EXERCISE IN ATRIAL FIBRILLATION

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STUDENT DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree. I give consent to this copy of my thesis when deposited in the University Library, being made available for loan and photocopying, subject to the provisions of the Copyright Act 1968. The author acknowledges that copyright of published works contained within this thesis resides with the copyright holder(s) of those works. I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and through web search engines, unless permission has been granted by the University to restrict access for a period of time. I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Signed:

______________________________

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ABSTRACT

Atrial Fibrillation (AF) is the most common sustained cardiac arrhythmia affecting 1-2% of the global population. Up until recently the treatment of the condition has been centred around either rate or rhythm control strategies in the form of pharmacological or surgical approaches. Emerging studies have demonstrated the importance of treating the underlying cause of the arrhythmia; focusing on the risk factors that are known to predispose to AF. These include obesity, obstructive sleep apnoea, type II diabetes mellitus, dyslipidaemia, alcohol and smoking. This new approach to focus on risk factor management has shown positive outcomes in the management of AF with a reduction in symptoms and burden, but also a reversal of the atrial substrate and subsequent reversal of the disease progression.

Physical inactivity is increasingly recognised to contribute to many of these predisposing conditions but also as an independent risk factor for AF. Therefore, the potential role of physical activity and exercise in both the prevention and management of AF is gaining attention. This thesis focuses on the relationship of physical activity and exercise in both the prevention and management of AF and aims to extend our understanding of the role exercise can play within this emerging field.

Chapter 1 presents an initial insight into the growing prevalence of AF, its related risk factors and a detailed summary on the pathophysiological remodelling within the heart that leads to AF. Then this chapter aims to provide a comprehensive literature review of the current relationship of physical activity and exercise in the causation and prevention of AF and aims to provide comprehensive insight into this relationship that currently exists. This chapter also summarises the current studies that investigate an exercise led intervention in those with AF both in persistent and non-persistent AF, which then provides the rationale of the proposed series of studies and the main part of the PhD project being the ACTIVE-AF study.
Chapters 2 and 3 are meta-analyses that aim to provide important information on those studies that have assessed cardiorespiratory fitness at baseline testing and its relationship to both AF and stroke incidence. These chapters aim to provide further rationale on how exercise and improvements in cardiorespiratory fitness can reduce the risk of AF, and furthermore reduce the risk of stroke, especially that stroke is associated with AF and the risk is severely heightened in those with the cardiac arrhythmia.

Chapter 4 is a study in which we assessed the use of a heart rate marker typically used to prescribe exercise target intensities in healthy populations. Heart rate reserve is a measure that assumes equivalence to one’s corresponding oxygen update or VO$_2$ and has yet to be investigated to assess its validity in the AF patient cohort, whether the two measures are in fact equal. This study found that the use of heart rate reserve cannot assume its equivalence to a corresponding VO$_2$ and therefore must be calculated on an individual basis following a cardiopulmonary exercise test, which can then allow for the prescription of individualised exercise targets in patients with AF.

Chapter 5 is a study which evaluates the association between AF symptom burden using the University of Toronto AFSS questionnaire and cardiorespiratory fitness levels. Further to this, the study also assesses whether subjective assessment of exercise dyspnea and exercise intolerance relates to cardiopulmonary derived measures. The purpose of this study is to provide insight whether objective assessment of cardiorespiratory fitness can predict one’s degree of AF symptom severity calculated using the AFSS questionnaire.

Chapter 6 then aims to further assess the role of rhythm status on cardiopulmonary gas exchange measures, with attention in VO$_{2peak}$ and ventilatory efficiency. There have been several studies to date which have assessed the immediate changes to VO$_{2peak}$ following successful restoration of sinus rhythm via direct current cardioversion or catheter ablation;
however, very few have assessed for any changes also within a measure of ventilatory efficiency reflected by $V_t/VCO_2$ in patients with ‘asymptomatic’ AF. This study therefore aims to assess in more detail besides cardiorespiratory fitness changes, whether other cardiopulmonary gas exchange markers improve after 4-week after successful restoration of sinus rhythm by cardioversion in patients with ‘asymptomatic’ AF and aims to provide new insight in whether this patient cohort do in fact exhibit symptoms that can be detected during cardiopulmonary exercise testing.

Finally, in Chapter 7 we assessed an exercise intervention in the management of AF. The findings of study have been to date the largest randomised controlled trial to assess a physical activity intervention in patients with symptomatic AF. The study’s primary end points showed significant improvements in exercise capacity following 6-month intervention period in those patients within the intervention group compared to controls. This study was able to further assess and validate the role of an exercise led-intervention in AF patients, as improvements to exercise capacity and subsequent volume of oxygen uptake have a direct effect in improving AF known risk factors and should be a part of the newly adopted risk factor management approach within this disease population.

In conclusion, we assess and summarise the current link between exercise in the prevention and management of AF. We also address the proposed link in athletic cohorts where exercise is purported to promote AF, however there is still more to be done to effectively assess this relationship. However, for the general population where obesity and physical inactivity rates are growing there is no doubt that the benefits of engaging in regular exercise far outweigh any potential risk.
CHAPTER 1 - EXERCISE AND ATRIAL FIBRILLATION: PROTECTIVE OR CAUSATIVE! A
COMPREHENSIVE LITERATURE REVIEW OF THE CURRENT STUDIES.

1.1 Prevalence and Global Burden of Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia affecting 1-2% of the
global population. [1] AF is directly associated with an increased risk of stroke, cardiovascular
disease (CVD) and all-cause mortality. [2-4] Patients with AF commonly experience a broad
range of symptoms including; palpitations, shortness of breath, dizziness, reduced exercise
capacity and fatigue and an overall decreased quality of life. [5] The risk of developing AF is
increased in presence of established coexisting morbidities such as; hypertension, [6] type II
diabetes, [7] alcohol and smoking. [8, 9] However, there are now newly emerged risk factors
that have been associated with AF that include; obesity, [10, 11] obstructive sleep apnoea, [12]
pre-hypertension, [13] physical inactivity, [14] genetics and increasing age. [15-17] Indeed, as
the community prevalence of some of these new risk factors increase, it is likely that obesity
and physical inactivity are poised to become dominant attributable risks for AF. Not only have
these risk factors been associated with an additive risk of developing AF, [18] but evidence
suggests that the number of co-existing risk factors determine the onset of persistent AF and
determines the progression of the AF disease process. [19]

At present there is an exponential rise in the prevalence of AF worldwide, which
subsequently increases the frequency of AF-related hospitalisations and demands on
healthcare systems. [1, 3, 20, 21] In large review of population-based data of AF over a 30-year
period, Chugh et al., assessed the global burden of AF across this period with the final analysis
of the 184 included studies showing a significant increase in AF prevalence and incidence
across both sexes from 1990 to 2010. [3] Furthermore, it was shown that AF prevalence was
significantly higher in males aged >75-years, further reinforcing the relationship of age as an AF risk factor. [3] Within the US Olmsted County cohort-study assessed AF prevalence from 1980 to 2000 they noted a significant increase in AF incidence from 3.04 to 3.68 (per 1000 person-years), with a projected increase of 300% in AF diagnosis based on their results up to the year 2050. [22] This increasing prevalence naturally places severe pressures within the healthcare system and within a prospective study in the US analysing AF-related hospitalisations between 1985 until 1999 they showed that there was a 3-fold increase in the recent years, with more than 50% of hospitalisations occurring in those aged >75-years, which is no surprise given previously published data on the growing prevalence of AF worldwide. [23] Further to this, we are seeing a similar picture within the Australian population with recent data showing a high prevalence of AF in people aged >55-years of 5.4%, with a forecasted 120% increase to 6.4% by 2034 [15]. Additionally, the rate of hospitalisation for AF in Australia has now exceeded those for heart failure and myocardial infarction between 1993 and 2007, with an increase of 203% of AF hospitalisations, compared to only 4.5% and 17% for heart failure and myocardial infarction respectively. [24, 25] There is no doubt that within Australia and globally with the increasing prevalence and hospitalisations related to AF also have a huge economic implication for healthcare costs. Healthcare costs associated with AF doubled in the UK from 1.2% the total national health care budget to account for 2.4% only five-years later in 2000. [26] Similarly, the US have experienced similar increases in medical costs associated with AF which is predicted to increase simultaneously with the growing prevalence and burden. [27] This growing epidemic of AF has been continuing for some time now and is expected to further increase over the coming decades in conjunction with the growing prevalence of obesity and other CVDs which are now shown to be risk factors of AF. It is key that we require stronger primary preventative strategies via improved public policy strategies and awareness campaigns
to address the growing strain on the already fragile healthcare systems worldwide, and to reduce AF-related morbidity and mortality.

1.2 Exercise and Cardiovascular Disease

Regular exercise is well established as a key component in the prevention and treatment of CVD, with greater cardiorespiratory fitness (CRF) inversely related to the incidence of CVD and all-cause mortality. [28, 29] At present, physical inactivity is estimated to be responsible for 9% of world’s premature mortality, and 10% of the major forms of heart disease. [30] The current benefits of exercise both within the prevention and treatment of AF is receiving growing attention given the favourable impact exercise has on AF modifiable, lifestyle-based risk factors.

Exercise is well established as a form of preventative or adjunct treatment for CVD, with higher levels of physical activity independently associated with reduced cardiac morbidity, cardiac and all-cause mortality. [29, 31, 32] The WHO guidelines promote 150 mins of aerobic physical activity per week due to its benefits in improving CVD outcomes and minimising CVD incidence. [33]

Data from large cohort studies has revealed the benefits of even modest amounts of physical activity. In population data from Taiwan, Wen et al., demonstrated that as little as 15-minutes of daily aerobic exercise reduced all-cause mortality by 14% compared to sedentary people. [34] Further studies have extended these findings showing significant risk reductions in all-cause mortality in individuals those individuals who are the most active compared to sedentary individuals. [31, 32, 35]

Similarly, other studies have demonstrated an inverse relationship between CRF and CVD, with reduced CVD risk, cardiac and all-cause mortality in individuals with high CRF. [29,
In a meta-analysis, Kodama et al. analysed 33 studies that assessed CRF by an exercise stress test, and demonstrated a significant lower risk of CVD and all-cause mortality in those with higher CRF. [29] The analysis also highlighted a significant reduction in CVD and all-cause mortality per 1-MET increase in aerobic capacity of 15% and 13% respectively. [29] More recently, Bhella et al. assessed the long-term benefits associated with lifelong exercise of 4-5 times per week. They showed that lifelong regular exercise resulted in improved cardiac function by ways of; improved levels of LV stiffness and distensibility, higher stroke volume and greater LV end-diastolic and end-systolic volumes, which are known to be associated with incident AF. [36] Therefore, it is plausible to suggest the important role exercise and improved CRF can play in the prevention and treatment of both CVD and AF.

1.3 Risk Factors of Atrial Fibrillation

Cardiac disease and cardiovascular risk factors are independently associated with the development of AF. While age remains a significant risk for AF, heart failure, valvular heart disease and coronary artery disease have long been associated with the development of AF. In recent years, the risk of AF has been shown to be greatly increased in those with known CVD risk factors such as; hypertension, [13] obesity, [11] obstructive sleep apnoea, [37] type II diabetes, [38] alcohol and smoking. [8, 9] Typically, these risk factors often co-exist and results in an additive risk of developing AF. In addition, the number of risk factors that co-exist has been associated with the development and progression of more persistent forms of the disease. [19]
**Hypertension**

Epidemiological data supports a strong association between hypertension and AF. [39] In a prospective study assessing of 34,000 females in the Women’s Health Study, the presence of hypertension was associated with a two-fold increase in AF risk. [13, 40] There was graded increase in risk of incident AF, with a 37% increased risk in the lower ranges of what is now classed as hypertension (Systolic BP 130-139mmHg), up to a 121% increased risk in presence of established hypertension >140mmHg. [13] These results seem consistent with early population data from the Framingham Heart Study which showed that hypertension yielded a 50% and 40% increased risk of AF in males and females respectively across 180,158 person-years of follow-up. [41] Based on this data there is no doubt that hypertension significantly contributes the highest attributable risk of AF. This provides important information in the need to monitor and prevent hypertension if possible, especially now with the newly updated guidelines which have lowered the bar in terms of diagnosed hypertension with a systolic cut-off of 130mmHg, compared to 140mmHg previously. [42] Therefore given this, there is no doubt that many more people may be at risk of AF given this lower threshold to diagnose hypertension, which provides further importance in controlling blood pressure as early as possible to minimise AF onset.

**Obesity**

Global obesity rates have grown concurrently with an increasing burden of AF. [43] Obesity is a strong predictor of AF, with those with a BMI > 30 along with every one-unit increase in BMI being a significant accentuated risk of AF. [44-46] This data has been further supported in a recent meta-analysis by Wong et al., which assessed the association between BMI to incident AF, and showed a significant increased risk of AF by 29% for every 5-unit increase in BMI,
highlighting the importance that even modest reductions in weight can have a significant clinical impact. [47] By the exponential growth in the burden of individuals globally who are overweight or obese, this is poised to contribute the greatest attributable risk in

**Sleep disordered breathing**

There is strong epidemiological data linking obstructive sleep apnoea and AF with recent data to suggest that it exists in up to 74% of AF patients. [48] Patients with OSA are over two-fold more likely to be diagnosed with AF, and in turn those with AF are more likely to be diagnosed with OSA, with data suggesting 21-93% of patients with AF are likely to be diagnosed with the sleep disorder. [37, 49] Gami et al., assessed the role of OSA, obesity and risk in incident AF, finding a three-fold increased risk of AF in those with OSA. Notably, the magnitude of nocturnal oxygen desaturation was an independent predictor of AF. [50] Not only has OSA had significant contribution to the development of AF, there is evidence to suggest it has implications to our ability to maintain sinus rhythm after cardioversion or catheter ablation. [51-53] OSA has shown to play an important role in the promotion and recurrence of AF. [51, 54]

**Diabetes Mellitus**

Early observational data has showed a strong relationship between Type II Diabetes Mellitus (Type II DM) and AF which is now established it as an independent risk factor for AF. [55] In a case control study conducted by Dublin, et al., showing that those who suffer from DM had a 40% increased risk of incident AF. [56] These results were consistent to the Atherosclerosis Risk in Communities (ARIC) study by Huxley at al., where they showed that those who suffered from DM had a 35% increased risk of AF. Additionally, within the study, a linear relationship was observed between HbA1c and AF risk in those with DM, with the results highlighting a 13%
increased risk of AF for every 1% increase in HbA1c. Thus giving important insight into the association between glycaemic control and AF incidence. [38] Similarly, a meta-analysis within this relationship confirms this relationship presenting that those who suffer from the condition having up to a 40% increase in incident AF. [7]

**Physical Activity and Endurance Sport**

Whilst in the general population increasing levels of physical activity and exercise have shown to reduce the risk of AF, there is conflicting data in elite endurance cohorts that chronic exercise at these upper intensities and frequencies may in fact be a predisposing risk factor to AF. This relationship is discussed in greater detail below.

**Other emerging risk factors**

Additionally, there is data to suggest that there is an increased risk of AF associated with alcohol intake and smoking. [8, 9, 57, 58] ‘Holiday Heart’ or an alcohol binge was initially proposed by Ettinger et al., assessing the phenomenon whereby AF hospitalisations increased within a group of 24 patients following a weekend or holiday-season binges raising the link between binge drinking and AF. [59] In a recent meta-analysis assessing the association between alcohol and AF, there was no risk seen in low alcohol intake over a week. However, there was a moderate increase seen in the males only of 11%, with a significant 34% increased risk of AF seen in both genders who consume more than 2-3 standard drinks per day. [60] In patients with AF regular moderate alcohol intake has been associated with a significantly increased left atrial size and impaired atrial mechanical function compared to non-drinkers, providing important insight in the link between alcohol as a risk factor for AF and its role in progressing AF substrate. [61]
Limited studies have been unclear with the relationship between smoking and AF incidence; however, new studies have shown that smokers and former-smokers having a 1.5-2-fold increased risk of AF. [8, 62]

Finally, there has been little conclusive data to date to link excessive caffeine intake as a risk factor for AF. In an early cohort study by Frost et al., within the Danish Diet, Cancer and Health Study, they found no evidence to suggest that higher amounts of caffeine were linked to AF. [63] However, growing attention now is focused around energy drink consumption given their naturally higher caffeine concentration and the high consumption rates amongst young adults. Recent case reports have shown a link between energy drink consumption and arrhythmias or sudden cardiac death, with no study to date actually producing any data or cutoff around caffeine level intake and arrhythmia risk. [64] Future randomised controlled trials within this area would be required to quantify this relationship.

1.4 Mechanisms of Atrial Fibrillation

The onset of AF is associated with underlying remodelling to the atria which results in the establishment of the substrate and triggers that promote AF.

**Structural Remodelling**

Structural remodelling is seen to be a key mediator in AF onset and progression that is caused by atrial dilatation, fibrosis and inflammation, all of which result in local conduction disturbances thus increasing the likelihood of re-entry circuits. [65, 66] Atrial fibrosis is a common component of structural remodelling seen in patients with AF. [67] Fibrosis is physiologically the excess deposition of extracellular matrix proteins by fibroblasts (cardiac) which result in poor tissue compliance and function. [68] The progression of fibrosis (either
reactive or reparative), it can lead to slower conduction, increased conduction heterogeneity and promote re-entry or ectopic activity, which in turn promotes arrhythmogenesis, and in longer-term results in the substrate progression of AF from paroxysmal to more chronic forms of the disease. [69-72] The promotion of fibrosis in AF over the past decade has received widespread attention suggesting that the increased production of profibrotic markers of both angiotensin II and transforming growth factor-β1 are responsible system pathways that leads to the fibrosis. [73] Increases in both of these profibrotic markers have shown to be associated with atrial enlargement, increased conduction heterogeneity and increased AF. [74]

**Autonomic Remodelling**

The interplay between the parasympathetic and sympathetic arms of the autonomic nervous system has shown to have an important role in the promotion of AF, with the Euro Heart Survey by de Vos et al., showing one-third of their paroxysmal AF patients had an autonomic trigger associated with their AF onset. [65, 66, 75, 76] It has been postulated that the vagal effects on AF physiology play a key part in the onset of the arrhythmia especially during times of peak dominance at night, during rest and within the post-prandial period, with increases in vagal activity casing shortening of the atrial effective refractory period and action potential durations and delayed after depolarization which promote premature atrial electrical signalling. [77, 78] There is also the adrenergic (sympathetic) effects which typically occur following period of exercise, emotional stress or during the day mainly in patients with existing heart disease, which these sympathetic increases resulting in delayed after depolarizations and increased Ca²⁺ channel loading thus leading to the arrhythmia. [78, 79] It seems that both vagal and sympathetic influences play an overlapping role in contributing to the initiation of AF and
maintenance, with data suggesting an initial increase in sympathetic activation followed by increased vagal activity prior to triggering AF. [77]

**Electrical Remodelling**

There is much data that has established AF as a progressive disease that if left untreated with concomitant risk factors it can become more sustained and lead to more persistent (or permanent) forms. [65] Studies have now shown that ‘AF begets AF’ with longer durations of the arrhythmia associated with a slower restoration of positive electrical remodelling upon restoration of sinus rhythm. [80-82] The electrical remodelling of the atria that occurs that promotes the arrhythmia is associated with increases in atrial conduction time and atrial effective refractory periods, decreases in conduction velocities and prolongation of p-wave duration which promote ectopic firing and can precipitate AF. [83-85]

**Ionic Remodelling**

There is some overlap between the electrical and ionic changes associated with the promotion of AF, as many electrical changes may in fact be caused by underlying ionic channel alterations. There are three key ion currents that have been associated in the promotion of AF.

Calcium (Ca²⁺) is seen as one of the key ions involved in the underlying ionic remodelling of AF, both via the inactivation or downregulation of L-type Ca²⁺ channel current channels (I_{Ca,L}). [67, 86] I_{Ca,L} is responsible for the plateau phase of the action potential and in the release of Ca²⁺ from the sarcoplasmic reticulum resulting in excitation-contraction coupling. [86] In the onset of AF there is significant increase in intracellular Ca²⁺ loading in the sarcoplasmic reticulum, which results in a downregulation of I_{Ca,L}, which reduces action potential duration and favours AF continuation. [73, 87] Furthermore, this increased loading subsequently leads
to Ca\(^{2+}\) channel handling abnormalities resulting in abnormal release of Ca\(^{2+}\) from the sarcoplasmic reticulum causing delayed after depolarizations, ectopic firing and re-entry further promoting or perpetuating AF. [83, 88, 89]

Potassium (K\(^{+}\)) is another ion involved in AF attributed to both inward rectifying potassium currents (I\(_{K_{\text{ach}}}\)) and outward potassium currents which are responsible for maintaining and the repolarization of the action potential respectively. [83] In patients with AF, inward rectifying potassium currents is enhanced leading to hyperpolarization and excitability which reduces action potential durations and sustains re-entry therefore contributing to AF onset and maintenance. [89-91]

Sodium (Na\(^{+}\)) in the context of AF is not as key as the previously mentioned, however it plays a part as sodium current (I\(_{Na}\)) is an important contributor in the action potential upstroke. [89] The sodium-calcium exchange (NCX) is responsible for maintaining homeostasis of the update of Ca\(^{2+}\) into the sarcoplasmic reticulum, and during Ca\(^{2+}\) leakage due to handling abnormalities this activates NCX producing an inward-current to trigger an action potential that causes delayed after depolarisations which are known triggers of ectopic firing and subsequent promotion and maintenance of AF. [92, 93].

**Mechanical Remodelling**

AF has also shown to result in a loss of contractile function of the atria which can lead to the formation of an atrial thrombus and increased risk of thromboembolic stroke due to the inefficient pumping of blood from the atria. [94] This loss of atrial contraction function was first proposed by Logan et al., and has since been shown to be greatest in patients with longer forms of AF episodes, with successful restoration of sinus rhythm via cardioversion shown to restore atrial mechanical function in those patients with smaller degrees of AF, compared to
those with a higher degree of burden having a significant delay in the complete restoration of contractile function. [94-97]

1.5 Atrial Remodelling with Cardio-metabolic Risk Factors

Cardio-metabolic risk factors result in remodelling of the atria to establish the substrate for AF. These alterations include changes to the structural, autonomic and electrical properties of the atria which results in the milieu that forms the substrate for AF. Interacting with this substrate are the various triggers or drivers of AF that results in clinical episodes of AF. [67, 98]

Hypertension

In an early study Kistler et al., used an ovine model to assess the effect of elevated BP on electrical and structural changes in promoting AF. At final analysis, they found that the sheep with elevated BP compared to controls had significant; atrial dilatation, conduction heterogeneity, reduced atrial conduction, conduction slowing, interstitial fibrosis and increased AF inducibility. [99] This study provided useful insight into the underlying role of hypertension in the role of atrial structural and electrical remodelling responsible for promoting AF. Following this, Lau et al., again in an ovine model assessed the role of short-term hypertension in the promotion of AF. Sixteen sheep were studied, with 10 sheep having hypertension induced over a 7-week period, and the remaining being controls. [100] The hypertensive group compared to controls had significant; atrial dilatation, reduced conduction velocities, conduction heterogeneity, greater AF inducibility, increased AF durations and fibrosis. [100] Further to this, in a chronic ovine model, Lau et al., assessed the degree of atrial remodelling across various time points. The group found that early hypertension (<5-weeks) was associated with significant; atrial dilation and hypertrophy, higher refractoriness and
increased inflammation, whereas after 10-weeks of sustained hypertension there was significant atrial interstitial fibrosis, conduction slowing and increased heterogeneity, showing the progressive changes associated with chronic hypertension. [6] Similarly in hypertensive rats, these structural and electrical changes were also observed with significant bi-atrial enlargement, atrial conduction heterogeneity, reduced atrial refractoriness, and increased atrial interstitial fibrosis. [101] To further support the remodelling of the atria caused by hypertension but in humans, Medi el a., (201) conducted an electrophysiologic and electroanatomic study to quantify the changes to the atria in patients with longstanding chronically treated hypertension, compared to age-matched controls. In patients with hypertension compared to controls there was a significant reduction atrial conduction, an increase in areas of low voltage and an increased tendency and duration of induced AF. [102] These studies strongly link hypertension, and even short-term hypertension as a key driver in the onset and progression of AF, with hypertension resulting in significant structural and electrical remodelling of the atria. Therefore, target therapies that aim to treat hypertension have been shown to be effective in management of AF. [98]

**Obesity**

Obesity has now been newly established to be strong risk factor for AF development and maintenance. In the pivotal animal study, which laid the foundations linking obesity to AF development and maintenance, Abed at al., examined the effect of progressive weight gain on the substrate for AF in a sheep model. Thirty sheep were induced with a high-calorie diet across an 8-month period, with sustained obesity shown to have severe consequences for the electrophysiological, electro-anatomical and structural remodelling of the atria. [10] The chronically obese sheep demonstrated significant; left-atrial enlargement, conduction slowing,
interstitial atrial fibrosis, increased profibrotic TGF-β1 expression and greater AF inducibility. [10] This study established the importance of obesity in the direct role of promoting the AF substrate. Further to this Mahajan et al., looked at sustained chronic obesity in an animal model, which resulted in the sheep having significantly increased; left atrial volumes and pressures, interstitial fibrosis and conduction heterogeneity, all of which contribute to the substrate for AF. [11] In addition, this study demonstrated a unique substrate with an increase in pericardial fat volumes associated with infiltration of the adjacent atrial myocardium; potentially forming a part of the unique substrate in obesity. In humans, there have been suggestion of atrial electrical remodelling. In obese patients with AF undergoing catheter ablation Munger et al., set out to quantify the electrophysiological changes associated with obesity in this cohort compared to those with a normal BMI. Similarly, to the previous animal studies, this study found significant conduction slowing, shorter ERP, increased left atrial volume and higher degree of atrial remodelling in the obese cohort, and therefore provide important insight in the role of obesity and AF in humans. [103] Recently, Mahajan et al., have extended their observations in the ovine model to demonstrate similar increases in pericardial fat being associated with areas of low voltage on electroanatomic mapping. [11]

Based on these studies showing the direct role of obesity in the development of the AF substrate, it would seem plausible to then look at interventions that target weight-loss. Emerging studies have shown the role of weight management plays in the treatment of AF. [104, 105]

**Obstructive Sleep Apnoea**

In a first study to assess the underlying mechanisms of this association Ghias et al., in a canine model established that recorded ganglionated plexi neural activity increased before the onset
of AF during apnoea. However, after neural ablation of the ganglionated plexi or autonomic blockade, AF onset was inhibited. [106] Further to this, Stevenson et al., assessed the acute effects of hypoxemia and hypercapnia in the development of AF in a sheep model. The study found that in fact hypercapnia was associated with a significant increase in atrial refractoriness and conduction slowing, compared to hypoxemia and control groups, which summarised that in fact hypercapnia episodes may in fact promote AF. [107] In a pre-clinical rat model by Iwasaki et al., they showed that AF was not inducible in obese or lean rats, however AF was induced in 86% of the obese rats during OSA in comparison to only 28% within the lean rats (p<0.001). This study highlighted the key role OSA plays to promote AF in both obese and non-obese rats, however the effect was further enhanced in combination with obesity. [108] In a pig-model Linz et al., showed that negative tracheal pressure during OSA was a strong trigger for AF onset due to enhanced vagal activation and atrial refractory period shortening. [109] Given the strong association of OSA and AF development, Iwasaki et al., again in a rat-model aimed to assess the underlying remodelling that promotes the arrhythmia. The study showed that OSA caused significant AF-related cardiac structural changes which resulted in conduction slowing, increased fibrosis and diastolic dysfunction leading to an increase in AF duration and inducibility. [110]

Within the clinical setting, Dimitri et al., assessed the impact of OSA on the atrial substrate promoting AF. Forty patients with paroxysmal AF who underwent ablation were dichotomised into an OSA group with an AHI>15 or a reference group with an AHI<15. Following the electrophysiological study, it was revealed that the OSA patients compared to controls had a significantly enlarged left atrium, reduced bipolar voltage within both atria, increased atrial conduction time, sinus node remodelling and slower conduction velocity, thus contributing to the substrate to promote and maintain AF. [111] More recently, in paroxysmal
AF patients undergoing pulmonary vein isolation, Anter et al., reported that in those patients with OSA (AHI>15) had significantly lower atrial voltage amplitude, slower conduction velocities and higher amount of fractionated electrograms. Interestingly the study also showed that in the OSA patients they had significantly more PV-triggers of AF, and ablation of these extra PV-triggers led to greater improved clinical outcomes compared to standard pulmonary vein isolation alone, thus further highlighting the added complexities OSA plays in underpinning atrial remodelling that predisposes AF. [112] These clinical studies clearly highlight the importance of OSA in the development and maintenance of AF.

