Heart Failure with Preserved Ejection Fraction in Atrial Fibrillation

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“With man this is impossible, but not with God; all things are possible with God”

Bible NIV, Mark 10:27

For Joanna

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Abstract

Heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) are two highly prevalent chronic cardiovascular conditions associated with significant morbidity and mortality. It is increasingly recognised that these two conditions are closely linked and commonly coexist. This thesis investigates the influence of HFpEF in patients with AF, exploring its prevalence, risk factors, pathophysiological mechanisms, diagnostic challenges and influence on patient symptoms and potential outcomes. A cohort of 125 patients in total, taken from 177 screened patients with AF undergoing AF ablation was used to investigate these aims.

Utilising invasive haemodynamic testing, **chapter 2** investigates the prevalence of HFpEF in a cohort of patients with symptomatic AF and no clinical features of heart failure. Almost three quarters of this cohort (73%) demonstrated haemodynamic features of HFpEF. HFpEF was associated with increased symptoms of AF and poorer exercise tolerance providing insight into the previously unrecognised role that HFpEF plays in patient functional capacity. In addition, HFpEF was associated structural, mechanical and electrical dysfunction of the left atrium (LA) highlighting the role of LA cardiomyopathy in linking AF and HFpEF.

AF and HFpEF share several cardiovascular risk factors. In **chapter 3,** the role of obesity in linking AF and HFpEF is explored. The study shows that, compared to non-obese AF patients, obese patients with AF are more likely to demonstrate HFpEF with higher left ventricular filling pressures, worse symptoms and poorer quality of life. These differences are underpinned by a unique obese phenotype characterised by left atrial enlargement, increased epicardial adipose tissue and therefore increased pericardial restraint. C**hapter 4** explores the role of reduced cardiorespiratory fitness (CRF) on LA myopathy in AF. The study identifies reduced CRF as an independent contributor to LA myopathy, incorporating mechanical and

electrical dysfunction, and therefore highlights the influence of reduced CRF on the development of HFpEF in AF.

Chapter 5 explores the non-invasive diagnosis of HFpEF in AF, which represents a significant clinical challenge. The diagnostic accuracy of two validated HFpEF scoring systems (the HFA-PEFF score and the H_2FPEF score) for the non-invasive diagnosis of HFpEF in AF is evaluated. Overall diagnostic accuracy of both scoring systems was found to be only moderate compared to haemodynamic testing, highlighting both the ongoing need for invasive testing in patients with AF as well as the need for the development of novel scoring systems targeted to this specific cohort of patients.

Exercise intolerance is an important feature of AF and HFpEF. **Chapter 6** investigates the role that LA mechanical dysfunction plays on exercise intolerance in patients with AF. LA dysfunction was associated with reduced exercise capacity in patients presenting in both AF and SR, suggesting that HFpEF plays a role in exercise intolerance in patients with AF.

Stroke and systemic thromboembolism remain the most feared complications of AF. **Chapter 7** investigates the potential role that HFpEF may play in stroke risk in patients with AF. Using multimodality imaging of the left atrial appendage (LAA), this study shows that the presence of HFpEF in patients with AF is associated with reduced LAA function, suggesting that HFpEF may be a significant risk factor for stroke in patients with AF.

Finally, the thesis discusses avenues for further investigation with a focus on the influence that HFpEF may play in affecting outcomes in patients with AF and exploring the potential for HFpEF to be a novel therapeutic target to improve outcomes in patients with AF.

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 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 also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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Publications and Communications to Learned Societies

Chapter 1

- **Manuscript:** Ariyaratnam JP, Elliott AD, Mishima RS, Gallagher C, Lau DH, Sanders P. Heart failure with preserved ejection fraction: An alternative paradigm to explain the clinical implications of atrial fibrillation. Heart Rhythm O2. 2021 Dec 17;2(6Part B):771-783. doi: 10.1016/j.hroo.2021.09.015. PMID: 34988529; PMCID: PMC8710629.
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- **Manuscript:** Middeldorp ME, Ariyaratnam JP, Kamsani SH, Albert CM, Sanders P. Hypertension and atrial fibrillation. J Hypertens. 2022 Dec 1;40(12):2337-2352. doi: 10.1097/HJH.0000000000003278. Epub 2022 Oct 4. PMID: 36204994.

Chapter 2

- **Manuscript:** Ariyaratnam JP, Elliott AD, Mishima RS, Kadhim K, McNamee O, Kuklik P, Emami M, Malik V, Fitzgerald JL, Gallagher C, Lau DH, Sanders P. Identification of Subclinical Heart Failure With Preserved Ejection Fraction in Patients With Symptomatic Atrial Fibrillation. JACC Heart Fail. 2023 Nov;11(11):1626-1638. doi: 10.1016/j.jchf.2023.07.019. Epub 2023 Sep 6. PMID: 37676212.
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Chapter 3

- **Manuscript:** Ariyaratnam JP, Elliott AD, Mishima RS, Kadhim K, Emami M, Fitzgerald JL, Thiyagarajah A, Dziano JK, Howie JO, Middeldorp ME, Sanders P. The Influence of Obesity and Epicardial Adipose Tissue on HFpEF in AF. **In Review**.

Chapter 4

- **Manuscript:** Ariyaratnam JP, Elliott AD, Mishima RS, Kadhim K, Emami M, Fitzgerald JL, Thiyagarajah A, Dziano JK, Howie JO, Middeldorp ME, Sanders P. Influence of Cardiorespiratory Fitness on LA Remodeling, Cardiomyopathy and HFpEF. **In Review**.
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Chapter 5

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Chapter 7

- **Manuscript:** Ariyaratnam JP, Elliott AD, Mishima RS, McNamee O, Emami M, Thiyagarajah A, Fitzgerald JL, Dziano JK, Howie JO, Middeldorp ME, Lau DH, Sanders P. HFpEF in AF is Associated with Structural and Functional Remodelling of the Left Atrial Appendage: Implications for Stroke Risk. **In Review.**
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Other Publications During Candidature

1. Middeldorp ME, **Ariyaratnam J**, Lau D, Sanders P. Lifestyle modifications for treatment of atrial fibrillation. Heart. 2020 Mar;106(5):325-332. doi: 10.1136/heartjnl-2019-315327. Epub 2019 Nov 11. PMID: 31712316.
2. **Ariyaratnam JP**, Middeldorp M, Thomas G, Noubiap JJ, Lau D, Sanders P. Risk Factor Management Before and After Atrial Fibrillation Ablation. Card Electrophysiol Clin. 2020 Jun;12(2):141-154. doi: 10.1016/j.ccep.2020.02.009. PMID: 32451099.
3. **Ariyaratnam JP**, Sanders P. Protecting the oesophagus during left atrial ablation: A surplus of options but an absence of evidence. Indian Pacing Electrophysiol J. 2020 Nov-Dec;20(6):219-220. doi: 10.1016/j.ipej.2020.09.001. Epub 2020 Sep 29. PMID: 32979484; PMCID: PMC7691772.
4. Mishima RS, Verdicchio CV, Noubiap JJ, **Ariyaratnam JP**, Gallagher C, Jones D, Malik V, Agbaedeng TA, Middeldorp ME, Lau DH, Sanders P, Elliott AD. Self-reported physical activity and atrial fibrillation risk: A systematic review and meta-analysis. Heart Rhythm. 2021 Apr;18(4):520-528. doi: 10.1016/j.hrthm.2020.12.017. Epub 2020 Dec 19. PMID: 33348059.
5. **Ariyaratnam JP**, Stokes MB, Lau DH. Implantable cardioverter-defibrillator in patients awaiting heart transplantation: Reinforcing the bridge to transplant. Heart Rhythm O2. 2021 Dec 17;2(6Part B):719-720. doi: 10.1016/j.hroo.2021.11.003. PMID: 34988521; PMCID: PMC8710616.
6. Emami M, **Ariyaratnam JP**, Pitman BM, Lau DH. Tailored Cryoballoon Pulmonary Vein Ablation for Atrial Fibrillation: When to Stop the Freeze? Heart Lung Circ. 2022 Apr;31(4):457-459. doi: 10.1016/j.hlc.2022.01.004. Epub 2022 Feb 10. PMID: 35153148.

7. Noubiap JJ, Nyaga UF, Middeldorp ME, Fitzgerald JL, **Ariyaratnam JP**, Thomas G, Sanders P. Frequency and prognostic significance of atrial fibrillation in acute pulmonary embolism: A pooled analysis. Respir Med. 2022 Aug;199:106862. doi: 10.1016/j.rmed.2022.106862. Epub 2022 May 13. PMID: 35636098.
8. **Ariyaratnam JP**, Sanders P, Elliott AD. Atrial fibrillation ablation in patients with heart failure with preserved ejection fraction: Complexities in diagnosis and treatment. Heart Rhythm O2. 2022 Sep 5;3(5):509-510. doi: 10.1016/j.hroo.2022.08.008. PMID: 36340498; PMCID: PMC9626876.
9. Mishima RS, **Ariyaratnam JP**, Pitman BM, Malik V, Emami M, McNamee O, Stokes MB, Lau DH, Sanders P, Elliott AD. Cardiorespiratory fitness, obesity and left atrial function in patients with atrial fibrillation. Int J Cardiol Heart Vasc. 2022 Aug 6;42:101083. doi: 10.1016/j.ijcha.2022.101083. PMID: 35971520; PMCID: PMC9375161.
10. Pitman BM, **Ariyaratnam J**, Williams K, Evans M, Reid-Smith N, Wilson L, Teo K, Young GD, Roberts-Thomson KC, Wong CX, Sanders P, Lau DH. The Burden of Cardiac Implantable Electronic Device Checks in the Peri-MRI Setting: The CHECK-MRI Study. Heart Lung Circ. 2023 Feb;32(2):252-260. doi: 10.1016/j.hlc.2022.10.005. Epub 2022 Nov 25. PMID: 36443175.
11. Elliott AD, **Ariyaratnam J**, Howden EJ, La Gerche A, Sanders P. Influence of exercise training on the left atrium: implications for atrial fibrillation, heart failure, and stroke. Am J Physiol Heart Circ Physiol. 2023 Oct 1;325(4):H822-H836. doi: 10.1152/ajpheart.00322.2023. Epub 2023 Jul 28. PMID: 37505470

Abbreviations

AF	Atrial fibrillation
AFSS	Atrial fibrillation severity scale
BMI	Body mass index
CPET	Cardiopulmonary exercise test
EAT	Epicardial adipose tissue
EAM	Electroanatomical mapping
HFpEF	Heart failure with preserved ejection fraction
LA	Left atrium
LAEF	Left atrial emptying fraction
LV	Left ventricle
LVEF	Left ventricular ejection fraction
mLAP	Mean left atrial pressure
MLWHF	Minnesota living with heart failure
SR	Sinus rhythm
TMWP	Transmural wall pressure
VO_{2peak}	Peak oxygen consumption

CHAPTER 1 Literature Review

1.1 INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac rhythm disorder of adults, affecting up to 60 million people worldwide.[1] It is characterised by an irregular heartbeat, generated by chaotic electrical activity in the atrial chambers. When AF develops, it can cause symptoms of palpitations, breathlessness, chest pains, exercise intolerance, fatigue and has been shown to have a detrimental impact on patient quality of life.[2,3] In addition, AF carries significant prognostic implications, increasing risk of all-cause and cardiovascular mortality, stroke and heart failure.[4]

Whilst normal sinus rhythm involves regular electrical impulse generation and coordinated conduction through the atria to the ventricles, the chaotic atrial electrical activity of AF results in irregular and often rapid conduction to the ventricles. In addition, the absence of coordinated conduction through the atria results in loss of atrial contractility which not only reduces overall cardiac output,[5,6] but may also increase LA thrombus formation and therefore increase risk of stroke. This electrical dysfunction therefore has a significant impact on the morbidity and mortality associated with AF.

However, AF is not limited to electrical dysfunction of the atria. Patients with AF also demonstrate significant structural and functional remodelling of the left atrium, even after sinus rhythm has been restored.[7] This remodelling of the LA is often referred to as LA myopathy and is characterised by LA fibrosis, dilatation, mechanical dysfunction, endothelial dysfunction and alterations in prothrombotic factors.[8] These non-electrical features of AF may also contribute to the morbidity and mortality associated with AF.

LA myopathy is also a recognised a hallmark of another chronic cardiovascular condition, heart failure with preserved ejection fraction (HFpEF).[9] HFpEF is defined as the inability of the heart to supply sufficient blood to the body in the context of a preserved left

ventricular ejection fraction. Haemodynamically, HFpEF is characterised by elevated left ventricular filling pressures either at rest or with exertion and invasive assessment of filling pressures remains the gold-standard diagnostic test for HFpEF. Several studies have now identified LA myopathy as a common pathophysiological feature of HFpEF.[10-13]

LA myopathy is not the only link between AF and HFpEF. Clinically, patients with AF and HFpEF have overlapping symptoms including dyspnoea, exercise intolerance and fatigue. In addition, both conditions share similar risk factors including hypertension, obesity, diabetes mellitus, obstructive sleep apnoea, physical inactivity and sedentary lifestyle. Growing epidemiological evidence suggests that both conditions commonly coexist and that patients with HFpEF are at increased risk of developing AF and vice versa.[14-17] However, the precise role that HFpEF plays in contributing to the morbidity and mortality of patients with AF remains unknown.

The focus of this thesis is to investigate the influence of HFpEF in patients with AF. We sought to determine the prevalence of HFpEF in patients with AF and its contribution to patient symptoms and outcomes. In addition, we investigate the role of LA myopathy in linking AF and HFpEF and the roles that specific risk factors play in the development of LA myopathy and HFpEF in patients with AF.

1.2 EPIDEMIOLOGY OF AF AND HFPEF

1.2.1 Atrial Fibrillation

AF represents a growing worldwide epidemic. Current estimates suggest that 59.7 million people (0.72% of the worldwide population) suffer with AF globally with 4.72 million new cases diagnosed each year.[1] Prevalence and incidence of AF have risen dramatically over the past 20 years and are projected to continue to increase exponentially in the coming years, reaching an estimated incidence of 33 million new cases each year by 2034 and a 60% increase

in total AF burden by 2050.[1,18] Lifetime risk for AF is now estimated to be around 37% in those aged older than 55,[19] increasing from around 25% in 2004.[20] These ever-rising numbers place a significant burden on healthcare resources, with costs associated with AF hospitalisations now outstripping those of ischaemic heart disease and heart failure.[21] Despite great advances in the diagnosis and management of AF in recent times, global AF-related deaths and disability associated life years (DALYs) have also climbed significantly over the past 20 years, reflecting the ongoing challenges associated with this important cardiovascular condition.

1.2.2 Heart Failure with Preserved Ejection Fraction

Heart failure also represents a global epidemic, with an estimated 64.3 million people (0.9% of worldwide population) affected worldwide.[22] HFpEF is thought to account for at least half of these cases.[23,24] As with AF, prevalence and incidence of HFpEF continue to rise each year with standardised incidence rates growing from 4.7 per 1000 in the 1990s to 6.8 per 1000 in the 2000s.[25] HFpEF is also associated with significant mortality and morbity, with 1-year and 5-year all-cause mortality rates of 29% and 65% respectively and hospitalisation rates of 1.39 times per year after diagnosis.[26] Interestingly, regional differences in clinical characteristics of HFpEF have been identified, with Western Europeans being older, Central/Eastern Europeans being younger and North Americans having higher prevalence of obesity and diabetes.[27]

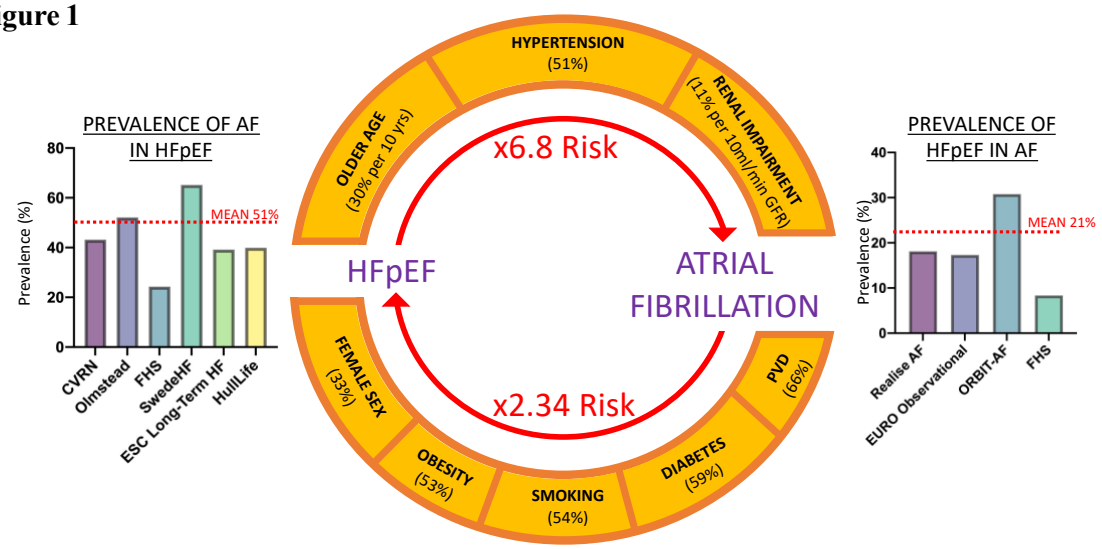
1.2.3 AF and HFpEF

In addition to being highly prevalent conditions independently, epidemiological studies show that AF and HFpEF frequently coexist. **Figure 1** shows the epidemiological relationship between both conditions.[28] In large heart failure registries recruiting both inpatients and outpatients, the overall prevalence of AF is estimated to be around 51%.[14-17,29,30] Similarly, in AF cohorts, the average prevalence of HFpEF is around 21%.[14,31-33] Both values are likely to

represent underestimates; the diagnosis of AF in patients with HFpEF is often limited by its paroxysmal nature and the absence of continuous rhythm monitoring whilst the diagnosis of HFpEF in patients with AF is challenged by the overlapping symptomatology and clinical presentation. As a result, the nature of the close relationship between the two conditions may be significantly underappreciated epidemiologically.

Community cohort studies examining the temporal relationship between AF and HFpEF provide unique insight into the bidirectional relationship between the two conditions. The Framingham Heart Study, which followed individuals with new-onset AF or heart failure for up to 7.5 years, showed that patients with AF had more than double the risk of developing HFpEF compared to those without AF.[14] Similarly, patients with HFpEF were more than three times more likely to develop AF. The PREVEND study, which invited the entire population of the city of Groningen, the Netherlands, to participate showed that AF increased the risk of HFpEF development by almost seven times compared to those without AF over the course of a longer follow-up period (almost ten years).[16] These studies highlight the synergetic nature of the relationship between AF and HFpEF and the impact that each condition has on the progression of the other.

Figure 1



Epidemiology of coexisting atrial fibrillation and heart failure with preserved ejection fraction (AF-HFpEF); HFpEF is associated with increased prevalence of AF and vice versa. The presence of HFpEF increases the risk of incident AF by 6.8 times. Similarly, the presence of AF increases the risk of HFpEF by 2.34 times. These increased risks are driven by several underlying risk factors.

1.3 PATHOPHYSIOLOGY OF AF AND HFPEF

1.3.1 Atrial Fibrillation

1.3.1.1 Electrophysiological Mechanisms

The electrophysiological mechanisms underlying the chaotic electrical activity of AF are numerous, complex and, despite extensive investigation to-date, remain incompletely understood. Current understanding is that distinct mechanisms are responsible for the initiation and maintenance of AF.

1.3.1.1.1 Initiation

Early experimental models raised the possibility that AF could be triggered by ectopic electrical activity from a single focus.[34] However, conflicting theories persisted for many years until the pioneering work of Haissaguerre and colleagues in the 1990s revolutionised our understanding of AF. Using intracardiac mapping during initiation of AF, they showed that 94% of ectopic foci triggering AF were located in the pulmonary veins.[35] Pulmonary veins are particularly arrhythmogenic structures, owing to sleeves of myocardial tissue which display disorganised myofiber arrangement creating the substrate for anisotropic conduction and micro-reentrant circuits.[36-38] In addition, they have been shown to contain spontaneously depolarising nodal-like cells which have the potential to be sources of arrhythmogenicity.[39] Importantly, Haissaguerre and colleagues also found that radiofrequency ablation at the site of these ectopic foci within the pulmonary veins could reduce the burden of AF during follow-up, leading to the development of interventional techniques for pulmonary vein isolation to treat AF, the cornerstone for current AF rhythm management strategies.

