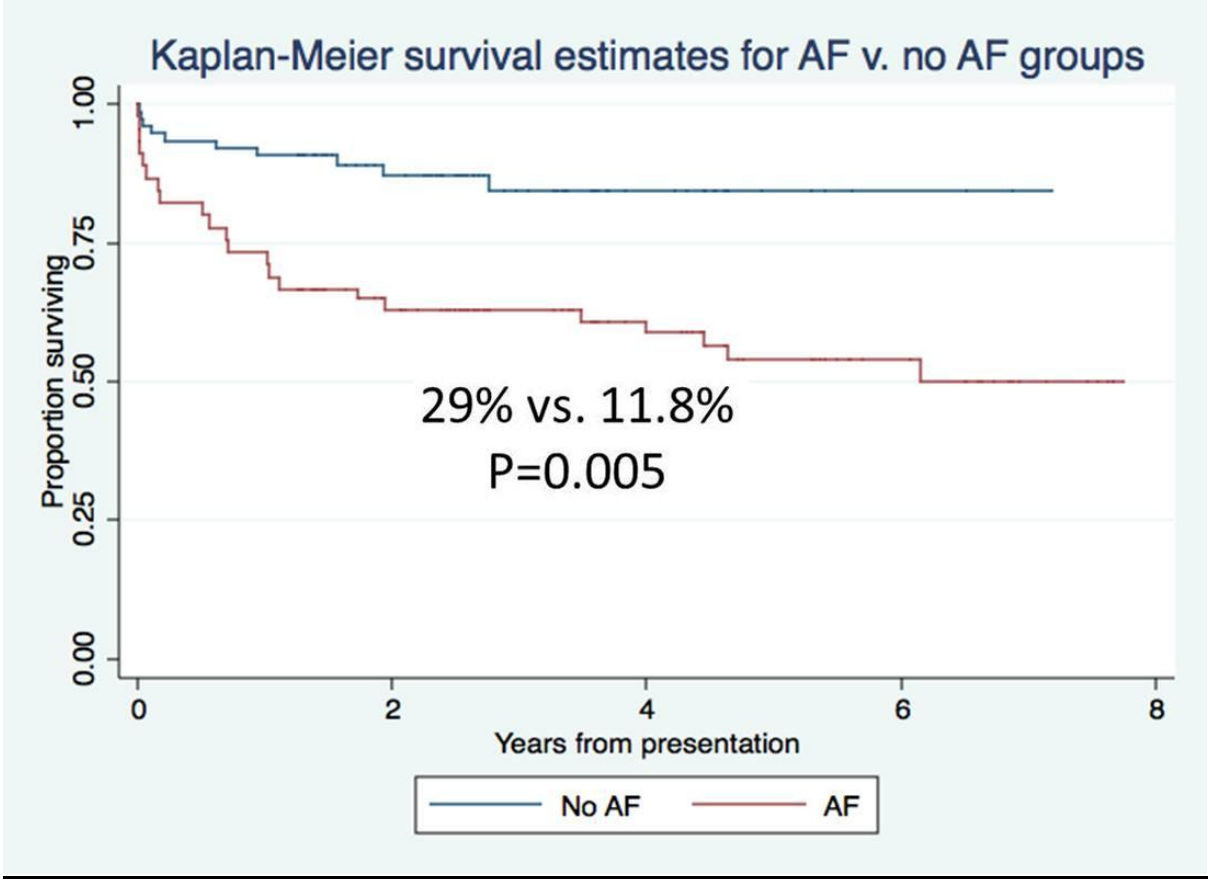


Figure 3: Kaplan –Meier survival estimates for AF group vs non AF post MI over 5.5 years.

Chapter 7

7.1 Conclusion and future directions

This thesis focused on the mechanistic link between atrial fibrillation and acute myocardial infarction. Although AF is a common complication during AMI, our knowledge of the mechanism by which AMI leads to AF is incomplete. This thesis evaluated the pathophysiological process of AF during AMI in the clinical and bench side setting. It also examined the incidence and the prognostic value of AF post AMI.

The incidence of AF after AMI has significantly decreased over the last 30 years as demonstrated in our systematic review and meta-analysis in chapter 2. However, the mortality remains significantly higher in AF patients post MI compared to non-AF patients with MI. This association has not changed when we compared patients during the prethrombolytic (1980s) vs. thrombolytic era (1990s) or even coronary angioplasty era (2000s). While this may be attributed to the fact that AF patients are older with more comorbidities and had less coronary intervention compared to non-AF patients, more work is required to address this issue. The role of anticoagulation with warfarin or the new novel anticoagulation in AF patients after MI needs further research, particularly in AF patients who require dual antiplatelets post coronary intervention with stenting.

The mechanism of AF during MI was also studied in the ovine model of myocardial infarction as well as in the clinical setting when patients presented with MI and the lesion involved the proximal right coronary artery or left circumflex artery where the atria get their blood supply. In both settings (Ovine chapter 3 & Clinical chapter 4) atrial ischaemia or infarction was found to play an important role in the pathogenesis of AF post MI. Atrial ischaemia resulted in multiple electrophysiological changes such as shortening of atrial effective refractory period, prolongation of conduction velocity and increase in conduction heterogeneity index (CHI). These electrical changes predisposed to re-entry and AF. In addition, left atrial stretch as demonstrated by raised left atrial pressure was also an important determinant in the development of AF after MI. The studies clearly demonstrated that AF aetiology during MI is

multifactorial and related to atrial ischaemia, hemodynamic changes and the neurohumoral response during MI. Early coronary intervention may reduce the atrial ischaemic burden and improve patients' overall prognosis as shown in chapter 4.

AF with rapid ventricular response increased the incidence rate of in-hospital VF arrest during MI as demonstrated in chapter 6. This association was independent of left ventricular ejection fraction. Increased oxygen demand during tachycardia, ventricular stretch due to irregular rhythm and short-long-short sequences during AF might all facilitate ventricular arrhythmia.

Finally, the management of AF post MI is suboptimal with a lack of evidence-based medicine. Further studies require determining the optimal antiarrhythmic as well as the best anticoagulation regime, especially in those who require dual antiplatelet therapy.

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