**Type II Diabetes Mellitus**

Several physiological mechanisms have been proposed regarding the link between Type II DM and AF. Kato et al., in a rat model aimed to assess the degree of structural remodelling associated with diabetes. In this RCT study after 24-weeks the diabetic rats had significant degree of structural remodelling of the atria characterised by interstitial fibrosis, compared to controls. [113] In a further physiological study in diabetic rats, Otake et al., established that neural remodelling may play a role for the increased vulnerability to AF in diabetes. The diabetic rats compared to controls had significant heterogeneity of the atrial effective refractory period and enhanced adrenergic activation which promoted the arrhythmia. [114]

Furthermore, those diagnosed with Type II DM seem to have elevated circulating inflammatory markers, which may contribute to promoting fibrosis. [56, 113] Atrial enlargement, autonomic remodelling, changes in vagal tone and conduction slowing have also been observed in those with DM and are key factors in the development of AF. [67, 114-116]
Other risk factors

To date there is essentially no or very limited data at assessing the remodelling associated with the other AF risk factors. Alcohol as a risk factor for AF is still not well defined but has been attributed to alcohol shortening the atrial refractory period, autonomic nervous system disturbances, and also serves as a risk factor for other known CVD. [58, 117] This risk of AF onset has been linked to cigarette smoking causing autonomic nervous system disturbances, in particular increased sympathetic activity and endothelial dysfunction, oxidative stress and atrial fibrosis, as well as predisposing as a risk factor to other known CVD also related to AF. [62, 118]

1.6 Risk Factor Management in AF

From what we have seen above there is now an established strong link to lifestyle-based CVD conditions as a risk factor for AF. Therefore, if we manage these risk factors one can reduce their risk of AF. However, in those with established AF a new paradigm has shaped the way we treat the disease termed ‘Risk Factor Management’.

In the first study to assess weight-loss as a therapy for AF treatment, Abed at al., conducted an RCT amongst 150 patients to assess weight-loss intervention versus controls who were provided with information regarding diet and exercise. After 3-months, weight-loss resulted in a significant reduction in AF burden, symptom severity and cardiovascular risk factors. [10]

Similarly, in the LEGACY study which was an observational study assessing the long-term effect of weight management in 355 patients with symptomatic AF, showed that those who achieved >10% weight-loss compared to those who did not or gained weight at final 4-year follow-up had significant; reductions in left atrial volumes and pressures, improvements
in AFSS symptom severity and burden scores and higher AF freedom of 86% compared to 40%. [104] Importantly, these benefits are maintained in the long-term but may be dampened by weight fluctuation. [119] Additionally, weight loss and aggressive risk factor management also improves outcomes following catheter ablation, reducing AF recurrences. [120]

More recently, in the REVERSE-AF study a sub-study from the LEGACY study, it evaluated the impact of weight-loss and risk factor management in the progression of AF. [105] The study showed that AF is reversed in patients who lost >10% body weight, with 88% of patients moving from persistent to paroxysmal AF. In contrast, only 3% of patients progressed from paroxysmal to persistent AF, compared to 48% of patients who failed to lose or gained weight. [105]

These studies clearly establish obesity as a key risk factor in the development and progression of AF, via the altering of the atrial substrate responsible for the arrhythmia. It is quite evident now, that therapies that target weight-loss and at improving the individual profiles of other risk factors within each patient is in fact effective in negating the effects of AF and can reverse AF and achieve freedom from an arrhythmia that has previously been known to be solely progressive in nature. [98] It must be highlighted that weight-loss, in conjunction with managing and improving all the other identifiable AF risk factors in an individual patient is crucial in reducing AF burden which includes; improving BP <130mmHg, treating OSA with CPAP therapy, lowering of blood glucose and cholesterol levels and improving cardiorespiratory fitness levels. [104, 121, 122] In fact, recent guidelines have since incorporated risk factor management as a key treatment strategy in AF management. [123]
1.7 Effect of Exercise on AF Cardio-metabolic Risk Factors

Physical inactivity is well established to increase obesity, OSA, hypertension and type II DM incidence, which are also known AF risk factors. [124, 125] Given, the strong evidence highlighting the relationship with these cardio-metabolic risk factors and AF incidence, it’s important that we assess the efficacy of exercise and the associated physiological benefits it plays in improving these known risk factor profiles in both the prevention and management of AF.

Hypertension

In both the prevention and management of hypertension exercise has been shown to play a key role. In an early study by Duncan et al., which assessed the effect of a 16-week aerobic exercise program within 56 mild-essential hypertensive patients with a baseline diastolic BP >90mmHg. At final follow-up the exercise group significantly improved their cardiorespiratory fitness and had significant reductions in both systolic and diastolic BP. [126]

Similar results were also echoed in an RCT study amongst 46 middle-aged African-American men with severe hypertension. [127] The study assessed the role of a 16-week aerobic exercise programme performed three-days per week at an intensity of 60-80%HR$_{max}$ in conjunction with antihypertensive medication, compared to the control group solely using medication. After 16-weeks the exercise group significantly increased their peak oxygen uptake and significantly lowered their diastolic BP. [127] Even, after 32-weeks the exercise group still maintained a significant lower diastolic BP even in the presence of a lowered medication dose compared to controls. [127] Furthermore, systolic BP at peak and during submaximal exercise significantly decreased within the exercise group compared to controls, showing further
benefit associated with an aerobic exercise intervention in patients with severe hypertension. [127]

More recently, Dimeo et al., conducted a 12-week RCT amongst 50 patients with resistant hypertension and assessed a 12-week aerobic exercise intervention which consisted of three sessions per week. At the end of the intervention, the patients in the exercise group significantly increased their CRF but also had significant decreases in both systolic and diastolic ambulatory blood pressures, which was attributed to exercise led improvements in systemic vascular resistance and sympathetic tone. [128]

This was also evaluated in an early meta-analysis of 30 studies conducted by Cornelissen et al., which assessed the effect of aerobic exercise on BP. The analysis revealed that aerobic exercise training greater than 12-weeks resulted in a significant decrease of both systolic and diastolic blood pressures in hypertensive patients. [129] The reported magnitude of change was -6.9mmHg (-9.1 to -4.6) and -4.9mmHg (-6.5 to -3.3) in both systolic and diastolic blood pressures following aerobic exercise training. [129]

The consensus within these studies allude that 12-16 weeks of aerobic exercise at least three-times per week can lead to significant improvements in both systolic and diastolic BP, making it an effective therapy in conjunction with antihypertensives to further manage this condition.

**Obesity**

Obesity has now been shown to play a key role in AF, and any therapies that are able to offset this are extremely important in the prevention, management and reversal of AF. Regular exercise is well established to reduce total body fat, waist circumference, aid in weight loss and reduce visceral and abdominal adipose tissue (even without loss of total body weight). [130,
In a murine model by Wang et al., they assessed the effect of a six-week exercise training on T-regulatory cells and showed that high-intensity training resulted in increased anti-inflammatory cytokine expression and increased number of circulating T-cells. In combination with one another these two marked increases are known to reduce systemic inflammation and indirectly lower the amount of stored adipose tissue within the body. Furthermore, in obese female adolescents two-months of aerobic exercise and reduced caloric diet resulted in significant reduction in the levels of circulating pro-inflammatory adipokines and improved lipid oxidation. These studies provide insightful information in the underlying physiological changes associated with exercise regarding obesity profiles.

In fact, engaging in 150 minutes per week of aerobic exercise over 12-months without changes to diet in post-menopausal women (who are known to be susceptible to weight gain) has led to significant reductions in total body fat and abdominal fat, with superior reductions seen in those who engaged in more than 300mins per week. Further to this, Jakicic et al., showed that exercise and physical activity can be pivotal in weight-loss and maintenance, with significant improvements seen in moderate-vigorous physical activity >200-mins per week. Earlier to these studies, Jakicic et al., assessed difference exercise target intensities and durations on weight-loss and cardiorespiratory fitness across 12-months in overweight women. Interestingly, the study showed that across all four groups weight-loss was statistically significant, but there was no difference between the groups. Ultimately this provided important data that any form of exercise over long-term does result in weight-loss and improvements in cardiorespiratory fitness.

Based on this, exercise plays a very important part in order to aid weight-loss and importantly maintain weight after such improvements are achieved. However, with regards to this there are some limitations that need to be noted in the long-term sustainability of weight-
loss following the short clinician-led exercise and diet interventions. In a meta-analysis of studies by Johns et al., that assessed the efficacy of diet or exercise interventions versus combined behavioural weight management programs, it showed that there was no difference in weight-loss in the short-term of 3-6-months. However the greatest differences were shown at 12 and 18-months with significantly better achievement of weight-loss in the combined behavioural weight management programs, compared to solely diet or exercise interventions. [137] This depicts the importance to incorporate exercise, diet and behavioural changes to achieve sustainable long-term improvements in weight management.

**Obstructive and Sleep Apnoea**

The role of continuous positive airway pressure (CPAP) as the key treatment option for OSA is well-established with many studies proving its effectiveness in managing the sleep disorder, however there is emerging data that has looked at the role of exercise in the management of OSA. [110]

In an early study in this field by Sengul et al., they assessed the effect of an exercise intervention on apnea-hypopnea index (AHI) and quality-of-life in patients with OSA. Patients were randomised to control or exercise group which consisted of 45-60-minutes aerobic exercise three-times per week over 12-weeks and they showed that the exercise group significantly improved their AHI from 15.2 to 11 (p=0.02), compared to no changes in the control group (p=0.11) at follow-up. [138] The study further reported improvements in VO$_{2\text{max}}$ and SF-36 vitality and mental health domains in the exercise group compared to controls (p<0.05). [138]

Following on from this, Kline et al., underwent an RCT of 43 overweight/obese and sedentary adults with moderate-severe untreated OSA. Those randomised to exercise training
completed four sessions per week across 12-weeks targeting a total of 150-minutes of aerobic physical activity per week, in conjunction with two-days of resistance-based exercise sessions. [139] At follow-up exercise patients significantly reduced their AHI by 7.6±2.5 compared to controls whom in fact increased their AHI by 4.5±2.4 (p<0.01). [139] Further to this, there were also significant improvements in self-reported sleep quality index markers from the Pittsburgh Sleep Quality Index in areas of; sleep quality, latency and disturbances (p<0.05). [139]

These studies highlight that exercise can in fact play a part in the management of OSA, and aerobic exercise >150-minutes per week may be able to illicit greater improvements in AHI in conjunction with CPAP therapy.

**Type II Diabetes Mellitus**

The prescription of aerobic exercise has shown to be favourable in the treatment and management of DM, due to its ability to reduce HbA1c profiles irrespective of weight-loss. [125] Current ACSM guidelines do recommend exercise to be taken up on most days in the aim to prevent and treat Type II DM given the benefits of exercise are known to have on improving blood glucose control and insulin sensitivity. [140] Many studies have shown the importance of aerobic exercise in conjunction with resistance-based exercises to improve blood glucose profiles and management of DM. Church et al., in a RCT assessed the efficacy of a combined aerobic and resistance based training program across 9-months and showed significant reductions in HbA1c levels compared to control subjects. [141] In the LOOK AHEAD study, which assessed the role of weight-loss in conjunction with a physical activity program, after one-year this lifestyle intervention group showed a significant improvement in HbA1c control compared to controls. [142] However, in contrast, a recent RCT study by Johansen et al., (2017) showed that a 12-month lifestyle intervention program which predominantly consisted of
weekly aerobic sessions did not result in a statistical difference in HbA1c between groups at
time of follow-up. The lifestyle group did have a larger reduction in HbA1c compared to
controls, but was not significant, although the lifestyle group did also result in a substantial
reduction in glucose-lowering medications being taken compared to controls. [143]
Irrespective, of this study, the literature in this field strongly supports the role of exercise in
the role of diabetes management with favourable improvements across all demographics.

1.8 Exercise and Atrial Fibrillation – Protective or Causative?

1.8.1 Physical Inactivity as an AF Risk Factor

There is a growing body of epidemiological evidence identifying physical inactivity as a
potential risk factor for incident AF, with most studies quantifying levels of physical activity
through self-reported modes. [144] In a prospective observational study, Mozaffarian et al.,
assessed the relationship between self-reported physical activity levels and AF risk. Across 12-
years follow-up, participants with the greatest dose of physical activity (combined distance and
pace walked), had a 48% lower risk of AF compared to those with the lowest levels of reported
activity. Importantly, there was a dose-dependent effect across quartiles of physical activity.
[145] In a later prospective study, Everett et al., noted that those who accumulated average
physical activity levels >7.5MET-h/week, consistent with current recommended guidelines,
across the study’s median follow-up period of 14-years had a 14% decreased risk of AF
incidence, in contrast to those who were sedentary. [146] Similarly, Azarbal et al.,
demonstrated that >9 MET hours of physical activity per week was associated with a 22%
reduction in incident AF compared to those who were sedentary over a 11.5-year period. [144]
The Multi-Ethnic Study of Atherosclerosis by Bapat et al., showed a 54% reduction in AF
incidence between those who engaged in high levels of intentional vigorous physical activity,
compared to none. [147] Even more recently Andersen et al., in a cohort study of 1.1 million young men assessed the interplay between exercise capacity and muscular strength on the risk of arrhythmia, with the study showing that higher exercise capacity and muscle strength being associated with a 8% reduction in AF incidence. [148] These results were much lower compared to previous studies. However, this can be attributed to the younger-age of baseline testing for those recruited within the army, and the relatively lower presence of other known AF risk factors that you would typically see in an older population. Therefore, given the general healthier status of this study cohort, the actual results may be underestimated in comparison to others. [149]

In addition to the above-mentioned findings strongly favouring physical activity in reducing the risk of incident AF, Drca et al., reported lack of benefit from physical activity in reducing incident AF. However, they did show that at older ages >60 that regular exercise did slightly lower AF risk in males. [150] When assessing females, Drca et al., found strong evidence that increasing levels of physical activity correlated with a decreased AF risk. [151] Despite previous studies showing risk reductions with physical activity, Aizer et al., showed those who underwent vigorous exercise which was defined as exercise able to work up a sweat and greater than 5-times a week across 9-years had a slightly increased risk of AF, although at older ages the same amount of exercise slightly lowered AF risk. [152]

In two studies, there was some indication of an interplay between physical activity and obesity. Huxley et al., showed that excess body weight on its own without any physical activity is an important risk factor for AF, as the risk nearly doubles in those who were overweight or obese (HR: 1.20 and 1.95 respectively). [153] However, in overweight and obese men undertaking an ideal level of physical activity, exercise played a protective role against AF, countering the effect of excess body weight with an attenuated risk of AF. [153] This was
further supported by Azarbal et al., that similarly assessed obesity and physical activity, and its effect on AF risk in women. [144] The highest risk was in the obese and physically inactive (0-3MET-h/week) group compared to the obese and most active (>9MET-h/week) with a relative risk of 1.44 and 1.17 respectively. [144] Therefore, these studies show that exercise may blunt the arrhythmogenic effects of other risk factors such as obesity.

Although large epidemiological studies provide rich data regarding the role of measurable risk factors and incident AF, they are subject to limitations regarding the method of assessing physical activity on a large scale. In all studies, physical activity was assessed by self-report, thus leading to potential bias. An alternative method of examining the role between exercise, physical activity and AF is to record exercise capacity by way of an exercise stress test. This approach offers a more objective way of examining the role physical activity plays in reducing AF risk, if those who are physically active will typically have greater cardiorespiratory fitness and exercise tolerance.

Six studies have demonstrated the protective role of CRF against incident AF. [14, 154-158] These studies typically included patients who were referred for exercise stress testing for potential heightened risk of AF, with underlying CVD risk factors such as hypertension and Type II DM. CRF was determined at baseline and may have varied across the course of the study, and AF was diagnosed by hospital medical records and/or study ECG at various time-points. In the largest observational study so far of approximately 550,000 individuals from the UK Biobank Tikkanen et al., showed favourably that those with highest CRF had a significantly lower risk of AF incidence (HR: 0.40 95% CI 0.30 to 0.53). Similarly, Hussain et al., in a retrospective study assessed CRF and AF incidence over a median follow-up period of 14-years and found that again there was an inverse relationship between CRF and incident AF, with a higher CRF resulting in a significantly lowered risk in AF incidence (HR: 0.64 95% CI 0.57 to
Qureshi et al., also examined the association between baseline CRF and incident AF measured via a baseline exercise stress test and showed an independent relationship between a higher CRF and a decreased incidence of AF (HR: 0.44 95% CI 0.39 to 0.50). [155] These results are further supported by Faselis et al., and Khan et al., which again supported a higher CRF protecting against incident AF. [14, 159] These reductions in incident AF may be attributed to the increased CRF improving other known AF risk factors and therefore may be a target for improving outcomes in patients at risk or with AF. However, even though AF risk has been moderately lower in these previously mentioned studies, there was a negative study by Alonso et al., where their data did not reach any significance. For this study, it can be plausible to suggest that this may be attributed to their study design as it did not solely assess CRF and AF, but also assessed lifestyle intervention in patients with Type II DM, whom are already known to be at risk of AF. [156] Overall, these findings may be subject to limitations as there was a large difference between follow-up duration across the 6 studies, with 5.4-years being the shortest and 19.5-years being the longest, which may influence the findings of this analysis, in conjunction with the diagnosis of AF events across the follow-up period via study ECG or hospital medical records. However, these studies do show that there is an independent relationship between a higher CRF and a decreased incidence in AF.

Finally, ageing has been well-established as risk factor for AF above the age of 55-years, with a 9% increased risk of AF associated with a per-year increase in age. [41, 98] In an aged rodent model published recently, Malmo et al., assessed ageing in the promotion of AF and whether long-term aerobic training could counteract the effects associated with the ageing process. In this randomised control trial the older rodents were randomised to either a control arm or 16-week aerobic interval training programme. At follow-up the exercise intervention group had a significantly higher VO$_{2\max}$ than the controls, with the control group having a
significantly higher AF susceptibility and slower atrial conduction velocity. [160] It was shown that the long-term aerobic exercise training in fact had a protective effect against ageing, with the exercise group having an increased atrial conduction velocity and prolongation of the action potentials and reduction of action potential alternans, irrespective of both groups having significant fibrosis associated with age. [160] Therefore, this data supports previous findings that aerobic physical activity can protect against AF even within the ageing population.

1.8.2 Exercise Contributing to AF

Epidemiological evidence
Despite the growing evidence indicating physical activity as a preventative strategy to reduce both incident AF and outcomes in those with established AF, high-volume endurance exercise may potentially carry an elevated risk of incident AF. An early study by Karjalainen et al., compared the prevalence of AF in middle-aged men in those undergoing intense endurance training to that of the general population. AF was diagnosed in 5.3% and 0.9% of athletes and controls, respectively. The relative risk of endurance exercise was increased by over five-fold, showing an association between chronic endurance training and AF. [161]

In addition, Elosua et al., in a prospective case-control study evaluated the association between sports practice and the prevalence of lone AF in men and reported a three-fold increase in lone AF in those who engaged in more than 1500-hours of sports, with similar AF rates also reported in Baldesberger et al. [162, 163] Similarly, Molina et al., assessed the incidence of lone-AF in a retrospective cohort study of marathon runners and sedentary males. After follow-up there was a four-fold increase in the risk of lone-AF within marathon runners, with larger left atrial size being an independent predictor of AF within this cohort.[164] Wilhelm et al., also demonstrated that endurance training history was associated with greater
AF incidence, along with increased atrial size and elevated vagal tone. Endurance athletes had significantly greater AF risk compared to the sedentary subjects with 6.7% and 0.5% prevalence, respectively. [165]

In the largest cohort-study to date Andersen et al., looked at the relationship between the number of completed races and finishing times against the risk of arrhythmias in 52,755 long distance cross-country skiers. [166] This data showed that incident AF risk is increased in those who completed a higher number of races which may be taken as surrogates of endurance training history. [166] Myrstad et al., also supported these previous findings between endurance exercise and increased AF incidence in men, with every 10-years of endurance exercise related to a 16% increase in risk of AF. [167].

To shed further light on this relationship, Calvo et al., assessed the role of exercise intensity and cumulative duration on lone-AF risk in a prospective case-control design. Greater than 2000 hours of accumulated high-intensity aerobic exercise over a lifetime had the greatest relative risk of AF (OR 3.88 95% CI 1.55 to 9.73), compared to those who were less than 2000 hours (OR 0.38 95% CI 0.12 to 0.98). [168] The risk of AF also increased in those suffering from two or more known AF risk factors, thus stressing the important role other known risk factors play in the development of AF. [168]

In the most recent study, Morseth et al., further assessed various exercise levels to AF incidence, and found that vigorous exercise defined as hard training or competitive sports several times weekly attributed to only a slight elevated risk of AF (OR 1.29 95% CI 0.73 to 2.30). In comparison, with high (recreational sports at least 4-hours per week) and moderate (general aerobic exercise) levels of exercise in fact having a protective effect against AF risk of 0.94 and 0.81 respectively. [169] This low increase in AF risk is vastly different from previous studies within the field, which could be attributed to the younger mean age and overall better
health status of the recruited individuals. Therefore, leading to a population bias and underrepresentation of true AF risk.

**Exercise induced remodelling of the atria to predispose AF**

An animal study by Guasch et al., assessed the mechanisms underlying AF promotion from chronic endurance exercise, by randomly assigning rats to a control or exercise group which entailed one-hour a day, five-days per week of aerobic treadmill exercise across 16-weeks. Cardiac structure and function were assessed using transthoracic echocardiography, autonomic tone was quantified as the difference between heart rate after propranolol and hear rate after propranolol and atropine, and fibrosis was quantified by histology samples from the atria. [170] After the 16-week training period the exercise group compared to controls had significant; left atrial dilation (LADd: 1.17±0.03 vs 0.86±0.03mm/kg, p<0.001), atrial fibrosis (2.5% vs 1.3%, p<0.001) and enhanced parasympathetic tone (60 vs 35bpm, p<0.001). [170] Further to this, a key summary of this study was that AF susceptibility following chronic endurance exercise was significantly attributed to atrial fibrosis, vagal enhancement and was caused by increased baroreflex and cardiomyocyte sensitivity due to cholinergic stimulation potentially due to RGS-protein downregulation. [170] Strikingly, the paper also displayed that by 4-weeks of cessation of exercise (detraining) the electrophysiological and autonomic tone differences reversed with no differences between groups (p>0.05). In contrast, the structural remodelling components of fibrosis and left atrial size remained significantly higher than the control group following 4 and 8-weeks of ceased exercise (p<0.01). These changes following the training stimuli coupled with the suppressive response of atropine highlighted a key finding of this study that vagal enhancement is an important factor in the promotion of the arrhythmia in this exercise cohort. [170]
In a murine model Aschar-Sobbi et al., assessed a six-week intense aerobic training program and they found that the exercise group compared to sedentary controls had a significant increased susceptibility of AF. The exercised mice either completed 90-minutes of swimming or 120-minutes of treadmill running daily and as a consequence was associated with an increase in parasympathetic nerve activity (p<0.01), slower conduction velocities (p=0.02), atrial hypertrophy (p=0.02) and atrial fibrosis (p=0.03). [171] The study showed that atropine did not abolish AF inducibility via its inhibition of the parasympathetic nerve activity which has typically been associated within this population as a key mechanism for arrhythmia occurrence and may suggest in turn from other studies namely Guasch et al., that in fact vagal tone alone is not sufficient enough to promote AF, rather it needs another stimuli from a structural and/or electrical change. [171] Furthermore, the study provided mechanistic insight that an inflammatory cytokine is central to the physiology of AF susceptibility that is induced with endurance exercise, however upon inhibiting TNFα pathway during exercise AF susceptibility was reduced and atrial remodelling was prevented, without affecting the beneficial physiological responses linked with exercise training. [171]

In a newly published study by Elliott et al., in 99 recreational endurance athletes, which assessed the degree of atrial remodelling associated with lifetime training hours, they found that those athletes with the highest (>6000) and even moderate amount (3000-6000) of training hours both had a significantly increased LA size compared to a low degree of training. Interestingly, this change to LA size was independent of changes in vagal tone, LV remodelling and increased atrial ectopics. [172] This provides important insight to suggest that increases in LA size may in fact be the precursor for the increased risk of AF in this cohort before electrical and autonomic remodelling takes place which in combination may trigger AF. [172]
The increased risk of AF may be attributed by both the increase in parasympathetic tone and left atrial size, which are both well-known established aerobic exercise training adaptations. [152, 171, 173] It is well-established now that endurance exercise significantly increases vagal tone, resulting in bradycardia, and this enhanced parasympathetic tone has shown to be a key autonomic cause in AF onset, as it can cause a shortened atrial refractory period by reducing the inward current via L-type calcium channels, potentially promoting re-entry. [92, 174] Biatrial dilatation is a typical adaptation within the athlete’s heart to long-term exercise training in conjunction with left ventricular hypertrophy and left ventricular dilation. [152, 170, 173, 175] Of these changes, a primary measurable structural change that is an independent risk factor for AF onset is an increased size of the left atria; however, alone does not guarantee AF. [176] However, further investigations are required to understand the electrostructural remodelling with endurance exercise. [146, 152, 164, 168]

In addition, although we typically associate this population to be healthy, there are also ‘hidden risk factors’ of AF that may be present such as, aortic stiffness, type II DM, OSA, body stature, high alcohol intake and a genetic predisposition. Evaluation of traditional risk factors, particularly in the elderly athlete should be undertaken as part of the management of AF.