More recently, several non-pulmonary vein triggers for AF have also been identified. It is thought that these may be particularly influential in patients with higher burden AF, with

evidence suggesting that they may play a role in up to 73% of patients with persistent AF. Recognised non-pulmonary vein triggers include the LA posterior wall,[40] the proximal superior vena cava,[41] the coronary sinus ostium,[42,43] left atrial appendage,[44] the Crista terminalis[45] and the mitral annulus,[46] with some evidence to suggest that these triggers play important roles in patients with persistent AF.[47] However, evidence to support ablation of these non-pulmonary vein triggers remains lacking.

1.3.1.1.2 Maintenance

The earliest theory to explain how AF sustains itself beyond the initial trigger was provided by Gordon Moe in the late 1950s when he described his 'multiple wavelet hypothesis'. This hypothesis, derived from both experimental and computational models of AF, postulated that AF was sustained by multiple fibrillatory wavefronts wandering through the atria in chaotic fashion.[48,49] These reentrant wavefronts could undergo complex interactions to either produce new wavefronts or eliminate wavefronts and the persistence of AF would depend on the number of wavefronts remaining above a critical level. Investigating this hypothesis further, Allessie and colleagues showed in their canine model that 4-6 of these simultaneously circulating wavefronts were required to sustain AF.[50] Factors favouring the maintenance of AF according to this hypothesis include increased tissue mass, slowed conduction, heterogeneous conduction and shortening of refractory periods. [48,49] Some of these factors have proved to be effective targets for the treatment of AF; class III antiarrhythmic medications prolong refractory periods[51] whilst the surgical Cox-Maze procedure reduces the atrial tissue mass available for depolarisation and remains the most effective method for reducing AF burden.[52]

1.3.1.2 Atrial Remodelling

It is now recognised that remodelling of the atria underpins these electrophysiological mechanisms, providing the atrial substrate necessary for the development of AF. Atrial remodelling is defined as any persistent change in atrial structure and function and is consistently present in AF.[53] At a molecular level, atrial remodelling is characterised by widespread ion channel dysregulation, gap junction remodelling and interstitial fibrotic change. At a macroscopic level, LA dilatation, mechanical dysfunction and electrical dysfunction involving conduction abnormalities are observed.

Several factors have been identified as drivers of this atrial remodelling process, including modifiable and non-modifiable risk factors such as ageing, hypertension and obesity. In addition, AF itself has been implicated in the progression of the atrial substrate with evidence to suggest that AF induces alterations in intracellular calcium handling and other ion channels resulting in shortened atrial action potentials and refractory periods.[53,54] These changes underpin the seminal findings of Wijffels and colleagues who found that artificial maintenance of AF resulted in greater inducibility and stability of AF, thereby creating the mantra 'AF begets AF'.[55] Further evidence for the influence of increased AF burden on atrial remodelling is the finding that patients with persistent AF demonstrate greater elctroanatomic remodelling compared with age-matched paroxysmal AF patients.[56]

1.3.2 HFpEF

The oedematous and congestive condition of heart failure has been recognised for centuries and was initially labelled dropsy, derived from the Greek word for water ("*hypdrops"*). Early haemodynamic studies highlighted that the core mechanism underlying the heart failure syndrome was elevated left ventricular filling pressures, usually in combination with reduced left ventricular ejection fraction.[57] The concept of HFpEF developed much later, after Luchi et

al described a group of patients with typical heart failure symptoms but preserved left ventricular ejection fraction on cardiac imaging.[58]

Early theories regarding the mechanisms underlying HFpEF pertained to impairment in diastolic LV function, with specific abnormalities identified in active relaxation and passive stiffness.[59] However, HFpEF is now recognised as a complex interplay of various factors incorporating both cardiac and non-cardiac elements. Several abnormalities of cardiac function in addition to LV diastolic dysfunction have now been established in HFpEF, including subtle LV systolic limitations,[60] RV dysfunction and pulmonary vascular disease,[61] endothelial dysfunction,[62] abnormal ventricular-arterial coupling[63], chronotropic incompetence[64] and LA myopathy.[10,13] Extra-cardiac abnormalities associated with HFpEF include metabolic abnormalities such as diabetes[65] and obesity,[66] renal dysfunction,[67] peripheral vascular disease[68] and skeletal muscle dysfunction.[69,70] The heterogeneous nature of HFpEF has recently led to the search for and identification of several distinct but overlapping clinical phenotypes, which has the potential to lead to phenotype-targeted treatments for HFpEF in the future.[71]

1.3.3 Mechanisms Linking AF and HFpEF

AF and HFpEF share several similar pathophysiological processes, all of which appear to be inextricably linked (**Figure 2)**. Systemic inflammation, hemodynamic alterations, microvascular dysfunction, epicardial adiposity and myocardial fibrosis all play key roles in the development of the atrial myopathy underlying both AF and HFpEF. However, these mechanisms are not independent of each other but rather represent a complex network of interacting processes. In addition to these mechanisms, development of AF and HFpEF potentiate the development and progression of each other, resulting in the creation of a vicious cycle in which, left untreated, AF and HFpEF continue to rapidly progress unabated. The final common pathway of all these mechanisms appears to be the development and progression of

LA disease which is increasingly recognised as the most important linking factor between AF and HFpEF.

1.3.3.1 Left Atrial Myopathy

In health, LA mechanical function is a vital contributor to cardiac function.[72] First, it serves as a reservoir receiving and storing blood from the pulmonary veins. Second, through its conduit and booster functions, it contributes to LV filling and up to 15-30% of LV stroke volume. Finally, in conjunction with the mitral valve, it shields the pulmonary vasculature from large left ventricular pressure oscillations. Disease of the LA, resulting in LA myopathy and impaired LA function, therefore has significant physiological repercussions culminating in symptomatic and prognostic implications for the patient.

LA myopathy is a characteristic hallmark of both AF and HFpEF. As discussed above, AF is underpinned by atrial remodelling; LA dilatation and dysfunction represent key features of this remodelling. Growing evidence suggests that HFpEF is also associated with a significant LA myopathy. Indeed, one of the key HFpEF phenotypes is the atrial myopathy phenotype, characterised by LA dilatation, mechanical dysfunction and, often, AF.[73] Patients with the atrial myopathy HFpEF phenotype have been shown to demonstrate significantly worse haemodynamics compared to other HFpEF patients,[74] leading to reduced exercise capacity and poorer prognosis.[75,76] Clinical and experimental models of HFpEF have identified significant atrial fibrosis.[77-79] whilst HFpEF patients demonstrate significantly larger LAs.[80] and reduced LA systolic and diastolic function compared with non-HFpEF controls.[81]

Importantly, the LA myopathy underlying both AF and HFpEF is a progressive condition, and this is reflected in the disease processes of both AF and HFpEF. AF is characterised by the gradual progression from short, intermittent episodes (paroxysmal AF) to longer-lasting episodes (persistent AF) and finally to permanent AF. This clinical progression

is associated not only with worsening electrical disease (lower LA voltages, conduction heterogeneity, increasing fractionation)[56] but also LA dilatation and[82] impaired mechanical function[83]. Similarly, progressive worsening of LV diastolic dysfunction, which is characteristic of HFpEF, is associated with LA enlargement and reducing LA function as determined by echocardiographic measures of LA strain.[84,85]

1.3.3.2 Systemic Inflammation

Systemic inflammation plays a central role in the pathophysiology of both AF and HFpEF. The role of systemic inflammation is highlighted by observational studies in which systemic inflammatory mediators were used to predict the onset of the two conditions. In large population-based cohorts, elevated plasma levels of proinflammatory TNFa, E-Selectin, ICAM-1 and VCAM were all found to be associated with increased risk of incident HFpEF during long-term follow-up.[86-88] Similarly, elevated levels of numerous inflammatory biomarkers, including TNFa, CRP and IL-6, as well as increased white blood cell count have been shown to be associated with increased risk of incident AF.[89,90] In addition, they have been shown to be associated with increased AF recurrence after ablation or electrical cardioversion.[89] Furthermore, patients with systemic inflammatory disorders such as rheumatoid arthritis and systemic sclerosis have been shown to be at significantly increased risk of both incident AF and HFpEF.[91,92] These studies highlight the significance of systemic inflammatory processes in patients with AF and HFpEF. Whilst strong data regarding anti-inflammatory agents for the treatment of AF or HFpEF remain lacking, there is some evidence to suggest that steroids may reduce post-ablation and post-surgical AF[93,94] and studies investigating the use of anti-inflammatory agents in HFpEF are underway.[95]

1.3.3.3 Haemodyanamic Alterations

Several cardiovascular risk factors are associated with significant intracardiac hemodynamic changes which promote the development of both AF and HFpEF. Chronic hypertension is associated increased afterload and left ventricular hypertrophy, impaired left ventricular filling and the raised left ventricular diastolic pressures diagnostic of HFpEF.[96,97] Moreover, these mechanisms further lead to increased left atrial stretch, dilatation and increased risk of AF.[98] In spontaneously hypertensive rats, similar LV and LA structural changes were identified and these were associated with lower atrial effective refractory period (ERP), increased atrial interstitial fibrosis and increased inducibility of AF.[99] In addition to the direct effects of pressure changes on cardiac structure, these hemodynamic alterations are also associated with neurohormonal activation of the renin-angiotensin-aldosterone system (RAAS), which has been shown in animal models to cause atrial and ventricular myocardial remodelling.[100]

Similarly, obesity is also associated with significant haemodynamic alterations leading to AF and HFpEF.[101] Chronically obese sheep exhibited raised left atrial pressures and significant electroanatomical mapping consisting of reduced conduction velocities and increased conduction heterogeneity, resulting in more frequent and prolonged episodes of AF.[102] Furthermore, obese patients with AF have been shown to exhibit raised LA pressures and shorter effective refractory periods compared to non-obese patients with AF.[101] These studies highlight the important influence of obesity on LA haemodynamics and the development in AF. Obesity is also closely associated with diastolic function and HFpEF; obesity has been shown to be associated with concentric LV remodelling, reduced LV diastolic function and raised LV end-diastolic pressures.[103-105] Furthermore, recent data suggests that haemodynamic effects of obesity represent a specific phenotype of HFpEF patients within the heterogeneous HFpEF clinical syndrome.[66] Patients with obesity-related HFpEF exhibited markedly different haemodynamics compared with non-obese HFpEF, including greater

plasma volume expansion, worse RV dysfunction, higher intracardiac pressures at rest and during exercise and increased exertion-induced pericardial restraint.[66] These findings highlight the marked effects of obesity on intracardiac haemodynamics which contribute to the development of both AF and HFpEF.

1.3.3.4 Coronary Microvascular Dysfunction

Myocardial ischemia in the absence of macrovascular epicardial coronary artery disease is defined as coronary microvascular dysfunction (CMD).[106] CMD has been shown to be highly prevalent in patients with both HFpEF and AF and has been shown to be associated with systemic and local inflammatory processes resulting from the presence of cardiovascular risk factors.[107] CMD causes abnormalities in left ventricular systolic function despite the presence of normal ejection fraction. These abnormalities in systolic function are subtle and include reduced left ventricular longitudinal strain,[108] midwall fractional shortening[109] and mitral annular systolic excursion[110]. In addition, CMD likely accounts for the exercise-induced myocardial ischemia and subendocardial systolic dysfunction often seen with HFpEF.[111] These subtle deficits result in the impaired systolic reserve characteristic of patients with HFpEF and AF.

CMD has been shown to be closely associated with elevated left ventricular filling pressures at rest and during exercise and reduced cardiorespiratory fitness.[112] The most extensive clinical investigation of CMD in HFpEF, showed that up to 75% of patients with HFpEF had underlying CMD.[113] Of note, 58% of these patients had coexisting AF whilst the prevalence of AF in those without CMD was only 25%. Furthermore, atrial microvascular dysfunction has been identified in patients with AF but without HFpEF.[114] These findings suggest that CMD may play a significant role in the pathogenesis of both AF and HFpEF and could also be potential targets for treatment.

1.3.3.5 Epicardial Adiposity

Adipose tissue has important proinflammatory, neurohormonal and hemodynamic effects on the cardiovascular system, all of which increase the risk of both AF and HFpEF. However, deposition of adipose tissue around the heart (epicardial adipose tissue [EAT]) is particularly relevant to both. When compared with overall BMI, EAT confers a 2-fold increased risk of AF,[115] whilst patients with HFpEF have almost 40% more EAT compared to non-HFpEF patients with matched BMI.[116]

EAT has several characteristics which render it detrimental to cardiac structure and function and increasing the risk of both AF and HFpEF. Anatomically, there is no fascial plane separating the adipose tissue from the myocardium meaning adipocytes can communicate directly with cardiac myocytes. As a result, EAT can directly infiltrate the myocardium, causing reduced voltages and conduction heterogeneity and thereby creating the electrophysiological milieu for the development of AF.[117,118] Additionally, EAT and the myocardium share the same microcirculation, leaving the myocardium vulnerable to paracrine effects from the adipose tissue. EAT is a particularly active secretory tissue (more than visceral adipose tissue), expressing high levels of pro-inflammatory cytokines and atherogenic molecules, which lead to local inflammation, tissue fibrosis, cardiomyocyte dysfunction.[119,120] Finally, the presence of EAT can directly affect cardiac mechanics, its encasing of the myocardium causing pericardial restraint and increased left-sided pressures at rest and during exercise.[121]

1.3.3.6 Fibrosis

Cardiac fibrosis is a histological hallmark of both AF and HFpEF and is closely linked with the presence of cardiovascular risk factors. Fibrotic change is driven by neurohormonal and

inflammatory mediators released in response to cardiovascular risk factors.[122] Animal models of hypertension, diabetes, obesity and sleep apnoea have all demonstrated increased levels of atrial fibrosis on histology.[123] Furthermore, clinical electroanatomical mapping studies show increased low voltage areas and complex fractionated atrial electrograms associated with chronic hypertension[124], obesity[125] and obstructive sleep apnoea,[126] findings which have been associated with increased fibrosis, increased intracellular space, increased myofibrillar loss and reduced nuclear density on histology and electron microscopy.[127] These changes in the cardiac architecture lead to anistropic conduction, facilitating the stabilization of electrical reentry and the development of AF.

Patients with AF exhibit both atrial and ventricular myocardial fibrosis, suggesting a ubiquitous rather than localized phenomenon, possibly in response to systemic disease. HFpEF is also characterised by global myocardial fibrosis. An autopsy study comparing ventricular histology between HFpEF patients and age-matched controls demonstrated significantly increased ventricular fibrosis in HFpEF.[128] Ventricular fibrosis has been linked with LV stiffening,[129] which is a characteristic feature of the HFpEF syndrome.[109] Moreover, both clinical studies and experimental models of HFpEF have identified significant atrial fibrosis,[77-79] which likely contributes to the increased left atrial stiffness seen in patients with HFpEF. Global myocardial fibrosis is therefore a common pathophysiological mechanism in both AF and HFpEF, causing both mechanical and electrical dysfunction and likely contributing to the epidemiological overlap between the two conditions. Fibrosis likely represents the final common pathway of all the pathophysiological mechanisms described above but non-invasive methods for quantifying fibrotic change within the atria remain rudimentary. Given the association between increasing fibrosis and poorer outcomes, novel methods to quantify atrial fibrosis have the potential to provide new possibilities for the investigation and management of both AF and HFpEF.

1.3.3.7 Vicious Cycle

Whilst common pathophysiological mechanisms contribute significantly to the frequent coexistence of AF and HFpEF, additional and important contributory factors are the direct influences that each condition has on the other.[130] The two conditions interact with each other in a vicious cycle, each potentiating the risk of the other.

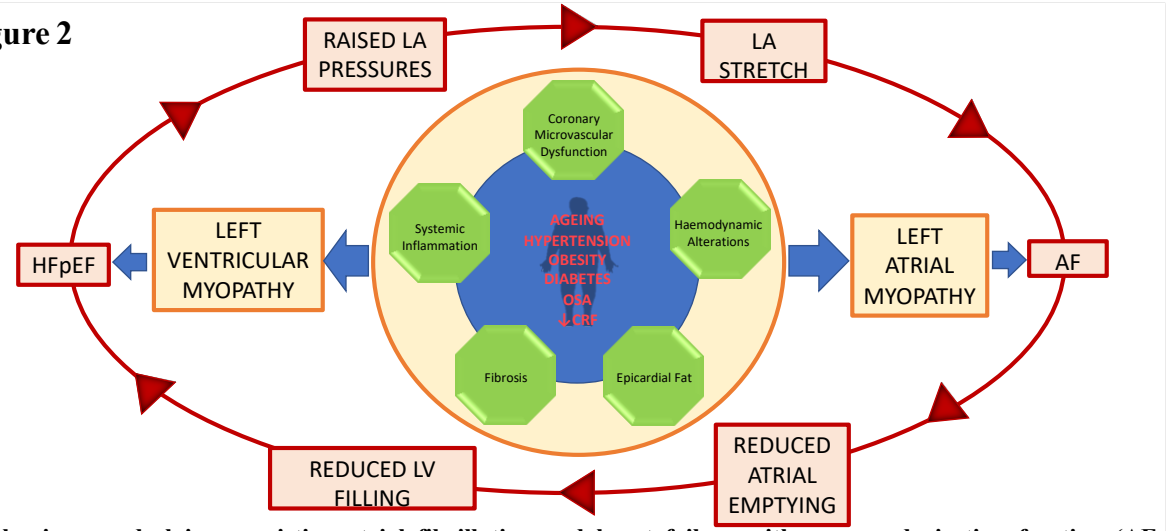
The unifying hemodynamic abnormality in HFpEF is raised left ventricular end diastolic pressure and this inevitably increases LA pressures. Increased LA pressures lead to LA stretch, dilatation and structural remodelling. LA stretch activates stretch-sensitive ion channels and promotes ion channel dysregulation within the LA, altering ionic currents and resulting in reduced LA voltages, slowed conduction and increased susceptibility to AF.[131,132] In addition, HFpEF results in neurohormonal activation of the renin-angiotensin aldosterone system (RAAS) due to renal underperfusion. RAAS activation is associated with fibrotic change within the LA,[133] partly mediated through inflammatory cytokines.[134] Hemodynamic, neurohormonal and proinflammatory mechanisms therefore all contribute to the development and potentiation of AF in patients with HFpEF.

Similarly, AF can promote the development of HFpEF. The loss of atrial systole associated with AF results in a 20% reduction in cardiac output due to reduced ventricular filling.[135] This reduced left ventricular filling results in impaired cardiac output at normal diastolic filling pressures, leading to HFpEF.[136] Furthermore, AF has been shown to be associated with increased left ventricular fibrotic change which is known to cause left ventricular stiffening and therefore elevated left ventricular end-diastolic pressures.[137] Finally, the fast ventricular rate and irregularity associated with AF can result in abnormal hemodynamics, structural remodelling and neurohormonal activation, all of which can increase the risk of HFpEF in patients with AF.[138]

1.4 SHARED RISK FACTORS

Both AF and HFpEF are underpinned by a group of shared cardiovascular risk factors which contribute to the mechanisms linking AF and HFpEF described above (**Figure 2**). This group of risk factors includes both modifiable as well as non-modifiable risk factors.

Figure 2



Mechanisms underlying coexisting atrial fibrillation and heart failure with preserved ejection fraction (AF-HFpEF); both AF and HFpEF are underpinned by the presence of multiple cardiovascular risk factors. These risk factors drive several processes leading to atrial and ventricular myopathies and resultant AF and HFpEF. AF and HFpEF interact with each other in a vicious cycle through reduced left atrial function.