Aortic stiffness has been shown to be a relatively ‘silent’ AF risk factor and may be an underlying contributor in this athletic cohort which typically don’t have any of the other known AF/CVD risk factors. [177] In an early observational study by Mitchell et., which assessed pulse pressures (a reflection of aortic stiffness) within 5331 participants, they found that pulse pressure was significantly related to incident AF, with a 26% increased risk of AF per-every 20mmHg increase. Further supporting these findings, Lau et al., assessed aortic stiffness using pulse pressure, augmentation pressure and augmentation index amongst 68 lone-AF patients undergoing catheter ablation compared to age-matched controls. Following ablation in
patients with no structural heart disease or known AF risk factors, they found that in the lone-
AF patients compared to controls, there was significant increases in pulse pressures and
subsequent presence of aortic stiffness (p<0.05). [178] Furthermore, these patients also had
significant increases in left atrial dimensions compared to controls, and further reinforced
aortic stiffness as an underlying risk factor of AF. [178] The elevation in pulse pressures which
is reflective of aortic stiffness and increased cardiac load seems to precede increases in left
atrial size, left-ventricular hypertrophy and consequently the onset of AF. [177-179]

Type II DM and OSA cannot be ignored to occur in healthy athletic individuals, especially
amongst the older cohorts whom are more susceptible to these forms of CVDs. Although the
burden is significantly lower within this cohort compared to sedentary individuals, there is no
denying that these diseases can be present and potentially an underlying contributor to AF as
long-term exercise can reduce the risk but unfortunately not completely protect against Type
II DM and OSA. [110, 180] Body stature or lean body mass has been assessed as a link to AF
incidence, with recent data suggesting that a higher lean body mass was a significant predictor
for AF. [181] With many competitive athletes having leaner body mass, this may also be a
contributing risk within this population. What also should be considered is excessive alcohol
intake in these athletic individuals, especially with the ‘binge-drinking’ culture that exists within
has shown that within males a high and moderate weekly intake of alcohol was associated with
a 34% and 26% increase in AF risk respectively (p<0.01). [60]

Therefore, when assessing contributors for AF within this cohort, the changes
associated with long-term endurance exercise on the heart should not be the only assumption,
with the investigation of other underlying risk factors potentially present that is contributing
to the AF.
1.8.3 Summary of the U-Shape Relationship

Based on the presented studies above there is a defined U-shape relationship that represents the ideal point of which exercise protects against AF before it may in fact promote AF. Several studies have aimed to quantify this relationship using total amount of lifetime exercise, with a training history of >1500-2000 hours being noted to increase the risk of lone-AF. [162, 168] However, there are some limitations associated with this quantification of ideal training durations. Firstly, these studies utilised a self-reporting to quantify training history which presents a bias. Furthermore, these studies to date have not yet defined a specific intensities or weekly frequencies of exercise that could potentially elicit an increased risk of arrhythmia. Therefore, given competitive endurance athletes would train more than 20-hours per week, and based on the current data it would only take two-years of training to achieve this point which presents some limitation of this current data and the need to further assess this proposed relationship. [183] Given that the overall benefits of exercise are quite positive for overall health and has shown to play an important role in improving AF known risk factors, exercise should be strongly promoted in populations at risk of AF.

1.9 Exercise in the Management of Atrial Fibrillation

1.9.1 Exercise in the Management of Permanent AF

In a modern publication, the National Heart Foundation of Australia for the first time incorporated the promotion of exercise in the management of AF within the newly adopted guidelines. [123] Up until recently, the role of exercise training has primarily been assessed in patients with permanent AF. In early observational studies by Mertens and Kavanagh and Vanhees et al., they simply showed that an exercise intervention within permanent AF patients significantly improved their fitness performance measures to no detriment of the patient. [184,
Later on in a more defined observational study, Plisiene et al., noted that exercise training resulted in improvements in exercise capacity, health-related quality of life, and ventricular rate control both at rest and during exercise. In this study, which initially aimed to assess changes to parasympathetic tone in response to regular exercise, found that two 45-min sessions per week at moderate intensity over 4-months significantly improved exercise capacity, with general health perception rating trending to significance but most likely did not reach this due to small sample size of only ten patients. [186-188] Further to this, there was a small randomised controlled trial conducted by Hegbom et al., which assessed a short-term exercise training intervention in patients with permanent AF. In total, 28 patients were enrolled in the study, with the exercise group undergoing an 8-week aerobic exercise program consisting of 3 sessions of 75-mins. At the end of the 2-month intervention the exercise group compared to controls significantly improved their exercise capacity, along with four categories of their SF-36 questionnaires which included; physical functioning, bodily pain, vitality and emotional well-being. [187] Following on from this, Osbak et al., underwent a similar RCT in 47 patients, which assessed a 12-week intervention of 3 exercise sessions of 60-mins per week, and similarly reported significant improvements in exercise capacity and health-related quality of life for the permanent AF patients randomized to exercise. These two latter RCTs provided useful insight in the plausibility to prescribe exercise to patients with AF, without any contraindications to the training stimulus. It is therefore reasonable to conclude that in those with permanent AF, exercise training can improve functional quality of life. However, this data sheds little insight into the role of exercise for patients with paroxysmal or persistent AF.
1.9.2 Exercise in the Management of Non-Permanent AF

In a large observational study on the role of cardiorespiratory fitness for long-term AF outcomes. The CARDIO-FIT study prescribed a total weekly target of 200-minutes of aerobic exercise and showed that both high baseline CRF and an improvement in fitness over a 4-year follow-up in obese individuals with symptomatic, non-permanent AF improved AF-free survival both with and without rhythm control. [122] Additionally, symptom burden and severity significantly decreased in those who gained >2METs in CRF over the study time course, compared to those with a <2MET gain. Strikingly, of those who concurrently gained fitness and lost >10% of initial body weight, over 90% were free from AF at final follow-up. Patients who gained CRF also demonstrated significant improvements in known risk factors including BMI, blood pressure, LA volume, lipid profile, glycaemic control and systemic inflammation even after adjustment for weight-loss. [10, 119, 122] An important feature to highlight is that those patients who stayed connected with their treating physician on a regular basis and continually received the consistent message of achieving weekly exercise and weight-loss targets, were more likely to sustain the results achieved. This sheds the importance of this long-term study to suggest the need of education and behavioural management in the long-term benefits to manage AF by empowering the patient to take responsibility of their health.

In 2016 Malmo et al., assessed the effects of a short-term 12-week aerobic interval training intervention for paroxysmal and persistent AF patients in a randomised controlled trial. This study assessed aerobic interval training in which patients exercise for four minutes at >90% of their heart reserve, repeated four times during each session and interspersed by three minutes of active recovery. Exercise training resulted in a significantly greater reduction in AF burden in the intervention arm from 8.1% to 4.8% (p<0.01), compared to controls who increased their time in AF from 10.4% to 14.6% (p<001). Self-reported AF symptoms using the
AFSS questionnaire also significantly decreased in those within the exercise group compared to controls. Additionally, patients in the exercise group increased left atrial function and left ventricular ejection fraction, along with overall improvements in VO$_{2\text{peak}}$, lipid profiles and quality of life.[189] In a more recent RCT by Skielboe et al., compared the intensity of two exercise interventions. Over 12-weeks participants were randomised to a program of exercise at either 50% or 80% of maximal perceived exertion. At the end of the study there was no difference in AF burden from pre to post exercise intervention, with the primary outcome being that both sets of exercise groups statistically improving their VO$_{2\text{peak}}$ with no adverse effects. [190] The measurement of AF by means of a daily-ECG and lower volume of exercise per week in comparison to the Malmo et al., may be the plausible suggestions why there were no differences seen in AF burden. As the study may have underestimated the amount of AF from the start, as the Malmo et al., study undertook implantable loop recorders for each of their participants which allowed for continuous monitoring of AF burden. However, given the improvements seen in VO$_{2\text{peak}}$ with no adverse effects within the study population, the study further supports to promote exercise intervention within AF patients.

Furthering the benefits for exercise in patients with AF, the EURObservational Research Programme Pilot Study on Atrial Fibrillation showed that regular exercise in patients with AF results in lower risk of all-cause death, irrespective of gender, age, clinical presentation and stoke risk. [191] Similarly, in the CopenHeart$_{\text{RFA}}$ RCT trial which assessed the role of an exercise program compared to usual medical care in AF patients following catheter ablation. The study’s primary outcome was VO$_{2\text{peak}}$ with the premise to support the role of exercise in conjunction with standard surgical AF management strategies to improve patient outcomes. Patients randomised in the exercise arm underwent a 12-week exercise programme with three session’s per-week and at follow-up testing the group significantly improved their VO$_{2\text{peak}}$ and
physical capacity compared to the usual care control patients. [192] Consequently, highlighting the important need to incorporate exercise as a part of the treatment strategy to further improve patient outcomes.

The current literature shows that exercise in AF patients can lead to improvements in AF symptom severity, burden, pathophysiology, VO$_{2peak}$ and AF related risk factors (Table 1.1). [122, 189] These improvements mechanistically can be attributed to exercise knowingly able to directly improve AF known risk factors such as; diastolic blood pressure, systemic inflammatory markers, glycaemic control and lipid profile (Figure 1.1). [122] In CARDIO-FIT patients with the higher CRF improvements had improved AF symptoms and burden, along with reverse atrial remodelling with a significant decreased left atrial size and left ventricular end-diastolic diameter at follow-up. [122] However, Malmo et al., showed in its short-term study that AF symptoms and burden significantly improved. However, there were no structural changes observed compared to the CARDIO-FIT study which reported these such as; a reduced left atrial size, improved blood pressure and inflammatory markers. The lack of these structural changes can be attributed to the short-term nature of the study intervention. This therefore, sheds some insight that the improvements seen so far by exercise are not solely attributed via the improvement of AF related risk factors, but instead may play a direct role on improving AF via autonomic or intrinsic electrophysiological changes. [189]

Overall these studies provide a much-needed insight into the incorporation of aerobic exercise in patients with symptomatic, permanent and non-permanent AF. Although, lacking in the literature so far is the assessment of resistance-based training in AF management. What we have seen so far based on this data is that exercise should not be deterred in any way in this patient cohort, as there is no evidence so show any contraindications to exercise prescription, irrespective if patients have either paroxysmal, persistent or permanent AF.
Further to this, what these studies do highlight, is the essential need to include exercise in the management of AF as it does improve AF outcomes, and exercise capacity, irrespective of the lack of data showing whether it can assist in AF freedom. To move forward from here, larger randomised, intervention studies with a longer degree of follow-up are required to thoroughly assess the degree to which an aerobic exercise intervention can improve AF outcomes within this population, in conjunction with the development of sustainable behavioural changes to maintain adequate ongoing physical activity levels.

1.10 Clinical Significance

Based on current evidence, physical inactivity and low-CRF is an independent risk factor for incident AF. Therefore, strategies that increase physical activity and induce sustainable exercise habits are urgently needed to help curtail the rising tide of AF incidence. Given this growing demand on the healthcare systems globally we need to accept that AF is a serious growing epidemic and it is only expected to increase further. There is a strong need for increased awareness of AF and its associated lifestyle-based risk factors from a primary prevention standpoint would be essential to start to address this growing prevalence. The adoption of public healthcare policies that can promote and fund lifestyle-based interventions in those at risk or diagnosed with AF would be ideal to lower the healthcare system burden and AF-related hospitalisations. However, without more public awareness of AF, without public policies that will fund exercise physiology or dietitian services to prevent or manage AF, there will no doubt be a continual increase in AF as projected and a naturally increased burden on the healthcare system. We should be aiming to keep these patients away from hospital and prevent or manage appropriately, instead of filling up what is already a fragile healthcare system.
Recent studies by Pathak et al., and Malmo et al., have promoted the role of an exercise intervention in the management and treatment of paroxysmal and persistent AF. [122, 189] These studies have highlighted the benefits of exercise as a non-invasive, non-pharmacological approach for the reduction of AF burden and recurrences in both short and long-term follow-ups. Future studies will hopefully continue to prove evidence for the efficacy of exercise training in patients with AF whilst also investigating the mechanism(s) driving these benefits.

Existing evidence suggests that high levels of endurance exercise over many years leads to an increased risk of AF onset. [168, 169] This is possibly attributed to the physiological and autonomic changes that are associated within chronic aerobic exercise training that includes atrial enlargement, increased vagal activity and altered left atrial substrate, which are all known AF risk factors. [164, 165] This could also be associated to other ‘hidden’ AF risk factors that are not typically associated with a healthier population such as; underlying aortic stiffness, Type II DM, OSA or increased alcohol intake. However, this population is only representative of a small elite group of endurance athletes and does not represent the larger population of people who do not partake in any if not modest amounts of exercise, with even high amounts of exercise also seem to be protective against AF. [169]

Clinically this literature review shows and supports that exercise in conjunction with aggressive risk factor management can have positive effects, by either minimising the potential risk of AF onset or serve as an adjunct form of treatment within the management of AF.

1.11 Conclusion

Extensive risk factor management and prescribed exercise has shown to be an important component in minimising the prevalence of AF, and within AF patients improving both pathophysiology and outcomes. Despite long standing research showing that high levels of
chronic endurance exercise seem to have a negative effect in increasing the risk of AF onset, this is only a small population who compete in elite endurance events, and thus it is not representative of the wider general population. Therefore, exercise should not be deterred in any way possible in those who are at risk or who suffer from AF, as it has been shown that exercise and improvements in CFR decreases AF incidence and improves AF outcomes serving as a pivotal adjunct treatment in AF patients. More studies are warranted to further evaluate the role of a specific exercise intervention within AF sufferers to support its role in the adopted treatment strategies within this cohort.
1.12 Figures and Tables

Figure 1.1: Summary of Benefits of Exercise in AF

![Diagram showing benefits of exercise in AF patients compared to general population]

- **General Population**
  - Reduces Risk of AF

- **In AF Patients**
  - Short Term (<6 months)
    - Reduces AF Burden
    - Reduces Symptom Severity
    - Improves CRF and QoL
  - Long-Term (>4 years)
    - Increases AF Freedom
    - Reduces Symptom Severity
    - Improves CRF and QoL

**Benefits of Exercise in AF**

- Aerobic Exercise >210-mins/week
- Improves
  - Weight Loss
  - Blood Pressure
  - Mortality Risk
  - CRF
  - HbA1c
  - Systemic Inflammation
  - Apnea-Hypopnea Index
  - PNS Tone
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>AF Type</th>
<th>Size (n)</th>
<th>Intervention Duration</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mertens and Kavanagh (1996)</td>
<td>Obs</td>
<td>Permanent</td>
<td>20</td>
<td>52 weeks</td>
<td>Walking 5x per week 60-80% VO&lt;sub&gt;2peak&lt;/sub&gt;</td>
<td>Improved: Peak VO&lt;sub&gt;2&lt;/sub&gt;, peak work (watts), work at ventilatory threshold,</td>
</tr>
<tr>
<td>Vanhees et al., (2000)</td>
<td>Obs</td>
<td>Permanent</td>
<td>19</td>
<td>12 weeks</td>
<td>Aerobic 3x90mins per wk 80%HR&lt;sub&gt;peak&lt;/sub&gt;</td>
<td>31% increase in peak VO&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Plisiene et al., (2008)</td>
<td>Obs</td>
<td>Permanent</td>
<td>10</td>
<td>16 weeks</td>
<td>Aerobic 2x45mins per wk Moderate intensity</td>
<td>Improved: SF-36 questionnaire, resting ventricular rate, max ex. capacity, lactate threshold speed</td>
</tr>
<tr>
<td>Hegbom et al., (2007)</td>
<td>RCT</td>
<td>Permanent</td>
<td>28</td>
<td>8 weeks</td>
<td>Aerobic 3x75mins per wk 70-90% HR&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Improved: Exercise capacity, SF-36 and SSCL questionnaires</td>
</tr>
<tr>
<td>Osbak et al., (2011)</td>
<td>RCT</td>
<td>Permanent</td>
<td>47</td>
<td>12 weeks</td>
<td>Aerobic 3x60mins per wk 70% Max Exercise Capacity</td>
<td>Improved: Exercise capacity (watts), 6MWT distance, resting HR, QoL questionnaire</td>
</tr>
<tr>
<td>Pathak et al., (2015)</td>
<td>RCT</td>
<td>Non-Permanent</td>
<td>308</td>
<td>49 months (follow-up)</td>
<td>Recommended aerobic exercise of 200mins per wk</td>
<td>Greatest CRF Gain &gt;2METs improved: AF burden and symptom severity</td>
</tr>
<tr>
<td>Malmo et al., (2016)</td>
<td>RCT</td>
<td>Non-Permanent</td>
<td>51</td>
<td>12 weeks</td>
<td>Aerobic 3x40mins per wk 4x4min intervals at 85-95% HR&lt;sub&gt;peak&lt;/sub&gt;</td>
<td>Decreased: AF Burden (Time in AF), total cholesterol. Improved: Exercise capacity and SF-36 questionnaire - AF symptoms</td>
</tr>
<tr>
<td>Risom et al., (2016)</td>
<td>RCT</td>
<td>Non-Permanent</td>
<td>210</td>
<td>12 weeks</td>
<td>Aerobic 3x30mins per wk 60-70% VO&lt;sub&gt;2peak&lt;/sub&gt;</td>
<td>Improved: Peak VO&lt;sub&gt;2&lt;/sub&gt;, 6MWT, Sit-to-Stand, SF-36 (general health perception rating)</td>
</tr>
<tr>
<td>Skielboe et al., (2017)</td>
<td>RCT</td>
<td>Non-Permanent</td>
<td>76</td>
<td>12 weeks</td>
<td>Aerobic exercise 2x60mins HI group – 80% RPE (Borg 16-18) LI group – 50% RPE (Borg 11-13)</td>
<td>Improved: Peak VO&lt;sub&gt;2&lt;/sub&gt; across both groups with no statistical difference between either.</td>
</tr>
</tbody>
</table>
CHAPTER 2 - GREATER CARDIORESPIRATORY FITNESS REDUCES INCIDENCE OF ATRIAL FIBRILLATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

2.1 Introduction

AF is the most common sustained cardiac arrhythmia affecting 1-2% of the global population. [1] Since 1990, the prevalence and incidence of AF has risen 18% amongst men and women. [1] AF is directly associated with an increased risk of stroke, cardiovascular disease (CVD) and all-cause mortality. [2-4] The risk of AF onset is strongly related to age, with data now showing that one-third of people above 65-years being at risk of AF onset. [193] Furthermore, the risk of developing AF is increased in those suffering from coexisting morbidities including; obesity, [10] type II diabetes, [7] hypertension, [13] obstructive sleep apnoea, [12] alcohol and smoking. [8, 9] The rising AF prevalence has resulted in a growing AF-related health burden leading to increased hospitalisations and demand on healthcare systems. [25, 194] Notably, the rise in AF hospitalisations is outgrowing that for seen for heart failure and myocardial infarction. [24] Therefore, strategies to offset the growing burden of AF are warranted to reduce both disease morbidity and healthcare demands.

Recent studies have shown the importance of greater physical activity for the reduction in AF incidence. [147] This data is also consistent with other observational data which shows regular physical activity to reduce incidence of AF. [145, 151] Regular exercise is well established as a key component in the prevention and treatment of CVD, with greater cardiorespiratory fitness (CRF) inversely related to the onset of CVD and all-cause mortality. [28, 29, 195]

In fact, CRF has been shown to be a stronger predictor of CVD onset compared to self-reported physical activity levels as it known to have many physiological benefits that reduce
the risk of developing known CVDs and all-cause mortality. [32, 196] A meta-analysis by Kodama et al., which assessed this showed that patients with a high-CRF were associated with a significantly lower risk of CVD and all-cause mortality compared to those with low-CRF. The study also went further to categorise that those above a CRF level of 7-METs had a significant lower rate of all-cause mortality and CVD onset, compared to those below, which supports previous studies. [29]

Although low-CRF and lack of exercise are predictive of cardiovascular disease onset and mortality, only recently has this also emerged as a potential risk factor for AF. However, recent studies have provided some support for the role of CRF in modulating AF incidence. With no prior analysis of studies completed to date, the aim of this meta-analysis was therefore to quantify the relationship between CRF, measured by a symptom limited exercise stress test, and AF incidence. We hypothesised that there would be an inverse linear relationship that a higher CRF will have a lower AF incidence.

2.2 Methods

Search Strategy

The systematic literature review was conducted using PUBMED, MEDLINE and EMBASE databases searching for studies reporting AF incidence according to categories of baseline CRF up until 30th August 2018. The following search terms were used: atrial fibrillation, (OR) atrial flutter, (OR) arrhythmia, (AND) cardiorespiratory fitness, (OR) exercise, (OR) physical activity, (AND) risk, (OR) relative risk (OR) incidences. We then searched the reference lists of all retrieved articles for additional studies meeting our eligibility criteria. The review was registered in PROSPERO (Registration Number CRD42018109066), and the studies were
assessed for quality using the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist. [197]

**Study Eligibility**

To determine the relationship between CRF and AF risk we included prospective cohort studies examining the relationship of CRF quantified at baseline by a symptom-limited exercise stress test, with AF detected during follow-up via electrocardiograms, physician diagnosis, hospital or medical records to stipulate AF incidence. Studies were excluded if they failed to specifically quantify CRF at baseline by a symptom-limited stress test, a review, a case report or if the study was not published in English. The primary defined endpoint of this analysis was AF incidence with regards to corresponding CRF measured at baseline.

**Data Extraction**

Two authors (Christian Verdicchio and Adrian Elliott) performed the search and data extraction independently. We then extracted the multivariate-adjusted risk estimated where reported or the number of AF cases and total number of participants per group within each study. Baseline data of patient characteristics, follow-up duration, AF detection modes and the number of AF cases was extracted.

**Definition of CRF**

For the CRF analysis, we extracted the data from the lowest CRF group, an intermediate group – defined as the median group (i.e. 3rd out of 5 groups) or the group below the median (i.e. the 2nd out of 4 groups), and the highest CRF group within each study. Across the studies, CRF was defined in METs and VO₂, with AF diagnosis detected via medical records and/or study ECG.
For the meta-analysis that defined levels of CRF, low CRF was <6METs, intermediate CRF was defined as ≥6 to <9 with high CRF being ≥9METs.

**Data Analysis**

Following data extraction, we used RevMan 5.0 to perform a random-effects meta-analysis using the inverse variance method for pooled risk ratios. Data was entered as relative risk log(RR) and the standard error (SE), based on the multivariate adjusted values shown in each study. Where this was not available, we entered raw outcome data to calculate unadjusted risk estimates, which we then entered as log(RR) and SE. We then evaluated the lowest CRF group from each cohort with the group of the highest CRF and performed a random-effects meta-analysis to compare the multivariate risk estimates of each group with I² used to assess heterogeneity between studies.

**2.3 Results**

In total 3343 studies were retrieved from the search, with 3322 studies removed by title and abstract, leaving 21 studies. After accessing full-texts 16 studies were removed for not meeting the inclusion criteria as they did not quantify levels of CRF or were interventional studies. Five studies met the inclusion criteria which assessed baseline CRF using exercise stress testing and its relationship to AF incidence in a general population setting, with one study having three groups of data comparing CRF and AF incidence see figure 2.1. [14, 155, 157-159]

**Study population**

Of the identified 5 studies that met the inclusion criteria (Table 2.1), there were a total of 150,684 individuals (47.8% males) used for data analysis with a mean age of 55±2 years and a
median follow-up period of 8-years (range 5-20-years). The total number of AF events across the studies was 16,701. In terms of baseline AF risk factors 24.3% of the total individuals had hypertension with 7.6% having type II diabetes mellitus. The characteristics of these studies are shown in Table 2.1.

**High-CRF and risk of AF**

AF incidence rates demonstrated an overall decline in rates across the CRF quartiles from low to high CRF in those studies who reported this variable. Calculated mean incidence rates for low-CRF was 21±13.4 compared for high-CRF of 6.9±0.7 per 1000 person-years (p=0.03). The overall pooled risk of AF in the high-CRF group versus the low-CRF group showed a significant lower risk of incident AF (OR: 0.49, 95% CI, 0.39-0.61, p<0.01, Figure 2.3).

There was evidence of statistical heterogeneity between the studies (I²=86%, p<0.01). In the three studies that reported METs, the mean CRF values in the high-CRF was 10.5, compared to 5.5 in the low-CRF group.

**Intermediate-CRF and risk of AF**

A secondary analysis was completed comparing the intermediate-CRF group versus the low-CRF group. All the studies reported values of intermediate-CRF and again, there was a significant lowered risk in AF incidence (OR: 0.70, 95% CI, 0.61-0.81, p<0.01, Figure 2.4), with evidence of statistical heterogeneity across the studies (I²=73%, p<0.01). Figure 2.2 shows these findings graphically of a graded inverse risk of incident AF with CRF.
2.4 Discussion

**Major Findings**

The principal finding from this meta-analysis is CRF is inversely correlated with the risk of developing AF. Indeed, we observed a graded response to the level of CRF, when measured by an objective exercise stress test. High CRF being associated with a 51% reduction in the risk of incident AF when compared to individuals with low-CRF. These findings are important in developing preventative strategies for AF. In addition, it may be an important use in screening individuals at risk of developing AF. This data further supports the growing body of evidence identifying physical inactivity and poor CRF, alongside other clinical risk factors such as obesity and hypertension, as a risk factor for incident AF. [144]

**Cardiorespiratory Fitness and AF**

The findings of our analysis show that regular exercise leading to improvements in CRF confers a lower risk of incident AF. In a prospective observational study, Mozaffarian et al., assessed the relationship between levels of exercise and AF risk. Participants with the greatest dose of exercise (combined distance and pace walked), had a significantly lower risk of AF compared to those with the lowest levels of reported activity. Importantly, there was a dose-dependent effect across quartiles of exercise levels. [145] This was further supported in The Multi-Ethnic Study of Atherosclerosis by Bapat et al., which showed a 54% reduction in AF incidence between those who engaged in high levels of intentional vigorous exercise, compared to none. [147] The following results of a lower AF risk with a higher reporting of subjective physical activity levels, are similar to the results within our analysis which showed a 51% reduction in the risk of AF in those with the highest CRF (p<0.01). However, it must be noted that overall the benefits of exercise on AF incidence across all studies have been modestly favourable.
Although these large epidemiological studies provide rich data regarding the role of measurable risk factors and incident AF, they are subject to limitations regarding the method of assessing levels of exercise on a large scale. In all studies, exercise was assessed by self-report, thus leading to potential bias. An alternative method of examining the role between exercise, and AF is to record exercise capacity by way of an exercise stress test. This approach offers a more objective way of examining the role physical activity plays in reducing AF risk, if those who are physically active will typically have greater cardiorespiratory fitness and exercise tolerance. In fact higher fitness levels measured by symptom limited exercise stress test also showed that higher fitness group conferred a 53% reduction in all-cause mortality, which further sheds insight into the importance of a higher-CRF mediating benefits for both AF and all-cause mortality, as well as other cardiovascular diseases. [198]

**Exercise in the Treatment of AF**

In addition to a preventative benefit as we have highlighted from this analysis, increasing CRF has also shown to have favourable effects in the treatment and management in patients with AF. In an observational study of over 300, symptomatic, overweight or obese AF patients, both high baseline CRF and an improvement in fitness over a 4-year follow-up, improved AF-free survival both with and without rhythm control. [122] Additionally, symptom burden and severity significantly decreased in those who gained >2METs in CRF over the study time course, compared to those without. [10, 119, 122] More recently, a randomised controlled trial revealed that exercise training and subsequent improvements in CRF resulted in a significantly greater reduction in AF burden and AF symptoms, in conjunction with improvements in left atrial function, left ventricular ejection fraction, VO$_2$peak, lipid profiles and quality of life. [189]
Mechanisms by which exercise reduces AF risk

The proposed mechanisms by which improvements seen in CRF have on reducing AF risk may be attributed to a few factors; Firstly, the benefits on cardiac function, as exercise is known to improve diastolic function and subsequent left ventricular filling which lowers the workload in the left atrium and subsequent structural remodelling which is a known predisposed risk of AF. [199, 200] Secondly, the benefits to known AF risk factors, as an enhanced CRF improves systemic inflammation by reducing C-reactive protein, which is an inflammatory marker strongly associated with AF, in conjunction with improvements in other risk factor profiles such as; blood pressure regulation, blood lipids, HbA1c profile and autonomic control. [7, 122, 128, 201, 202] Therefore, improving CRF may work by driving improvements in cardiac function and individual risk factors of AF resulting in blunting the overall effect size of these risk factors on promoting arrhythmogenesis and in turn reducing AF onset.

Based on our analysis, it shows that higher-CRF results in a reduction in AF incidence. Within the limits of the included studies, we did not observe any evidence that a higher-CRF results in a less favourable AF outcome. However, we must point out the growing evidence of incident AF in endurance athletes with endurance exercise training across many years seems to lead to an increased risk in AF, with most studies to date showing a heightened occurrence in veteran endurance marathon runners and cross-country skiers. [161, 164, 167] It would be plausible to suggest, that this phenomenon would not have been noticed in our population because many of these patients would not be as healthy as these “athletes”, and therefore the active promotion of exercise plays a stronger role in preventing and reducing the arrhythmia as previously highlighted. In a general population, with known AF risk factors, exercise should be promoted to assist in the prevention of AF and improve other known CVD profiles.
Clinical Implications

This study adds valuable information in the need to adopt regular exercise and improve CRF as a primary prevention strategy for AF. This analysis in conjunction with newly emerging studies are showing a protective effect of improvements in CRF against AF. This has enormous implications as now we can promote exercise to prevent AF risk which only a decade ago was not possible due to lack of studies and poorer understanding on mechanisms that contributed to the arrhythmia. Given the growing prevalence of obesity and CVD onset not only in Australia but worldwide, the targeting approach of AF awareness campaigns that promote good lifestyle habits such as diet and exercise would help minimise the already growing global burden of AF by further re-enforcing to the general public the added benefit of exercise and physical activity can play in protecting against AF along with protecting against other forms of CVD. It would seem now that more awareness campaigns should be adopted by national heart organisations and governments should be lobbied for improved community sporting facilities to further promote and enhance daily exercising habits within the general community to fight against AF and turn the tide on a growing epidemic.

Limitations

Despite our findings on the link between CRF and AF risk, these findings may be subject to limitations in the included studies. At present there are only 5 studies that currently have assessed AF incidence based on a measured and quantified CRF following a baseline exercise stress test, with the CRF at follow-up unknown and subsequently may not be reflective of the baseline CRF value. Secondly, there was a large difference between follow-up duration across the studies, with 5.4-years being the shortest and 19.5-years being the longest, which may
influence the findings of this analysis. The quantification of CRF quartiles and ascertainment of AF also differed across the studies causing variability within the results.

2.5 Conclusion

There is an independent relationship between a lower CRF and an increased risk of AF. Therefore, a higher CRF is protective against AF. Increased CRF is known to improve other known AF risk factors and may be a target for improving outcomes in patients at risk of or with AF. Therefore, exercise interventions should be promoted in those at risk of developing AF with known risk factors, or who suffer from AF. Future studies are warranted to identify the mechanism(s) through which improved CRF confers a reduction in AF incidence.
2.6 Figures and Tables

Figure 2.1: Flowchart of search strategy
**Table 2.1:** Summary of Studies and Patient Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yrs)</td>
<td>55±13</td>
<td>53±5</td>
<td>57±11</td>
<td>52±13</td>
<td>57±8</td>
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<tr>
<td>Participants (N)</td>
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<td>1,950</td>
<td>5,692</td>
<td>12,043</td>
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<td>Follow-up (Yrs)</td>
<td>5.4</td>
<td>19.5</td>
<td>8.3</td>
<td>14</td>
<td>6.1</td>
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<tr>
<td>Hypertension (%)</td>
<td>64</td>
<td>31</td>
<td>59</td>
<td>27.4</td>
<td>19.7</td>
</tr>
<tr>
<td>Type II DM (%)</td>
<td>19</td>
<td>5</td>
<td>41</td>
<td>26</td>
<td>5.3</td>
</tr>
<tr>
<td>AF Diagnosis</td>
<td>Medical Records</td>
<td>Medical Records &amp; Study ECG</td>
<td>Medical Records</td>
<td>Study ECG</td>
<td>Medical Records</td>
</tr>
<tr>
<td>AF Events (N)</td>
<td>4,616</td>
<td>305</td>
<td>722</td>
<td>1,222</td>
<td>9,836</td>
</tr>
</tbody>
</table>

(*) denotes three groups within the study
Figure 2.2: Graph and Summary of AF Incidence Across the CRF Quartiles

<table>
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<tr>
<th>CRF Quartile</th>
<th>MET Range</th>
<th>Incidence Rates</th>
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<tr>
<td>Low (Q1)</td>
<td>&lt;5</td>
<td>21</td>
</tr>
<tr>
<td>Intermediate (Q2-3)</td>
<td>6-9</td>
<td>9</td>
</tr>
<tr>
<td>High (Q4)</td>
<td>&gt;9</td>
<td>6.9</td>
</tr>
</tbody>
</table>
Figure 2.3: Forest Plot of AF Risk Between High and Low CRF
**Figure 2.4:** Forest Plot of AF Risk Between Intermediate and Low CRF

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Fasulis et al</td>
<td>-0.2231</td>
<td>0.0905</td>
<td>16.1%</td>
<td>0.80 [0.67, 0.96]</td>
</tr>
<tr>
<td>Hussain et al</td>
<td>-0.2877</td>
<td>0.073</td>
<td>17.8%</td>
<td>0.75 [0.65, 0.87]</td>
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<tr>
<td>Khan et al</td>
<td>-0.1278</td>
<td>0.1546</td>
<td>10.6%</td>
<td>0.88 [0.65, 1.19]</td>
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<td>Qureshi et al</td>
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<td>0.0398</td>
<td>20.7%</td>
<td>0.80 [0.74, 0.86]</td>
</tr>
<tr>
<td>Tikkanen et al</td>
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<td>0.1672</td>
<td>9.8%</td>
<td>0.68 [0.49, 0.94]</td>
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<tr>
<td>Tikkanen et al</td>
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<td>0.1369</td>
<td>12.0%</td>
<td>0.51 [0.39, 0.67]</td>
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<tr>
<td>Tikkanen et al</td>
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<td>0.124</td>
<td>13.0%</td>
<td>0.51 [0.40, 0.65]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.70 [0.61, 0.81]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.02; Chi² = 22.13, df = 6 (P = 0.001); I² = 73%

Test for overall effect: Z = 5.06 (P < 0.00001)
CHAPTER 3 - GREATER CARDIORESPIRATORY FITNESS REDUCES STROKE INCIDENCE: A SYSTEMATIC REVIEW AND META-ANALYSIS

3.1 Introduction

Stroke is a leading cause of death worldwide with a yearly 6.4 million deaths attributed to the disease accounting for 11.8% of all deaths, and a common cause of disability. [194, 203] Since 1990 there has been an increase in the incidence and burden of stroke worldwide. Especially in developing countries due to a lack of adequate healthcare available. [204] Because of the rising stroke prevalence there is a growing stroke related health burden resulting in increased frequency of hospitalisations and substantial demands on healthcare systems globally. [194, 204] Those who suffer from a stroke typically experience symptoms such as; slurred speech, drooped mouth, dizziness or loss of balance, headache and paralysis to their limbs. [205] The risk of suffering from a stroke is increased in those suffering from coexisting cardiovascular disease (CVD) morbidities including; hypertension [206], smoking [207], Type II DM [206] and dyslipidaemia [207]. Stroke risk is also strongly correlated with age, with an increased prevalence of stroke events of 1 in 6 in those aged between 55-75 years of age. [208]

In general, in AF patients, stroke risk is amplified 5-fold in those without valvular heart disease, and 17.5-fold in those with valvular AF. However, it is well recognised that the risk of stroke is additive commiserate with the number of risk factors and individual has, as depicted in the CHADS-VA scoring system. [123] Current AF guidelines strongly recommending anticoagulation in AF patients with known risk factors for stroke. [209] In fact, data from CRYSTAL AF has showed that 30% of patients admitted into hospital for embolic stroke of unknown source (ESUS) had underlying AF when investigated using implantable cardiac monitors. [210] These findings importantly highlight the current underestimation of AF within
the general population, but also shed light into the increasing rates of stroke attributed to the underlying arrhythmia. [210]

Regular exercise is well established as a key component in the prevention and treatment of cardiovascular disease (CVD), with greater cardiorespiratory fitness (CRF) inversely related to the onset of CVD and all-cause mortality. [28, 29] Emerging studies have shown the importance in improved levels of physical activity and subsequent CRF can play in the reduction in stroke incidence, with The Cardiovascular Health Study conducted by Soares-Miranda et al., showing that regular physical activity reduced stroke risk by 44% compared to those who were sedentary. [211]

The interaction between exercise and stroke is receiving growing attention given the positive role exercise is known to have on the stroke related, lifestyle-based risk factors. Exercise may be able to play a potential role in the management of patients with AF at risk of stroke. The aim of this meta-analysis was therefore to thoroughly assess the current literature to characterise the relationship between CRF measured by a symptom limited exercise stress test and stroke incidence. We hypothesised that there would be an inverse linear relationship that a higher CRF will have a lower stroke incidence.

3.2 Methods

Search Strategy

The systematic literature review was conducted using PUBMED, MEDLINE and EMBASE databases searching for studies reporting stroke incidence according to categories of baseline CRF up until the 30th August 2018. The following search terms were used: stroke, (OR) cerebrovascular accident, (AND) physical fitness, (OR) cardiorespiratory fitness, (OR) exercise, (AND) risk, (OR) incidences. We then searched the reference lists of all retrieved articles for
additional studies meeting our eligibility criteria. The review was registered in PROSPERO (Registration Number CRD42018109071) and study quality was assessed using the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist. [197]

**Study Eligibility**

To determine the relationship between CRF and stroke risk we included prospective cohort studies examining the relationship of CRF quantified at baseline by a symptom-limited exercise stress test, with stroke detected during follow-up via hospitalisation or medical records to stipulate stroke incidence. Studies were excluded if they failed to specifically quantify CRF at baseline by a symptom-limited stress test, were a review or case report study, or if the study was not published in English. The primary defined endpoint of this analysis was stroke incidence with regards to corresponding CRF measured at baseline.

**Data Extraction**

Two authors (Christian Verdicchio and Xiao Fan Ng) performed the search and data extraction independently. We then extracted the multivariate-adjusted risk estimated where reported or the number of stroke cases and total number of participants per group within each study. Baseline data of patient characteristics, follow-up duration, stroke detection modes and the number of stroke cases was extracted.

**Definitions of CRF**

For the CRF analysis, we extracted data from the lowest CRF group, an intermediate group – defined as the median group (i.e. 3rd out of 5 groups) or the group above the median (i.e. the 3rd out of 4 groups), and the highest CRF group within each study. Across the studies CRF was
defined in METs, VO\textsubscript{2max}, Watts or functional aerobic capacity, with stroke diagnosis detected via medical records or the national death registries.

**Data Analysis**

Following data extraction, we used RevMan 5.0 to perform a random-effects meta-analysis using the inverse variance method for pooled risk ratios. Data was entered as relative risk log(RR) and the standard error (SE), based on the multivariate adjusted values shown in each study. Where this was not available, we entered raw outcome data to calculate unadjusted risk estimates, which we then entered as log(RR) and SE. We then evaluated the lowest CRF group from each cohort with the group of the highest CRF and performed a random-effects meta-analysis to compare the multivariate risk estimates of each group with I\textsuperscript{2} used to assess heterogeneity between studies.

**3.3 Results**

In total 8240 studies were retrieved from the search, with 7923 studies removed by title and abstract, leaving 317 studies. After accessing the 317 full-texts, 309 studies were removed for not meeting the inclusion criteria. Eight studies met the inclusion criteria which were used for this meta-analysis that assessed baseline CRF using exercise stress testing and its relationship to stroke incidence see figure 3.1.

**Study population**

Of the identified 8 studies that met the inclusion criteria there were a total of 1,628,883 individuals (99% males) used for data analysis with a mean age of 46.5±14 years and a mean
follow-up period of 16.3±5.4 years. The total number of stroke events across the studies was 19,903. The characteristics of these studies are shown in Table 3.1.

**Incidence rates**

The incidence rates per 1,000 person-years was calculated from the studies between low and high-CRF groups (Figure 3.2). There was a significant lower incidence rates of stroke per 1,000 person-years in the high-CRF of 2.3 compared to low-CRF of 4.7 (p=0.04). The pooled risk of stroke in the high-CRF group versus the low-CRF group showed a significant lowered risk of stroke incidence of 0.62 (95% CI, 0.58-0.65, p<0.01, Figure 3.3), thus favouring high-CRF, with no presence of any significant difference in the heterogeneity across the studies (I²=0%, p=0.53). A secondary analysis was completed comparing the intermediate-CRF group versus the low-CRF group. Again, there was a significant lowered risk in stroke incidence of 0.78 (95% CI, 0.73-0.85, p<0.01, Figure 3.4), with no presence of any statistical difference in the heterogeneity across the studies (I²=18%, p=0.28).

**Effect of exercise capacity on types of stroke**

A sub-analysis was completed in those studies which categorised ischemic, fatal and non-fatal stroke incidence between high and low-CRF groups. In two studies that categorised ischaemic stroke incidence, there was a significant lowered risk of ischaemic stroke in the high-CRF of 0.35 (95%CI, 0.19-0.65, p<0.01, Figure 3.5). In the three studies that categorised fatal and non-fatal stroke incidence according to levels of CRF, again there was a statistically reduced risk of fatal (RR 0.57 95%CI, 0.38-0.84, p<0.01, Figure 3.6) and non-fatal strokes (RR 0.71 95%CI, 0.58-0.88, p<0.01, Figure 3.7) in those with high-CRF compared to low-CRF.
3.4 Discussion

Major findings

This meta-analysis demonstrates that high-CRF is associated with a 38% reduced risk of stroke when compared to individuals with low-CRF. Furthermore, high-CRF lowered the risk of ischaemic, fatal and non-fatal strokes compared to those with low-CRF.

Cardiorespiratory Fitness and stroke

Our findings demonstrate that higher-CRF reduces stroke risk. Regular exercise has been well established to prevent CVD, and even improve outcomes in those with a CVD event including stroke and myocardial infarction. [212] A population-based cohort study in men (free from known CVD) assessed the time spent walking and its associated risk of stroke, which showed a significant 65% reduced risk of stroke in those who spent more than 22-hours of walking. [213] More current, in the Cardiovascular Health Study greater levels of exercise was inversely associated with a reduced stroke risk, with those completing the highest amount of leisure-time activity per week having a 44% reduced risk of stroke. [211] These studies substantiate our results where our analysis showed a 38% reduction in stroke risk in those with higher levels of CRF.

Interestingly, CRF has been strongly correlated to be the key prognostic tool for all-cause mortality both within the healthy and CVD populations, and an even stronger predictor of mortality in comparison to known CVD risk factors. [214] In a meta-analysis by Kodama et al., individuals with low-CRF <7.9METs had a substantially higher risk of all-cause mortality and CVD events compared to those with a higher-CRF >10.9METs. [29] This data seems to correlate with our results, when you compare the mean values of CRF between the high and low ranges,
which seems to suggest that CRF above 10METs also confers a lower risk of stroke, along with CVD and all-cause mortality. [29, 198]

Although these large epidemiological studies provide rich data, they are subject to limitations regarding the method of assessing levels of exercise on a large scale. In these studies, physical activity was assessed by self-report through subjective questionnaires, thus leading to potential bias and misrepresentation of a true CRF. It has been evaluated that the direct measurement of CRF via CardioPulmonary Exercise Testing (CPET) is closer associated with cardiac events in comparison to leisure time physical activity defined by questionnaires, with higher CRF but not a higher leisure time associated with fewer cardiac events in those <65-years of age. [215] It could be said that based on this that CRF is a better representative of physical fitness and is primarily influenced by exercise training irrespective of body weight which is already factored when expressed in ml/kg/min⁻¹. In fact higher fitness levels measured by symptom limited exercise stress test also showed that higher fitness group conferred a 53% reduction in all-cause mortality, which further sheds insight into the importance of a higher-CRF mediating benefits for both AF and all-cause mortality, yet alone other cardiovascular diseases. [198] This, may be able to shed some light why our analysis conferred a lowered reduced risk of stroke of 38% compared to the above-mentioned studies. Based on this, our meta-analysis of the current studies within the literature that directly assess CRF utilising CPET may in fact better predict stroke risk and provide a better insight into the mechanisms that may be responsible for this reduced risk. Increased CRF has shown to reduce the risk of CVD and is well established to also play a key role on modifiable stroke (and CVD) risk factors such as; hypertension, [128] obesity and systemic inflammation. [216, 217] Mechanistically the main driver in the reduction in stroke caused by improvements in CRF may be linked to an improved endothelial function associated with exercise, since exercise causes an increase in vascular
nitric oxide (NO) levels which are known to promote vasodilation and lower peripheral resistance, thus improving blood flow. [212] Furthermore, improvements in CRF also reduce systemic inflammation via its ability to increase the production and release of anti-inflammatory cytokines from skeletal muscle, reduce the number of circulating pro-inflammatory monocytes and increase the number of regulatory T-cells within the bloodstream. [216] Exercise and improvements in CRF should be promoted in populations with known CVD and stroke risk factors, given the central role it can play to minimise the risk of stroke, CVD events and improve mortality. [29, 214]

**Clinical Implications**

Clinically this data further supports established data of exercise protecting against CVD and more specifically now protecting against stroke. This re-iterates the importance for governments to adopt policy that further promotes increasing levels of CRF through exercise interventions within the general community, and for medical practitioners to continually educate and prescribe exercise to their patients as a primary or secondary prevention measure against stroke, AF and other CVDs. Given the heightened risk of stroke in patients diagnosed with AF, it is even more vital within this patient cohort to promote exercise in order to protect against stroke and for exercise to even act as a secondary or tertiary prevention in those with established AF or other CVDs.

**Limitations**

Despite our findings this analysis may be subject to limitations associated in the individual included studies. Firstly, there was a large range associated with mean follow-up for stroke incidence. A possible bias associated with this analysis is that not all categories of high and low-
CRF levels were equally defined across the studies with a standard range. Another limitation associated with the study is the small number of studies that sub-classified their events across ischaemic strokes and fatal vs non-fatal stokes. Further studies would be recommended to classify the type of stroke, which could allow for a more detailed insight within this area.

3.5 Conclusion

There is an independent relationship between a lower CRF and an increased risk in stroke. Hence, high CRF protects against stroke. Increased CRF is known to improve other known stroke risk factors and may be a target for improving outcomes in patients at risk of stroke. Therefore, exercise interventions that aim to improve CRF should be promoted in those at risk of CVD and subsequent stroke event. Future studies are warranted that directly assess CRF and stroke incidence within the general population.
3.6 Figures and Tables

Figure 3.1: Flowchart of search strategy
<table>
<thead>
<tr>
<th>Study</th>
<th>Age (Yrs)</th>
<th>Participants (N)</th>
<th>Follow-up (Yrs)</th>
<th>Stroke Events (N)</th>
<th>Low-CRF</th>
<th>High-CRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurl et al., (2003)</td>
<td>53±11</td>
<td>2,011</td>
<td>11</td>
<td>110</td>
<td>&lt;25ml/kg/min</td>
<td>&gt;35ml/kg/min</td>
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<tr>
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<td>51±5</td>
<td>1,639</td>
<td>16.6</td>
<td>97</td>
<td>&lt;162Watts</td>
<td>&gt;230Watts</td>
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<tr>
<td>Hooker et al., (2008)</td>
<td>44±10</td>
<td>46,405</td>
<td>18.8</td>
<td>692</td>
<td>8.6 METs</td>
<td>15 METs</td>
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<tr>
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<td>42±11</td>
<td>15,282</td>
<td>17.4</td>
<td>171</td>
<td>6.8 METs</td>
<td>12.6 METs</td>
</tr>
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<td>Sieverdes et al (2015)</td>
<td>43±10</td>
<td>45689</td>
<td>17.5</td>
<td>619</td>
<td>8.5 METs</td>
<td>13.7 METs</td>
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<tr>
<td>Crump et al., (2016)</td>
<td>18±8</td>
<td>1,530,315</td>
<td>25.6</td>
<td>16,979</td>
<td>&lt;240Watts</td>
<td>&gt;289Watts</td>
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<tr>
<td>Pandey et al., (2016)</td>
<td>68±5</td>
<td>19,815</td>
<td>6.5</td>
<td>808</td>
<td>8.3 METs</td>
<td>12.9 METs</td>
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<td>Khan et al., (2017)</td>
<td>53±5</td>
<td>2,089</td>
<td>19.1</td>
<td>198</td>
<td>5.8 METs</td>
<td>11.6 METs</td>
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<tr>
<td>Hussain et al., (2018)</td>
<td>52±13</td>
<td>12,043</td>
<td>14</td>
<td>1128</td>
<td>Aerobic Capacity &lt;75%</td>
<td>Aerobic Capacity &gt;105%</td>
</tr>
</tbody>
</table>
Figure 3.2: Incidence Rates Per 1,000 Person-Years in Low Vs High-CRF Groups

- Kurl et al., (2008)
- Hooker et al., (2008)
- Hooker et al., (2008)*
- Sieverdes et al., (2015)
- Crump et al., (2016)
- Pandey et al., (2016)
- Khan et al., (2017)
- Hussain et al., (2018)
Figure 3.3: Forest Plot of Stroke Risk Between High and Low CRF

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 7.09$, df = 8 ($P = 0.53$); $I^2 = 0\%$
Test for overall effect: $Z = 16.68$ ($P < 0.00001$)
Figure 3.4: Forest Plot of Stroke Risk Between Intermediate and Low CRF

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
<th>Odds Ratio IV, Random, 95% CI</th>
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<td>Crump et al 2016</td>
<td>-0.1863</td>
<td>0.0317</td>
<td>44.8%</td>
<td>0.83 [0.78, 0.88]</td>
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<tr>
<td>Hooker et al 2008</td>
<td>-0.1625</td>
<td>0.1139</td>
<td>10.2%</td>
<td>0.85 [0.68, 1.06]</td>
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<tr>
<td>Hooker et al 2008*</td>
<td>-0.844</td>
<td>0.2975</td>
<td>1.7%</td>
<td>0.43 [0.24, 0.77]</td>
<td></td>
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<tr>
<td>Hussain et al 2018</td>
<td>-0.3857</td>
<td>0.09</td>
<td>14.9%</td>
<td>0.68 [0.57, 0.81]</td>
<td></td>
</tr>
<tr>
<td>Khan et al 2017</td>
<td>-0.2357</td>
<td>0.2334</td>
<td>2.8%</td>
<td>0.79 [0.50, 1.25]</td>
<td></td>
</tr>
<tr>
<td>Kurl et al 2003</td>
<td>-0.3285</td>
<td>0.3537</td>
<td>1.2%</td>
<td>0.72 [0.36, 1.44]</td>
<td></td>
</tr>
<tr>
<td>Kurl et al 2008</td>
<td>-0.3567</td>
<td>0.3537</td>
<td>1.2%</td>
<td>0.70 [0.35, 1.40]</td>
<td></td>
</tr>
<tr>
<td>Pandey et al 2016</td>
<td>-0.2744</td>
<td>0.0957</td>
<td>13.5%</td>
<td>0.76 [0.63, 0.92]</td>
<td></td>
</tr>
<tr>
<td>Sieverdes et al 2015</td>
<td>-0.1985</td>
<td>0.1185</td>
<td>9.6%</td>
<td>0.82 [0.65, 1.03]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.78</strong></td>
<td><strong>0.73, 0.85</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.00 \); \( \chi^2 = 9.77 \), df = 8 (\( P = 0.28 \)); \( I^2 = 18\%

Test for overall effect: \( Z = 6.11 \) (\( P < 0.00001 \))
**Figure 3.5:** Forest Plot of Ischaemic Stroke Risk Between High and Low CRF

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurl et al 2003</td>
<td>-0.8347</td>
<td>0.2897</td>
<td>67.0%</td>
<td>0.43 [0.25, 0.77]</td>
<td></td>
</tr>
<tr>
<td>Kurl et al 2008</td>
<td>-1.5141</td>
<td>0.4912</td>
<td>33.0%</td>
<td>0.22 [0.08, 0.58]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>0.35 [0.19, 0.65]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.07; \chi^2 = 1.42, \text{df} = 1 (P = 0.23); I^2 = 30\%$

Test for overall effect: $Z = 3.31 (P = 0.0009)$
Figure 3.6: Forest Plot of Fatal Stroke Risk Between High and Low CRF

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hooker et al 2008</td>
<td>-0.6931</td>
<td>0.3537</td>
<td>31.2%</td>
<td>0.50 [0.25, 1.00]</td>
</tr>
<tr>
<td>Hooker et al 2008*</td>
<td>-0.844</td>
<td>0.798</td>
<td>6.1%</td>
<td>0.43 [0.09, 2.05]</td>
</tr>
<tr>
<td>Sieverdes et al 2015</td>
<td>-0.478</td>
<td>0.2498</td>
<td>62.6%</td>
<td>0.62 [0.38, 1.01]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.57 [0.38, 0.84]</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0\%$, $Q = 0.37$, df = 2 ($P = 0.83$); $I^2 = 0\%$

Test for overall effect: $Z = 2.87$ ($P = 0.004$)
**Figure 3.7:** Forest Plot of Non-Fatal Stroke Risk Between High and Low CRF

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hooker et al 2008</td>
<td>-0.478</td>
<td>0.1867</td>
<td>31.9%</td>
<td>0.62 [0.43, 0.89]</td>
</tr>
<tr>
<td>Hooker et al 2008*</td>
<td>-0.5798</td>
<td>0.3915</td>
<td>7.3%</td>
<td>0.56 [0.26, 1.21]</td>
</tr>
<tr>
<td>Khan et al 2017</td>
<td>-0.1054</td>
<td>0.2606</td>
<td>16.4%</td>
<td>0.90 [0.54, 1.50]</td>
</tr>
<tr>
<td>Sieverdes et al 2015</td>
<td>-0.2877</td>
<td>0.1582</td>
<td>44.4%</td>
<td>0.75 [0.55, 1.02]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.71 [0.58, 0.88]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.84, df = 3 (P = 0.61); I² = 0%
Test for overall effect: Z = 3.22 (P = 0.001)
CHAPTER 4 - USE OF HEART RATE FOR GUIDING EXERCISE TRAINING IN PATIENTS WITH ATRIAL FIBRILLATION

4.1 Introduction

Exercise in AF is receiving growing worldwide attention, with more studies now assessing the efficacy of an exercise intervention in this patient cohort. At present exercise training in patients with non-permanent AF contributes to a reduction in AF burden and AF recurrences. [122, 147, 189] In the CARDIOFIT study, the gain of cardiorespiratory fitness over a 4-year follow-up improved freedom from AF. [122] Likewise, AF burden was reduced in patients randomised to 12-weeks of aerobic interval training at an intensity of 85-95% of HRpeak. [189] In fact, newly published guidelines by the National Heart Foundation of Australia for the first time recommend exercise prescription in the management of AF. [123] However, the intensity of exercise that promotes the greatest clinical benefit has yet to be defined.