1.4.1 Aging

AF and HFpEF are predominantly diseases of the elderly and aging is recognised as the most prominent risk factor for both conditions. AF incidence rates rise rapidly with age[139,140] with those aged 80-84 almost twenty times more likely to develop AF as those aged 55-59 each year.[141] Similarly, incidence of HFpEF is also closely associated with age, with a seven-fold increased risk at 85 years of age compared to 45-54 years.[142] Importantly, the impact of age on the prevalence and incidence of AF and HFpEF has been shown to be independent of other predisposing conditions.[143,144] Mechanistically, the aging process has been shown to be associated with several of the pathophysiological mechanisms linking AF and HFpEF. Age-related atrial electrophysiological dysfunction has been identified in several human studies of

AF[145-147] whilst aging is also associated with chronic low-grade systemic inflammation,[148] abnormal intracardiac haemodynamics,[149] coronary microvascular dysfunction[150] and myocardial fibrosis.[151]

1.4.2 Hypertension

Hypertension is the most prevalent modifiable risk factor underlying both AF and HFpEF; hypertension is present in 40% of patients with AF[152] and 64% of patients with HFpEF.[152] Longitudinal cohort studies show that the presence of hypertension is associated with a 50% increased risk of AF for each decade of advancing age[153] and a 3-fold increased risk of HFpEF development after multivariable adjustement.[154] In addition to established hypertension, growing evidence suggests that pre-hypertension, defined as a systolic BP greater than 120 mmHg but less than 140 mmHg or a diastolic blood pressure greater than 80 mmHg but less than 90 mmHg, is also associated with increased AF risk.[155] Importantly, treatment of hypertension has been shown to significantly reduce the risk of both AF[156] and HFpEF,[157] further highlighting the influence of uncontrolled hypertension on the development of both conditions.

The mechanisms by which hypertension can lead to the development of AF and HFpEF is driven largely by haemodynamic alterations. Hypertension results in increased afterload causing left ventricular hypertrophy and increased ventricular stiffness.[158] This increased ventricular stiffness not only leads to diastolic dysfunction and HFpEF but can also result in LA stretch, dilatation and myopathy resulting in the development of AF.[98,124,159,160] In addition to these haemodynamic effects, further mechanisms linking hypertension to AF and HFpEF include cardiac fibrosis related to activation of the neurohormonal renin-angiotensin-aldosterone system[161,162] and a hypertension-induced systemic inflammatory response.[163]

1.4.3 Diabetes Mellitus

Diabetes mellitus has also been identified as an important independent predictor of incident AF and HFpEF. The Framingham Heart Study showed that a diagnosis of diabetes was associated with a significantly increased risk of AF, reaching 40% in men and 60% in women.[143] Similarly, type 2 diabetes is associated with a 2-fold increase in heart failure risk in men and 5-fold increase in women[164] whilst up to 45% of patients with HFpEF demonstrate comorbid type 2 diabetes,[165] Effective treatment of diabetes also appears to be important with poorer HbA1c control associated with increased risk of both AF[166] and HFPEF[167]. In addition, the diabetic precursor, impaired fasting glucose, has also been associated with increased risk of both AF and HFpEF.[168] Diabetes, like all the other cardiovascular risk factors described in this section, influences the development of AF and HFpEF through several of the pathophysiological pathways described above, with evidence for associations with left atrial electrical and mechanical dysfunction,[169,170] systemic inflammation,[171] coronary microvascular dysfunction,[172] epicardial adiposity[173] and cardiac fibrosis.[174,175]

1.4.4 Obesity and Increased BMI

Obesity represents another metabolic risk factor which is closely associated with the development of AF and HFpEF. The presence of obesity has been shown to be associated with a 50% increased risk of incident AF,[176] whilst each unit increase in BMI is independently associated with a 4% increased risk of AF[177] and represents the second highest population attributable risk factor for AF after hypertension.[178] Increasing BMI also represents a significant risk factor for HFpEF and has been shown to be independently associated with a 66% increased risk of incident HFpEF.[179]

Obesity places unique stresses on the myocardium which increases the risk of both AF and HFpEF. Obesity is associated with plasma volume expansion, resulting in a

hypercirculatory state, deleterious haemodynamic changes and gross cardiac remodelling.[180] Specifically, obesity results in left ventricular hypertrophy, dilatation and diastolic dysfunction.[181] As with hypertension, this left ventricular remodelling is accompanied by significant left atrial changes including dilatation, dysfunction and electroanatomical remodelling.[102,125,182,183] The hypercirculatory state of obesity is also associated with right ventricular hypertrophy and enlargement, resulting in pericardial constriction, greater interventricular dependence, higher left ventricular filling pressures and the development of a unique phenotype of HFpEF associated with obesity.[66] The increased epicardial adipose tissue of obesity likely also contributes to this pericardial restriction[121] and HFpEF whilst also communicating directly with cardiac tissues as described above. In addition, obesity has also been associated with systemic inflammation,[184] microvascular dysfunction[185] and cardiac fibrosis.[186]

1.4.5 Obstructive Sleep Apnoea

Obstructive sleep apnoea (OSA), characterised by repetitive partial or complete obstruction of the upper airway during sleep, is another cardiovascular risk factor associated with both AF and HFpEF. Recent data suggests that OSA is highly prevalent amongst patients with AF, with up to 72% of patients demonstrating at least mild OSA and 40% with moderate-to-severe OSA.[187] HFpEF is similarly associated with OSA with almost 70% of patients with HFpEF demonstrating objective evidence of OSA.[188] Additionally, OSA has been shown to be independently associated with a 1.7-fold increased risk of incident HFpEF[154] and 2.4-fold increased risk of AF.[189]

Several pathophysiological mechanisms link OSA with structural and functional cardiac remodelling, leading to the development of both AF and HFpEF. This cardiac remodelling develops as a result of both acute and chronic effects of OSA and involve

haemodynamic, inflammatory and neurohormonal mechanisms. One of the consequences of repetitive hypoxic episodes in OSA is chronic pulmonary vasoconstriction, leading to increased right heart afterload, right heart dilatation and leftward septal displacement causing increased left ventricular filling pressures and HFpEF.[190-192] In addition, chronic exposure to repetitive hypoxic episodes is associated with high levels of reactive oxygen species, inflammation and hypertension, all of which contribute to cardiac remodelling.[193] Repetitive respiratory events cause large oscillations in intrathorcacic pressures, resulting in myocardial stress affecting the thin-walled left atrium preferentially and left atrial stretch and dilatation.[194] In addition, it has been noted that paroxysms of AF are often temporally associated with obstructive respiratory events,[195] highlighting the acute effects of each obstructive episode on atrial electrophysiology.[196]

1.4.6 Physical Activity and Cardiorespiratory Fitness

Physical activity and cardiorespiratory fitness represent further modifiable risk factors with strong associations with both AF and HFpEF.[197] Higher leisure-time physical activity levels have been associated with a 19% reduction in the risk of HFpEF[198] whilst guideline-recommended levels (500-1500 MET-min/week) of physical activity are associated with a 5-10% reduction in incident AF in men and 6-15% reduction in women.[199] Similarly, objectively measured cardiorespiratory fitness has been shown to be independently associated with HFpEF; moderate and high fitness individuals (as defined objectively measured peak oxygen consumption) are at 40% and 77% lower risk respectively of developing HFpEF compared to those with low fitness[200] whilst an inverse dose-dependent relationship between cardiorespiratory fitness and incident AF has also been demonstrated with each unit increase in metabolic equivalents achieved on treadmill testing associated with a 7% reduced risk of incident AF.[201] The relationship between physical activity, cardiorespiratory fitness and AF

and HFpEF is likely mediated by several factors; regular exercise has been shown to be associated with improved autonomic function,[202] insulin sensitivity,[203] vascular function[204] and less inflammation[205] whilst higher cardiorespiratory fitness is associated with better blood pressure and diabetes control, improved lipid metabolism and lower BMI,[206] all of which are known to contribute to AF and HFpEF risk.

1.5 CHALLENGES OF DIAGNOSING HFPEF IN PATIENTS WITH AF

Despite its clinical importance, the diagnosis of HFpEF in patients with AF remains a complex clinical challenge. Symptoms of AF and HFpEF overlap significantly; in patients with known AF, symptoms such as shortness of breath or exercise intolerance will often be attributed to the AF rather than a new diagnosis of HFpEF. Furthermore, routine diagnostic tests normally used for the diagnosis of HFpEF, such as serum natriuretic peptide levels and echocardiographic assessment of left ventricular diastolic dysfunction, are often altered by the presence of AF, meaning that their values are less clinically useful in the context of AF.[207] The gold-standard criteria for diagnosis of HFpEF involves invasive hemodynamic estimation or measurement of left ventricular end diastolic pressures at rest (>15mmHg) and during exercise (>25mmHg); this testing is largely restricted to specialist, high-volume centres and therefore unavailable to the majority of the population. Historically, therefore, the coexistence of HFpEF in patients with AF has been difficult to identify.

1.5.1 Non-Invasive Diagnosis

Recently, two novel scoring systems utilizing integrated diagnostic approaches have been developed to assist in the diagnosis of HFpEF.[208,209] The first scoring system, the HFA-PEFF algorithm, was developed as part of an expert-directed consensus guideline for the diagnosis of HFpEF. This scoring system involves pre-test probability assessment followed by diagnostic

work-up involving resting echocardiography and serum natriuretic peptide assessment. Importantly, this scoring system accounts for alterations caused by AF by incorporating different cut-off levels for BNP and LA volume according to the presence or absence of AF. A high score reflects a definitive diagnosis of HFpEF whilst a low score represents low likelihood of HFpEF. However, an intermediate score necessitates further investigation involving exercise testing with either stress echocardiography or invasive hemodynamic cardiopulmonary exercise testing. Whilst invasive hemodynamic cardiopulmonary exercise testing is a proven diagnostic tool in HFpEF, stress echocardiography currently lacks the convincing evidence to support its use for this purpose.[136]

The second diagnostic algorithm for HFpEF is the H_2FPEF scoring system derived by Reddy et al.[208] This algorithm was developed using clinical data from a cohort of 414 consecutive patients with unexplained dyspnoea undergoing invasive hemodynamic assessment. A total of 267 of these patients were found to have HFpEF on the basis of their intracardiac hemodynamics whilst the remaining 147 were diagnosed with non-cardiac dyspnoea. All clinical variables were then reviewed, and multivariate logistic regression performed to identify those variables which reliably discriminated between HFpEF and non-cardiac dyspnoea. Interestingly, the variables which discriminated best were largely cardiovascular risk factors including obesity, hypertension and advancing age. Important components of the HFA-PEFF scoring system such as LA volume and natriuretic peptides were found to be poorly discriminative and not included in this algorithm. The most important multivariate predictor of HFpEF was found to be AF, providing further evidence for the close association between AF and HFpEF. Indeed, the presence of AF scores 3 points in the H2FPEF system, conferring a minimum intermediate probability of HFpEF in all patients with AF. As with the HFA-PEFF algorithm, intermediate scores necessitates further evaluation with invasive exercise hemodynamics.

A recent retrospective analysis of patients with suspected HFpEF showed that both scoring systems for HFpEF accurately identified those at highest risk for heart failure hospitalizations and all-cause mortality.[210] Importantly, a significant proportion of these patients had coexistent AF, raising hopes that the diagnosis of AF-HFpEF has been made simpler with the use of these two scoring systems. However, a large proportion of the AF cohort had intermediate HFpEF scores according to these models. A definitive diagnosis of HFpEF would therefore require invasive hemodynamic testing in many AF patients.

1.5.2 Invasive Diagnosis

Several recent investigations have utilized invasive hemodynamic studies to identify the true proportion of AF patients with underlying HFpEF. Table 2 provides an overview of these studies. Two of the studies investigated patients going for AF ablation and assessed mLAP following transseptal puncture.[211,212] In the remaining two studies, patients with AF underwent invasive right heart catheter for assessment of mean pulmonary capillary wedge catheter (PCWP).[213,214] The response of intracardiac pressures to exercise were also assessed in all studies; studies involving right heart catheter utilized supine bicycle ergometer whereas those involving AF ablation utilized arm exercises done in the supine position following transseptal puncture.

In all four studies, a high proportion of AF patients exhibited the raised intracardiac pressures diagnostic of HFpEF. The highest proportion of AF patients meeting HFpEF criteria was seen in the study by Reddy et al. who demonstrated elevated pressures in 94.1% of AF patients. However, it is unlikely that this study was representative of the general AF population; the patients included in this study had significant dyspnoea of uncertain cause and had been investigated extensively prior to referral for invasive hemodynamic studies. Sugumar et al. included a smaller number (54) patients awaiting first-time AF ablation and found that 64%

met the criteria for HFpEF diagnosis. However, again this study was limited by a highly selected population of AF patients (only 20% of patients referred for AF ablation were ultimately included in the study). Of note, the majority of those meeting HFpEF criteria in this study were identified only on exercise, suggesting that these patients had early rather than established HFpEF, representing perhaps early LA remodelling. Importantly, all studies showed that AF cohorts exhibited a broad spectrum of LA pressures, highlighting the fact that despite the diagnosis of HFpEF being reliant on meeting strict LA pressure cutoffs, the reality is that the LA myopathy progresses on a more continuous spectrum.

The studies measuring transseptal LA pressures rather than PCWP identified similar proportions of HFPEF patients at rest but lower proportions of patients meeting criteria with exercise. There are several possible reasons for these differences in prevalence: 1) the studies involving LA pressures involved larger and more representative AF populations, 2) the methods of exercise used in the transseptal studies (arm exercises) were less exhaustive than bicycle ergometry and therefore elevated intracardiac pressures to a lesser extent 3) exercise studies undertaken immediately prior to AF ablation likely involved some level of sedation (although this was not explicitly stated in either study) which may have had some impact on exertional levels 4) invasive cardiopulmonary exercise was performed in the supine position thereby elevating LV filling pressures to a greater extent than would be seen with upright exercise[215] and 5) the mean PCWP values were overestimates of left ventricular end-diastolic pressures; an investigation into the relationship between mean PCWP and LVEDP in showed that PCWP was consistently higher than LVEDP in patients in AF, likely due to the poor operating compliance of a stiff LA and the uncoupling of LVEDP from PCWP.[216]

Aside from the prevalence of HFpEF in patients with AF, these invasive hemodynamic studies provide numerous additional insights into the association between AF and HFpEF. Sramko et al showed that elevated LA pressures were independently associated with an

increased risk of AF recurrence following ablation.[211] Sugumar et al. further showed that patients without AF recurrence had reduced mean PCWP at follow-up whilst symptomatic improvement following ablation was also associated with significantly reduced mean PCWP.[213] In another invasive hemodynamic study investigating the impact of progressively increasing AF burden in patients with a known diagnosis of HFpEF, higher AF burden was associated with progressively increased intracardiac pressures, reduced LA function and worse long-term survival.[13] Taken together, these findings not only highlight the close links between LA myopathy, AF and HFpEF and the progressive nature of all three conditions, but also suggest that reversal of this progression is possible and may be related to a reduction in LA myopathy.

1.6 CLINICAL IMPLICATIONS OF AF; THE POTENTIAL ROLE OF HFPEF

Atrial fibrillation is associated with several important clinical implications associated with poorer quality of life and prognosis. Two of the key clinical implications of AF are exercise intolerance and systemic thromboembolism. The mechanisms underlying both of these clinical implications in AF remain unclear. Evidence suggests that the dysrhythmia of AF is the causal mechanism underlying exercise intolerance and thromboembolism in AF. On the other hand, given the close association between AF and HFpEF, there is also evidence to suggest that the LA myopathy of HFpEF also plays a key role in the development of these clinical implications.

1.6.1 Exercise Intolerance

Exercise intolerance is highly prevalent in patients with AF; more than 60% of patients with symptomatic AF suffer with exertional dyspnoea or exercise intolerance and these symptoms are closely associated with reduced quality of life.[31] The mechanisms of exercise intolerance in AF remain unclear however. Rhythm at the time of exercise likely plays an important role.

Indeed, exercise intolerance is closely linked with AF burden and DC cardioversion from AF rhythm to sinus rhythm has been shown to result in dramatic improvements in exercise capacity.[217] On the other hand, patients with a history of AF but maintaining sinus rhythm may also demonstrate exercise intolerance. Recent data from a large cohort of AF patients either in AF or maintaining sinus rhythm identified diastolic dysfunction and chronotropic incompetence as the only independent predictors of cardiorespiratory fitness.[218] Diastolic dysfunction and chronotropic incompetence are both hallmarks of HFpEF, suggesting that the coexistence of HFpEF may play a role in exercise intolerance in patients with AF.

Exercise intolerance is a cardinal feature of HFpEF. Unlike in AF, the mechanisms of exercise intolerance in HFpEF have been extensively studied. Several mechanisms have been elucidated including cardiac and non-cardiac contributors.[219,220] For a significant proportion of HFpEF patients, exercise intolerance appears to be driven by impaired cardiac reserve as a result of reduced stroke volumes during exercise and/or chronotropic incompetence.[221,222] Several factors may underlie reduced stroke volumes during exercise in patients with HFpEF including both systolic[221] and diastolic impairments,[223] inducible myocardial ischaemia,[224] dynamic mitral regurgitation,[225] left atrial dysfunction[226,227] and ventriculo-arterial uncoupling.[228] Chronotropic incompetence, established as a major contributor to exercise intolerance in HFpEF, is thought to be related to a reduction autonomic imbalance and downregulation of beta-adrenergic receptors.[229]

Non-cardiac contributors to exercise intolerance in HFpEF include reduced pulmonary reserve and skeletal muscle dysfunction. Mechanisms of reduced pulmonary reserve include impaired gas exchange at the alveoli caused by pulmonary congestion or pulmonary capillary stress failure and respiratory muscle weakness.[230,231] In addition, there is a growing body of evidence to suggest that exercise intolerance may be related to impaired oxygen uptake at the level of the skeletal muscles during exercise.[220] Both structural and functional maladaptations

of skeletal muscle have been identified in HFpEF including reduced capillary density, reduced lean muscle mass, increased intermuscular fat, impaired skeletal muscle mitochondrial function, reduced muscle oxygen diffusive capacitance and reduced oxidative capacity.[69,232,233] Whether these factors contribute to exercise intolerance in patients with symptomatic AF remains unclear.

1.6.2 Stroke and Systemic Thromboembolism

AF is associated with a 5-fold increased risk of stroke or systemic thromboembolism and as many as 20-30% of all ischaemic strokes occur in patients with AF.[234-236] Whilst the mechanism ischaemic stroke in AF is known to be cardioembolic, the precise causes of atrial thrombus formation in AF remain contested.

1.6.2.1 Atrial dysrhythmia or LA myopathy

Traditional thinking was that the fibrillating atrium was a necessary condition for the formation of thrombus within the left atrium, with evidence to suggest that it was associated with stasis of blood, endothelial dysfunction and hypercoagulability, all three components of Virchow's triad.[237] However, early studies investigating the temporal relationship between short paroxysms of AF and subsequent development of stroke suggested that there was no direct link between episodes of AF and stroke.[238-240]

As a result, a competing theory developed to suggest that AF was simply a marker of stroke risk rather than a causal factor. This theory suggested that it was the underlying atrial myopathy and the presence of HFpEF, rather than the AF dysrhythmia itself, which was associated with thrombus formation. To support this theory were the findings that atrial fibrosis and reduced LA strain in sinus rhythm are both associated with increased risk of stroke in patients with a history of AF.[241,242] Furthermore, rhythm control strategies to reduce the burden

of AF, including catheter ablation, have not been shown to reduce the risk of stroke significantly,[243,244] necessitating the need for ongoing anticoagulation beyond the AF ablation procedure.

The debate continues to-date. More recent data suggests that longer multi-hour episodes of AF may be temporally associated with the development of ischaemic stroke, indicating that prolonged dysrhythmia plays a mechanistic role in thromboembolism.[245] On the other hand, anticoagulation of patients with device-detected AF has not been shown to significantly reduce stroke risk whilst a diagnosis cryptogenic stroke, in which no AF has been identified on prolonged ambulatory monitoring, has been associated with reduced left atrial function and LA myopathy. Overall, therefore, there is evidence to suggest that both the atrial dysrhythmia of AF and the LA myopathy of HFpEF may both contribute to stroke risk in patients with AF; further investigation into the relative contributions of these factors in generating LA thrombus is required to determine novel methods of stroke reduction in AF.