The current guidelines for the prescription of exercise in patients in cardiovascular disease rehabilitation programs recommend heart rate reserve (HRR) as the primary method for guiding exercise intensity. [218] In this context, HRR is adopted as a surrogate measure of the oxygen uptake reserve (VO₂R). In patients with heart failure and ischemic heart disease, Brawner et al., showed that %HRR to closely approximate %VO₂R irrespective of beta-blockade medication. [219] This data justified the use of %HRR for prescribing exercise intensity in patients with cardiovascular disease. In contrast, Mezzani et al., showed that amongst chronic heart failure patients there is an unreliable relationship between %HRR and %VO₂R, which can be attributable to left ventricular dysfunction, reduced stroke volume and impaired oxygen transport and utilisation. [220]

Given the growing role exercise is now receiving in AF and its incorporation into latest AF guidelines, there is an absence of data which have assessed the relationship between HRR
and VO₂R in patients with AF to assess its validity as a metric for guided exercise prescription as already seen in healthy and CVD populations. [123] The use of HRR allows the ability the closely guide exercise target intensities to correspond with VO₂ without the need to conduct cardiopulmonary exercise testing (CPET) which is not always readily accessible within the general population. [218]

Therefore, we hypothesize that the relationship between %HRR and %VO₂R may be disturbed by variation in the underlying rhythm, rate control medication, or sinus node dysfunction, which remains prevalent amongst AF patients. [221] The aims of this study were therefore to: 1) assess the relationship between %HRR and %VO₂R in patients with AF, and 2) to determine whether rhythm, medication use, and sinus node dysfunction may influence this relationship.

4.2 Methods

Study Population

The study comprised of patients with non-permanent AF referred for a cardiopulmonary exercise stress test (CPET) with regards to their medical care to the Centre for Heart Rhythm Disorders at the University of Adelaide, Adelaide, Australia. All patients provided written informed consent, with the study protocol approved by The Human Research Ethics Committee of the Royal Adelaide Hospital and the University of Adelaide, Adelaide, Australia. The trial was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12615000734561).

Consecutive patients meeting the following inclusion criteria were recruited: (i) they were able to complete a CPET on a treadmill ergometer and (ii) diagnosed with paroxysmal or persistent AF. The exclusion criteria were: permanent AF, rapid AF at time of testing, active malignancy, autoimmune or systemic inflammatory diseases, severe renal or hepatic failure
and left ventricular ejection fraction <45%, decompensated heart failure and mitral valve disease. Furthermore, patients who could not perform an exercise stress test due to neuromuscular or musculoskeletal problems were also excluded. Baseline patient characteristics were recorded including height, weight, BMI, medical history and medications relating to their AF management.

Endpoints

The primary endpoint of this study was to assess the validity of the relationship between %HRR and %VO₂R in patients with AF. The secondary endpoints of the study were to assess this same relationship within a.) those who were in AF compared to sinus rhythm (SR) at testing b.) beta-blockade adrenergic therapy, and c.) those who were defined with chronotropic incompetence.

Cardiopulmonary exercise test (CPET)

All patients prior to the test were connected to a twelve-lead ECG (Mortara, USA) to assess rhythm and heart rate, in conjunction with the use of the Oxycon Mobile (Jaeger, Germany) breath-by-breath wireless transfer to assess and measure continuous cardiopulmonary gases at rest and throughout exercise.

A symptom-limited maximal CPET on the treadmill following a modified Balke protocol was utilised in all patients. The test was ceased once the patient was unable to continue exercise due to fatigue and was deemed to have satisfied the maximal CPET criteria by achieving a respiratory exchange ratio (RER) >1.1. Chronotropic incompetence (CI) was defined in those patients failing to reach 80% age-predicted HR, or 62% age-predicted HR in those on beta-blockade therapy. [222]
HR and gas exchange data during the CPET tests were recorded at 20-second intervals and exported into a spreadsheet (Excel, Microsoft, USA). After five minutes of seated rest, pre-exercise data was obtained in standing position. Peak HR and VO$_2$ values, averaged across the final 20s of each 1-minute stage of the CPET were used to for analysis to calculate the percentages of peak HRR and VO$_2$R.

**Calculation of HRR-VO$_2$R slope**

Linear regression using the minute to minute HR and VO$_2$ data from each of the individual CPETs was used to calculate the slope and y-intercept for %HRR versus %VO$_2$R. A slope of 1.0 and a y-intercept of 0 represented equivalence between %HRR and % VO$_2$R. The resulting straight-line formula was used to determine %VO$_2$R and %HRR.

**Statistical analysis**

All values were shown as mean and standard deviation. To assess the relationship between %HRR and %VO$_2$R a one-sample t-test was used to evaluate the overall difference of our calculated slopes against the hypothetical values of equivalence. Three pre-specified analyses were subsequently performed to assess the relationship between %HRR and %VO$_2$R in those a.) in AF compared to sinus rhythm (SR) at time of testing, b.) with beta-blockade adrenergic therapy and c.) with CI. Two-tailed P<0.05 was specified as statistically significant. Statistical analysis was performed with SPSS version 21 (SPSS 24 Inc., Chicago, IL, USA).

4.3 Results

**Study Population**

The study comprised of 112 patients scheduled for CPET, however 11 patients were excluded from the study for; being in rapid AF (n=4), having decompensated heart failure (n=2) and
unable to exercise (n=5). Figure 4.1 demonstrates the CONSORT diagram for recruitment. In total there were 101 patients who met the inclusion criteria and underwent and completed CPET whom had a mean age of 66±9 years, mean BMI of 29.4±4.4. Mean VO_{2peak} and HR_{peak} were 21.1±6.3ml/kg/min and 137±24bpm, respectively. Table 4.1 shows the patient characteristics based on rhythm at the time of CPET.

**Primary analysis - %HRR and %VO_{2R}**

Overall there was poor correlation between %HRR and %VO_{2R} (r^2=0.16, figure 4.2). Of the entire 101 patients there was a mean slope of 0.79±0.4. The slope of %HRR - %VO_{2R} significantly differed from an assumed slope of 1.0 (mean difference: -0.21, 95% CI -0.30 to -0.12, p<0.001). The mean y-intercept slope calculated amongst the patients was 20.1±41.6, which significantly differed from a hypothetical value of 0 (mean difference: 20.1, 95% CI 11.9 to 28.3, p<0.001). These findings were maintained when resting VO_{2} measures were substituted with a value of 3.5ml.kg.min^{-1} (1-MET), with no statistical difference between the calculated slopes (0.78±0.4) and y-intercepts (21.7±41.3) (p>0.05).

Our primary findings of the study show that our calculated slope of 0.79±0.4 and y-intercept 20.1±41.6 is statistically different from a hypothetical equal slope and y-intercept of 1 and 0 respectively (p<0.01). This data further shows that even though %HRR may lack validity for %VO_{2R} across the lower ranges of HR, in contrast during higher ranges of HR there was a closer alignment of the %HRR and %VO2R relationship based on visual assessment.

**Influence of rhythm status on the relationship between %HRR and %VO_{2R}**

The influence of underlying rhythm was assessed by comparing the slope of %HRR to %VO_{2R} in patients in AF and SR at the time of their CPET. The mean slopes for patients in AF and SR were 0.75±0.3 (n=28) and 0.81±0.4 (n=73), respectively. There was no significant difference
between both groups (mean difference: 0.06, 95% CI -0.34 to 0.25, p=0.53), showing that rhythm status did not have an impact on this relationship. The calculated y-intercepts for patients in AF and SR were not significantly different (26±27 and 18±46, respectively, p=0.41) (Table 4.2). The HR_{peak} was higher in patients who were in AF at the time of CPET as compared to those in SR (148±27bpm vs 133±22bpm, p<0.01, figure 4.3) However, no significant difference was noted in VO_{2peak} between patients in AF or SR at time of CPET (p=0.81, figure 4.4).

**Influence of beta-blockers on the relationship between %HRR and %VO_{2R} in AF patients**

The slope of %HRR to %VO_{2R} was assessed in patients for differences in those with and without beta-blockade therapy. Calculated mean slopes for both groups were 0.74±0.6 (n=50) and 0.84±0.2 (n=51) for those with and without beta-blockade therapy respectively. There was no statistical difference between both groups (mean difference: 0.1, 95% CI -0.07 to 0.27, p=0.23, table 4.2). Both HR_{peak} (143±23bpm vs 131±24bpm, p=0.02) and VO_{2peak} (22.6±6.7ml/kg/min v 19.6±5.4ml/kg/min, p=0.02) parameters were statistically higher in those patients without beta-blockade therapy compared to those with beta-blockade (Figures 4.3 and 4.4, respectively).

**Influence of CI on the relationship between %HRR and %VO_{2R} in AF patients**

The slope of %HRR and %VO_{2R} was assessed in those with and without CI during CPET. Calculated mean slopes for both groups were 0.93±0.5 (n=21) and 0.75±0.4 (n=80) for those with detected CI and those without respectively, with no statistical difference between both
groups (mean difference: -0.18, 95% CI -0.39 to 0.03, p=0.10, table 4.2). There was a significant difference in \( \text{HR}_{\text{peak}} \) values between patients with and without CI (117±20bpm and 143±22bpm, p<0.001, figure 4.3) respectively. Despite the difference in \( \text{HR}_{\text{peak}} \), there was no difference in \( \text{VO}_{2}\text{peak} \) between the two groups (p=0.30, figure 4.4).

### 4.4 Discussion

#### Major Findings

Based on prior studies in health individuals, studies have demonstrated that %HRR corresponds closely to %\( \text{VO}_{2} \text{R} \) making it a suitable metric to prescribe target appropriate exercise intensities in both healthy individuals and patients with cardiovascular disease. [223, 224] However, whether these same guides can be used in disease states has not been evaluated. This prospective clinical study shows that relationship between %HRR and %\( \text{VO}_{2} \text{R} \) cannot be generalised for individuals with AF. Indeed, it raises that individuals with AF should be evaluated using a CPET to appropriately guide exercise behaviour change.

#### Utility of %HRR a surrogate for %\( \text{VO}_{2} \text{R} \) for continuous exercise training

Our results show that the %HRR lacks assumed equivalence to a corresponding %\( \text{VO}_{2} \text{R} \). Our data suggests that across lower ranges of HR and subsequent exercise intensities during exercise the %HRR overestimates %\( \text{VO}_{2} \text{R} \). This has important consequences in that HR based training in the low to moderate intensity range may not provide a sufficient training stimulus. In contrast, %HRR demonstrated improved validity across the higher ranges of HR. This may indicate that %HRR may be more appropriate in guiding exercise across the range of intensities employed in more vigorous interventions such as >70% of a HRR where the greatest cardiorespiratory gains are seen. This has important considerations given the absence of
guidelines regarding the prescription of exercise intensity in this cohort. However, general guidelines for exercise prescription commonly incorporate HR based measures such as HRR, which may lack equivalence with VO$_2$ based measures, when used within AF patients. The American College of Sports Medicine guidelines on exercise prescription in cardiovascular disease cohorts, in fact identify target exercise intensities between 50-85% of ones’ %HRR when prescribing aerobic exercise in patients with cardiovascular disease. [195] In AF patients the limited studies to date which have prescribed exercise target intensities have done so by using the percentages of maximal HR as a general guide and not have assessed the use of %HRR yet within this cohort. [189]

**Factors determining relationship between HRR and VO$_2$R**

In AF the typical management entails rate or rhythm control strategies either pharmacological or surgical. [225] Rhythm status and rate control medication can present a degree of complexity when prescribing exercise due to the varying or strongly controlled low HR with increasing exercise intensities; however, these factors do not seem to affect exercise capacity and do not negate the benefits of aerobic exercise training within these patients. [187, 188, 226] Furthermore, sinus node disease (SND) is common in AF patients, leading to CI with exercise. [221] Similarly AF is present in 40-70% of patients at the time of diagnosis of SND, and another 22% develop AF over time. [221, 227] Consistent with the previous data, CI was noted in 30% of our patients. CI has been proposed to contribute to exercise intolerance, in heart failure and other cardiovascular disease. However, there is conflicting data from a new study by showing that neither rate adaptive pacing nor ivabradine-mediated HR suppression altered peak VO$_2$. [228] The current study shows that the HR$_{peak}$ was reduced in patients with beta-blockade therapy, chronotropic incompetence, and increased when exercise was
performed in AF. However, despite differences in HRpeak, CI alone or AF did not influence VO2peak. The current study also shows poor correlation between HRR and VO2R in patients with AF. This lack of correlation was not influenced by beta blockers, chronotropic incompetence and even rhythm, which is interesting as these three factors are all well known to mediate HR responses. This study has important implications for exercise prescription in AF patients reinforcing the importance of personalised exercise prescription for patients with AF.

**Mechanism for dissociation between %HRR and %VO2R in AF patients**

The mechanisms contributing to the dissociation between %HRR and %VO2R at submaximal exercise intensities are unclear. The HR response at lower exercise intensities is considered to depend primarily on vagal withdrawal with sympathetic drive increasing as the exercise intensity rises. Autonomic nervous system disturbances have been widely reported in patients with AF and may contribute to a HR response at the onset of exercise that is less closely matched to metabolic demand. [89] Alternatively, the disparity between HR and VO2 measures may be due to mismatch between O2 delivery and utilization in the early exercise response, although this has not been widely studied. [229] Further studies characterising the physiological response to exercise in AF patients may be warranted.

**Limitations**

There are a few study limitations that should be considered. Firstly, the beat-to-beat variability in RR intervals during AF episodes may limit accurate heart rate determination during exercise. Secondly, we did not systematically record rating of perceived exertion during each exercise
stage, which would enable the evaluation of alternative exercise prescription tools. Additionally, we did not recruit a healthy, age-matched control group for direct comparison, although this should not influence the interpretation of our results for practical implementation. Finally, it may have been advantageous to record haemodynamic responses to exercise, including stroke volume and cardiac output, which may have enabled further investigation into the mechanisms contributing to disparity between %HRR and %VO$_2$R.

### 4.5 Conclusion

In individuals with AF, %HRR is not equivalent to %VO$_2$R, with wide variation at different exercise intensities. There was no significant effect of rhythm at time of testing, presence of chronotropic incompetence or beta-blockers on the relationship between %HRR and %VO$_2$R in AF patients. These findings highlight that the HR prescription of exercise intensity in AF patients should be guided by the individualised HR-VO2 relationship assessed by a CPET rather than assumed equivalence. More studies are strongly promoted to further assess methods of guiding exercise intensity in AF patients.
### 4.6 Figures and Tables

**Table 4.1: Baseline Patient Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>All (n=101)</th>
<th>AF at time of test (n=28)</th>
<th>SR at time of test (n=73)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66±9</td>
<td>67±8</td>
<td>66±9</td>
<td>0.4</td>
</tr>
<tr>
<td>Male (%)</td>
<td>71 (70.2)</td>
<td>22 (78.5)</td>
<td>49 (67.1)</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI</td>
<td>29.4±4.4</td>
<td>29.7±4.3</td>
<td>29.3±4.5</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>63 (62.4)</td>
<td>17 (60.7)</td>
<td>46 (63)</td>
<td>0.8</td>
</tr>
<tr>
<td>Diabetes Mellitus, N (%)</td>
<td>11 (10.9)</td>
<td>2 (7.1)</td>
<td>9 (12.3)</td>
<td>0.4</td>
</tr>
<tr>
<td>Obstructive Sleep Apnoea, N (%)</td>
<td>22 (21.8)</td>
<td>6 (21.4)</td>
<td>16 (21.9)</td>
<td>0.9</td>
</tr>
<tr>
<td>Previous AF Ablation, N (%)</td>
<td>29 (28.7)</td>
<td>2 (7.1)</td>
<td>27 (37)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Beta-blockade therapy, N (%)</td>
<td>50 (49.5)</td>
<td>15 (53.6)</td>
<td>35 (47.9)</td>
<td>0.6</td>
</tr>
<tr>
<td>Calcium-Channel therapy, N (%)</td>
<td>16 (15.8)</td>
<td>4 (14.2)</td>
<td>12 (16.4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Anti-arrhythmic therapy, N (%)</td>
<td>41 (40.5)</td>
<td>12 (42.8)</td>
<td>29 (39.7)</td>
<td>0.4</td>
</tr>
<tr>
<td>LV Ejection Fraction (%)</td>
<td>62.2±6.2</td>
<td>59.4±5.1*</td>
<td>63.2±6.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>VO_2peak (ml/kg/min)</td>
<td>21.1±6.3</td>
<td>20.9±7.2</td>
<td>21.2±5.9</td>
<td>0.8</td>
</tr>
<tr>
<td>HR peak (bpm)</td>
<td>137±24</td>
<td>148±27*</td>
<td>133±22</td>
<td>0.02</td>
</tr>
<tr>
<td>Chronotropic Incompetence, N (%)</td>
<td>21 (20.8%)</td>
<td>6 (7.1%)</td>
<td>21 (28.8%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
**Figure 4.1:** CONSORT Diagram of Participant Recruitment

- **Enrollment**
  - Assessed for eligibility (n=112)
  - Excluded for not meeting inclusion criteria (n=11)
    - Rapid AF (n=4)
    - Decompensated HF (n=2)
    - Unable to exercise (n=5)

- **Testing**
  - Treadmill CPET (n=101)

- **Analysis**
  - Analyzed (n=101)
**Figure 4.2**: Relationship Between %HRR and %VO$_2$R In All Patients

Dashed line represents equivalence with a slope = 1 and y-intercept = 0

The solid line represents our calculated slope and y-intercept
Table 4.2: Summary of Sub-Analysis Results

(* denotes statistically significant difference p<0.05)

<table>
<thead>
<tr>
<th>Patient Subgroups</th>
<th>Slope</th>
<th>p-value</th>
<th>HR$_{peak}$ (bpm)</th>
<th>p-value</th>
<th>VO$_{2peak}$ (ml/kg/min)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rhythm Status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AF</td>
<td>0.75±0.3</td>
<td>0.53</td>
<td>147.5±26.5</td>
<td>0.006*</td>
<td>20.9±7.2</td>
<td>0.81</td>
</tr>
<tr>
<td>SR</td>
<td>0.81±0.4</td>
<td></td>
<td>133.1±21.6</td>
<td></td>
<td>21.2±5.9</td>
<td></td>
</tr>
<tr>
<td><strong>Beta-Blocker Therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-Blockade</td>
<td>0.74±0.6</td>
<td>0.23</td>
<td>131.1±24.1</td>
<td>0.02*</td>
<td>19.6±5.4</td>
<td>0.02*</td>
</tr>
<tr>
<td>No Beta-Blockade</td>
<td>0.84±0.2</td>
<td></td>
<td>142.5±22.5</td>
<td></td>
<td>22.6±6.7</td>
<td></td>
</tr>
<tr>
<td><strong>Chronotropic Response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CI</td>
<td>0.93±0.5</td>
<td>0.10</td>
<td>117.1±19.6</td>
<td>&lt;0.001*</td>
<td>19.8±5.0</td>
<td>0.30</td>
</tr>
<tr>
<td>No-CI</td>
<td>0.75±0.4</td>
<td></td>
<td>142.8±21.9</td>
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<td>21.4±6.6</td>
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</tr>
</tbody>
</table>
**Figure 4.3**: Peak Heart Rate

- **AF vs. SR**:
  - Peak Heart Rate (HRpeak) for AF and SR.
  - Significance: *p < 0.01.

- **BB vs. No-BB**:
  - Peak Heart Rate (HRpeak) for BB and No-BB.
  - Significance: *p < 0.01.

- **CI vs. No-CI**:
  - Peak Heart Rate (HRpeak) for CI and No-CI.
  - Significance: *p < 0.01.
Figure 4.4: Peak VO$_2$
CHAPTER 5 – ROLE OF CARDIOPULMONARY EXERCISE TESTING AND VO\textsubscript{2peak} IN PREDICTING ATRIAL FIBRILLATION SYMPTOMS SEVERITY AND EXERCISE INTOLERANCE IN PATIENTS WITH ATRIAL FIBRILLATION

5.1 Introduction

AF has been shown to significantly impair quality-of-life. Registry data from the ORBIT-AF study has shown that nearly two-thirds of patients with AF are symptomatic and have an impaired quality-of-life, with the most prevalent symptoms including; dyspnea, shortness of breath, fatigue, anxiety and palpitations. [230] These symptoms also typically present in clusters with one another which further exacerbates the symptom burden within this cohort. [231, 232]

Cardiopulmonary exercise testing (CPET) has shown to be an important prognostic and diagnostic tool in patients with cardiovascular disease. [233-235] Peak oxygen consumption (VO\textsubscript{2peak}), derived from CPET, provides as accurate assessment of an individual’s aerobic capacity. Those with AF have been shown to have a reduced VO\textsubscript{2peak} by approximately 10%, which has been attributed to the underlying mechanical remodeling and haemodynamic impairment. [236-238]. Within heart failure patients there are studies that have established an inverse relationship between the degree of self-reported symptoms using the NYHA (New York Heart Association) classification system and exercise capacity derived from CPET. [239, 240] CPET has been proposed as a method to identify individuals who may benefit from the maintenance of sinus rhythm. To date there is no data that has examined the relationship between VO\textsubscript{2peak} derived from CPET and reported AF symptoms and exercise intolerance.

The aims of this study were to assess whether AF symptom severity correlates with CPET derived measures. Furthermore, we wish to assess whether the subjective assessment of exercise-related symptoms from the AFSS correlated with CPET derived measures. We
hypothesised that there would be an inverse relationship with AFSS symptom severity score and exercise-related symptoms in relation to VO$_{2\text{peak}}$.

5.2 Methods

Participant Recruitment

The study comprised of consecutive paroxysmal or persistent AF patients referred for CPET at the Centre for Heart Rhythm Disorders, Adelaide, Australia. Patients were excluded from this study if they met any of the following criteria; left ventricular ejection fraction <50%, mitral valve disease, permanent AF, clinical heart failure (HFP EF and HFr EF), congenital heart disease, recent cancer diagnosis or ongoing cancer treatment, failure to complete AFSS questionnaire and musculoskeletal disease/injury limiting exercise. Additionally, to minimise the influence of exercise training on exercise capacity, we excluded patients participating in structured, supervised exercise study interventions. All patients provided written informed consent to take part in the study that was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and the University of Adelaide. The trial was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12615000734561).

Clinical Examination

All participants underwent clinical evaluation of their rhythm disturbance and for prevalent cardiovascular risk factors. [241] Clinical characteristics were obtained during a formal consultation prior to the CPET, with cardiologist and general practitioner records used to classify the presence of other co-morbidities. A review of anthropometrical measures, including height and weight, and current medications was performed on the day of CPET.

Cardiopulmonary Exercise Testing
Cardiopulmonary exercise testing was performed on a treadmill using the modified-Balke protocol, with treadmill speed modified to optimise the test duration to 8-15 minutes. Resting measures were obtained during two-minutes of standing, following a period of 3-minutes seated rest. The treadmill exercise then commenced at the desired speed, with gradient increasing by 1% per minute from an initial gradient of 1%. A minimum of 2-minutes recovery at a speed of 2.4km/h, gradient 0% was commenced after the participants attained peak exercise. Twelve-lead ECG (Mortara, USA) was monitored to record heart rate and rhythm throughout rest, exercise and recovery. Pulmonary gas exchange was recorded continuously through a metabolic cart (Oxycon Mobile, Carefusion, Germany). Oxygen consumption and carbon dioxide production were averaged over 20s intervals, with subsequent calculation of ventilatory equivalent for CO$_2$ ($V_E/VCO_2$), and respiratory exchange ratio (RER). VO$_2$peak was taken as the highest attained VO$_2$ during peak exercise. $V_E/VCO_2$ was calculated by using a linear regression slope between both minute ventilation and CO$_2$ output between rest and peak exercise.

**AF Symptom Severity**

The AF Symptom Severity Scale (AFSS, University of Toronto, Canada) was administered on the day of the CPET prior to the test. The AFSS is a validated self-reported questionnaire that quantifies three areas of AF-related burden and symptoms being; frequency, duration and severity. [242] For the purpose of our study, this tool was used to assess the total symptom severity through a symptom-specific continuous subscale with a score of 0 reflecting no symptoms to the maximal score of 35 reflecting highly symptomatic. Furthermore, we assessed specifically two questions of AF-symptoms in relation to shortness of breath during exercise and exercise intolerance and assessed its relationship to VO$_2$. Within each sub-score of
symptoms classed from 0 (no symptoms) to 5 (highly symptomatic), a score of 0-1 was classed as mildly symptomatic, 2-3 moderately symptomatic and 4-5 highly symptomatic. With regards to the overall scores of symptom severity we classed three cut-off scores of ≤11 (mildly symptomatic), ≤22 (moderately symptomatic) and ≥23 (highly symptomatic).

**Transthoracic Echocardiography**

Resting transthoracic echocardiography was performed in the 30 days prior to CPET with a 3.5-MHz probe (Vivid7, GE Medical Systems). Transthoracic images were obtained in the apical four- and two-chamber views, as well as the parasternal long and short axis views. Tissue doppler imaging was utilised to assess and quantify systolic and diastolic function. All measurements were performed according to American Society for Echocardiography guidelines. [243] In patients with AF during echocardiography, all measures were averaged over a minimum of 5 cardiac cycles. Fifteen clinical and echocardiographic variables including; LA and LV sizes, RV function, diastolic filling pressures and ejection fraction were analysed by an experienced sonographer, blinded to all exercise data, obtained all images. The images were subsequently analysed by a cardiologist blinded to exercise test outcomes.

**Statistical Analysis**

Statistical analysis was performed using SPSS Version 24 (SPSS Inc., Chicago, USA). All data were assessed for normality using the Shapiro-Wilk test. Continuous variables were reported as mean ± standard deviation. Between-groups differences were assessed using the chi-squared test for categorical variables and the independent t-test for normally distributed continuous variables. Statistical significance was set at p<0.05. To assess factors relating to VO\textsubscript{2}peak, candidate clinical and echocardiographic variables were assessed my univariate linear
regression. Significant univariate predictors were then entered into a multivariate regression, including age and gender as known determinants of VO$_{2peak}$.

5.3 Results

Study Population

Overall, 132 patients with AF and free from diagnosed HF were included in the analysis. Figure 5.1 demonstrates the CONSORT diagram for recruitment. The mean age of the participants was 66±9 years and 62% were males (n=83). The mean body mass index was 30±4.9Kg/m$^2$. Other baseline patient characteristics are presented in Table 5.1.

There were no major cardiac events during CPET. Across the entire cohort the mean VO$_{2peak}$ was 1858±652ml/min or 94.1±19.1% of age and gender predicted values, with 34 patients (26%) meeting the definition of exercise intolerance (<85% age and gender predicted values). The mean VE/VCO$_2$ slope was 31.2±5.9 and mean peak heart rate achieved was 136±24bpm.

Primary Outcomes

AFSS Symptom Severity and VO$_{2peak}$

In our primary analysis there was no statistical relationship between the three defined classes of mild, moderate and highly total symptomatic scores of the AFSS symptom severity metric and VO$_{2peak}$ (p=0.9) (Figure 5.2). There were 89 patients with mild reported AFSS symptoms scores with a mean VO$_{2peak}$ of 1863±698ml/min, 33 patients with moderate reported AFSS symptoms with a mean VO$_{2peak}$ of 1860±549ml/min and only 10 patients highly symptomatic with a mean VO$_{2peak}$ of 1803±595ml/min.
We then assessed the individual sub-categories of exertional symptoms and VO$_{2peak}$.

There was no significant relationship between the degree of AFSS self-reported dyspnea upon exertion and VO$_{2peak}$ ($p=0.5$) (Figure 5.3). There were 56 patients with mild reported dyspnea upon exertion with exercise with a mean VO$_{2peak}$ of 1840±722ml/min, 55 patients with moderate reported symptoms with a mean VO$_{2peak}$ of 1920±637ml/min and only 21 patients highly symptomatic in relation to dyspnea upon exertion with a mean VO$_{2peak}$ of 1744±478ml/min.

Finally, when we assessed for a relationship between the degree of AFSS self-reported exercise intolerance and VO$_{2peak}$ there was no statistical relationship between the two parameters ($p=0.6$) (Figure 5.4). There were 64 patients with mild reported exercise intolerance with a mean VO$_{2peak}$ of 1911±736ml/min, 51 patients with moderate level of exercise intolerance symptoms with a mean VO$_{2peak}$ of 1831±529ml/min and only 17 patients reporting high levels of exercise intolerance with a mean VO$_{2peak}$ of 1740±668ml/min.

**Secondary Outcomes - Predictors of VO$_{2peak}$**

**Effect of Rhythm Status**

At time of testing 38 patients (29%) of patients were in AF. Resting heart rates were significantly lower in those patients in SR compared to AF (Mean Difference: -12.5, 95%CI -19.4 to -5.6bpm, $p<0.01$). Similarly, peak heart rates were significantly lower in those in SR at time of testing (Mean Difference: -16.5, 95%CI -27.6 to -5.3bpm, $p<0.01$). There was no significant difference in VO$_{2peak}$ between either group ($p=0.6$), however $V_{E}/V_{CO2}$ was significantly higher in patients with AF compared to SR (Mean Difference: -2.2, 95%CI -4.3 to -0.05, $p=0.04$). The number of patients meeting the criteria for exercise intolerance was significantly greater in patients with AF compared to SR (36.8% v 24.7%, $p<0.05$).
Effect of Cardiac Structure and Function

Fifteen clinical and echocardiographic variables were analysed for their correlation with VO$_{2peak}$. Beyond age and gender, significant univariate predictors of VO$_{2peak}$ included the presence of a pacemaker, E/E’, chronotropic index (CI), LVEDD (indexed to body surface area) and RV S’. In a multivariate analysis, the presence of a pacemaker, chronotropic index (CI), indexed LVEDD and RVS’ remained significant predictors of VO$_{2peak}$ ($r^2=0.63$, Table 5.5).

Likewise, all the echocardiographic variables were analysed for their correlation with V$_{E}$/VCO$_2$. In univariate analysis, the significant predictors of V$_{E}$/VCO$_2$ were age, rhythm status which also remained significant following the multivariate analysis. (Table 5.6)

5.4 Discussion

Primary Findings

There are several key findings from this study;

1. AFSS symptom severity score does not correlate with VO$_{2peak}$.

2. Self-reported symptoms of exertional symptoms within the AFSS do not correlate with VO$_{2peak}$.

3. A significant proportion of patients with non-permanent AF demonstrated an impaired VO$_{2peak}$ and ventilatory efficiency, which may reflect poor long-term outcomes.

4. Rhythm status at time of testing was not a significant predictor of VO$_{2peak}$.

5. Age, female gender, pacemaker, reduced RV function, reduced chronotropic response and increased LV size were all significantly associated with a lower VO$_{2peak}$. 
AFSS Symptoms and VO\textsubscript{2peak}

Our primary focus of this study was to assess the relationship whether subjective assessment of AF symptom severity from the AFSS correlates with CPET derived measures. In relation to this, we found that self-reported symptoms are not associated with objectively quantified measures of cardiorespiratory fitness. As we observed within our cohort the mean VO\textsubscript{2} was lower across the higher classes of symptoms; however, this was not significant, and if we see in those with the highest reported symptoms there were only 10 patients within this group which would underpower any chance to statistically detect any difference across the groups. Similarly, there was no relationship between VO\textsubscript{2peak} and the degree of exertional symptoms from the AFSS. Our data was not significant when we compare to previous studies within heart failure cohorts which have shown an inverse relationship between the lowest and highest degree of symptoms reported using the NYHA questionnaire and VO\textsubscript{2peak}. [239, 244, 245]

Ultimately, these studies like ours are assessing a subjective assessment of subjective symptoms and exercise related symptoms against an objective measure of cardiorespiratory fitness, which in a disease cohort would naturally be expected to vary significantly. Within our patients exercise intolerance was a commonly reported symptom in AF patients with 68 (52%) patients reporting moderate to high degree of symptoms. However, only 37 (28%) patients met the clinical definition of exercise intolerance (VO\textsubscript{2peak} <85% age-gender predicted and <62% in beta-blocker patients), which suggest that there is a large discrepancy between self-reported symptoms and perceptions of exercise intolerance and objective capacity in patients with AF. [246] This finding further supports our data of subjective questionnaires not correlating with objective measures of exercise capacity within this cohort.
Effect of Rhythm Status

In patients with AF, the absence of active atrial filling, impairs stroke volume and reduces ventricular filling times with the high heart rates and consequently leads to a reduced VO$_{2}^{\text{peak}}$. [238, 247] In previous studies, successful restoration of SR by electrical cardioversion improves VO$_{2}^{\text{peak}}$, thus suggesting that the presence of AF is the primary driver of exercise intolerance in this cohort. [238, 248] However, we found no significant difference in VO$_{2}^{\text{peak}}$ between patients in AF or SR at time of testing. We observed a significant increased V$_{E}$/VCO$_{2}$ slope in patients with AF compared to SR. V$_{E}$/VCO$_{2}$ slope has been shown to be elevated in patients with heart failure and is inversely related to cardiac output. [249, 250] The prognostic value of this slope has been well established to predict long-term outcomes and in AF patients this elevation may be due to alterations in central respiratory control or altered pulmonary vascular tone, which has been shown in patients with HFP EF. [251-254]

Cardiac structure and function and the relationship to VO$_{2}^{\text{peak}}$

Following on from our primary analysis, our study then assessed for any clinical and echocardiographic measures that may in fact be correlated with VO$_{2}^{\text{peak}}$. Importantly, our findings show that echocardiographic parameters of RV function and LV size along with chronotropic response were all significant predictors of VO$_{2}^{\text{peak}}$ in patients with AF.

Therefore, therapies that target improvements in RV and LV function may in fact be beneficial for the alleviation of exercise intolerance within this cohort. [199, 255-257]

Limitations

The main limitation of this study was the number of recruited patients especially in relation to the low numbers within the high self-report AF symptom severity group. Another limitation of
this study was that we assessed cardiac function with resting transthoracic echocardiography, which did not allow us to identify those potentially with an abnormal response to exercise with normal resting values.

5.5 Conclusion

In patients with AF, CPET derived measures of exercise capacity does not correlate with AF symptom severity and exercise-related symptoms from the AFSS. AF at time of testing was associated with a reduced ventilatory efficiency (increased V̇E/V̇CO₂ slope); however, rhythm status at time of testing was not a significant predictor of VO₂peak. Lower RV function reduced chronotropic response and increased LV size were all significantly associated with lower VO₂peak. Further larger trials are further warranted to assess whether subjective measures of AF symptoms can correlate to exercise capacity within this patient cohort.
5.6 Figures and Tables

Figure 5.1 CONSORT Flow Diagram of Patient Recruitment and Attrition

**Enrollment**

- Assessed for eligibility (n=150)

- Excluded for not meeting inclusion criteria (n=18)
  - Permanent AF (n=4)
  - HFrEF (n=5)
  - Unable to exercise (n=5)
  - Did not complete AFSS (n=4)

**Testing**

- Treadmill CPET (n=132)

**Analysis**

- Analysed (n=132)
<table>
<thead>
<tr>
<th>Table 5.1 Baseline Patient Characteristics</th>
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</thead>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>SR Patients</strong> (n=94)</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Gender (Male n, (%))</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
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<tr>
<td>Type II DM, n (%)</td>
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<tr>
<td>Obstructive Sleep Apnoea, n (%)</td>
</tr>
<tr>
<td>Permanent Pacemaker, n (%)</td>
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<tr>
<td>Previous Ablation, n (%)</td>
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</table>

**MEDICATIONS**

<table>
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<tr>
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<th>SR Patients (n=94)</th>
<th>AF Patients (n=38)</th>
<th>All Patients (n=132)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Beta-Blockers, n (%)</td>
<td>38 (40.4)</td>
<td>17 (44.7)</td>
<td>55 (42)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Calcium-Channel Blocker, n (%)</td>
<td>20 (21.2)</td>
<td>9 (23.6)</td>
<td>29 (22)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Sotalol, n (%)</td>
<td>19 (20.2)</td>
<td>9 (23.6)</td>
<td>28 (21)</td>
<td>p&gt;0.05</td>
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<td>Flecainide, n (%)</td>
<td>22 (23.4)</td>
<td>7 (18.4)</td>
<td>29 (22)</td>
<td>p&gt;0.05</td>
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Figure 5.2: AFSS total symptom score and corresponding VO$_{2\text{peak}}$

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<tr>
<th>Mildly Symptomatic (n=89)</th>
<th>Moderately Symptomatic (n=33)</th>
<th>Highly Symptomatic (n=10)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>VO$_{2\text{peak}}$ (ml/min)</td>
<td>1863.9±698.3</td>
<td>1860.2±549.6</td>
<td>1803±595.2</td>
</tr>
</tbody>
</table>
Figure 5.3: AFSS Degree of shortness of breath during exercise and corresponding VO$_{2\text{peak}}$

<table>
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<th>Moderately Symptomatic (n=55)</th>
<th>Highly Symptomatic (n=21)</th>
<th>p-value</th>
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<tr>
<td>VO$_{2\text{peak}}$ (ml/min)</td>
<td>1840.4±722.8</td>
<td>1920.5±537.9</td>
<td>1744.1±478.7</td>
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Figure 5.4: AFSS Degree of exercise intolerance and corresponding VO$_{2}$peak

<table>
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<th>Mildly Symptomatic (n=64)</th>
<th>Moderately Symptomatic (n=51)</th>
<th>Highly Symptomatic (n=17)</th>
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<tr>
<td>VO$_{2}$peak (ml/min)</td>
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<tr>
<td>1911.1±736.4</td>
<td>1831.7±529.6</td>
<td>1740.5±668.9</td>
<td>0.6</td>
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Table 5.5 Predictors of Exercise Intolerance

<table>
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<th>Variable</th>
<th>UNIVARIATE</th>
<th></th>
<th>MULTIVARIATE</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (B)</td>
<td>SE</td>
<td>P</td>
<td>Coefficient (B)</td>
</tr>
<tr>
<td>Gender</td>
<td>-684.4</td>
<td>72.8</td>
<td>&lt;0.001</td>
<td>-670.3</td>
</tr>
<tr>
<td>Age</td>
<td>-35.3</td>
<td>3.8</td>
<td>&lt;0.001</td>
<td>-34.4</td>
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<td>Pacemaker</td>
<td>-198.7</td>
<td>77.5</td>
<td>0.01</td>
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<td>LVEDD Indexed</td>
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<td>122.1</td>
<td>0.01</td>
<td>-361.1</td>
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<td>RVS'</td>
<td>28.9</td>
<td>13.3</td>
<td>0.03</td>
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<td>Chronotropic Index</td>
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<td>88.8</td>
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<td>E/E'</td>
<td>-20.1</td>
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Univariate adjusted-analysis: Age and Gender
Multivariate adjusted-analysis: Univariate + Hypertension, Obstructive Sleep Apnoea, Type II DM and Sotalol
### Table 5.6 Predictors of $V_e/VCO_2$

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<th>MULTIVARIATE</th>
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<td></td>
<td>Coefficient (B)</td>
<td>SE</td>
<td>P</td>
<td>Coefficient (B)</td>
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<td>P</td>
</tr>
<tr>
<td>Age</td>
<td>0.2</td>
<td>0.1</td>
<td>&lt;0.001</td>
<td>0.2</td>
<td>0.6</td>
<td>&lt;0.001</td>
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<tr>
<td>Rhythm Status</td>
<td>2.4</td>
<td>1.1</td>
<td>0.03</td>
<td>2.4</td>
<td>1.0</td>
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</table>

Univariate adjusted-analysis: Age and Gender
Multivariate adjusted-analysis: Univariate + Hypertension, Obstructive Sleep Apnoea, Type II DM and Sotalol
CHAPTER 6 – RESTORATION OF SINUS RHYTHM IMPROVES CARDIORESPIRATORY FITNESS AND VENTILATORY EFFICIENCY IN ASYMPTOMATIC PATIENTS WITH ATRIAL FIBRILLATION

6.1 Introduction

In patients with AF exercise intolerance, dyspnea and reduced quality-of-life are commonly reported symptoms. [230] Dyspnea or exercise intolerance amongst AF patients are estimated to affect up to two-thirds of this cohort, which may be attributed to haemodynamic impairments during exertion. [237, 238, 258]

Cardiopulmonary exercise testing (CPET) is the gold-standard assessment in measuring aerobic capacity. Over the past three decades, parameters measured during CPET, such as peak oxygen consumption (VO$_{2peak}$) have demonstrated strong diagnostic and prognostic value. [214, 235] However, there have been few studies to date which have assessed the use of CPET within AF patients to quantify the impaired exercise tolerance amongst AF patients. [234, 250, 259, 260]

It has been well described that AF results in a loss of atrial kick and impairs cardiac output, an effect that would subsequently limit VO$_{2peak}$. [238] In an early study, Gosselink et al., investigated the effect of sinus rhythm restoration on VO$_{2peak}$ amongst patients with long-standing persistent AF. In those patients who maintained SR following cardioversion, VO$_{2peak}$ improved by 11% compared to those who remained in AF. [261] Subsequent studies further supported these early studies demonstrating the beneficial effect of SR restoration in predominantly symptomatic patients with AF. [262-264] More recently, Gilbert el al., showed that within 2-weeks following successful cardioversion resulted in a significant 14% improvement in VO$_{2peak}$. However, the study also reported that from 2-8 weeks there were no significant differences to VO$_{2peak}$ across these two-timepoints suggesting that the improvements to cardiac function are quite immediate and may be caused by the restoration
of atrial kick or improved diastolic filling. [265] Other studies have also shown the beneficial effect of SR restoration on VO_{2peak} following catheter ablation. [266, 267] However, only one study to date within AF patients have assessed changes to the ventilatory efficiency derived from \( V_{E}/V_{CO_2} \), showing significant improvements in this variable following successful restoration of sinus rhythm following cardioversion. [268]

Symptom status and self-reported burden of AF plays a key role by the treating physician to select the appropriate management strategy for the individual patient. Patients that are typically symptomatic are referred for rhythm control strategies much quicker to alleviate the burden; however, when it comes to ‘asymptomatic patients’ management strategies alter given the fact that patients are not seen to be affected. However, with the known presence of underlying dyspnea and exercise intolerance that exists within this cohort, are ‘asymptomatic patients’ truly asymptomatic? Could these patients in fact have symptoms of dyspnea and exercise intolerance and be missed due to lack of adequate cardiopulmonary exercise assessment. To date the current studies within this field have primarily assessed symptomatic AF patients with a focus on VO_{2peak}. However, there is no study to date to assess these changes in patients with ‘asymptomatic AF’, which may in result in this group of patients exhibiting symptoms that were not typically detected within the standard assessments.

Therefore, our study aims to assess the changes to both VO_{2peak} and \( V_{E}/V_{CO_2} \) in asymptomatic patients with persistent AF undergoing electrical cardioversion. Where, we hypothesized that restoration of SR would improve these cardiopulmonary measures one-month following cardioversion.
6.2 Methods

Participant Recruitment

The study comprised of consecutive patients referred for direct current cardioversion for the management of their persistent AF at the Centre for Heart Rhythm Disorders, Adelaide, Australia. Patients were excluded from this study if they met any of the following criteria; left ventricular ejection fraction <50%, mitral valve disease, permanent AF, heart failure with preserved ejection fraction, congenital heart disease, recent cancer diagnosis or ongoing cancer treatment, and musculoskeletal disease/injury limiting exercise. Since we were assessing asymptomatic patients with AF, patients who scored >7 on the total severity score or recorded a score of >2 (>2 reflects the patient reporting a symptom associated with their AF) on an individual AF symptom on the University of Toronto AFSS questionnaire were also excluded. All patients provided written informed consent to take part in the study that was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and the University of Adelaide. The trial was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12615000734561).

Clinical Examination

All participants underwent clinical evaluation of their rhythm disturbance and a detailed review of prevalent cardiovascular risk factors. Clinical characteristics were obtained during a formal consultation prior to the CPET, with cardiologist and general practitioner records used to classify the presence of other co-morbidities. A review of anthropometrical measures, including height and weight, and current medications was performed on the day of CPET.
University of Toronto AF Severity Scale Questionnaire

For quantification of baseline patient self-report AF symptom severity, the University of Toronto AFSS questionnaire was administered prior to the CPET. All patients completed the severity scale which consists of 7 questions assessing a range of AF-related symptoms and its impact on the patient within the previous 4-weeks of their lives.

Since we were assessing asymptomatic patients, any patients were removed from the study if they scored >7 for the overall score or >2 for any individual sub-scale score.

Cardiopulmonary Exercise Testing

Testing pre and post cardioversion was performed at the Centre for Heart Rhythm Disorders, Adelaide, Australia. CPET was conducted on a treadmill using the modified-Balke protocol, with treadmill speed modified to optimise the test duration to 8-15 minutes. [269] Resting measures were obtained in the minute prior to exercise initiation, following a period of 3-minutes seated rest. The treadmill then commenced at the desired speed, with gradient increasing by 1% per minute from a starting gradient of 1%. A minimum of 2-minutes recovery at a speed of 2.4km/h, gradient 0% was commenced after the participants attained peak exercise. Twelve-lead ECG (Mortara, USA) was monitored to record heart rate and rhythm. Blood pressure was recorded at standing rest pre-exercise, every 2-minutes throughout exercise and 2-minutes into recovery. Pulmonary gas exchange was recorded continuously through a metabolic cart (Oxycon Mobile, Carefusion, Germany). Oxygen consumption and carbon dioxide production were averaged over 20s intervals, with subsequent calculation of ventilatory equivalent for CO₂ (VE/VCO₂), and respiratory exchange ratio (RER). O₂ pulse was calculated as the absolute VO₂peak (ml/min) divided by peak heart rate and expressed as ml of O₂ per heartbeat. VO₂peak was taken
as the highest attained VO$_2$ during peak exercise. CPET was completed at baseline within the 2-weeks prior to cardioversion and repeated 4-weeks post cardioversion.

**Direct Current Cardioversion**

All procedures were conducted at the Royal Adelaide Hospital, Adelaide South Australia. In all cases, patients had been on either uninterrupted oral anticoagulation or underwent transoesophageal examination prior to cardioversion to exclude the presence of left atrial thrombus. In all cases under anaesthesia, 200 J biphasic shocks were delivered to restore sinus rhythm. Given the possibility of atrial mechanical stunning developing post cardioversion, follow-up was defined as four-weeks post cardioversion, with the patients reverting into AF classed as the control group and used to compare differences in those who remained in SR following successful cardioversion. [97]

**Statistical Analysis**

Categorical variables are represented by frequencies and percentages. Continuous variables are summarised by mean ± standard deviation. All outcomes were assessed for normality using a Shapiro-Wilks test for normal distribution. To assess changes between groups following cardioversion an independent samples t-test was utilised, with a paired samples t-test used to assess within group differences from both testing timepoints. Two-tailed p<0.05 was considered statistically significant. Statistical analysis was performed with SPSS Version 21.0 (SPSS, Inc., Chicago, Illinois).
6.3 Results

In total 34 patients took part in the study who completed both pre and post CPET following cardioversion. Figure 6.1 demonstrates the CONSORT diagram for recruitment. The mean age of the participants was 67±7 years and 70% were males (n=24). There were 23 patients who successfully maintained SR (SR group) compared to 11 patients who reverted to AF (control group) at follow-up testing. Baseline patient characteristics are presented in Table 6.1 and outcomes of all measures are presented in Table 6.2.

**Primary Outcomes**

**VO\textsubscript{2peak}**

At baseline there was no differences in VO\textsubscript{2peak} between groups (p>0.05). Similarly, at follow-up there were no significant differences in VO\textsubscript{2peak} between groups in those patients who successfully maintained SR or reverted into AF (mean difference: 2.2, 95% CI -2.1 to 6.5ml/kg/min, p=0.2, figures 6.2). For the absolute VO\textsubscript{2peak} changes between groups there were no differences between the SR or control group at time of follow-up testing (mean difference: 117.9, 95%CI -348.2 to 584.1ml/min, p=0.6, figure 6.3).

For individual group changes there was a significant improvement in VO\textsubscript{2peak} in those who maintained SR (mean difference: 1.4, 95% CI 0.4 to 2.4ml/kg/min, p<0.01), with no changes within the control group (mean difference: -0.7, 95% CI -2.5 to 1.1ml/kg/min, p=0.3). However, for individual group changes in relation to absolute VO\textsubscript{2peak} there was a significant improvement within the group who maintained SR (mean difference: 127.5, 95% CI 36.6 to 218.6ml/min, p<0.01), compared to no changes within those who reverted back into AF (mean difference: -62.9, 95% CI -252.1 to 126.3ml/min, p=0.4).
**Ve/VCO₂**

From baseline results there were no differences between groups in relation to their Ve/VCO₂ (p>0.05); however, following on from cardioversion there were significant differences between groups in relation to the Ve/VCO₂ with those patients who maintained SR having a significantly lower Ve/VCO₂ (improved) compared to those who reverted into AF (mean difference: -6.3, 95% CI -11.6 to -0.9, p<0.01, figure 6.4).

When we assessed for individual group changes, those patients who maintained SR significantly lowered their Ve/VCO₂ (p<0.01) compared to the control group who significantly increased their Ve/VCO₂ (p=0.03).

**Secondary Outcomes**

**Minute Ventilation (Ve)**

At baseline there were no differences between groups in relation to Ve (p>0.05). At follow-up there were no significant differences in those patients who successfully maintained SR and those who reverted into AF (mean difference: -2.5, 95% CI -21.5 to 16.5L/min, p=0.7, figure 6.5).

When we assessed the individual group changes at follow-up there were no changed observed in those patients who maintained SR at time (p=0.5), however in those patients who reverted into AF there was a significant increase in the Ve (p=0.05).

**Resting and Peak Heart Rates**

With regards to heart rate values there were no differences in relation to both peak and resting HR values at baseline exercise testing (p>0.05). Following cardioversion, there was a significant
reduction in resting heart rate upon successful maintenance of SR compared to those who reverted into AF (mean difference: -13.4, 95%CI -20.8 to -5.9, p<0.001).

In relation to individual group differences at follow up there was a significant reduction seen in resting HR in those patients who maintained SR (mean difference: -23.5, 95%CI -29.3 to -17.8, p<0.001), with no differences in those who reverted into AF.

For peak HR there was no statistical level of significance reached in relation to difference between groups at follow-up testing (mean difference: -15.3, 95%CI -30.9 to 0.3, p=0.055), however the data does suggest that peak HR does seem to decrease following maintenance of SR.