1.6.2.2 The role of the Left Atrial Appendage

The left atrial appendage (LAA), an embryological remnant forming a small finger-like outpouching of the left atrium, plays a critical role in thrombus formation in patients with AF. Up to 90% of all LA thrombus in patients with AF arise in the LAA.[246] Growing evidence suggests that specific features of LAA structure and function may be associated with increased risk of thrombus formation and stroke risk. It has been suggested for example that increased LAA size is directly correlated with thromboembolic risk, with increased LAA volume,[247] neck size[248] and orifice area[249] all associated with increased risk of thrombus formation. Additionally, LAA morphology has been associated with stroke risk. Several LAA morphological types have been identified, including chicken wing, windsock, cauliflower and cactus morphologies, with increased thromboembolic risk associated with cauliflower

appearance and reduced risk with chicken-wing morphology.[250] Finally, reduced LAA function is strongly correlated with increased stroke risk in patients with AF, with reduced emptying velocities on echocardiographic Doppler analysis associated with increased risk of thrombus formation.[251] The role that HFpEF plays on LAA structure and function is unclear and may provide information regarding the role that HFpEF plays in thromboembolisms in AF.

1.7 TREATMENT STRATEGIES FOR HFPEF IN AF

Management of AF has traditionally focussed on stroke prevention and symptom control via rate or rhythm control. However, emerging data suggests that a progressive LA myopathy and HFpEF may underlie many, if not all of the prognostic consequences of AF, suggesting that a re-evaluation of the treatment strategies for AF may be needed, with renewed focus on reversal of the progressive LA myopathy. Evidence suggests that many of the established treatments for AF may already involve reversal of the LA myopathy and treatment of the occult underlying HFpEF. Whilst these treatments have not yet shown any proven benefit in stroke risk reduction, a number of proven treatments may exert their effects through reversal of the HFpEF process. These treatments include risk factor management, novel pharmacological therapies and catheter ablation for AF.

1.7.1 Lifestyle Modification and Risk Factor Management

Numerous observational and randomized studies have demonstrated the significant benefits of aggressive risk factor management (RFM) in patients with AF.[252-255] The symptomatic and quality of life benefits seen with RFM have been consistently associated with reductions in AF burden. However, RFM has also been associated with reverse remodelling of the LA. The LEGACY study showed that substantial weight loss was associated with structural reverse remodelling of the LA; weight loss of more than 10% resulted in significant reductions in LA

volumes and improvements in left ventricular diastolic function.[252] Furthermore, the REVERSE-AF study showed that this weight loss could actually result in reversal of the natural progression of AF with 88% of patients losing >10% of weight regressing from persistent to paroxysmal AF. Animal studies of AF have also demonstrated significant reversal of the LA myopathy with weight loss.[125] Whilst the symptomatic and quality of life benefits associated with RFM may be due to the significant reduction in AF burden, there is evidence to suggest that LA myopathy reversal and, therefore, improved HFpEF management, may also underlie the benefits of RFM. There is also evidence to support aggressive RFM in HFpEF cohorts; a twenty week supervised exercise program and/or hypocaloric diet regimes were associated with significant improvements in exercise tolerance as measured by cardiopulmonary exercise testing compared to a control group who did not make any lifestyle changes.[256] The majority of these patients did not have a history of AF and the improvements in exercise tolerance were not accompanied by significant changes in LA size and changes in LA function were not assessed. Further research is therefore required to delineate the precise mechanisms underlying the efficacy of RFM in HFpEF and whether lifestyle changes can result in improvements in exercise capacity in AF as has been shown in HFpEF. In addition further research is required to establish whether any long-term mortality or thromboembolic benefits can be obtained from lifestyle treatments.

1.7.2 Pharmacological Therapy

Historically, despite a vast number of clinical trials investigating a variety of different medications, proven pharmacological therapies for patients with HFpEF have been lacking. However, in recent years there has been great development in this area, with SGLT2 inhibitors providing most success to-date. Both empagliflozin and dapagliflozin have been shown to significantly reduce hard cardiovascular endpoints in patients with HFpEF.[257,258] Similarly,

GLP1 inhibitors also show great promise in HFpEF, with the recent STEP-HFpEF trial showing significant weight loss and symptom improvements in patients with the obesity phenotype of HFpEF.[259] Given the close association between HFpEF and AF, these novel classes of medications may provide significant benefit in patients with AF and future studies should investigate their utility in this cohort of patients

Beta-blocker use in patients with AF is common. However, in HFpEF, beta-blocker use is increasingly discouraged due to their impact on chronotropic incompetence and exercise intolerance. Indeed, beta-blocker withdrawal resulted in profound improvements in maximal functional capacity in patients with HFpEF.[229] In addition, increasing pacing rates in HFpEF patients with pre-existing pacemakers was also associated with improved quality of life and physical activity levels, further highlighting the significance of chronotropic incompetence in patients with HFpEF.[260] Whether these findings would extend to patients with symptomatic AF remains unclear.

1.7.3 Early Rhythm Control

Rhythm control has long been established as an important treatment strategy in AF to improve symptoms and quality of life.[261] Recent data suggests that early rhythm control may also reduce major cardiovascular events including cardiovascular mortality, stroke and heart failure hospitalization.[262] The mechanisms for these improvements in outcomes are purported to be related to a reduction in AF burden but could also be attributable to reverse remodelling and treatment of the underlying LA myopathy. It is well-known that duration of time in AF is directly correlated with structural, contractile and electrical remodelling of the LA.[263] Indeed, it has been shown that longer times to treatment of AF is associated with increased risk of AF recurrence.[264] Early rhythm control of AF may therefore halt progression of adverse LA remodelling, resulting in reduced likelihood of developing HFpEF and improved outcomes.

1.7.4 Catheter Ablation

Catheter ablation for rhythm control has also been consistently associated with improvements in symptoms and quality of life.[261] Again, catheter ablation has been shown to not only reduce AF burden but also result in reverse remodelling of the LA. The imaging substudy of the Catheter Ablation Versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial showed that catheter ablation was associated with significantly reduced LA volumes compared with antiarrhythmic drug therapy.[265] This suggests that catheter ablation may be associated with a significant reverse remodelling process resulting in reduced LA myopathy and therefore improved outcomes. Evidence regarding left atrial mechanical function following ablation is less clear; early studies suggested that LA function decreased after ablation[266] although a more recent study suggested that LA strain may improve at six months post-ablation in patients with less atrial fibrosis on cardiac MRI at baseline..[267] Two meta-analyses investigating left atrial function post-ablation delivered conflicting results.[268,269] More data is required to determine the effect of catheter ablation on overall LA function.

Symptomatic benefits may therefore arise from reduced LA myopathy in addition to reduced AF burden. In their hemodynamic assessment of patients with AF pre- and post-ablation, albeit in a relatively small cohort, Sugumar et al showed that patients remaining arrhythmia free post-ablation showed significant reductions in their mean PCWP with exercise, reflecting an improvement in their underlying HFpEF.[213] The resultant improvement in their heart failure symptoms was therefore possibly related to both reduced arrhythmia burden as well as improved LA myopathy. Whilst there can be little doubt that catheter ablation is an effective strategy in the treatment of patients with AF, the precise mechanisms of its efficacy remain unclear.

CHAPTER 2 Identification of Subclinical Heart Failure with Preserved Ejection Fraction in Patients with Symptomatic Atrial Fibrillation

Statement of Authorship

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2.1 INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac rhythm disorder, associated with increased risk of stroke, heart failure (HF) and mortality.[4] Heart failure with preserved ejection fraction (HFpEF) represents a constellation of signs and symptoms attributable to raised left ventricular filling pressures.[270] Epidemiologic and experimental studies suggest that AF and HFpEF may be closely related but the prevalence of HFpEF in patients with symptomatic AF and its clinical implications remain unclear.[28]

Both AF and HFpEF are associated with significant LA dysfunction. AF is characterised by progressive electrical, structural and mechanical remodelling of the left atrium (LA),[271] whilst LA dysfunction is a hallmark of certain HFpEF phenotypes.[272] We hypothesize that a significant proportion of symptomatic AF patients who do not display overt clinical features of HF, demonstrate subclinical HFpEF, defined as Stage B HF in the current AHA/ACC/HFSA guidelines,[273] due to hemodynamic, mechanical and electrical remodelling of the LA. The aim of this study was to 1) utilize invasive hemodynamic testing to determine the prevalence of subclinical HFpEF in a cohort of patients with symptomatic AF; 2) comprehensively characterize LA cardiomyopathy in patients with AF and subclinical HFpEF with invasive and non-invasive investigations; and 3) identify the functional consequences of subclinical HFpEF in patients with AF.

2.2 METHODS

2.2.1 Study Design

This was a prospective clinical study undertaken at the Centre for Heart Rhythm Disorders at the University of Adelaide. All patients provided written informed consent. The study protocol was approved by the Human Research Ethics Committee of the Central Adelaide Local Health

Network and the University of Adelaide. The study was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12620000639921).

2.2.2 Study Population

Consecutive individuals with symptomatic paroxysmal or persistent AF due to undergo an AF ablation were eligible to participate. Patients were excluded if they had: 1) reduced left ventricular ejection fraction (<50%); 2) previous diagnosis of cardiomyopathy; 3) moderate-to-severe valvulopathy; 4) previous diagnosis of pulmonary hypertension; 5) active malignancy; 6) severe chronic obstructive airways disease; 7) inability to exercise; or 8) inability to provide written informed consent.

2.2.3 Study Procedures

Participants underwent invasive investigations at their AF ablation procedure and non-invasive investigations in the 4-week period prior to AF ablation (Figure 1).

2.2.4 Invasive Investiatigations

All participants underwent invasive hemodynamic assessment at the AF ablation procedure in order to; 1) diagnose the presence of subclinical HFpEF, 2) assess LA compliance and 3) assess LA electrical remodelling. Invasive procedures were undertaken in the fasted state under general anaesthesia.

2.2.4.1 Patient Preparation

All participants underwent invasive investigation at the AF ablation procedure having fasted for at least 6 hours. All anti-arrhythmic drugs were withheld for ≥5 half-lives prior to the procedure. Anaesthetic agents used for induction and maintenance of anaesthesia were standardised across all cases. All procedures were undertaken with uninterrupted oral

anticoagulation. An arterial line was placed for continuous monitoring of arterial blood pressure. All patients underwent transesophageal echocardiography (TOE) at the start of the procedure to ensure there was no atrial thrombus. In all patients, heparin was administered to maintain the activated clotting time over 350 seconds. Access was via the right femoral vein with ultrasound guidance. Transseptal puncture was performed using a SLO sheath and BRK1 needle (Abbott, Minneapolis, MN) under TOE guidance allowing access to the LA. An Agilis sheath (Abbott, Minneapolis, MN) was placed in the LA and a 6F pigtail catheter in the RA for simultaneous pressure monitoring.

2.2.4.2 Haemodynamic Diagnosis of Subclinical HFpEF

In this study of patients without overt clinical features of heart failure other than symptoms of AF, we diagnosed subclinical HFpEF according to established hemodynamc criteria.[273] Diagnosis of subclinical HFpEF was based on invasive measurement of mean LA pressure (mLAP) undertaken at the AF ablation procedure. Mean LAP provides an exact measurement of left ventricular filling pressures which has previously been defined as the gold-standard method for the diagnosis of HFpEF.[209,274]

All hemodynamic measurements were performed at the AF ablation procedure following transseptal puncture and after confirming hemodynamic stability for a 10-minute period. Inotropic and vasopressor medications were withheld during hemodynamic assessment. The LA, right atrial (RA) and arterial catheters were attached to pressure transducers and zeroed at the level of the mid-thorax, allowing the recording of LA, RA and arterial pressures. Pressures were recorded (240 Hz) on the WorkMate Claris^{TM} Electrophysiology System (Abbott, Minneapolis, MN) and analysed offline. Pressures were measured at end-expiration and averaged over 3 cardiac cycles for patients in sinus rhythm and over 6 cycles for patients in AF. From the LA pressure waveform mLAP, peak V-wave and the nadir Y-descent were

measured. Mean LAP was taken at the start of the C-wave. In the absence of a visible C wave, mLAP was taken midway between the peak and trough of the A-wave in those with sinus rhythm or 130-160ms after the onset of the QRS in those in AF.[275] The peak A-wave and the nadir X-descent were additionally measured in patients in sinus rhythm. RA and arterial pressures were collected in the same way.

Participants were assigned to the 'HFpEF' group if mLAP at baseline was greater than 15mmHg and to the 'Early HFpEF' group if mLAP was less than 15mmHg at baseline but rose to above 15mmHg following infusion of 500mls of saline, as defined previously.[276,277] All other patients were placed in the 'No HFpEF' group. Throughout this manuscript, the 'HFpEF' and 'early HFpEF' classification refers to patients with subclinical HFpEF only, given the exclusion of patients with overt features of heart failure.

2.2.4.3 Invasive Assessment of LA Compliance

LA compliance was assessed invasively and involved direct LA fluid loading using a body mass-adjusted volume (15mls/kg) of normal saline infused directly into the LA over an 8-minute period. After the initial 500ml rapid fluid challenge for diagnosis of subclinical HFpEF, the remainder of the fluid required for LA compliance assessment was given, with the entire fluid load occurring within 8 minutes. LA, RA and arterial pressures were recorded throughout this infusion and evaluated at 2-minute intervals. At the same time, the TOE probe was used to monitor anteroposterior LA diameter. The 120-degree mid-esophageal view was chosen for this analysis due to its with minimal underestimation of LA size and using the aortic valve as a landmark to ensure consistency of measurements.[278] This view was maintained throughout the infusion protocol and images were recorded at the same time intervals as the pressure measurements (0, 2, 4, 6 and 8 minutes). LA diameter was measured at end- atrial diastole and averaged over 3 cardiac cycles at each infusion time-point. LA dilatation over the course of the

infusion was recorded as percent change from baseline LA dimension. All measurements were verified by a second independent reviewer. All measurements were undertaken by investigators blinded to the clinical characteristics and non-invasive evaluations. LA compliance was calculated as:

$$\text{LA Compliance} = \Delta\text{LA Diameter}/\Delta\text{Peak LA Pressure}$$

2.2.4.4 Electroanatomical Mapping

Three-dimensional electroanatomical mapping (EAM) was performed prior to ablation using the HD-32 Grid Catheter (Abbott, Minneapolis, MN) and the Ensite™ Precision EAM Cardiac Mapping System (Abbott, Minneapolis, MN). High-density voltage and activation maps were created during pacing at 600ms cycle length from the coronary sinus. Patients who had undergone previous AF ablation (n=46) and patients in AF at the time of mapping (n=27) were excluded from the electrical analysis. Automated collection of points was performed; points were only acquired if they met the internal and external projection criteria of 5mm with 5mm interpolation. These maps were then analysed offline for evaluation of global and regional bipolar voltages, conduction velocities (CV) and proportion of complex fractionated electrograms.

Electrogram analysis was meticulously performed offline to exclude ectopic beats and noise. The LA was divided into posterior, anterior, roof, inferior, septal and lateral segments. Regional bipolar peak-to-peak voltages were defined as the amplitude between the peak positive and peak negative deflections of the electrogram. Regional voltages were analysed offline using a custom made validated software.[279] Regional conduction velocities were analysed using isochronal activation maps. Conduction velocities (CV) were determined in the direction of wavefront propagation (least isochronal crowding) and calculated as the distance between two points divided by the difference in local activation times. Mean CV was

determined by averaging the CV over 5 pairs of points, as previously described.[183] The percentage of points exhibiting complex fractionated signals, defined as signals of more than 50ms duration with at least 3 deflections crossing the baseline, was also determined in each region. Overall LA voltage, CV and proportion of complex fractionated points were calculated by combining the data from all 6 regions.

2.2.5 Non-invasive Investigations

All participants underwent a series of non-invasive investigations in order to 1) further assess LA cardiomyopathy and 2) evaluate the functional consequences of subclinical HFpEF in AF. These non-invasive investigations took place in within a 4-week period prior to the AF ablation procedure. Rate-control and anti-arrhythmic medications were withheld for 48 hours prior to all non-invasive investigations.

2.2.5.1 Resting and exercise echocardiography

Resting and exercise echocardiography was performed according to a study specific protocol by an experienced sonographer. Images obtained focussed on left ventricular and left atrial structure and function. Transthoracic echocardiographic imaging involved parasternal and apical views. Left ventricular ejection fraction (LVEF) was measured by the Simpson's biplane method. Maximum (LA_{max}) and minimum LA (LA_{min}) volumes were obtained using the biplane area-length method and indexed to body surface area. LA emptying fraction (LAEF) was calculated using the formula:

$$LAEF = (LA_{max} - LA_{min})/LA_{max} \times 100.$$

LA strain was performed using a previously validated software.[280] For patients presenting in AF, LA booster strain was not evaluated but LAEF and reservoir strain were assessed as these functions do not depend on LA contractile function. Flow Doppler and tissue Doppler imaging

were used to calculate E/E'. All measurements were obtained according to the American Society for Echocardiography guidelines.[281,282] Measurements were averaged over 3 cardiac cycles in sinus rhythm and over 6 cycles in AF.

Exercise echocardiography was performed using a dedicated supine bicycle ergometer allowing echocardiographic imaging during exercise. Exercise protocol involved cycling at a workload of 20W, increasing by 20W every 2-minutes. Focussed TTE images were obtained during every second stage. Exercise was stopped just prior to fusion of the E and the A waves or when symptoms limited further exercise.

2.2.5.2 Cardiac Biomarker – NT-pro BNP

Blood sampling for analysis of NT-pro BNP levels was undertaken at rest in the fasting state prior to exercise testing.

2.2.5.3 Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed using an upright cycle ergometer (Lode Corival, Lode B. V., Netherlands). Pulmonary gas exchange was measured continuously using a metabolic cart (Vyntus CPX, Vyaire Medical). Oxygen consumption (VO_2) and carbon dioxide (VCO_2) production were averaged over 20 second intervals. Participants began cycling at a power of 20 Watts, incrementally increasing by 10 Watts per minute. Peak exercise was defined as the point at which the participant felt the need to stop due to symptoms or fatigue and a respiratory exchange ratio >1.05. Peak VO_2 (VO_{2peak}) was identified as the highest attained VO_2 during exercise. Chronotropic response was calculated as difference between the resting heart rate prior to exercise and the maximum heart rate achieved at peak exercise.

2.2.5.4 Symptom Questionnaires

Symptoms of heart failure and AF were quantified using the Minnesota Living with Heart Failure (MLHFQ) and the AF Severity Scale (AFSS) (University of Toronto, Toronto, Ontario, Canada) questionnaires. The MLWHF questionnaire quantifies the presence and significance of heart failure symptoms encountered over the preceding 4-weeks. The AFSS questionnaire quantifies AF-related symptom frequency, duration and severity in addition to providing information on specific AF-related symptom burden and global well-being. AF symptom burden encompassed symptoms experienced over the previous 4-week period, regardless of the presence/absence of AF episodes. Both questionnaires have been clinically validated for use in heart failure and AF respectively.[283,284]

2.2.6 Statistical Analysis

Continuous variables were reported as means ± standard deviation for normally distributed data or median and interquartile range for non-normally distributed data. Categorical variables were reported as frequencies and percentages. Normality of each continuous variable was assessed using the Shapiro-Wilk test. Continuous variables were compared across the three HFpEF groups using one-way analysis of variance (ANOVA) procedures or Kruskal-Wallis H test as appropriate. Independent-samples Student t-tests or Mann Whitney U tests were performed between each pair of groups. Categorical variables were compared across the three groups and each pair of groups using the chi-square test or Fisher's exact test (when cell size was less than 5). Linear regression analyses were used to assess LA pressure increases according to volume of saline infused (saline-pressure slopes). Univariable and multivariable predictors of HFpEF were investigated using binary logistic regression. P-values of ≤ 0.05 were considered statistically significant. Power analysis determined that a sample size of 93 would be required to identify a HFpEF prevalence of 40% with a desired precision of ±10% at the

95% confidence interval. All statistical analysis was performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

2.3 RESULTS

2.3.1 Participant Recruitment

Of 172 consecutive patients due to undergo AF ablation, 39 patients met pre-defined exclusion criteria and 13 declined participation, resulting in a final cohort of 120 patients included in the study. **Figure 2** demonstrates the CONSORT figure for screening, recruitment and classification.

2.3.2 HFpEF Diagnostic Groups

Amongst our cohort, 57 participants (47.5%) had a mLAP greater than 15mmHg at baseline and were therefore placed in the 'HFpEF group'. A further 31 (25.8%) participants exhibited baseline mLAP of less than 15mmHg but an increase to greater than 15mmHg following 500mls saline infusion and were classified as 'Early HFpEF'. The remaining 32 (26.7%) participants were classified as 'No HFpEF'.