Although, when we assess for individual group differences peak HR significantly decreases in those who maintained SR from baseline to follow-up (mean difference: -26.6, 95%CI -35.9 to -17.2, p<0.001) with no differences observed within the AF group (p>0.05).

**O₂ Pulse**

At baseline there was no difference between both groups in relation to their O₂ pulse. Following cardioversion, there were no significant differences seen in relation to O₂ pulse between both groups of patients who successfully maintained SR or who were in AF at time of follow-up (mean difference: 2.3, 95%CI -0.5 to 5.1, p=0.08, figure 6.6).

However, upon assessing individual group changes, there was a significant increase in O₂ pulse seen in those who maintained SR (p<0.001) compared to no differences within those who were in AF (p=0.7).
6.4 Discussion

Primary Findings

The primary findings of our study are that restoration of SR did not lead to any significant improvements in VO\textsubscript{2peak}, however, it does lead to significant improvements in ventilatory efficiency in asymptomatic patients with AF. Furthermore, successful restoration of SR significantly improves heart rate modulation with reductions in both resting and peak heart rates.

Restoration of SR and VO\textsubscript{2peak}

Our data is not entirely consistent with previous studies which have shown improvements in VO\textsubscript{2peak} following successful restoration of SR both with DCC and catheter ablation. [236, 238, 261, 263, 265, 267] Our primary analysis did not reach a level of significance between groups, however when we analysed for individual group changes there was a level of significance achieved with a 10-15% improvement in VO\textsubscript{2peak}. This improvement is consistent with previous studies reporting that the restoration of SR results in a 10% improvement in cardiac output and subsequently VO\textsubscript{2peak}. [238] However, the lack of significance achieved when assessing differences between groups could strongly be attributed to recruitment size and the unequal 2:1 allocation of patients in SR or AF at follow-up testing which is solely due to the success of the cardioversion itself.

Restoration of SR improves ventilatory efficiency

Our other primary finding of this study is that $\text{Ve/VCO}_2$ significantly improves in patients with AF after successful restoration of SR. This measure is reflective of ventilatory efficiency and serves as a prognostic tool in relation to mortality. [252, 270] Our results indicate that patients
significantly improved from an abnormal $V_E/VCO_2$ slope ($\geq 34$) in AF to within normal limits ($<34$) in SR. This is an important finding and provides new insight into this metric as it has not well been explored amongst AF patients, despite its prognostic value amongst HF patients. Only two previous studies to date in this setting have assessed changes to ventilatory efficiency in patients with AF following restoration of SR with Lundstrom et al., and Guazzi et al., both showing significant improvements. [271, 272] In patients with heart failure, $V_E/VCO_2$ is elevated and may lead to increased symptoms associated with reduced functional capacity. [273, 274] Improvements in ventilatory efficiency following successful restoration of SR have been previously noted to occur due to improvements in perfusion-ventilation matching in the lungs with decreased ventilatory dead space. [275] This has important clinical implications in the management and treatment in patients with asymptomatic AF, in that a rhythm control strategy may provide some cardiopulmonary improvements in a cohort that typically are not considered to be physically affected by the arrhythmia. Furthermore, the significant improvements seen in the ventilatory efficiency following restoration of SR also provides an important mechanistic insight into AF and its role in modulating abnormal ventilatory processes and may underpin the typical symptom observed within this cohort of breathlessness. What could be postulated based on previous work in this area is that the restoration of SR may in fact improve respiratory control pathways and pulmonary circulation, which in combination can lead to improvements in cardiopulmonary gas exchange and VO$_{2\text{peak}}$. [272]

**Restoration of SR and the effect on minute ventilation and stroke volume**

Additionally, our study did not see any differences in $V_E$ or $O_2$ pulse between patients in SR or AF at follow-up testing. Interestingly, there was no changes seen in $V_E$ which was not expected
given the improvement seen in ventilatory efficiency. In a similar study to ours the authors reported that the restoration of SR significantly reduced and improved \( V_E \) during both steady-state and above anaerobic threshold by 7%; however, this was not seen within our cohort. [271] Although, we did see a significant increase in \( V_E \) within the control group which supports previous data that AF can lead to altered ventilatory pathways. Based on our data it may suggest that improvements to \( V_E \) do not immediately occur following restoration of SR. It could be postulated that within AF cohorts there are other underlying mechanisms that may cause this altered ventilation response which may be explained by an augmented activation of the metaboreflex or central command response to increasing exercise demands and may require longer term sustainment of SR to exhibit improvements in these areas. [272, 276]

\( O_2 \) pulse is a measure purported to be reflective of stroke volume and this could also be related to the fact that we did not see statistically significant changes in \( VO_{2peak} \). When we assessed individual group differences the SR group did significantly increase their \( O_2 \) pulse by \( \approx 25\% \) compared to the AF group which remained unchanged. This degree of improvement has been similarly reported in other studies that have assessed changes following successful restoration of SR via both cardioversion and catheter ablation with an \( \approx 35\% \) improvement in \( O_2 \) pulse that was attributed to improvements in stroke volume and peripheral blood flow distribution and extraction. [266, 272] However, it is important to highlight that \( O_2 \) pulse is very much an indirect measure of stroke volume which assumes various variables within the Fick equation. Further to this, heart rate parameters of resting and peak also normalised in those again who restored SR, with resting and peak heart rates significantly lower at follow-up testing as previously established from previous studies when achieving SR. [261, 265, 266, 271, 272]
Limitations

A limitation of our study is the small sample size of patients that we have recruited, especially that our study had a 2:1 distribution regarding those patients who achieved SR and those who remained AF following cardioversion procedure. Echocardiographic measures would have been best to assess any underlying cardiac structural and functional improvements following cardioversion. Another limitation of the study was the ability to have a longer-term follow-up to further assess any further changes following longer sustained periods of SR compared to AF. Finally, another potential limitation of our study us that majority of our patients recruited were males, which may potentially cause a gender bias when trying to apply these findings to both genders.

6.5 Conclusion

In individuals with asymptomatic persistent AF, restoration of SR results in improvements in $V_e/\text{VCO}_2$, with no significant changes seen in VO$_{2\text{peak}}$. These results provide important insight into the underlying role of AF on ventilatory processes and drivers that may affect this cohort which can now be improved upon successful restoration of SR. Furthermore, this may shed some light that there may be in fact symptoms of AF in patients typically categorised as ‘asymptomatic’ which can be measured using CPET. More studies are required to directly assess ventilatory pathways in patients with AF and the prevalence of this within asymptomatic patients.
6.6 Figures and Tables

Figure 6.1: CONSORT Flow Diagram of Patient Recruitment and Attrition
Table 6.1: Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>SR Patients (n=23)</th>
<th>AF Patients (n=11)</th>
<th>All Patients (n=34)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.5±7.1</td>
<td>66.5±5.1</td>
<td>67.2±6.5</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Gender (Male n, (%))</td>
<td>17 (74)</td>
<td>7 (63.6)</td>
<td>24 (70)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Obesity, n (%)</td>
<td>8 (34.7)</td>
<td>6 (54.5)</td>
<td>14 (41.2)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>13 (56.5)</td>
<td>7 (63.6)</td>
<td>20 (58.8)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Obstructive Sleep Apnoea, n (%)</td>
<td>7 (30.4)</td>
<td>3 (27.2)</td>
<td>10 (29.4)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Type II DM, n (%)</td>
<td>4 (17.4)</td>
<td>2 (18.2)</td>
<td>6 (17.6)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td><strong>MEDICATIONS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-Blockers, n (%)</td>
<td>12 (52.1)</td>
<td>7 (63.6)</td>
<td>19 (55.9)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Calcium-Channel Blocker, n (%)</td>
<td>5 (21.7)</td>
<td>1 (9.1)</td>
<td>6 (17.6)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Anti-Arrhythmic, n (%)</td>
<td>14 (60.8)</td>
<td>8 (72.7)</td>
<td>22 (64.7)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Anti-Hypertensive, n (%)</td>
<td>10 (43.4)</td>
<td>3 (27.2)</td>
<td>13 (38.2)</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td><strong>ECHOCARDIOGRAPHIC MEASURES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA Volume Indexed (ml.m²)</td>
<td>38.7±8.1</td>
<td>41.8±11.5</td>
<td>39.7±9.2</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>IVSd (mm)</td>
<td>1±0.1</td>
<td>1.1±0.1</td>
<td>1±0.1</td>
<td>p&gt;0.05</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>59.5±6.8</td>
<td>62±4.4</td>
<td>60.3±6.1</td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>
Table 6.2: Results

<table>
<thead>
<tr>
<th></th>
<th>SR Group</th>
<th></th>
<th>Control Group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre DCC</td>
<td>Post DCC</td>
<td>Pre DCC</td>
<td>Post DCC</td>
<td>P-value</td>
</tr>
<tr>
<td>( \text{VO}_{2 \text{peak}} ) (ml/kg/min)</td>
<td>19.6±6.5</td>
<td>21±5.7*</td>
<td>18±5.8</td>
<td>18.8±5.7</td>
<td>0.2</td>
</tr>
<tr>
<td>( \text{VO}_{2 \text{peak}} ) (ml/min)</td>
<td>1785.9±705.6</td>
<td>1913.4±656.6</td>
<td>1732.5±612.7</td>
<td>1795.5±546.3</td>
<td>0.6</td>
</tr>
<tr>
<td>( \text{V} \text{e}/\text{VCO}_2 )</td>
<td>35.6±7.9</td>
<td>31.9±5.1*</td>
<td>34.5±9.5</td>
<td>38.2±10.4*</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>( \text{V} \text{e} ) (L/min)</td>
<td>75.1±26</td>
<td>76.5±23.7</td>
<td>70.6±26.1</td>
<td>79±12.1*</td>
<td>0.7</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>155.6±27.4</td>
<td>129.1±19.1*</td>
<td>141.4±33.1</td>
<td>144.4±24.6*</td>
<td>0.055</td>
</tr>
<tr>
<td>Resting HR (bpm)</td>
<td>88.4±14.5</td>
<td>64.8±8.7*</td>
<td>78±12.5</td>
<td>78.2±12.1*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>( \text{O}_2 ) Pulse</td>
<td>11.6±4.5</td>
<td>14.7±4.1*</td>
<td>12.3±3.2</td>
<td>12.4±3.1</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*denotes statistical differences within individual groups (p<0.05)
Figure 6.2a: Relative VO$_2$peak

![Graph showing relative VO$_2$peak before and after DCC with SR and AF groups compared.](image-url)
Figure 6.2b: SR Group Individual Patient Pre-Post Relative VO\textsubscript{2peak} (ml/kg/min)
Figure 6.2c: Control Group Individual Patient Pre-Post Relative VO$_{2peak}$ (ml/kg/min)
Figure 6.3: Absolute VO$_{2\text{peak}}$
Figure 6.4: $V_E/VCO_2$

![Graph showing $V_E/VCO_2$ before and after DCC with legend for SR and AF, marked as *p<0.01.](image)
Figure 6.6: O$_2$ Pulse

![Graph showing O$_2$ Pulse pre and post DCC for SR and AF groups with p=0.08](image-url)
CHAPTER 7 - A LIFESTYLE-BASED, EXERCISE & PHYSICAL ACTIVITY INTERVENTION IN PATIENTS WITH SYMPTOMATIC ATRIAL FIBRILLATION

7.1 Introduction

The growing prevalence of AF has resulted in a significant increase in the frequency of AF-related hospitalisations and subsequent healthcare burden. [15] Therefore, there is an urgent need to improve treatment and outcomes for patients with AF to reduce both disease morbidity and healthcare demands.

Exercise has been well-established in the prevention and treatment of CVD. [277] Higher levels of physical activity and cardiorespiratory fitness are independently associated with reduced CVD incidence, cardiac morbidity and cardiac and all-cause mortality. [29, 31, 32, 39, 278, 279] The risk of developing AF is significantly increased in those with underlying cardiovascular risk factors such as obesity, [10] type II diabetes mellitus, [38] hypertension and obstructive sleep apnoea. [12, 13] Given the identification of these risk factors in the development of AF, their underlying presence has also shown to be linked in the progression of the disease in those with existing AF. [10] As a result, recent studies that have focussed on weight loss and physical activity have shown the significant clinical benefit in the reduction of AF burden and symptom severity. [10, 104, 120]

Up until recently there were no adopted guidelines for the prescription of exercise in AF. However, in the latest Australian National Heart Foundation guidelines in recommends exercise that improves aerobic capacity in patients with symptomatic AF to reduce AF burden. [123] In the only randomised controlled trial to date amongst patients with non-permanent AF, Malmo et al., showed that AF burden was significantly reduced in patients randomised to 12-weeks of aerobic interval training at an intensity of 85-95% of HRpeak. [189] In addition to this, there were also significant improvements in peak VO₂, quality-of-life measures and left
atrial and ventricular function. [189] Furthermore, in an observational study of over 350 overweight or obese AF patients, an improvement in cardiorespiratory fitness (CRF) >2METs over a 4-year follow-up, led to improved sinus rhythm maintenance and a reduction in AF symptom severity, independent of weight-loss. [122]

Although these studies support the efficacy of exercise-based rehabilitation in the management of AF, there is an absence of randomised, controlled trials assessing longer exercise interventions combining both supervised and home exercise.[98] Such an intervention has several distinct advantages including the potential for greater translation into clinical care and less demand on resources for frequent, supervised exercise sessions. Previous studies have shown the strong efficacy of home-based exercise programs in the long-term to improve cardiorespiratory fitness, quality-of-life and outcomes following myocardial infarction, or in those with type 2 diabetes mellitus and peripheral artery disease. [280-282]

Therefore, this pilot randomised controlled trial aims to assess the efficacy of an exercise intervention in patients with symptomatic AF compared to usual care in improving cardiorespiratory fitness. The aims of this study were to (i) evaluate the impact of a structured exercise physiologist-led 6-month combined home and supervised physical activity intervention program on cardiorespiratory fitness when compared with usual care controls and (ii), to assess the impact of a physical activity intervention on changes related to arrhythmia burden and symptom severity, CVD risk factors and cardiac structure and function. We hypothesised that a physical activity-based lifestyle intervention would improve cardiorespiratory fitness, compared to usual medical care.

7.2 Methods

Study Population
The study comprised of patients referred for the management of symptomatic drug resistant persistent or paroxysmal AF at the Centre for Heart Rhythm Disorders, Adelaide, Australia. As per the 2017 HRS consensus guidelines, paroxysmal AF was defined as an AF episode that terminates spontaneously or with an intervention within a 7-day period, and persistent AF was defined as continuous AF that is sustained greater than 7-days. [283] The exclusion criteria were: permanent AF; >80 years of age; history of myocardial infarction, cardiac surgery, pacemaker insertion or ablation in the past 12 months; autoimmune or systemic inflammatory disease; active malignancy; left ventricular ejection fraction <40%; decompensated heart failure or unable to exercise due to an existing neuromuscular or musculoskeletal disorder. All patients provided written informed consent to take part in the study that was approved by the Human Research Ethics Committee of the Royal Adelaide Hospital and the University of Adelaide. The trial was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12615000734561).

**Study Protocol and Design**

This was a single-centre, randomised controlled trial. Eligible patients who consented to the study underwent 1:1 computer generated randomization to either the exercise intervention group or control group, with the treating physician blinded to patient group allocation. All patients were assessed at both baseline and at the completion of the six-month intervention period. Echocardiographers and cardiac technicians were blinded to patient randomisation. Figure 7.1 reflects the recruitment and randomisation of patients during the study. The primary endpoint for the study was cardiorespiratory fitness defined as peak oxygen consumption (VO\textsubscript{2peak}). Secondary endpoints were; AF burden, AF symptom severity, cardiac structure and function, quality-of-life assessment and CVD risk factors.
Physical Activity Intervention Group (PA)

Patients allocated to PA intervention group underwent a six-month physical activity-based lifestyle intervention with the aim of increasing their physical activity levels to ≥210 minutes/week. The rationale for this intervention is based on previous studies in which a target of 200 minutes per week led to significant weight loss, improved cardiorespiratory fitness and traditional cardiovascular risk factors including blood pressure, blood lipids and glycated haemoglobin. [284, 285]

The intervention included a 30-minute weekly supervised session with an exercise physiologist. During this session the patients were continuously counselled on achieving 30-minutes of moderate-to-vigorous aerobic exercise daily and asked to maintain a weekly journal detailing their physical activity and exercise habits for the remainder of that week, with a target exercise intensity prescribed either by the rate of perceived exertion or HR metrics if the patient had a HR device. This journal was passed onto the exercise physiologist at the weekly supervised exercise sessions.

All patients had constant telephone and email support in relation to any exercise training they were achieving on their own, and additional exercise sessions were made available if required. In those patients with a BMI >30, a target weight loss of 5% of initial weight was initiated by way of a meal plan and behavior modification program. [98]

Reduction of weekly alcohol intake was set at ≤3 standard drinks. Smoking cessation, where necessary, was targeted using the ‘5A’ (Ask, Assess, Advice, Assist and Arrange follow-up) framework.[286]

Usual medical care was also maintained in conjunction with the intervention, with the treating physician also providing further risk factor management and lifestyle health advice.
The Supervised Exercise Session

This session was conducted by an exercise physiologist with a total duration of 30-minutes. On a weekly basis the type of exercise was altered between treadmill walk or running, cycling, rowing and a combined arm-leg cycling ergometer.

This session included a 3-minute warm-up at 50% heart rate reserve (HRR), followed by four, four-minute bouts of aerobic intervals with a target heart rate of between 85-90% HRR and a two-minute low-intensity and slow-moving active recovery between each interval. This form of aerobic interval training has shown to be most effective mode of training in improving cardiorespiratory fitness in general cardiovascular disease and AF patients. [189, 287] Following the end of the intervals, the participant was given a 3-minute aerobic warm-down to assist in their recovery.

Control Group

Patients allocated to the control group were issued with initial written and verbal advice regarding health, nutrition and exercise guidelines upon enrolment into the study. The patients were strongly counselled on the importance of completing 30-minutes of daily moderate-to-vigorous aerobic exercise. During the study the patients randomized to this group continued with their usual medical care and received risk factor management at the discretion of their treating physician.

Arrhythmia Management
All patients within the study underwent guideline-directed arrhythmia management at the discretion of their treating physician who was blinded to group allocation. The use of rhythm and rate control strategies was at the discretion of the treating physician with those patient’s refractory to anti-arrhythmic agents being offered ablation. AF burden was determined by clinical review, 12-lead electrocardiogram and 4-day Holter monitoring. AF was taken as any AF episode ≥30 seconds. [283]

**Primary Outcomes**

**Cardiorespiratory Fitness**

Cardiorespiratory fitness was assessed by a symptom-limited maximal cardiopulmonary exercise stress test (CPET) on the treadmill following a modified Balke protocol initiating at a speed of 5.3km/h (incline 0%) and a continual 1% increase every minute. Cardiopulmonary gases were measured continuously using Oxycon Mobile (Jaeger, Germany) breath-by-breath wireless transfer, with cardiorespiratory fitness expressed as peak oxygen consumption (VO$_{2peak}$) recorded over a 20-second averaging interval. Peak minute ventilation was also assessed (VE$_{peak}$) along with slope of minute ventilation to carbon dioxide production ratio (VE/VCO$_2$). Twelve-lead ECG (Mortara, USA) was used to assess rhythm and heart rate at rest and throughout exercise. The test was ceased once the patient was unable to continue exercise due to fatigue and was deemed to have satisfied the maximal CPET criteria by achieving an RER >1.05 or a plateau in VO$_2$ response despite increasing workload. [195]

**Secondary Outcomes**
**AF Burden**

Arrhythmia duration was determined using 4-day Holter monitoring which assessed the presence of any AF episodes lasting >30secs. Analysis was performed by an independent technician reported by an electrophysiologist both of whom were blinded to participant randomization with the total duration of AF being the sum of all cumulative episodes.

**AF Symptom Severity**

The AF Severity Scale (AFSS, University of Toronto, Canada) is a validated self-reported questionnaire that quantifies three areas of AF-related symptoms being; frequency, duration and severity. [10, 242] For the purpose of our study, this tool was used to solely assess patient self-reported AF symptoms at both baseline and follow-up, using the severity score out of a total of 35. A score of 0 reflects no symptoms and a score of 35 reflects the highest symptom severity.

**Cardiac Function and Structure**

Transthoracic echocardiography was performed with a 3.5-MHzprobe (Vivid7, GE Medical Systems) at baseline and at 6-month follow-up by an independent sonographer blinded to participant randomization. Measures recorded included; left atrial volume, left ventricular wall thickness and diastolic function using LV diastolic filling pressure estimated by the ratio of early mitral inflow velocity to early mitral annular velocity (E/E’) with all values quantified as per American Society of Echocardiography guidelines. [243, 288]

**Quality of Life**
The impact of overall health related quality-of-life was determined by the self-administered questionnaire Atrial Fibrillation Effect on QualiTy-of-Life (AFEQT, St Jude Medical, USA). [289] A score of 100 reflects a good quality-of-life, with a score of 0 reflecting the worst quality-of-life caused by the condition.

**Cardiovascular Disease Risk Factors**

Assessment of AF related CVD risk factors were recorded at both baseline and follow-up. Regarding weight management we recorded both height and weight measurements to reflect body mass index (BMI) in Kg/m² in conjunction with waist circumference (cm). Resting blood pressures (mmHg) were also taken in a standing position pre-exercise at both baseline and follow-up. [104]

**Statistical Analysis**

Categorical variables are represented by frequencies and percentages. Continuous variables are summarised by mean ± standard deviation. All outcomes were assessed for normality using a Shapiro-Wilks test for normal distribution. Differences to assess changes within our primary and secondary outcomes from baseline to follow-up were assessed using analysis of variance procedures. Follow-up measures were compared with adjustment for baseline values as a covariate. Parameters that were significantly different from a normal distribution were reported as median and interquartile range. Two-tailed p<0.05 was considered statistically significant. Statistical analysis was performed with SPSS Version 21.0 (SPSS, Inc., Chicago, Illinois).
7.3 Results

In total 75 patients were recruited within the study. Figure 7.1 demonstrates the CONSORT diagram for recruitment. There were with similar baseline patient characteristics between groups which is shown in Table 7.1. The mean age of the entire cohort was 65±9 years and overall there were 44 (58.7%) males in the study. Of the patients that were randomised at baseline, there were 60 who completed testing both at baseline and at 6-month follow-up who were included in the final analysis. Table 7.2 reflects the overall analysis of all outcomes assessed from baseline to follow-up.

Primary Endpoint:

Cardiorespiratory Fitness (VO$_{2peak}$)

At baseline there was no difference between either group in relation to cardiorespiratory fitness (p=0.8). At follow-up, the intervention group completed an average weekly amount of 163±54 minutes of self-reported aerobic physical activity, which resulted in the group significantly improving VO$_{2peak}$ from 20.3±5.1 to 23.2±6.1ml.kg.min$^{-1}$ (p<0.01). Within the control group from baseline to follow-up VO$_{2peak}$ significantly decreased from 20±6.5 to 18.6±5.31ml.kg.min$^{-1}$ (p<0.05). Between groups there was a significant difference in VO$_{2peak}$ at final follow-up (Mean Difference: +4.6, 95%CI 1.6 to 7.7ml.kg.min$^{-1}$, p<0.01, figure 7.2).

In other secondary cardiopulmonary measures, VE$_{peak}$ significantly increased in the intervention group compared to controls (Mean Difference: +12.3, 95%CI 0.9 to 26.4, p<0.01), with no differences in Vt/VCO$_2$ between groups at follow-up (p=0.5). Peak exercise HR significantly increased in the intervention group compared to controls (Mean Difference: +18.2, 95%CI -7.4 to 29.1bpm, p=0.02), with no differences in resting HR values between groups (p=0.4).
Secondary Endpoints:

AF Burden

There was no difference between groups at baseline with regards to their AF burden expressed as percentage of recording time in AF (p=0.8). At follow-up both groups had significant reductions in AF burden with the intervention group reducing their time in AF from 34.4±46.9 to 14.7±33.8% (p<0.01), and the control group from 21.3±40.9 to 8.6±27% (p<0.05) (Figures 7.3). However, there was no significant difference between groups at follow-up with regards to AF burden (Mean Difference: -5.9, 95%CI -21.6 to 9.9%, p=0.51, figure 7.4). The number of AF episodes and longest AF episode were analysed with no significant difference within or between groups at follow-up (p>0.05).

AF Symptom Severity and Burden (AFSS)

In the AFSS self-reported questionnaire there was no difference between either group at baseline between both the symptom severity (p=0.9) and overall global well-being (p=0.7). From baseline to follow-up there was no significant changes within the intervention and control groups (p>0.05). There were no statistical differences between groups at final follow-up for symptom severity (Mean Difference: 1.9, 95%CI -1.7 to 5.6, p=0.2, figure 7.5) or overall global well-being (Mean Difference: -0.4, 95%CI -1.1 to 0.4, p=0.4).

Impact on Quality of Life (AFEQT)

At baseline there was no difference between groups for self-reported quality-of-life (p=0.8). At follow-up the invention group significantly improved quality of life (73±20 to 82±14, p<0.05), with no change within the control group (p>0.5). Irrespective of this, there were no statistical
differences between both groups at final follow-up (Mean Difference: -6.5, 95%CI -16.6 to 3.6, p=0.2, figure 7.6).

**Cardiovascular Disease Risk Factors**

At baseline there was no difference in BMI between both groups (p=0.8). Within the intervention group there was a significant decrease in BMI (30.1 ± 4.8 to 28.8 ± 4.5, p<0.01) with no difference within the control group. At final follow-up there was no statistical difference between groups (Mean Difference: 0.7, 95%CI -2.1 to 3.4, p=0.2). With regards to body weight there was no difference at baseline between groups (p=0.9). Both the intervention and control groups significantly decreased from 90.8±17.4 to 87.5±17.4kg (p<0.01) and 90.5±14.7 to 88.7±15.1kg (p<0.05), respectively. However, there was no significant difference between groups at follow-up (Mean Difference: 1.1, 95%CI -7.4 to 9.8, p=0.4). There was no difference at baseline between groups with regards to waist circumference (p=0.4), and at follow-up there was no change within groups (p>0.05). Furthermore, there was no significant difference between groups for waist circumference (Mean Difference: 0.8, 95%CI -6.1 to 7.7, p=0.8). Finally, at baseline there was no difference between groups in relation to Systolic BP (p=0.1). At follow-up the intervention group did significantly lower systolic BP from 136.7±16.8 to 129.3±13.6mmHg (p<0.01) in contrast to the control group (p>0.05). Furthermore, there was no significant differences present between either group in relation to systolic BP (Mean Difference: -0.7, 95%CI -9.7 to 8.3, p=0.3).

**Cardiac Structure and Function**

At baseline there was no difference in Ejection fraction (%EF) between groups (p=0.2). At follow-up %EF had significantly increased in the intervention arm from 60.7±8.8 to 63.3±6.5%
(p<0.05) with no changes within the control arm (p>0.05). There were no differences between groups at final follow-up (Mean Difference: -0.9, 95%CI -3.6 to 1.9, p=0.1). Across all other parameters recorded by echocardiogram of Indexed left atrial (LA) volume, interventricular septal thickness at diastole (IVSd) left-Ventricular end-diastolic volume (LVEDV) and E/E’ ratio, there were no significant differences; between groups at baseline, within individual groups, or between groups at follow-up (Table 7.2).

7.4 Discussion

Major Findings

This pilot study demonstrates that an exercise and home-based physical activity intervention in patients with symptomatic, paroxysmal and persistent AF leads to significant improvements in cardiorespiratory fitness. In addition, we observed that there were improvements in both the ventilatory and heart rate responses to maximal exercise.

These data highlight the feasibility of achieving improvements in exercise capacity with short term intervention to allow the development of randomised studies to evaluate the potential impact on AF burden.

Improvements in VO$_{2peak}$ and other exercise parameters

We found that home-based and supervised exercise training program leads to increase in VO$_{2peak}$ by ~15% across a 6-month period. This magnitude of change is like that reported in previous studies amongst patients with permanent and non-permanent AF, and further enforces the efficacy of exercise in patients with AF. [187-189] It seems evident that targeting >210-minutes per week of aerobic exercise can lead to significant improvements in cardiorespiratory fitness in a cohort that were typically inactive prior to study enrolment. [195,
Improving cardiorespiratory fitness is well-established to play an important role in reducing AF incidence, AF recurrence, and lowering the risk of CVD and all-cause mortality. [14, 29, 32, 122] This improvement seen in our cohort is clinically translational as a 1ml.kg.min\(^{-1}\) improvement in VO\(_2\) has a strong prognostic value being associated with a 10-15% reduction in CVD and all-cause mortality. [29, 235, 292] We also witnessed significant improvements in both VE\(_{\text{peak}}\) and HR\(_{\text{peak}}\) in the intervention group which are attributable physiological adaptations of the exercise training. An improved HR\(_{\text{peak}}\) is clinically relevant as an attenuated chronotropic response to increasing exercise demands can be a predictor of mortality and CVD events and is an important clinical outcome. [293, 294]

**AF burden and symptom severity**

Despite the positive improvements in cardiorespiratory fitness, we observed no significant difference between groups regarding AF burden. This finding contrasts with other studies in which exercise training improves aerobic capacity and concurrently reduces AF burden and arrhythmia recurrences. [122, 189] However, we observed a significant decline in AF burden within both groups, suggestive of improved rhythm control either through the optimisation of medical therapy or ongoing, physician-led multifactorial risk factor management, which has become our standard model of care. [98] This neutral effect of our results could be possibly attributed to our cohort having a significantly lower level of baseline exercise capacity (~20ml.kg.min\(^{-1}\) compared to ~33 ml.kg.min\(^{-1}\)) than in the previous randomised, controlled study. [189] Irrespective of the improved exercise capacity recorded in our intervention group they were still a significantly less fit cohort than in the previous study. This may reflect that the recruited patients in Malmo et al., had a healthier baseline status, lower disease morbidity and an ability to exercise at a greater intensity that may drive superior cardiac and physiological...
adaptations attributed to the greater training stimulus, compared to our patient cohort. [189] Finally, this neutral effect seen in AF burden may also be attributed to the higher amount of persistent AF patients that were recruited within our study. Our study compared to the previous randomised control trial had significantly more patients with persistent atrial fibrillation both at baseline and at follow-up which may be a key contributor as to why our study was unable to detect a difference between groups due to the higher degree of AF within our patient cohort. [189]

There were no differences in AF symptom severity within or between groups at final follow-up. In previous studies to date there has been a significant improvement seen in AF symptoms at time of follow-up. [122, 189]. However, the absence of between-group differences in our study could be due to our patient’s lower baseline AFSS scores in comparison to both Malmo et al., and Pathak et al., which may have blunted the effects of a lifestyle-based intervention in our population given the smaller degree of room to improve self-reported AF symptoms to begin with. [122, 189] Upon completing a power analysis to detect any significant differences of an exercise intervention on AF burden we would need to enrol approximately 130 patients (65 patients in each group), and therefore this suggests that possibly even previous studies also may have had a population bias in showing this and therefore provides insight that larger powered studies may be required to further address this disparity in the data thus far.

**Cardiac structural and functional changes**

Improvements in cardiac structural and functional parameters have previously been demonstrated as a result of exercise training. [295] In AF patients, improved diastolic function and reduced atrial dilatation have been associated with increased cardiorespiratory fitness.
However, we were unable to detect any differences between groups at time of follow-up. In previous studies amongst AF patients (Malmo et al.,) improvements in left atrial and ventricular function have been observed despite stable cardiac volumes, amongst those randomised to intensive exercise training. Likewise, similar studies in HFpEF cohorts have shown that exercise interventions lead to improvements in LA volume and E/E'. The absence of significant differences in our study potentially reflects differences in imaging modalities as well as variation in the exercise prescription.

**CVD risk factors**

Obesity and systolic blood pressure (BP) are key mediators in the promotion of AF and are primary targets in treatment strategies with a focus on lifestyle-based risk modification. [101, 104, 120] There were no differences between groups in BMI, but there were individual improvements within groups. This would suggest that the improvements in VO$_{2\text{max}}$ were in fact not driven by weight-loss, but purely by increasing levels of physical activity and training, therefore supporting our exercise intervention. Given that BMI was relatively stable with no differences across the groups, this could be another reason why we did not notice much difference between our groups across our measured outcomes. Perhaps it would be plausible to suggest that in future to add another intervention arm to assess the efficacy of exercise in conjunction with weight-loss. With regards to BP, there was only an improvement within the exercise group at time of follow-up, however between groups it was statistically trending and may reach a level of significance with a larger population size. This improvement within the exercise group sheds important light as a potential adjunct role within the standard care when targeting improvements in BP control, especially now with the newly adopted guidelines to diagnosis hypertension. [6, 297]

Page | 165
Clinical Implications

This study provides important information in the role of exercise within AF treatment and management streams. It supports the previous studies to date that exercise prescription within non-permanent AF cohort is safe and can lead to significant improvements in cardiorespiratory fitness, ventilation and HR response to peak exercise, which ultimately will improve patients’ long-term outcomes and activities of daily living.

This study incorporated only the single supervised session and educated and counselled the patients to engage in more physical activity within their own schedules, which will allow for an easy transition after the intervention period for the patients to continue in their new-daily exercise routine. This is in comparison to the previous studies which have supervised all the exercise sessions, therefore minimising the ability to translate that into normal daily routines for the patients after the intense intervention period ceased. It’s important that as clinicians the exercise session is an important time to use to empower and motivate the patient to engage in weekly targets of activity like our study, which in the long-term would translate into better longer-term outcomes. The premise of this study supports that within AF multidisciplinary groups we should promote exercise as a part of ‘Risk Factor Management’ approach as it can improve other related risk factor profiles that may in the long-term improve AF outcomes.

Study Limitations

Firstly, it’s important to highlight that our study was a pilot and is underpowered to detect a difference in both AF burden and AF symptom severity between both patient groups. This study has the potential for patient bias as we relied on a weekly self-reported model to quantify weekly physical activity levels within the intervention group. To add to this, we did not monitor...
the control group in terms of their daily activity levels. Therefore, it is plausible to suggest that some in fact may have become more active over the follow-up duration. Furthermore, our follow-up can be regarded as short in nature to detect chronic exercise induced cardiac adaptations. AF burden assessment using 4-day Holter may have missed AF episodes outside of this timeframe, however this was used across both study groups and was a limitation for both groups. Measurement bias has been reduced via standardised processes in our clinic and the evaluation by operators blinded to the patients’ randomisation.

7.5 Conclusion

This pilot randomised control trial shows that a supervised exercise and home-based physical-activity led intervention of patients with AF leads to significant improvements in cardiorespiratory fitness, ventilation and heart rate responses to maximal exercise over a six-month period. We did not observe any change in AF burden, potentially indicating that exercise training does not improve rhythm control. However, further studies are strongly recommended to assess the efficacy of longer intervention periods with enhanced follow-up.

Given the well-established general cardiovascular benefits associated with exercise and improved cardiorespiratory fitness, physical activity should continue to be strongly promoted and advocated amongst patients with AF to reduce overall CVD risk, improve mortality and promote greater risk factor control. This study further adds important data to the current literature that exercise is safe, effective and improves cardiorespiratory fitness in patients with AF with no exacerbation of the condition. Clinicians should look at ways to prescribe physical activity targets within their management of AF.
7.6 Figures and Tables

Figure 7.1: CONSORT Flow Diagram of Patient Recruitment and Attrition
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<thead>
<tr>
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<th>Intervention Group n=39</th>
<th>Control Group n=36</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
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<td>64.5 ± 9.6</td>
<td>.6</td>
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<tr>
<td>Male gender, n (%)</td>
<td>24 (62)</td>
<td>20 (56)</td>
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<tr>
<td>BMI (Kg/m²)</td>
<td>30.1 ± 4.8</td>
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<tr>
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<td>90.5 ± 14.7</td>
<td>.9</td>
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<tr>
<td>Waist Circumference (cm)</td>
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<td>SBP (mm Hg)</td>
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<td>Cardioversion Patients</td>
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**METABOLIC RISK FACTORS**

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<td>Obesity, n (%)</td>
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<td>Hypertension, n (%)</td>
<td>27 (69)</td>
<td>22 (61)</td>
<td>.5</td>
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<tr>
<td>Type II DM, n (%)</td>
<td>2 (5)</td>
<td>8 (22)</td>
<td>.01</td>
</tr>
<tr>
<td>OSA, n (%)</td>
<td>11 (28)</td>
<td>9 (25)</td>
<td>.4</td>
</tr>
<tr>
<td>Heart Failure, n (%)</td>
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<td>2 (6)</td>
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**MEDICATION USE**

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<tbody>
<tr>
<td>Beta-blockers, n (%)</td>
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<td>14 (40)</td>
<td>.4</td>
</tr>
<tr>
<td>CCBs, n (%)</td>
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<td>9 (30)</td>
<td>.4</td>
</tr>
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<td>AADs, n (%)</td>
<td>24 (62)</td>
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<td>.5</td>
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<td>Anti-HTN, n (%)</td>
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<td>20 (63)</td>
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**CARDIOPULMONARY MEASURES**

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<td>VO_{2peak} (ml.kg.min⁻¹)</td>
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<td>VO_{2peak} (ml.min)</td>
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<tr>
<td>VE_{peak} (litres)</td>
<td>70.2 ± 23.1</td>
<td>69.3 ± 24.6</td>
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<tr>
<td>V_{E}/VCO₂</td>
<td>29.4 ± 5</td>
<td>30.7 ± 5.4</td>
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**AF BURDEN**

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<tr>
<td>Time in AF (%)</td>
<td>34.4 ± 46.9</td>
<td>21.3 ± 40.9</td>
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Table 7.1: Patient Baseline Characteristics continued.

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<tr>
<td>LA Volume Indexed (ml.m²)</td>
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<tr>
<td>IVSd, (mm)</td>
<td>1.1 ± 0.2</td>
<td>1.0 ± 0.1</td>
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<td>LVEDV (ml)</td>
<td>107.3 ± 36.7</td>
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<td>Septal E/E’ ratio</td>
<td>11.6 ± 4.4</td>
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<tr>
<td>Lateral E/E’ ratio</td>
<td>8.9 ± 4.5</td>
<td>8.2 ± 3.4</td>
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<tr>
<td>EF (%)</td>
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<table>
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<th>ATRIAL FIBRILLATION SEVERITY SCALE (AFSS)</th>
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<th>Group 2</th>
<th>p-value</th>
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<tr>
<td>Symptoms (0-35)</td>
<td>9.6 ± 7</td>
<td>9.7 ± 9.1</td>
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<tr>
<td>Global well-being (0-10)</td>
<td>7.2 ± 1.4</td>
<td>7.1 ± 1.6</td>
<td>.7</td>
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<table>
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<th>ATRIAL FIBRILLATION EFFECT ON QUALITY OF LIFE (AFEQT)</th>
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<tr>
<td>Overall (0-100)</td>
<td>73 ± 19.7</td>
<td>71.6 ± 22.8</td>
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<td></td>
<td>Intervention Group</td>
<td>Control Group</td>
<td>p-value</td>
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<tr>
<td>-----------------------</td>
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<td>---------------</td>
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</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-Up</td>
<td>Baseline</td>
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<tr>
<td>BMI (Kg/m²)</td>
<td>30.1 ± 4.8</td>
<td>28.8 ± 4.5**</td>
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<td>Weight (Kg)</td>
<td>90.8 ± 17.4</td>
<td>87.5 ± 17.4**</td>
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<td>SBP (mm Hg)</td>
<td>136.7 ± 16.8</td>
<td>129.3 ± 13.6**</td>
<td>130.6 ± 15.6</td>
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<td><strong>CARDIOPULMONARY MEASURES</strong></td>
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<td>VO₂peak (ml.kg.min⁻¹)</td>
<td>20.3 ± 5.1</td>
<td>23.2 ± 6.1**</td>
<td>20 ± 6.5</td>
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<td>VO₂peak (ml.min)</td>
<td>1878 ± 646.1</td>
<td>2037 ± 744.1</td>
<td>1830.6 ± 653</td>
</tr>
<tr>
<td>VE peak (litres)</td>
<td>70.2 ± 23.1</td>
<td>78.5 ± 25.5**</td>
<td>69.3 ± 24.6</td>
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<tr>
<td>V̇e/VCO₂</td>
<td>29.4 ± 5</td>
<td>30.9 ± 5.5**</td>
<td>30.7 ± 5.4</td>
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<tr>
<td>HR peak</td>
<td>129 ± 19</td>
<td>139 ± 17**</td>
<td>132 ± 21</td>
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<td>HR rest</td>
<td>69 ± 12</td>
<td>70 ± 13</td>
<td>71 ± 13</td>
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<tr>
<td><strong>AF BURDEN</strong></td>
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<tr>
<td>Time in AF (%)</td>
<td>34.4 ± 46.9</td>
<td>14.7 ± 33.8**</td>
<td>21.3 ± 40.9</td>
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<tr>
<td>Change in Time in AF (%)</td>
<td>-21.9 ± 42.5**</td>
<td>-14 ± 36.7*</td>
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<td>Number of AF Episodes</td>
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<td>Longest AF Episode (mins)</td>
<td>804.3 ± 1420</td>
<td>696.9 ± 1708</td>
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**Table 7.2:** Outcomes continued.

<table>
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<tr>
<th>ECHOCARDIOGRAPHIC MEASURES</th>
<th>34 ± 9.2</th>
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<td>LA Volume Indexed (ml.m²)</td>
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<td>IVSd, (mm)</td>
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<td>1 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>1 ± 0.1</td>
<td>.4</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>107.3 ± 36.7</td>
<td>102.4 ± 40.2</td>
<td>97.1 ± 27.3</td>
<td>99.7 ± 26.2</td>
<td>.8</td>
</tr>
<tr>
<td>Septal E/E’ ratio</td>
<td>11.6 ± 4.4</td>
<td>12.6 ± 5.4</td>
<td>10.6 ± 3.8</td>
<td>12 ± 3.8</td>
<td>.9</td>
</tr>
<tr>
<td>Lateral E/E’ ratio</td>
<td>8.9 ± 4.5</td>
<td>10.1 ± 4.5</td>
<td>8.2 ± 3.4</td>
<td>10.8 ± 3.4</td>
<td>.9</td>
</tr>
<tr>
<td>EF (%)</td>
<td>60.7 ± 8.8</td>
<td>63.3 ± 6.5*</td>
<td>63 ± 6.4</td>
<td>62.3 ± 3.7</td>
<td>.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATRIAL FIBRILLATION SEVERITY SCALE (AFSS)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms (0-35)</td>
<td>9.6 ± 7</td>
<td>6.8 ± 5.1</td>
<td>9.7 ± 9.1</td>
<td>8.7 ± 8.1</td>
<td>.2</td>
</tr>
<tr>
<td>Global well-being (0-10)</td>
<td>7.2 ± 1.4</td>
<td>7.5 ± 1.5</td>
<td>7.1 ± 1.6</td>
<td>7.2 ± 1.3</td>
<td>.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ATRIAL FIBRILLATION EFFECT ON QUALITY OF LIFE (AFEQT)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (0-100)</td>
<td>73 ± 19.7</td>
<td>82.4 ± 14*</td>
<td>71.6 ± 22.8</td>
<td>75.3 ± 22.9</td>
<td>.2</td>
</tr>
</tbody>
</table>

(*) denotes changes in individual group between baseline to follow-up, p<0.05.
(***) denotes changes in individual group between baseline to follow-up, p<0.01
Figure 7.2: Cardiopulmonary Measure VO\textsubscript{2peak}
Figure 7.3a: Control Patient AF Burden – Individual Time in AF (%)

**AF Burden in Control Patients**

| Mean Change (%) | -14 ± 36.7 |

Baseline vs. Follow-Up

Time in AF (%)
Figure 7.3b: Intervention Patient AF Burden –Individual Time in AF (%)

AF Burden in Intervention Patients

Mean Change (%)  
-21.9 ± 42.5
Figure 7.4: AF Burden – Time in AF (%)
Figure 7.5: AFSS Symptom Severity Scale Score

AFSS Symptom Severity

Score of 35

Baseline  Follow-Up

Intervention  Control
Figure 7.6: AFEQT Impact on Quality of Life Score
CHAPTER 8 – FINAL DISCUSSIONS

This thesis presents a detailed appraisal of exercise in both the prevention and treatment strategy for patients at risk of, or with AF. This research has provided important insight into an area that has been receiving growing attention over the recent years.

The literature review in Chapter 1 summarises the current studies in the management of AF both permanent and non-permanent, which based on the limited research to date supports but does not provide a definitive answer for the use of exercise interventions in this cohort. Exercise in non-permanent AF studies so far have shown to increase exercise capacity, but also reduce both AF burden and symptoms. However, the research so far in this field is relatively new and with low patient numbers still leaves much more room to further assess the role of an exercise intervention in larger non-permanent AF cohorts and with a much larger degree of follow-up. This chapter then thoroughly assesses and summarises the current relationship of exercise studies in the prevention and in the contribution of AF. What this part of the chapter eloquently shows is that higher levels of physical activity and exercise capacity can have a protective effect against AF in the general population by improving individual risk factor profiles of AF, along with improvements in autonomic tone and inflammation. However, conflicting research has shown, albeit in a smaller population, endurance athletes, due to the excessive nature of the training stimuli, this can promote to the arrhythmia through other parameters by an increased vagal tone and atrial dilatation. Overall, what it’s important to clinically highlight, that the message of exercise and physical activity should be strongly promoted in the general population whom are at risk with or have AF, as these are the typical patient characteristics that present to a cardiology clinic.

Chapters 2 and 3 continue the theme of exercise and its preventative role both in AF and stroke incidence, given the close relationship between the two. These large populations
were able to show that higher levels of cardiorespiratory fitness objectively measured from an exercise stress test represented a reduced incidence of AF and stroke in the long-term. This sheds further light into the importance of exercise and fitness within the general population and long-term outcomes of those who are more active, which would typically reflect with a healthier phenotype and lower likelihood of having lifestyle-based CVDs which are also related risk factors for AF.

Chapter 4 provides clinically an important insight into using a heart rate-based metric to prescribe specific target intensities to improve cardiorespiratory fitness, that is already well-established across both healthy and heart disease patients. The use of HRR is important as typically it assumes reflects closely to ones VO$_2$ without the need for cardiopulmonary assessment. What we established in this novel study is that these two values cannot be assumed within the AF population, and that it in fact does need to be calculated by way of an individualised cardiopulmonary exercise test. Given the way our research is now emerging and given the role exercise seems to be playing in AF management, it’s important to investigate ways to enhance training adaptations and prescription of exercise, and this chapter was able to provide important founding research to suggest, that in the future management of AF the exercise prescription needs to be individualised.

Chapter 5 assessed whether AF symptoms can correlate with objectively measured cardiopulmonary measures. Our study showed that the AFSS symptom severity score, and self-reported symptoms of exercise related symptoms do not correlate with VO$_2$\textsubscript{peak}. Furthermore, we found that a significant proportion of AF patients do in fact have an impaired exercise capacity and ventilatory efficiency that may reflect poor long-term outcomes. Our study also showed that rhythm status at time of testing was not correlated with VO$_2$\textsubscript{peak}, however reduced RV function, increased LV size and blunted chronotropic response to exercise were all
significantly associated with a poor VO$_{2peak}$ and may ultimately serve as predictors for exercise capacity within AF patients. Therefore, this study provides a new insight that rhythm status itself may not responsible for the exercise intolerance or the symptoms of exercise related dyspnea within these patients, which may be in fact caused by underlying myocardial dysfunction.

Chapter 6 provides insight into the immediate changes to cardiopulmonary gas exchange parameters derived by CPET following successful restoration of SR within asymptomatic persistent AF patients undergoing cardioversion. Typically, previous studies have focussed on cardiorespiratory fitness improvements following restoration of SR. However, our findings show another important finding that V$_E$/V$CO_2$ significantly improves in patients who maintain SR at time of testing. This in fact supports the previous chapters findings that V$_E$/V$CO_2$ is significantly impaired in patients with AF at time of testing. Our data supports previous findings that AF can lead to an impairment in ventilatory pathways which may contribute to the typical reported symptoms of exercise intolerance or dyspnea within this patient cohort. More importantly, our findings have important clinical implications as this study was conducted in asymptomatic patients and therefore may provide new insight that this patient cohort may actually exhibit symptoms that can only be identified via cardiopulmonary exercise testing.

Finally, in Chapter 7 we present the findings from a pilot randomised control trial to date assessing a physical activity intervention in non-permanent AF patients. We were able to support previous research that cardiorespiratory fitness does significantly improve following an exercise physiologist-led home-based exercise intervention, which can be translational into one’s functional capacity. Our results did not show any differences associated with AF burden and symptoms between both groups; however, given the trending nature of the symptom
score it would be plausible to suggest that within a larger population this too would reach significance and further strengthen the benefits of incorporating exercise in the management of AF. What this study provides, that in conjunction with usual medical care, a supervised exercise intervention does positively improve patient outcomes and overall functional capacity. Exercise should not be deterred in this patient population, as it has shown to be safe and effective in its improvements in cardiorespiratory fitness, which translates into greater long-term outcomes in cardiac mortality and morbidity.
CHAPTER 9 - FUTURE DIRECTIONS

Improving our knowledge of the role exercise in both the prevention and management of this complex arrhythmia is crucial given the increasing prevalence of AF. We have seen now over the recent years that AF is directly associated with lifestyle-based CVD risk factors, and given the increasing global prevalence of obesity, AF also follows this trend. Therefore, strategies that can target and improve these known risk factors both within the primary prevention or management of the arrhythmia will play an important role.

Increasing levels of aerobic physical activity and exercise is well-established to improve CVD risk profiles such as; obesity, systolic blood pressure, HbA1c, sleep apnoea and hyperlipidaemia. Subsequently we have seen that higher levels of CRF is associated with a lower incidence of AF and stroke, which provides necessary insight into the importance of promoting physical activity to a population at risk of AF.

Furthermore, this thesis importantly highlights the role of aerobic exercise prescription in patients with AF, and its ability to improve CRF in a physical-activity led six-month intervention without any adverse effects in conjunction with the usual arrhythmia care. This supports emerging studies of the role exercise can play as an adjunct form of treatment in AF and can be emphasised to be a part of the risk factor model in AF management. However, irrespective of these improvements in cardiorespiratory fitness over a short six-month period, the important question to ask is whether these improvements are sustained in the long-term without any form of supervision. Perhaps, studies that aim to assess an exercise intervention in this cohort should incorporate a follow-up period post-intervention to assess whether the benefits are sustained in the longer term.

Furthermore, an important question that continues to exist is what is the optimal amount of exercise that should be prescribed in patients at risk or with AF? Based on the
current literature, and early studies in AF management it would seem plausible to recommend 210-minutes of aerobic physical activity per-week, which involves a combination of moderate and vigorous intensities. This form of exercise would improve cardiorespiratory fitness in patients with AF and would assist in the prevention of the disease whilst remaining in an area of exercise intensity that protects against AF and not causative as we have seen in elite endurance athletes.

Given the rising epidemic of AF globally, the need to adopt primary and secondary prevention strategies are paramount to reduce the burden on the global healthcare systems. Newly, adopted guidelines show the important need to utilise risk factor management in the treatment strategy for AF, and it seems plausible to suggest that exercise can be incorporated within that model to further enhance the management of the arrhythmia. However, further studies would be warranted to assess the role and strength of exercise in AF management on AF burden and symptom severity. Based on our pilot study, it would be fair to suggest that exercise may not have the same strong effect compared to weight-loss and the aggressive risk factor model but could surely play a strong role in improving functional capacity and subsequent self-reported AF symptom severity and can sit within the risk-factor paradigm.

Given the increasing attention exercise is receiving within this area, it should be said that in a population at risk or with AF, they should be exercising as much as possible and should not be deterred in any way from exercising irrespective of rhythm status or medication use. Exercise perhaps, should be prescribed by treating cardiologists to further stress the importance of exercise not only within AF management, but also for improving long-term CVD outcomes and mortality. Exercise can serve as a cost-effective way to protect against AF, as it has already shown in other CVDs and assist the economic strain associated with the growing number of AF hospitalisations worldwide. Clinicians around the world should be looking at
more effective ways to enhance patient awareness and understanding of AF to promote positive behavioural changes to address risk factors in across all three categories of primary, secondary and tertiary prevention models. Governments too should be playing their part in enhancing the awareness of AF and the ability to prevent the condition through lifestyle-modification and regular exercise habits, like what is already established in other CVDs. The adoption of public policy needs to address the new times of the ever-growing prevalence and burden of AF within healthcare systems, by looking at strategic ways to increase exercise levels of their respective communities whether through the education systems within schools, or adequate investment in infrastructure for cyclists on the roads or sporting hubs for both male and female populations. Given the fact that AF is linked to lifestyle-based risk factors, similar primary prevention policies such as for CAD and smoking should be assessed to address a new burden that has now rapidly surpassed heart failure and myocardial infarction hospitalisations over the last 20-years.

In summary, this thesis demonstrates the importance of incorporating exercise within AF patients, and the implementation of a multidisciplinary team would be highly recommended to maximise the patient’s ability to make informed decisions to improve their health. This thesis hopes to show the important link between exercise in protecting against AF in those at risk, but also playing an important part in the management in those with AF. Exercise is safe and should be prescribed in AF patients!
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