2.3.3 Baseline Characteristics

Table 1 shows the baseline characteristics of the study cohort according to the HFpEF groups. There were no significant differences across groups in age, gender, type of AF (paroxysmal or persistent AF), duration of AF or history of previous AF ablation. Participants in the HFpEF group also had significantly higher BMI (p=0.008), increased prevalence of hypertension (p=0.016) and higher CHA_2DS_2-Vasc scores (p=0.006). HFpEF participants were more likely to take angiotensin converting enzyme inhibitors or angiotensin receptor blockers (p=0.003) but there was no difference in the use of rate-controlling medications or antiarrhythmic drugs

across the three groups. 'Early HFpEF' did not differ significantly from 'No HFpEF' in terms of baseline characteristics, cardiovascular risk factors or medications.

2.3.4 LA Cardiomyopathy Assessment

2.3.4.1 LA Compliance and Invasive Hemodynamics

Table 2 shows the hemodynamic parameters across the three groups at baseline and following saline infusion. HFpEF was associated with significantly reduced LA compliance (**Figure 3A**, p=0.001) compared with the no HFpEF group. This difference in LA compliance was underpinned by exaggerated LA pressure responses to saline infusion; the HFpEF group exhibited significantly greater overall peak LA pressure increases with saline infusion (**Figure 3B,** p=0.005) compared with no HFpEF, despite no difference in RA (p=0.484) or mean arterial pressure changes (p=0.998). Additionally, LA dilatation with infusion was significantly reduced in the HFpEF group compared to the no HFpEF group (**Figure 3C**, p=0.001). For each ml/kg of saline infusion, LA pressure increases were higher in the HFpEF and early HFpEF groups (**Figure 3D).** Participants with early HFpEF also displayed reduced LA compliance compared with the no HFpEF group (p=0.005).

2.3.4.2 Resting Echocardiography

Table 3 shows the results of the non-invasive investigations. On resting echocardiography, LV systolic function was not different across the three groups (**Figure 4A**, p=0.315). Similarly, there was no difference in LA_{max} across the three groups (p=0.551). However, the HFpEF group was characterised by reduced LA reservoir strain (p=0.006) and reduced LAEF (**Figure 4B**, p=0.004). Participants with early HFpEF also demonstrated reduced LAEF (p=0.012) and LA reservoir strain (p=0.007) compared to those with no HFpEF. Average E/E' was also significantly higher in both the HFpEF and early HFpEF groups (**Figure 4C**, p<0.001). Of the

110 patients who completed the resting and exercise TTE analysis, 33 (30%) were in AF at the time of imaging. Including only patients in sinus rhythm did not alter the results; HFpEF remained associated with reduced LAEF (p=0.023), reduced LA reservoir strain (p=0.020) and increased E/E' (p<0.001) on echocardiography (**Table 4**).

2.3.4.3 Exercise Echocardiography

All groups had comparable LV systolic reserve during exercise (**Figure 4D**, p=0.381). However, patients with HFpEF demonstrated lower LAEF (**Figure 4E**, p=0.003) coupled with higher average E/E' (**Figure 4F**, p=0.014) at peak exercise. Early HFpEF was also associated with reduced LAEF (p=0.043) and E/E' (p=0.039) during exercise. HFpEF, but not early HFpEF was associated with reduced LV strain during exercise compared to no HFpEF (p=0.014). Excluding patients in AF had no impact on the effect of HFpEF and early HFpEF on LA function during exercise (**Table 4**).

2.3.4.4 Cardiac Biomarker

There was a trend towards increased NT-pro BNP in the HFpEF and early HFpEF groups, although this did not quite reach statistical significance (p=0.055).

2.3.4.5 Electroanatomic Mapping

Figure 5 and **Table 5** show the results of the EAM analysis. Amongst the 73 de novo AF ablation patients, 46 underwent EAM during sinus rhythm and were included in this analysis. Of these participants, 20 had HFpEF, 10 had early HFpEF and 16 had no HFpEF. HFpEF was associated with significantly reduced global bipolar LA voltage compared with no HFpEF (**Figure 5A and 5B**, p<0.001). Analysis of regional voltages revealed HFpEF was associated with significantly reduced voltage on the posterior wall (p=0.001) and roof (p=0.013). HFpEF

was also associated with significantly reduced global LA CV (**Figure 5C**, p=0.003) compared with no HFpEF and regional analysis revealed significantly lower CV on the posterior (p=0.014), inferior (p=0.004) and lateral (p=0.008) walls. Patients with 'Early HFpEF' demonstrated reduced LA voltages (p=0.025) but no differences in CV (p=0.145) compared with those with no HFpEF. There was no significant difference in percent of complex fractionated electrograms across the three groups (p=0.632).

2.3.5 Functional Consequences

2.3.5.1 Cardiopulmonary Exercise Testing

Table 6 shows the results of the non-invasive investigations used to identify the functional limiations associated with HFpEF. HFpEF was associated with significantly reduced VO_{2peak} (p<0.001) and percent of predicted VO_{2peak} achieved (p=0.006) compared with no HFpEF. HFpEF was also associated with reduced maximum heart rate achieved at peak exercise (p=0.007) and reduced chronotropic response (p=0.046). Early HFpEF was similarly associated with reduced VO_{2peak} (p=0.013), reduced percent of predicted VO_{2peak} (p=0.003) and reduced chronotropic response achieved at peak exercise (p=0.024).

2.3.5.2 Patient-Reported Symptoms

HFpEF (p=0.002) and early HFpEF (p=0.004) were associated with significantly higher AF symptom burden compared to no HFpEF. HFpEF (p=0.007) and early HFpEF (p=0.017) were also associated with significantly lower global well-being compared to no HFpEF.

2.3.6 Univariable and Multivariable Predictors of HFpEF

Univariable predictors of HFpEF were hypertension (p=0.006), BMI (p=0.003), and diabetes (p=0.021). Incorporating only these three variables into a multivariable model, BMI (p=0.016)

and a history of hypertension (p=0.025) remained significant independent predictors of HFpEF (**Table 7)**.

2.4 DISCUSSION

2.4.1 Major Findings

This prospective clinical study combining comprehensive assessment of left atrial hemodynamics, mechanical function and electroanatomical remodelling has several new findings that have significant implications for patients with symptomatic AF. We show that:

a) A significant proportion of patients with symptomatic AF without clinical features of HF display subclinical HFpEF with 73% of our cohort demonstrating hemodynamic features of HFpEF or early HFpEF.
b) Patients with subclinical HFpEF in AF are characterised by globally impaired LA hemodynamics and reduced LA compliance coupled with reduced LAEF, reduced LA strain and electrical remodelling of the LA.
c) HFpEF and early HFpEF are associated with important functional implications including reduced cardiopulmonary reserve and increased AF symptoms.

This study therefore demonstrates an unrecognized high prevalence of subclinical HFpEF in AF ablation cohorts. Additionally, we show an important association between the presence of subclinical HFpEF and functional capacity and suggest that early diagnosis and treatment of subclinical HFpEF in AF may improve patient symptoms and quality of life.

2.4.2 High Prevalence of Subclinical HFpEF in AF

In this cohort of symptomatic AF patients due to undergo AF ablation, we show that 47.5% have subclinical of HFpEF, based on invasive hemodynamic testing. A further 25.8% displayed exaggerated haemodynamic responses to 500mls fluid challenge and were considered to have

early HFpEF. Importantly, we have shown this high prevalence of hemodynamic HFpEF in a cohort of patients who did not display signs or symptoms of heart failure and demonstrated relatively low NT-pro BNP and preserved VO_{2peak} on non-invasive testing. According to current AHA/ACC/HFSA guidelines, these patients meet criteria for Stage B pre-heart failure, presenting without current or previous symptoms or signs of HF but demonstrating elevated LV filling pressures on invasive testing. This cohort therefore represents a population of patients at increased risk of progression to more advanced stages of HF.[273]

Although previous studies have attempted to assess the influence of HFpEF in patients with AF[211-214], these studies have been limited by non-consecutive selection of AF cohorts and indirect estimates of ventricular filling pressures using wedge pressures. Our consecutive AF ablation cohort included more patients with persistent AF and those undergoing redo AF ablation than prior studies. In addition, our use of direct LA pressure measurements allowed for more accurate identification of patients with HFpEF. This study therefore represents a more generalisable and accurate representation of the prevalence of HFpEF amongst patients with symptomatic AF and highlights the substantial prevalence of HFpEF in patients due to undergo AF ablation.

2.4.3 Early HFpEF

Using fluid challenge, we have been able to identify and characterize an additional cohort of patients with early HFpEF. Early HFpEF is a recognized clinical entity defined by the presence of elevated left ventricular filling pressures exclusively during exercise.[136] Early HFpEF diagnosed using invasive hemodynamic cardiopulmonary exercise testing has been shown to be associated reduced cardiac output during exercise and increased risk of long-term mortality.[285,286]

The challenge of diagnosing early HFpEF at AF ablation is the inability of the patient to carry out effective exercise testing under sedation or anaesthetic. Whilst previous studies have used isometric handgrip exercises,[211,212] these involve only small muscle mass and therefore likely do not sufficiently increase LA pressure in some patients. Fluid challenge provides a recognized alternative for the diagnosis of early HFpEF.[287] Although existing data suggests that fluid challenge may have reduced sensitivity for detecting early HFpEF compared to invasive hemodynamic exercise testing, we propose that our protocol is superior to previously examined fluid challenge protocols. By infusing saline directly into the LA rather than peripherally, we have been able to reduce the impact of differences in peripheral vascular resistance and pulmonary capacitance, thereby increasing the sensitivity to hemodynamic derangements within the LA. Importantly, we show that patients with both HFpEF and early HFpEF demonstrated increased AF symptom burden and reduced cardiopulmonary fitness, highlighting the functional limitations associated with elevated LA pressures at rest or with provocation.

2.4.4 LA Compliance

A key element of our study was the novel assessment of LA compliance, utilising LA pressure assessment coupled with changes in LA dimension during saline infusion. We demonstrate a significant reduction in LA compliance amongst those with subclinical HFpEF. Previous attempts at assessment of LA compliance or stiffness have involved either non-invasive evaluation or integrated assessments of separate stress imaging and invasive hemodynamic tests.[13,288] In this study, we have been able to simultaneously track pressure changes during volume stress with LA dimension, resulting in a more precise evaluation of LA compliance.

2.4.5 Clinical Implications

In this study we have shown that the presence of subclinical HFpEF is associated with significant morbidity, accounting for increased AF symptom burden and reduced exercise tolerance. We postulate that subclinical HFpEF may have additional mortality implications as many of the characteristics of subclinical HFpEF that we have found in this study have previously been shown to have prognostic significance. Reduced exercise tolerance in AF is associated with increased risk of all-cause and cardiovascular mortality [206,289] whilst reduced LA emptying fraction in AF is also associated with poorer long-term outcomes.[290] Furthermore, non-invasively assessed HFpEF has been shown to be associated with increased risk of all-cause mortality.[14] Future studies, involving long-term follow-up will be essential to further characterize the prognostic implications of abnormal hemodynamics in AF.

The presence of subclinical HFpEF may also correlate with risk of stroke and systemic thromboembolism. We have shown that subclinical HFpEF is associated with a LA cardiomyopathy involving LA mechanical dysfunction. Recent data suggests that reduced LA mechanical function is closely associated with increased risk of incident cardioembolic stroke.[291] Additionally, the atrial fibrosis which likely underlies the reduced LA compliance of subclinical HFpEF is also associated with an increased risk of stroke.[292] Taken together these data highlight the potential to identify patients at increased risk of stroke through invasive hemodynamic assessment for subclinical HFpEF.

Our findings may also have implications for the treatment of patients with AF. Many current treatments for AF, including AF ablation, focus on rhythm control for symptomatic benefit. Recent data suggests that whilst AF ablation remains superior to medical therapy in patients with coexistent HFpEF,[293] they may not necessarily obtain the same symptomatic benefit from rhythm control as those without HFpEF.[294] Our data suggests that an alternative approach to treatment in AF patients may be treatment of HFpEF via reversal of LA

cardiomyopathy. Recent experimental data suggests this may be achievable through simple interventions such as weight loss.[125] Similarly, clinical studies have shown that reduced LA volumes and improved LV filling pressures in patients with AF are achievable through weight-loss and improved cardiorespiratory fitness.[252-254] Finally, we postulate that therapies directed at the treatment of HFpEF may provide morbidity benefits in this cohort of patients; the identification of SGLT-2 inhibitors as the first medical therapy with proven benefit in HFpEF highlights the therapeutic potential for patients with symptomatic AF, given the high prevalence of subclinical HFpEF in this cohort.[257]

2.5 LIMITATIONS

Our findings should be considered in the context of the following limitations. The population studied included only patients going for AF ablation, thereby excluding older patients with permanent AF and larger LA volumes. However, this population represents a well-characterised cohort of patients with symptomatic AF requiring invasive therapy for treatment. We are also unable to extend these findings to patients with asymptomatic AF without indication for AF ablation. Additionally, despite exclusion of patients with a prior diagnosis of HFpEF, a small number of patients were taking mineralocorticoid receptor antagonists or loop diuretics for other diagnoses (eg. resistant hypertension, dependent leg oedema and nephrotic syndrome secondary to renal dysfunction). These medications may have artificially reduced baseline LA pressures in these patients. However, this only further highlights the prevalence of subclinical HFpEF in this cohort, with these patients likely to have higher LA pressures off these medications. The use of fluid challenge rather than exercise hemodynamic testing may underestimate the prevalence of early HFpEF.[295] However, obtaining direct measurements of LA pressure during exercise is unrealistic and alternatives to LA pressure such as pulmonary capillary wedge pressure may overestimate LA pressures in patients with AF due to poor atrial

operating compliance.[296] The absence of a control group of patients without AF is another limitation but the risks of transseptal puncture in patients without a clinical indication outweigh any research benefits. Finally, during saline infusion, volumetric assessment of the LA was not reproducibly possible in the context of ventilated and intubated supine patients. Instead, LA diameter taken from a standardized view in a consistent plane was used as an evidence-based alternative.[278]

2.6 CONCLUSIONS

A large proportion of symptomatic AF patients (73%) without clinical features of HF exhibit subclinical HFpEF based on established hemodynamic criteria. These patients exhibit a more advanced LA cardiomyopathy compared to those without HFpEF, incorporating structural, mechanical and electrical dysfunction assessed both invasively and non-invasively. Importantly, the presence of subclinical HFpEF in patients with symptomatic AF carries significant functional consequences, including reduced cardiopulmonary reserve and worse AF-related symptoms. Furthermore, subclinical HFpEF in AF may have additional prognostic implications including increased risk of progression to clinical HF and increased risk of mortality. Future studies should investigate the use of HFpEF specific therapies to improve outcomes for patients with AF and subclinical HFpEF.

2.7 TABLES AND FIGURES

Table 1

Baseline Cohort Characteristics. Values are mean ± SD, %, or median (IQR).

Baseline Characteristics	**No HFpEF (n=32)**	**Early HFpEF (n=31)**	**HFpEF (n=57)**	**p-value**
Age, (yrs)	60.6±11.0	64.3±9.4	65.3±11.9	0.153
Male Sex, n (%)	24 (77.4)	24 (82.8)	38 (69.1)	0.501
Paroxysmal AF, n (%)	16 (50)	15 (48.4)	29 (50.9)	0.992
Persistent AF, n (%)	16 (50)	16 (51.6)	28 (49.1)	0.992
Previous AF Ablation, n (%)	11 (34.4)	13 (41.9)	23 (40.4)	0.802
AF duration (months)	78.5±70.7	77.6±75.0	104.3±82.4	0.184
Cardiovascular Risk Factors				
BMI (kg/m^2)	27.6±4.5	27.6±4.2	30.3±5.0[ab]	0.008
Weight (kg)	89.7±17.0	84.9±15.3	93.7±21.3	0.114
Hypertension, n (%)	18 (56.3)	19 (61.3)	47 (82.5)[ab]	0.016
Diabetes, n (%)	2 (6.3)	1 (3.2)	11 (19.3)	0.056
Previous Stroke, n (%)	1 (3.1)	4 (12.9)	4 (7.0)	0.317
Coronary Artery Disease, n (%)	4 (12.5)	0 (0)	6 (10.5)	0.142
Obstructive Sleep Apnea, n (%)	10 (31.3)	9 (29.0)	15 (26.3)	0.880
History of Smoking, n (%)	6 (18.8)	6 (19.4)	16 (28.1)	0.505
Alcohol Excess (>30g/week), n (%)	17 (53.1)	11 (35.5)	23 (40.4)	0.331
CHA_2DS_2-Vasc Score	1.5 (1,2)	2 (1,2.5)[a]	2 (1,4)[a]	0.006
Medications				
ACEi/ARB	12 (37.5)	14 (45.2)	41 (71.9)[ab]	0.003
Beta-blocker	12 (37.5)	13 (41.9)	24 (42.1)	0.904
MRA	0 (0)	6 (19.4)[a]	4 (7.0)	0.019
Antiarrhythmic	22 (68.8)	26 (83.9)	42 (73.7)	0.364
Loop Diuretics	1 (3.1)	4 (12.9)	2 (3.5)	0.187
[a]p<0.05 compared to No HFpEF group; [b]p<0.05 compared to Early HFpEF group				

Abbreviations: HFpEF – Heart failure with preserved ejection fraction, HFpEF – Heart failure with preserved ejection fraction, AF – Atrial fibrillation, BMI – body mass index, ACEi – angiotensin converting enzyme inhibitor, HFA-PEFF score – Heart Failure Association diagnostic algorithm for diagnosis of HFpEF, ARB – angiotensin receptor blocker, MRA - mineralocorticoid receptor blocker.

Table 2

Invasive Hemodynamic Measurements at Baseline and with High Volume Saline Infusion.

Values are mean ± SD, %, or median (interquartile range).

Pressure	No HFpEF (n=32)	Early HFpEF (n=31)	HFpEF (n=57)	p-value
Baseline Pressures				
mLAP, mmHg	9.2 ± 2.5	12.5 ± 1.8[a]	17.6 ± 2.4[ab]	<0.001
LA Peak v wave, mmHg	16.6 ± 4.4	20.2 ± 6.1[a]	26.4 ± 6.4[ab]	<0.001
LA Nadir y-descent, mmHg	6.1 ± 3.1	9.1 ± 2.7[a]	13.2 ± 3.5[ab]	<0.001
mRAP, mmHg	7.0 ± 2.6	8.2 ± 2.8	12.2 ± 3.6[ab]	<0.001
RA:LA Ratio	0.76±0.19	0.65±0.20	0.69±0.18	0.090
MAP, mmHg	67±13	70±10	81±18[a]	<0.001
Pressure Increase from Baseline with Infusion				
Δ mLAP, mmHg	6.0 ± 2.7	8.5 ± 3.1[a]	7.5 ± 3.2 [a]	0.008
Δ LA Peak v wave, mmHg	11.4 ± 3.7	14.9 ± 5.7 [a]	16.1 ± 8.0 [a]	0.005
Δ LA Nadir y-descent, mmHg	4.3 ± 2.0	4.8 ± 2.0	5.4 ± 2.5	0.111
Δ mRAP, mmHg	5.8 ± 2.1	6.4 ± 2.2	6.3 ± 1.9	0.484
Δ MAP, mmHg	1.3±8.5	1.5±13.8	1.4±15.1	0.998
TOE LA Size				
Δ LA Diameter, mm	5.2±2.2	4.8±2.3	3.5±1.8[ab]	0.001
Compliance				
LA Compliance, mm/mmHg	0.49±0.24	0.34±0.18[a]	0.26±0.18[a]	<0.001
[a]p<0.05 compared to No HFpEF group; [b]p<0.05 compared to Early HFpEF group				

Abbreviations: LA- left atrium, RA – right atrium, MAP – mean arterial pressure.

Table 3

Resting and Exercise Echocardiography and Cardiac Biomarker Findings. In total, 110 patients (91.8%) completed resting and exercise echocardiography and 116 patients (96.7%) had NT-pro BNP analysis. Values are mean ± SD, %, or median (interquartile range).

	No HFpEF	Early HFpEF	HFpEF	p-value
Resting Echocardiography (n=110)				
LVEF (%)	58.0±6.4	58.0±6.3	56.2±5.1	0.315
LVEDV (ml)	101.9±27.6	91.4±29.2	91.5±33.4	0.303
LV Strain (%)	16.1±3.7	16.4±4.0	14.5±2.7	0.069
RWT	0.37±0.06	0.40±0.08	0.39±0.07	0.262
LV Mass Index (g/m^2)	79.5±19.6	88.7±27.2	83.0±20.4	0.262
LA_{max} (mL/m^2)	31.9±10.9	34.3±9.6	34.2±9.1	0.551
LA_{min} (mL/m^2)	17.7±7.5	22.1±7.6[a]	22.8±8.7[a]	0.024
LAEF(%)	44.5±12.8	36.2±11.5[a]	34.8±12.8[a]	0.004
Average E/E'	7.9±2.1	8.6±2.9	10.7±3.5[ab]	<0.001
LA Reservoir Strain (%)	25.1±11.1	18.4±7.6[a]	19.3±8.6[a]	0.006
LA Booster Strain (%)	13.8±6.3	9.4±3.8[a]	9.7±5.5[a]	0.007
LA Conduit Strain (%)	14.6±6.1	11.8±5.3	12.6±4.6	0.181
Cardiac Biomarker (n=116)				
NT-proBNP (pg/ml)	139 (58-341)	270 (110-645)	244 (115-695)	0.055
Exercise Echocardiography (n=110)				
Δ HR (bpm)	42.7±13.4	36.7±14.1	37.5±18.6	0.381
LVEF	64.1±6.3	63.3±5.1	63.1±5.9	0.588
LV Strain	19.3±4.0	18.8±3.3	16.1±3.6[ab]	0.014
Average E/E'	7.7±3.1	10.0±4.3[a]	11.1±4.9[a]	0.014
LAEF (%)	50.9±11.5	44.3±11.6[a]	40.1±13.7[a]	0.003
Reservoir Strain (%)	28.8±13.9	21.2±9.7[a]	21.6±10.4[a]	0.015
[a]p<0.05 compared to No HFpEF group; [b]p<0.05 compared to Early HFpEF group				

Abbreviations: LVEF – left ventricular ejection fraction, LVEDV – left ventricular end diastolic volume, RWT – relative wall thickness, LA – left atrium, LAEF – left atrial emptying fraction.

Table 4

Resting and exercise echocardiography results presented according to presenting rhythm.

Baseline Characteristics		**No HFpEF**	**Early HFpEF**	**HFpEF**	**p-value**
		SR=22 AF=7	**SR=20 AF=9**	**SR=35 AF=17**	
Resting LVEF (%)	SR	50	60.1±5.7	58.1±5.7	0.535
	AF	54.8±4.8	53.8±5.6	53.0±5.3	0.769
Resting LAEF (%)	SR	47.4±13.2	39.2±9.7[a]	38.0±13.3[a]	0.023
	AF	36.9±9.0	34.4±12.4	27.4±8.0	0.071
Resting E/E'	SR	8.2±2.2	8.0±1.9	10.9±3.6[ab]	<0.001
	AF	8.0±1.7	9.3±4.6	10.6±2.9	0.161
Resting Reservoir Strain (%)	SR	28.2±10.4	22.1±6.0[a]	22.3±8.0[a]	0.020
	AF	16.1±8.8	10.3±3.0	13.4±6.8	0.201
Exercise LVEF (%)	SR	67.6±5.2	63.3±8.9	63.5±6.7	0.181
	AF	58.3±6.8	55.2±9.9	60.0±9.2	0.63
Exercise LAEF (%)	SR	56.7±8.0	47.7±10.4 [a]	44.5±12.0 [a]	0.001
	AF	37.2±6.6	35.5±10.4	30.6±9.1	0.292
Exercise E/E'	SR	7.8±3.6	9.0±1.3	11.4±4.8 [a]	0.007
	AF	7.7±1.1	10.4±5.1	10.1±5.4	0.596
Exercise Reservoir Strain (%)	SR	35.7±11.6	24.9±8.4[a]	24.4±9.8[a]	0.002
	AF	15.5±6.1	11.2±4.4	12.5±6.5	0.415

Abbreviations: HFpEF – heart failure with preserved ejection fraction, SR – sinus rhythm, AF – atrial fibrillation, LVEF – left ventricular ejection fraction, LAEF – left atrial emptying fraction.

Table 5

Regional and global left atrial electrical parameters (voltage, conduction velocity and fractionation) across the three HFpEF groups.

Baseline Characteristics	No HFpEF (n=16)	Early HFpEF (n=10)	HFpEF (n=20)	p-value
Voltage (mV)				
Global	4.2±1.0	3.3±1.0[a]	2.9±1.[a]	0.001
Posterior	4.8±1.3	4.0±1.0	3.3±1.2[a]	0.003
Anterior	3.4±1.3	2.5±0.6	2.7±1.2	0.106
Roof	4.8±1.6	3.6±1.5	3.4±1.3[a]	0.027
Inferior	4.8±2.1	3.6±1.7	3.6±1.7	0.122
Septal	3.0 ±0.7	2.6±1.5	2.3±1.0	0.201
Lateral	3.6±1.3	2.6±0.8[a]	2.4±1.3[a]	0.020
Conduction Velocity (m/s)				
Global	1.04±0.16	0.96±0.12	0.86±0.13[a]	0.006
Posterior	1.03±0.21	0.92±0.17	0.76±0.30[a]	0.015
Anterior	1.02±0.25	0.93±0.12	0.88±0.18	0.176
Roof	0.90±0.37	0.88±0.17	0.78±0.30	0.538
Inferior	1.16±0.29	1.14±0.19	0.82±0.31[a]	0.003
Septal	0.99±0.24	0.91±0.17	0.88±0.20	0.358
Lateral	1.08±0.25	0.97±0.22	0.84±0.19[a]	0.026
Fractionated Points (%)				
Global	22±8	20±11	19±8	0.632
Posterior	23±11	17±9	21±11	0.547
Anterior	20±8	24±13	22±12	0.677
Roof	21±12	24±16	18±12	0.544
Inferior	23±16	22±12	18±12	0.527
Septal	37±13	30±17	21±12	0.021
Lateral	9±5	5±4	10±7	0.389
[a]p<0.05 compared to No HFpEF group; [b]p<0.05 compared to Early HFpEF group				

Table 6

Cardiopulmonary Exercise Test and Patient-Reported Symptom Evaluation Findings. In total, 100 patients (83.3%) satisfactorily completed CPET and 112 patients (93.3%) completed the symptom questionnaires.

	No HFpEF	Early HFpEF	HFpEF	p-value
CPET (n=100)				
VO_{2peak} (mL/kg/min)	25.3±7.3	20.2±7.6[a]	18.9±6.3[a]	<0.001
Percent Predicted VO_{2peak} (%)	104±24	84±23[a]	89±23[a]	0.006
Peak HR (bpm)	147±28	123±31 [a]	130±25 [a]	0.007
Percent predicted HR (%)	97±16	83±20[a]	85±16 [a]	0.008
HR increase (bpm)	75±31	55±29[a]	60±28	0.046
Symptom Questionnaire Scores (n=112)				
MLHFQ (0-105)	21.4±19.8	29.7±18.0	30.1±19.2	0.141
AFSS Frequency (1-10)	4.5±3.9	6.4±3.3	6.0±3.3	0.119
AFSS Duration (1-10)	6.8±3.1	7.8±2.3	6.9±3.2	0.379
AFSS Severity (1-10)	4.7±2.6	6.4±2.6	5.8±2.5	0.056
AFSS Symptoms (0-35)	6.9±7.3	14.2±7.5[a]	12.7±8.1[a]	0.002
AFSS Global Well-Being (1-10)	7.7±2.0	6.3±2.2 [a]	6.3±2.1 [a]	0.018
[a]p<0.05 compared to No HFpEF group; [b]p<0.05 compared to Early HFpEF group				

Abbreviations: HR – heart rate, AFSS – atrial fibrillation symptom severity questionnaire, MLHFQ – Minnesota Living with Heart Failure questionnaire.

Table 7

Univariate and Multivariate Predictors of HFpEF.

Variable	Univariate Regression Analysis		Multivariate Regression Analysis	
	Slope (95% CI)	**p-value**	**Slope (95% CI)**	**p-value**
Age	0.02 (-0.01 – 0.06)	0.156		
Gender	-0.47 (-1.28 – 0.33)	0.249		
BMI	**0.12 (0.05 – 0.21)**	**0.003**	**0.11 (0.02 – 0.20)**	**0.016**
Hypertension	**1.19 (0.37– 2.08)**	**0.006**	**1.01 (0.15 – 1.94)**	**0.025**
Diabetes	**1.56 (0.34 – 3.09)**	**0.021**	1.23 (-0.06– 2.80)	0.081
Alcohol	-0.16 (-0.89 – 0.56)	0.651		
Smoking	0.51 (-0.34 – 1.38)	0.246		
Type of AF	-0.003 (-0.72 – 0.72)	0.993		
Previous ablation	0.09 (-0.64 – 0.83)	0.800		
Duration of AF	0.004 (-0.00024 – 0.0094)	0.069		

Abbreviations: BMI, body mass index; AF, atrial fibrillation**.**

Figure 1

Experimental Flow Diagram. Following clinical decision to undertake an AF ablation, potential participants were enrolled if eligible. In the 4 weeks prior to the AF ablation date, participants would attend for the non-invasive assessments Invasive assessments would be undertaken at the AF ablation procedure

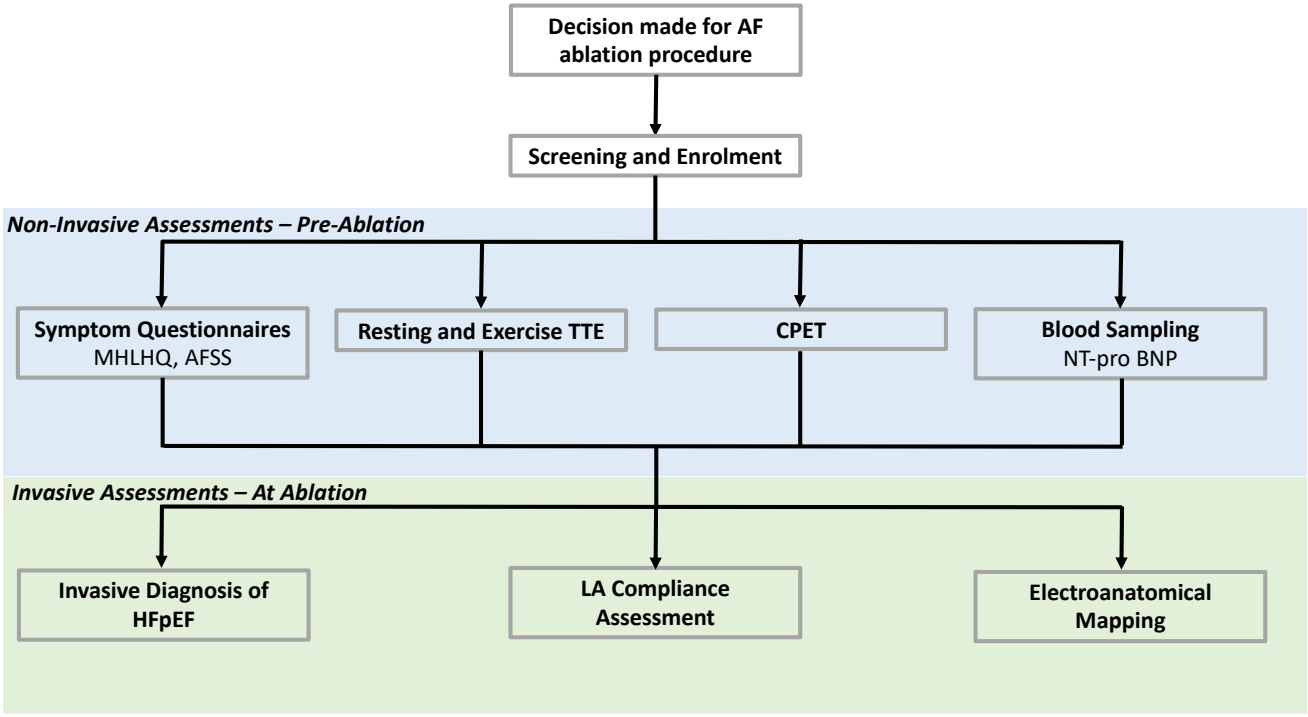


Figure 2

Study Consort Diagram. Of 172 patients screened for inclusion, 120 patients were included with 39 exclusions and an additional 13 patients who declined participation. Of the 120 inclusions, 57 had HFpEF, 31 had early HFpEF and 32 had no HFpEF based on the hemodynamic definitions. HFPEF – heart failure with preserved ejection fraction, LVEF – left ventricular emptying fraction.

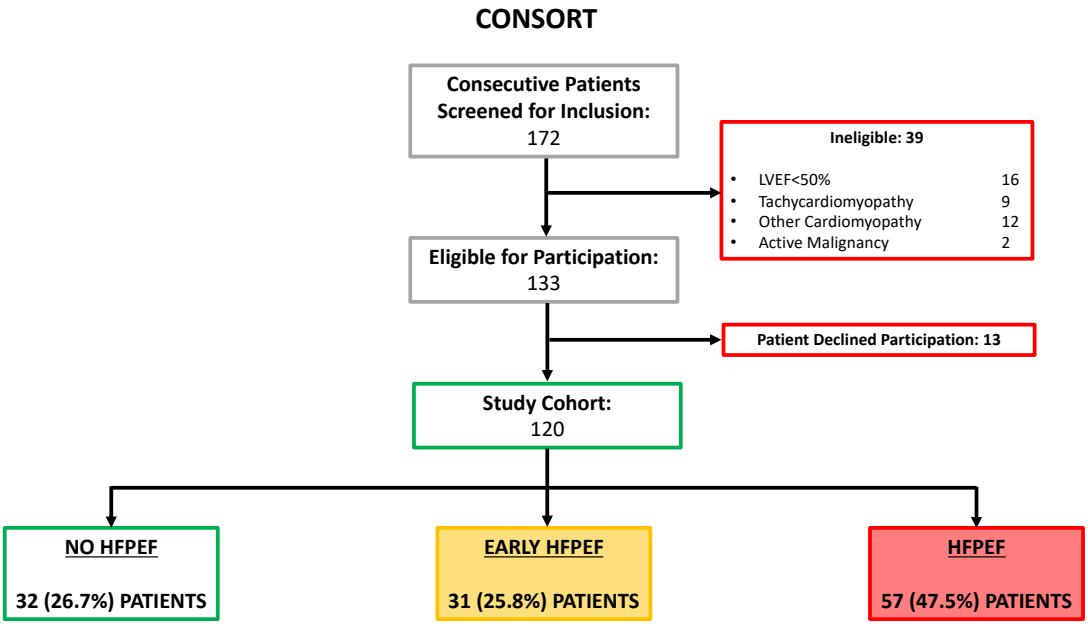


Figure 3

Invasive hemodynamics during high-volume fluid challenge. A) Patients with HFpEF and early HFpEF demonstrated significantly reduced LA compliance compare to those without HFpEF B) Underlying the differences in LA compliance were greater increases in LA pressure and C) reduced LA dilatation with fluid infusion in HFpEF and early HFpEF, D) Linear regression slopes showing rise in mLAP with 15ml/kg saline infusion according to HFpEF groups. LA – left atrium, LAD – left atrial diameter.

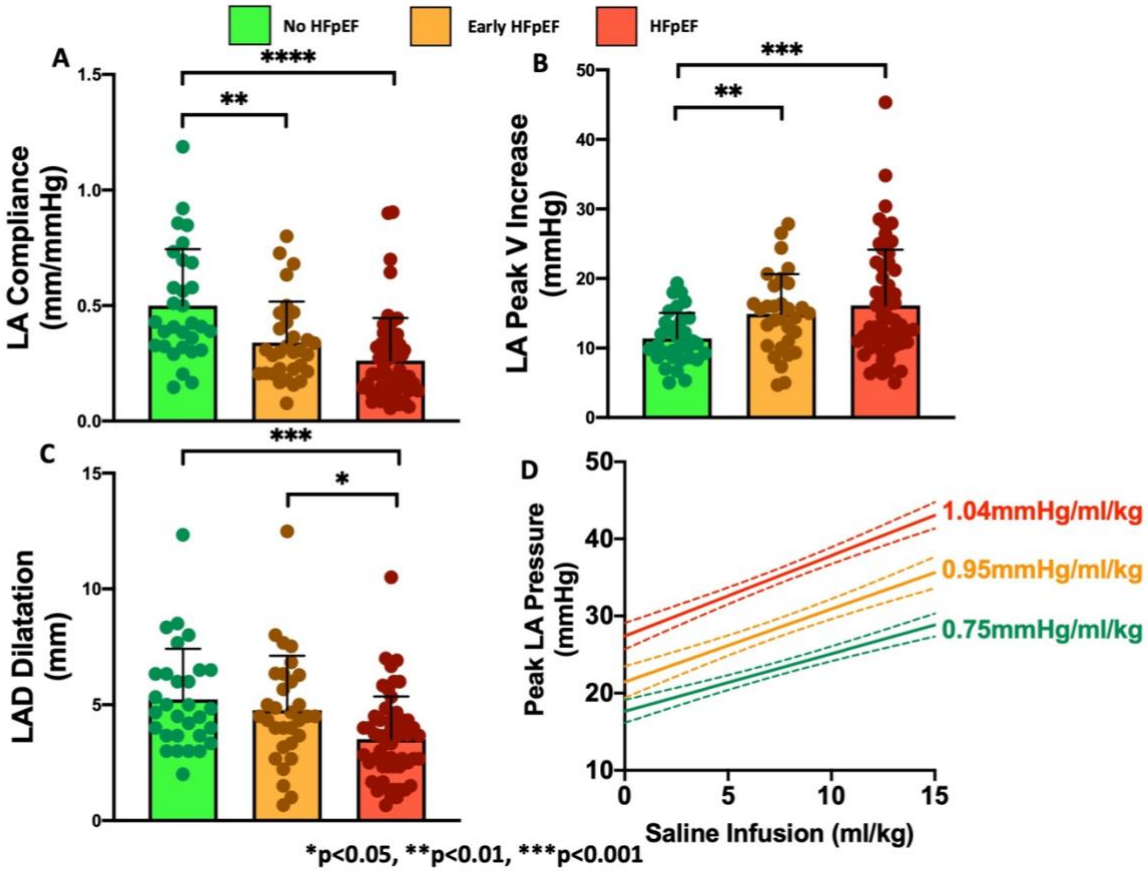


Figure 4

Non-invasive assessment of resting and exercise LV and LA function across the spectrum of HFpEF in AF. A) There were no differences in LV function assessed on resting echocardiography across the HFpEF groups. B, C) HFpEF and early HFpEF were associated with reduced LAEF at rest. C) HFpEF was also associated with increased E/E' at rest. D) On exercise echocardiography, LV systolic reserve was preserved in the three groups with LVEF at peak exercise similar across the three groups. E, F) LAEF was also significantly reduced in both HFpEF and early HFpEF during exercise whilst exercise E/E' was significantly increased in both groups. LVEF – left ventricular ejection fraction, LAEF – left atrial emptying fraction.

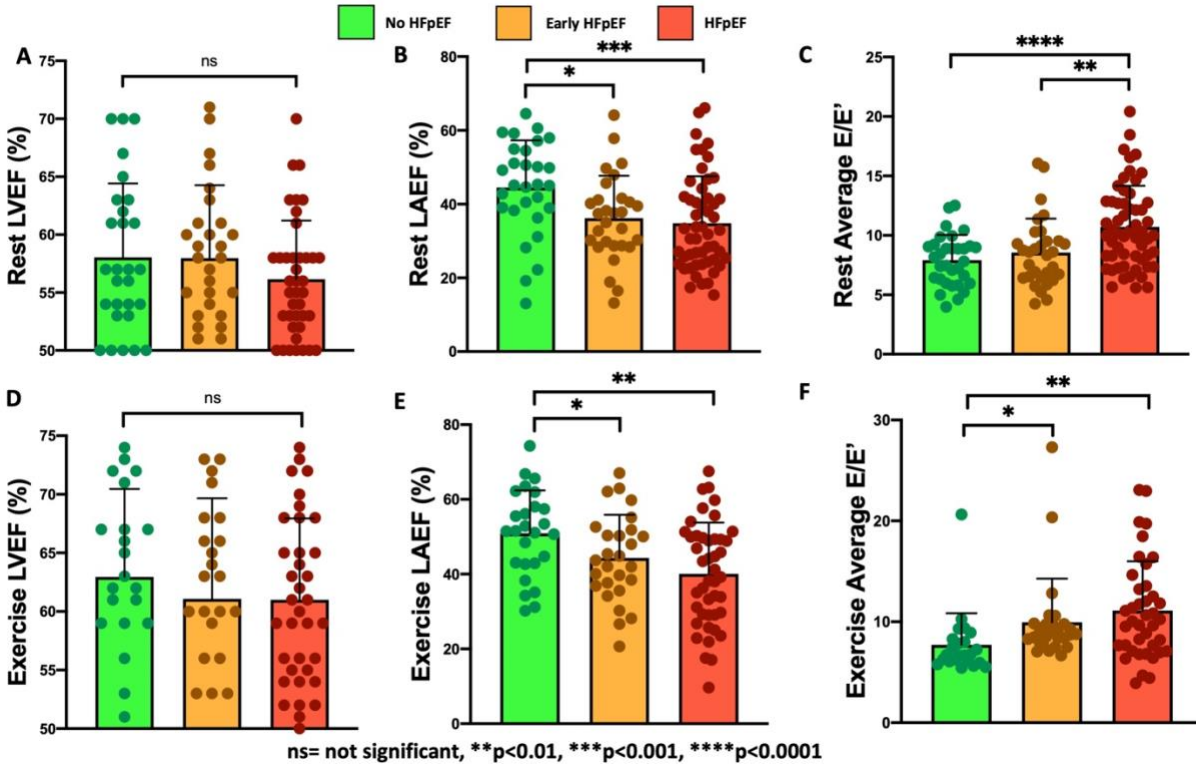
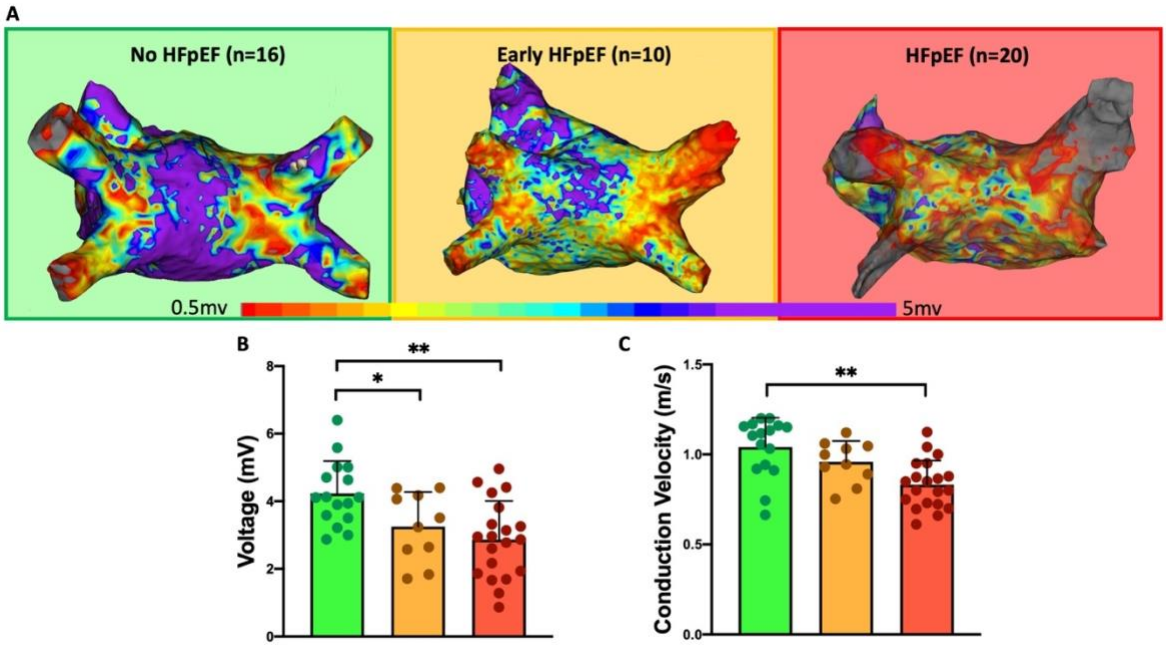


Figure 5

Electrical remodelling in HFpEF. A) Representative electroanatomical bipolar voltage maps according to HFpEF groups (scale - 0.5 – 5mV). B) Global LA bipolar voltage was reduced in both HFpEF and early HFpEF compared to no HFpEF. C) Global LA conduction velocity was also reduced in HFpEF but not early HFpEF compared to no HFpEF.



CHAPTER 3 The Influence of Obesity and Epicardial Adipose Tissue on HFpEF in AF

3.1 INTRODUCTION

Obesity represents one of the most significant cardiovascular risk factors underlying the development of atrial fibrillation (AF). Obesity has been shown to be associated with a 46-52% increased risk of incident AF[297] and is now the second highest population-attributable risk factor for AF after hypertension, accounting for up to 17.9% of all AF cases.[178] As worldwide obesity levels reach pandemic proportions,[298] the prevalence and incidence of AF also continue an inexorable rise, resulting in ever-rising AF-related healthcare costs.[21] Importantly, weight-loss has been shown to reduce AF recurrence and improve AF symptoms and is therefore advocated as a vital pillar in the guideline-directed management of patients with AF.[252,253]

The mechanisms underlying the relationship between obesity and AF have been extensively studied. Obesity has been shown to be associated with left atrial (LA) dilatation,[299] LA electroanatomical remodelling[183] and LA fibrotic change.[125] However, relatively sparse attention has been given to the influence of obesity on haemodynamics and the presence of HFpEF in AF. In HFpEF, obesity is associated with worse haemodynamics, increased pericardial restraint and ventricular interdependence due to larger total cardiac volumes and greater epicardial adipose tissue (EAT) volumes.[66] In **Chapter** 2 we showed that HFpEF was commonly present amongst patients with AF. The aim of this study was to investigate the influence of obesity and EAT on invasive haemodynamic parameters and the presence of HFpEF in AF.

3.2 METHODS

3.2.1 Study Design

This prospective study was undertaken at the Centre for Heart Rhythm Disorders, University of Adelaide. Ethical approval for the study was provided by both the Central Adelaide Local Health Network and the University of Adelaide. The study was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12620000639921).

3.2.2 Study Population

Consecutive patients with symptomatic paroxysmal or persistent AF due to undergo AF ablation at the Centre for Heart Rhythm Disorders between 2020-2022 were prospectively recruited. Pre-specified exclusion criteria included: 1) reduced left ventricular ejection fraction (<50%); 2) previous diagnosis of cardiomyopathy; 3) moderate-to-severe valvulopathy; 4) previous diagnosis of pulmonary hypertension; 5) active malignancy; 6) severe chronic obstructive airways disease; 7) inability to exercise; or 8) inability to provide written informed consent.

In order to establish the impact of obesity we classified patients according to body mass index (BMI). Participant height and weight were measured in a fasting state within 2 weeks of the AF ablation procedure and BMI was calculated from these measures. Participants were classified as obese if they had a BMI of $\geq 30 kg/m^2$. Participants with a BMI$<30 kg/m^2$ were classified as non-obese.

3.2.3 Invasive Haemodynamic Assessment

3.2.3.1 Patient Preparation

Invasive haemodynamic assessment was undertaken in the fasted state under general anaesthesia. Anaesthetic agents used for induction and maintenance of anaesthesia were

standardized across all cases. Tidal volumes were set at 7ml/kg, with respiration rates of 10-12 breaths per minute and positive end-expiratory pressure of 5cmH_2O. All anti-arrhythmic drugs were withheld for ≥5 half-lives prior to the procedure. No patients were on chronic amiodarone treatment. All procedures were undertaken with uninterrupted oral anticoagulation. An arterial line was placed for continuous monitoring of arterial blood pressure. All patients underwent transoesophageal echocardiography (TOE) at the start of the procedure to ensure there was no atrial thrombus. In all patients, heparin was administered to maintain the activated clotting time over 350 seconds. Access was via the right femoral vein with ultrasound guidance. Transseptal puncture was performed using a SLO sheath and BRK1 needle (Abbott, Minneapolis, MN) under TOE guidance allowing access to the LA. An Agilis sheath (Abbott, Minneapolis, MN) was placed in the LA and a 6F pigtail catheter in the RA for simultaneous pressure monitoring.

3.2.3.2 Haemodynamic Measurements

The LA, right atrial (RA) and arterial catheters were attached to pressure transducers and zeroed at the level of the mid-thorax, allowing the recording of LA, RA and arterial pressures. Pressures were recorded (240 Hz) on the WorkMate Claris^{TM} Electrophysiology System (Abbott, Minneapolis, MN) and analysed offline. Pressures were measured at end-expiration and averaged over 3 cardiac cycles for patients in sinus rhythm and over 6 cycles for patients in AF. From the LA pressure waveform mLAP, peak V-wave and the nadir Y-descent were measured. Mean LAP was taken at the start of the C-wave. In the absence of a visible C wave, mLAP was taken midway between the peak and trough of the A-wave in those with sinus rhythm or 130-160ms after the onset of the QRS in those in AF.[275] The peak A-wave and the nadir X-descent were additionally measured in patients in sinus rhythm. RA and arterial pressures were collected in the same way.

RA pressures were used to assess the influence of pericardial restraint whilst RA:LA pressure ratio was used to assess interventricular interdependence as has been previously described.[66] LA mean transmural wall pressure (mTMWP) was used to assess the direct influence of the LA myocardial wall on LA pressure, independent of the effect of pericardial restraint. mTMWP was calculated as:

$$mTMWP = mLAP - mRAP$$

HFpEF was diagnosed according to baseline mLAP and mLAP following infusion of 500mls saline directly into the LA via the Agilis sheath, as defined previously. HFpEF was diagnosed when mLAP ≥15mmHg or when mLAP rose to above 15mmHg following the 500ml bolus infusion.

3.2.4 Non-Invasive Investigations

All non-invasive investigations were performed in the 4-week period preceding the AF ablation procedure. These investigations included resting and exercise echocardiography, cardiopulmonary exercise testing (CPET), contrast-enhanced cardiac and pulmonary vein CT scans and blood sampling for the cardiac biomarker NT-pro BNP. We also assessed patient-reported symptoms using both the AF Symptom Severity Questionnaires and the Minnesota Living with Heart Failure Questionnaires. All rate-control and antiarrhythmic medications were withheld for 48 hours prior to these non-invasive investigations.

3.2.4.1 Resting echocardiography

Resting echocardiography was performed according to a study specific protocol by an experienced sonographer blinded to patient heart failure group. Images obtained included parasternal and apical views. Left ventricular ejection fraction (LVEF) was measured by the Simpson's biplane method. Maximum (LA_{max}) and minimum LA (LA_{min}) volumes were

obtained using the biplane area-length and indexed to body surface area. LA emptying fraction (LAEF) was calculated using the formula:

$$LAEF = (LA_{max} - LA_{min})/LA_{max} \times 100.$$

Flow Doppler and tissue Doppler imaging were used to calculate E/E'. LA strain was performed using a previously validated software.[280] All measurements were obtained according to the American Society for Echocardiography guidelines.[281,282] Measurements were averaged over 3 cardiac cycles in sinus rhythm and over 6 cycles in AF.

3.2.4.2 Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was performed using an upright cycle ergometer (Lode Corival, Lode B. V., Netherlands). Pulmonary gas exchange was measured continuously using a metabolic cart (Vyntus CPX, Vyaire Medical). Oxygen consumption (VO_2) and carbon dioxide (VCO_2) production were averaged over 20 second intervals. Participants began cycling at a power of 20 Watts, incrementally increasing by 10 Watts per minute. Peak exercise was defined as the point at which the participant felt the need to stop due to symptoms or fatigue. A maximal effort was defined as a respiratory exchange ratio >1.05. Peak VO_2 (VO_{2peak}) was identified as the highest attained VO_2 during exercise. Predicted VO_2 was calculated using the Wasserman-Hansen equation.[300] Chronotropic response was calculated as difference between the resting heart rate prior to exercise and the maximum heart rate achieved at peak exercise.

3.2.4.3 Contrast-Enhanced Cardiac CT Scans

Cross-sectional imaging was undertaken using dual source electrocardiographic-gated computed tomography (Siemens Somatom Force, Siemens, Forchheim, Germany). Contrast-enhanced imaging for cardiac anatomy were undertaken at end-expiration using a 64-slice scanner (2x192x0.6mm collimation, gantry rotation time of 250ms, tube voltage of 70 to

120kVp depending on patient size). Scans were triggered at 60% R-R interval on ECG in diastole and images were acquired in one heartbeat. A volume of 70mL iodinated contrast (Omnipaque 350) was infused at a flow rate of 6ml/sec with 50mL of normal saline solution at the same rate.

Offline analysis of CT scans were undertaken using the validated post-processing software 3D-slicer (v5.0.3) [301]. Images were reformatted from the raw data with 3mm slice thickness and 3mm intersection gaps. Manual segmentation of EAT volume was undertaken slice by slice using a paintbrush tool. The allowable attenuation range for identification of EAT was set to -190 to -30 Hounsfield units and EAT was defined as the adipose tissue between the myocardium from the surface of the heart to the visceral pericardium. EAT measurements extended from the level of the diaphragm to the pulmonary valve. Following manual segmentation, the EAT volume was obtained by multiplication with the section thickness.

3.2.4.4 Cardiac Biomarker – NT-pro BNP

Blood sampling for analysis of NT-pro BNP levels was undertaken at rest in the fasting state prior to exercise testing.

3.2.4.5 Symptom Questionnaires

Symptoms of heart failure and AF were quantified using the Minnesota Living with Heart Failure (MLWHF) and the AF Severity Scale (AFSS) (University of Toronto, Toronto, Ontario, Canada) questionnaires. The MLWHF questionnaire quantifies the presence and significance of heart failure symptoms encountered over the preceding 4-weeks. The AFSS questionnaire quantifies AF-related symptom frequency, duration and severity in addition to providing information on specific AF-related symptom burden and global well-being. AF symptom burden encompassed symptoms experienced over the previous 4-week period,

regardless of the presence/absence of AF episodes. Both questionnaires have been clinically validated for use in heart failure and AF respectively.[283,284]

3.2.5 Statistical Analysis

Continuous variables were tested for normality using the Shapiro-Wilk test and reported as means ± standard deviation for parametric data or median and interquartile range for non-parametric data. Categorical variables were reported as frequencies and percentages. Continuous variables were compared between obese and non-obese groups using independent-samples Student t-tests or Mann Whitney U tests as appropriate. Categorical variables were compared between groups using the chi-square test or Fisher's exact test as appropriate. Relationships between continuous variables were assessed using simple linear regression. P-values of ≤0.05 were considered statistically significant. All statistical analysis was performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

3.3 RESULTS

3.3.1 Recruitment and Classification

In total, after exclusion of patients meeting pre-specified exclusion criteria and those declining to participate, we included 120 consecutive AF patients undergoing AF ablation in our study cohort. Of these 120 participants, 76 (63.3%) had BMI<30kg/m^2 and were therefore non-obese and 44 (36.7%) had BMI≥30kg/m^2 and were therefore obese (**Figure 1**).

3.3.2 Baseline Characteristics

Table 1 shows the baseline characteristics of the cohort according to obesity classification. The obese patients were younger (59.4±13.0 vs 66.3±9.1, p=0.003) and had higher body mass (107.3±16.0 vs 80.6±12.8, p<0.001) and body surface area (2.3±0.2 vs 2.0±0.2, p=0.017)

compared to the non-obese patients. The only other difference between the two groups was a higher prevalence of previous stroke (9 [19.8%] vs 0 [0%], p<0.025) in the non-obese group.

3.3.3 Invasive Haemodynamics

Table 2 shows the invasive haemodynamic data for the obese and non-obese cohorts. Obesity was associated with significantly elevated mLAP (16.0±3.9 vs 12.9±4.0, p<0.001, **Figure 2A**), mRAP (12.0±3.8 vs 8.9±3.2, p<0.001, **Figure 2B**) and RA:LA pressure ratio (0.74±0.14 vs 0.67±0.20, p=0.017, **Figure 2C)** compared to non-obese patients. Obese participants were significantly more likely to have mLAP of ≥15mmHg either at rest or with 500ml saline infusion and therefore a coexistent diagnosis of HFpEF (84.1% vs 67.1%, p=0.043). In addition, as a continuous variable, BMI was positively associated with mLAP (R^2=0.104, p=0.003, **Figure 2D**), mRAP **(**R^2=0.,169, p<0.001**, Figure 2E**) and RA:LA pressure ratio (R^2=0.039, p=0.036, **Figure 2F**). However, obesity was not associated with differences in mTMWP compared to non-obese patients (R^2=0.,004, p=0.522).

3.3.4 Cardiac Structure and Function

Table 3 shows the results of resting echocardiography. Obesity was not associated with differences in LV structure or function, with no differences in LVEDV (97.1±32.3 vs 93.2±29.9, p=0.559), LVMI (83.6±20.1 vs 83.6±20.1, p=0.559), RWT (0.38±0.06 vs 0.39±0.08, p=0.354), LVEF (56.5±5.1 vs 57.6±6.2, p=0.381) or global longitudinal strain (15.2±3.2 vs 15.6±3.6). On assessment of LA structure, obesity was associated with larger maximum (76.7±25.3 vs 66.8±18.9, p=0.032) LA volumes, but no differences in LAEF (40.2±12.7 vs 36.2±13.1, p=0.121) or reservoir strain (20.2±8.6 vs 21.0±10.0, p=0.630). NT-pro BNP (207 [64-484] vs 239 [111-515], p=0.342) was also not significantly different between obese and non-obese patients in this cohort.

3.3.5 Functional Capacity

Table 4 shows the results of the functional assessments. Obesity was associated with significantly increased AF symptom burden (13.5 [7-22] vs 10.0 [4.0-15.3], p=0.357) and reduced global well-being (7 [5-7] vs 7 [6-8], p=0.017). In addition, there was a trend towards reduced VO_{2peak} (19.4±6.6 vs 22.1±7.7ml/kg/min, p=0.068) in the obese cohort despite no difference in peak HR (129±26 vs 135±30, p=0.360) achieved and chronotropic response (57±29 vs 67±30, p=0.100) during CPET. When VO_{2peak} was not adjusted for weight, the obese participants demonstrated a trend towards increased VO_{2peak} compared to the non-obese group (1813±735 vs 2130±858ml/min, p=0.093).

3.3.6 Epicardial Adipose Tissue Volume

Obese patients demonstrated significantly increased EAT volumes compared to non-obese patients (103.8 [82.8-123.6] vs 77.5 [56.1-95.2], p<0.001, **Figure 3A**) and BMI was closely correlated with EAT volume (R2=0.144, p<0.001, **Figure 3B**). On haemodynamic testing, increasing EAT volume was associated with both increasing mLAP (R^2=0.055, p=0.014, **Figure 3C**) and mRAP (R^2=0.071, p=0.007, **Figure 3D**). However, there was no relationship between EAT volume and RA:LA ratio (R2=0.015, p=0.225) or mean TMWP (R2=0.003, p=0.577). On non-invasive testing, increasing EAT volume was significantly associated larger LA volumes (R2=0.189, p<0.001) and reduced LA reservoir strain (R2=0.042, p=0.037, **Figure 3E**) coupled with reduced global longitudinal LV strain (R2=0.090, p=0.007, **Figure 3F**).

3.4 DISCUSSION

3.4.1 Major Findings

This prospective study investigating the influence of obesity on LA haemodynamics and LA cardiomyopathy in AF has identified the following novel findings:

a) Despite a younger age, obese AF patients demonstrate a worse haemodynamic profile involving elevated mLAP compared to non-obese patients. This was associated with functional limitations including worse AF symptoms and reduced quality of life.
b) Obesity was associated with higher mRAP and RA:LA pressure ratio highlighting the increased role of pericardial restraint. On the other hand, obese patients did not demonstrate a difference in mTMWP or non-invasive LA functional parameters suggesting no difference in LA cardiomyopathy between obese and non-obese patients.
c) EAT volume was significantly associated with LA and RA pressures suggesting a role in the development of HFpEF in patients with AF. In addition, EAT volume was associated with reduced LV and LA strain. This suggests a potential role of EAT on both myocardial function as well as pericardial restraint.

Taken together, our data shows that many AF patients demonstrate the obesity phenotype of HFpEF, characterised by increased pericardial restraint rather than increased LA cardiomyopathy. These findings have significant clinical implications, with the worse haemodynamics of obesity associated with increased AF symptom burden and a trend towards reduced exercise capacity. These data highlight the potential for novel and established weight-loss strategies to improve outcomes in obese patients with AF.

3.4.2 Obesity and AF

The relationship between obesity and AF is well-established. The Framingham Heart study showed that obese patients were 46-52% more likely to develop incident AF over the course of the next 13.7 years.[297] More recently, a large meta-analysis involving more than 50 observational analyses and investigating more than 600 thousand patients identified a 19-29% increased risk of incident AF for every 5 unit increase in BMI.[302] Conflicting data exists regarding the relationship between obesity and major cardiovascular outcomes (mortality, stroke and bleeding) in patients with AF. A number of studies have identified lower risk of major cardiovascular outcomes in patients with obesity, leading to the suggestion of an 'obesity paradox' in AF.[303-305] On the other hand, some studies have demonstrated no effect of obesity on the same outcomes.[306,307]

In our cohort of consecutive patients undergoing AF ablation procedures, 36.7% were obese, further highlighting the high prevalence of obesity in contemporary AF populations. Importantly, we found that obese patients were, on average, almost 7 years younger. These findings are comparable with other large clinical trials and observational studies of obesity in AF and highlight the fact that obese patients present with symptomatic AF at a younger age.[308,309] The younger age of obese AF patients likely contribute to the fact that outcomes often appear to be better in this cohort of patients.

3.4.3 Obesity and Invasive Haemodynamics

Obesity is associated with several haemodynamic circulatory changes resulting in substantial cardiac remodelling. The increased deposition of metabolically active visceral adipose tissue as well as increased lean body mass in obesity results in a hyperdynamic circulation with increased plasma volume.[310] Chronic exposure to these changes leads to substantial cardiac

remodelling, characterised by LV dilation and hypertrophy as well as LA and right heart enlargement.[311]

For the first time, we show that obesity in AF is associated with elevated mLAP compared to AF patients without obesity. Elevated mLAP has been consistently shown to be associated with worse symptoms and poorer prognosis in both AF and non-AF cohorts.[13,286] Our data contributes further to these previous findings, showing that the abnormal haemodynamics of obesity are associated with worse AF symptoms and reduced quality of life.

3.4.4 Obesity and Pericardial Restraint

Significantly, we have shown that the increase in mLAP in obesity was associated with higher mRAP and RA:LA pressure ratios. RAP is an established marker of pericardial restraint[312] and our data therefore suggests that the elevated mLAP of obesity is, at least in part, related to pericardial restraint. This is in keeping with previous studies which have identified a unique haemodynamic phenotype associated with obesity, involving biventricular hypertrophy and dilatation, plasma volume expansion, increased pericardial restraint, haemodynamic derangements and impaired pulmonary vasodilatation.[66] Our data suggests that the obesity phenotype of HFpEF is common amongst AF populations.

3.4.5 Obesity and LA Cardiomyopathy

Obesity was not associated with markers of worse LA cardiomyopathy. Mean TMWP provides an invasive measure of pressure exerted by the LA wall independent of pericardial restraint and this was not increased in obese patients. Similarly, there were no differences in any non-invasive markers of LA function including LA strain, emptying fraction or NT-pro BNP.

Our data conflicts somewhat with previous understanding of the implications of obesity in AF. Experimental models of obesity provide clear evidence of structural, functional and

electroanatomical remodelling of the LA associated with obesity.[102,125,313] Similarly, clinical studies confirm an association between obesity and LA disease.[183,299] We suggest that the lack of association of obesity with LA cardiomyopathy in this cohort, relates to the younger age of the obese AF patients. Future analyses incorporating age-matching may provide further insights into the independent effect of obesity on LA cardiomyopathy.

3.4.6 The Impact of Epicardial Adipose Tissue Volume

Whilst strong evidence suggests a close relationship between EAT and AF,[314-316] this is the first study to investigate the role of EAT volume in mediating invasive haemodynamics in patients with AF. Several previous studies have identified a relationship between EAT and haemodynamics in HFpEF[121,317,318]; our data extends these findings to an AF cohort. Given the association between EAT and RA pressures, there appears to be a relationship between EAT volume and pericardial restraint, which may contribute to the development of HFpEF and exercise intolerance in patients with AF. However, whether EAT exerts an independent effect on pericardial restraint remains unclear; other confounding factors for pericardial restraint include cardiomegaly, plasma volume expansion, mediastinal constraint and abdominal compression from visceral adipose tissue.[319] Interestingly, a clinical trial of weight loss in HFpEF demonstrated improved symptoms and exercise capacity despite no regression in epicardial fat volume, suggesting that functional limitations in HFpEF may be independent of EAT volume.[256] Further studies in patients with AF are required.

A relationship between EAT volume and both LA and LV strain was also identified. Similarly, EAT has also previously been shown to be associated with reduced RV strain and diastolic function.[320] Taken together, these data suggest that epicardial adiposity may have a direct influence of myocardial performance. Consistent with this are the findings that EAT is associated with myocardial inflammation, fibrosis and atrial and ventricular remodelling,

potentially mediated through direct infiltration or paracrine effects.[312,321,322] Our data suggests therefore that EAT may contribute to the relationship between HFpEF and AF through its direct influence on myocardial function as well as its influence on pericardial restraint and LA haemodynamics.

3.4.7 Clinical Implications

Our data suggests obese patients with AF demonstrate worse functional limitations despite presenting at a younger age. This is mediated through worse haemodynamic profiles rather than LA dysfunction, highlighting the fact that the obese phenotype of HFpEF is highly prevalent amongst AF patients. Interestingly, although there was a trend towards lower VO_{2peak} adjusted for body mass in the obese group, there was a trend towards higher unadjusted VO_{2peak} in the obese group than the non-obese group, possibly related to the increased lean body mass of obese individuals. It follows, therefore, that weight loss with maintenance of lean body mass should contribute to improved functional status in patients with AF. Prior studies have shown significant symptomatic improvement with weight loss driven by dietary modifications and exercise training in obese patients with both AF and HFpEF.[252,253,256] However, achieving sustained weight loss in obese patients with AF and HFpEF remains a significant clinical challenge. More recently, pharmacological therapies such as SGLT-2 inhibitors and GLP-1 antoagonists have demonstrated significant weight-loss in obese patients and demonstrate promise in achieving sustained weight loss in the obese phenotype of HFpEF.[259,323]This study provides further information to support the notion that weight reduction should be a therapeutic target in obese patients with AF, as obesity is associated with deranged haemodynamics and poor functional status. However, our data suggests that decreased fat but maintenance of lean body mass would be vital to improving the functional status of obese patients with AF.

3.5 LIMITATIONS

The results of this study should be interpreted in the context of its limitations. We only included patients undergoing AF ablation procedures, meaning the results may not be generalisable to the entire AF population. In addition, this is a substudy of an investigation powered to identify the prevalence of HFpEF in patients with AF. The study may therefore be underpowered to determine differences according to the presence or absence of obesity. In addition, whilst we have shown a correlation between obesity, invasive haemodynamics and functional limitations, we acknowledge that this does not necessarily mean that weight loss would significantly improve haemodynamics and functional capacity. Indeed, other factors such as skeletal muscle function may be additional important mediators of exercise capacity in obese patients and future research should investigate these factors. Finally, BMI is a notoriously limited measure of obesity-related dysmetabolism. Measurement of body fat percentage and lean body mass may have provided further important information.

3.6 CONCLUSIONS

In conclusion we have shown that obesity in AF is associated with abnormal intracardiac haemodynamics. We have shown that the obesity phenotype of HFpEF is common in AF, characterised by increased pericardial restraint and ventricular interdependence rather than poorer LA or LV function. These abnormal haemodynamics in obesity are associated with worse symptoms and reduced patient-reported quality of life. In addition, we show that increased EAT volumes in AF are also associated with deranged haemodynamics and impaired LV and LA strain Taken together our data provides potential mechanisms for the relationship between AF and HFpEF in obesity and further highlights the importance of weight reduction to improve symptoms and outcomes for patients with AF.

3.7 TABLES AND FIGURES

Table 1 - Baseline Characteristics. Baseline Characteristics in obese and non-obese individuals.

Baseline Characteristics	Non-Obese (n=76)	Obese (n=44)	p-value
Age, (yrs)	66.3±9.1[a]	59.4±13.0	0.003
Male Sex, n (%)	53 (69.7)	33 (75)	0.685
Persistent AF, n (%)	35 (46.1)	26 (59.1)	0.410
Previous AF Ablation, n (%)	31 (40.8)	16 (36.4)	0.776
AF duration (months)	65 (32-153)	58 (21-123)	0.293
Cardiovascular Risk Factors			
BMI (kg/m^2)	25.9±2.5	34.0±3.2	<0.001
Body Mass (kg)	80.6±12.8	107.3±16.0	<0.001
Height (cm)	176.1±10.6	177.2±10.2	0.554
BSA (m^2)	2.0± 0.2	2.3±0.2	0.017
Hypertension, n (%)	50 (65.8)	34 (77.3)	0.264
Diabetes, n (%)	6 (7.9)	9 (20.5)	0.082
Previous Stroke, n (%)	9 (11.8)	0 (0)	0.025
Coronary Artery Disease, n (%)	6 (7.9)	4 (9.1)	1
Obstructive Sleep Apnea, n (%)	17 (22.4)	17 (38.6)	0.090
History of Smoking, n (%)	13 (17.1)	15 (34.1)	0.058
Alcohol Excess (>30g/week), n (%)	30 (39.5)	21 (47.7)	0.490
CHA_2DS_2-Vasc Score	2 (1,3)	2 (1,3)	0.242

Abbrevations: AF – atrial fibrillation, BMI – body mass index, BSA – body surface area.

Table 2

Invasive haemodynamic results. Invasive haemodynamics in obese and non-obese participants.

Baseline Pressure	Non-Obese (n=76)	Obese (n=44)	p-value
mLAP, mmHg	12.9 ± 4.0	16.0 ± 3.9	<0.001
HFpEF, n (%)	51 (67.1)	37 (84.1)	0.043
LA Peak v wave, mmHg	21.2 ± 7.5	23.9 ± 6.3	0.038
LA Nadir y-descent, mmHg	8.9 ± 4.1	12.8 ± 3.6	<0.001
mRAP, mmHg	8.3 ± 3.2	12.0 ± 3.8	<0.001
RA:LA Ratio	0.67±0.20	0.74±0.14	0.017
m TMWP, mmHg	4.5±3.1	4.1±2.3	0.447
MAP, mmHg	71±14	80±18	0.008

Abbreviations: LA – left atrial, HFpEF – heart failure with preserved ejection fraction, RA – right atrial, TMWP – transmural wall pressure, MAP – mean arterial pressure.

Table 3

Non-Invasive Investigations. Results of transthoracic echocardiography and NT-pro BNP blood tests in obese and non-obese individuals.

Baseline Characteristics	Non-Obese (n=76)	Obese (n=44)	p-value
LVEDV (mL)	93.2±29.9	97.1±32.3	0.559
LVEF (%)	57.6±6.2	56.5±5.1	0.381
GLS (%)	15.6±3.6	15.2±3.2	0.607
LV Mass Index	83.6±23.6	83.6±20.1	0.559
Relative Wall Thickness	0.39±0.08	0.38±0.06	0.354
LA_{Max} (mL)	67.0±19.3	77.0±25.4	0.031
LA_{Min} (mL)	42.9±16.0	46.9±20.6	0.292
Resting LAEF (%)	36.2±13.1	40.2±12.7	0.121
Reservoir Strain (%)	21.0±10.0	20.2±8.6	0.630
Booster Strain (%)	11.5±6.1	9.8±4.9	0.155
Conduit Strain (%)	12.9±5.6	13.3±4.8	0.701
NT-pro BNP (pg/ml)	239 (111-515)	207 (64-484)	0.342

Abbreviations: LVEDV – left ventricular end diastolic volume, LVEF – left ventricular ejection fraction, GLS – global longitudinal strain, LA_{Max} – left atrial maximum volume, LA_{Min} – left atrial minimum volume, LAEF – left atrial emptying fraction.

Table 4

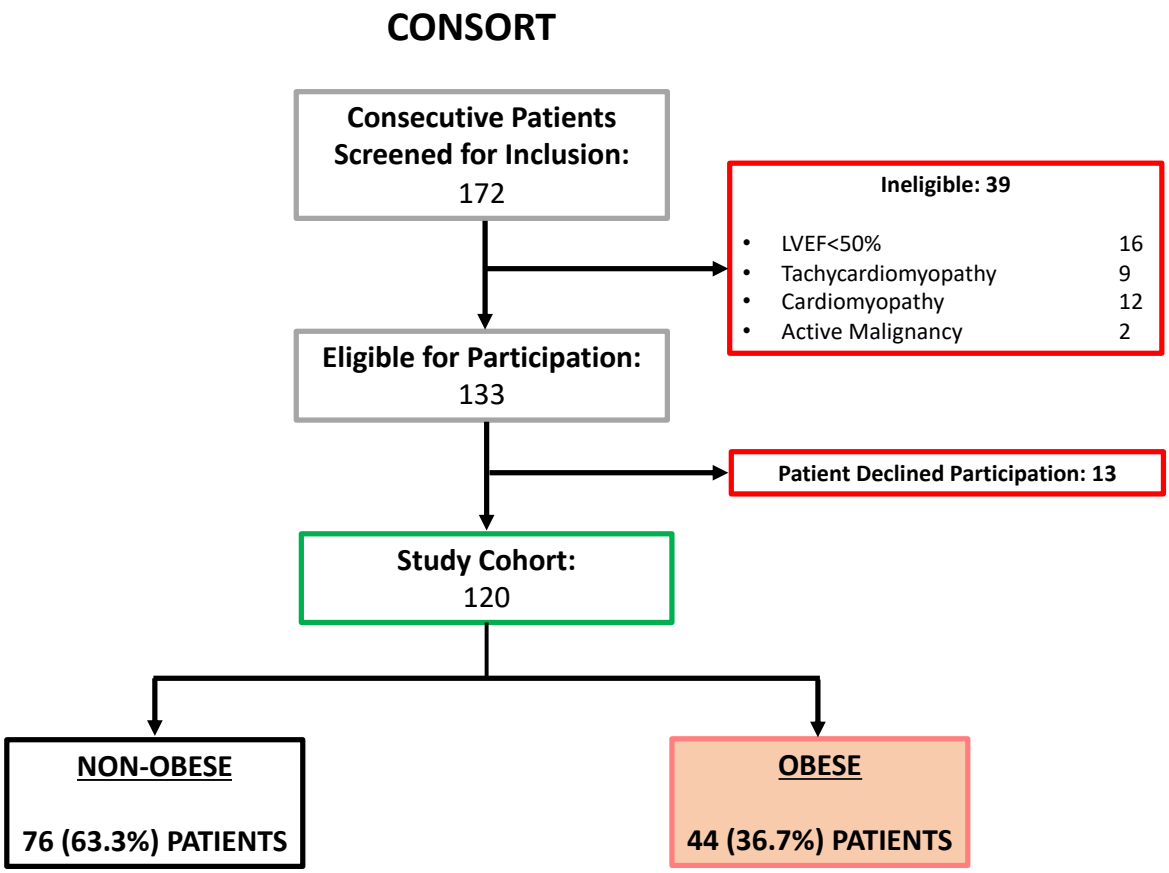
	Non-Obese (n=76)	Obese (n=44)	p-value
Symptoms			
MLWHF	24.0 (9.5-38.5)	25.0 (12.0 – 44.0)	0.234
AF Frequency	6.0 (1.8-8.3)	7.5 (3.5-10.0)	0.196
AF Duration	7.0 (6.0-9.3)	8.5 (7.0-10.0)	0.194
AF Severity	6.5 (4.0-8.0)	5.5 (4.5-7.0)	0.357
AF Symptom Burden	10.0 (4.0-15.3)	13.5 (7.0-22.0)	0.049
Global Well-Being	7.0 (6.0-8.0)	7.0 (5.0-7.0)	0.017
CPET			
VO_{2peak} (ml/kg/min)	22.1±7.7	19.4±6.6	0.068
VO_{2peak} (ml /min)	1813±735	2130±858	0.093
Predicted VO_{2peak}	91.9±26.0	91.7±22.3	0.970
Peak Heart Rate (bpm)	135±30	129±26	0.360
Chronotropic Response (bpm)	67±30	57±29	0.100

Functional Assessment. Results of the cardiopulmonary exercise test and MLWHF and AFSS symptom questionnaires in obese and non-obese individuals.

Abbreviations: MLWHF – Minnesota Living With Heart Failure, AFSS – Atrial Fibrillation Symptom Severity, AF – atrial fibrillation, CPET – cardiopulmonary exercise test, VO_{2peak} – maximal oxygen consumption.

Figure 1

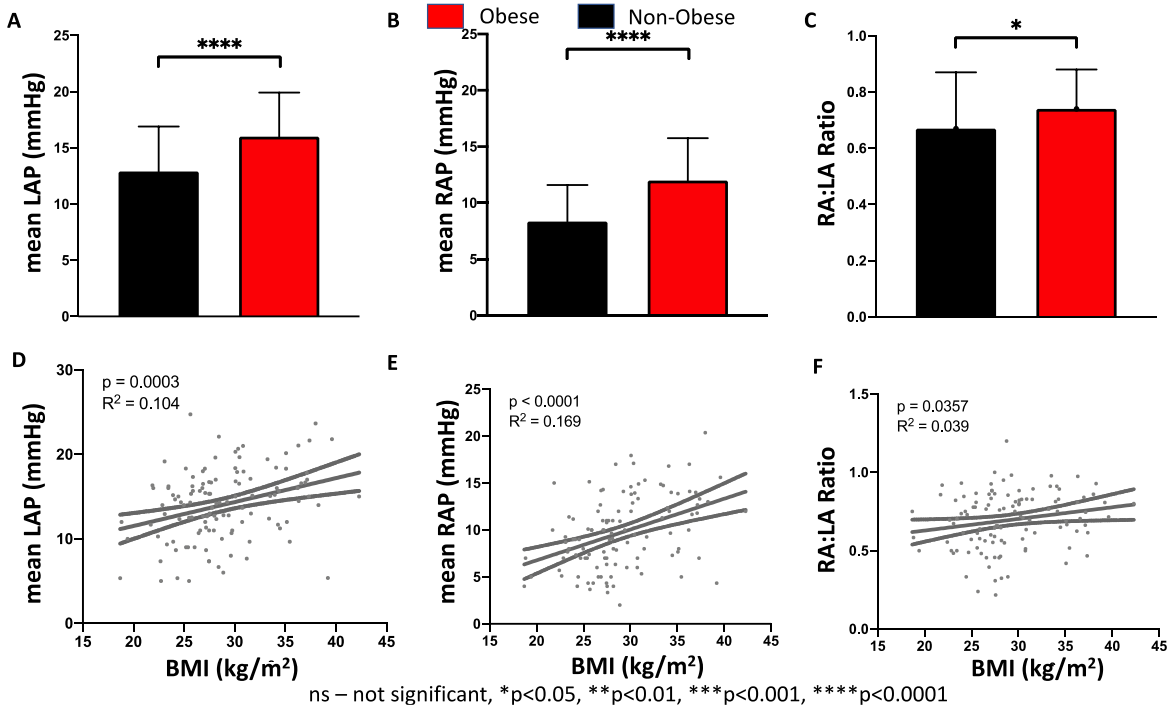
Study Consort Diagram. Of 172 patients screened for inclusion, 120 patients were included with 39 exclusions and an additional 13 patients who declined participation. Of the 120 inclusions, 44 were obese and 76 were not obese.



Abbreviations: LVEF – left ventricular ejection fraction.

Figure 2

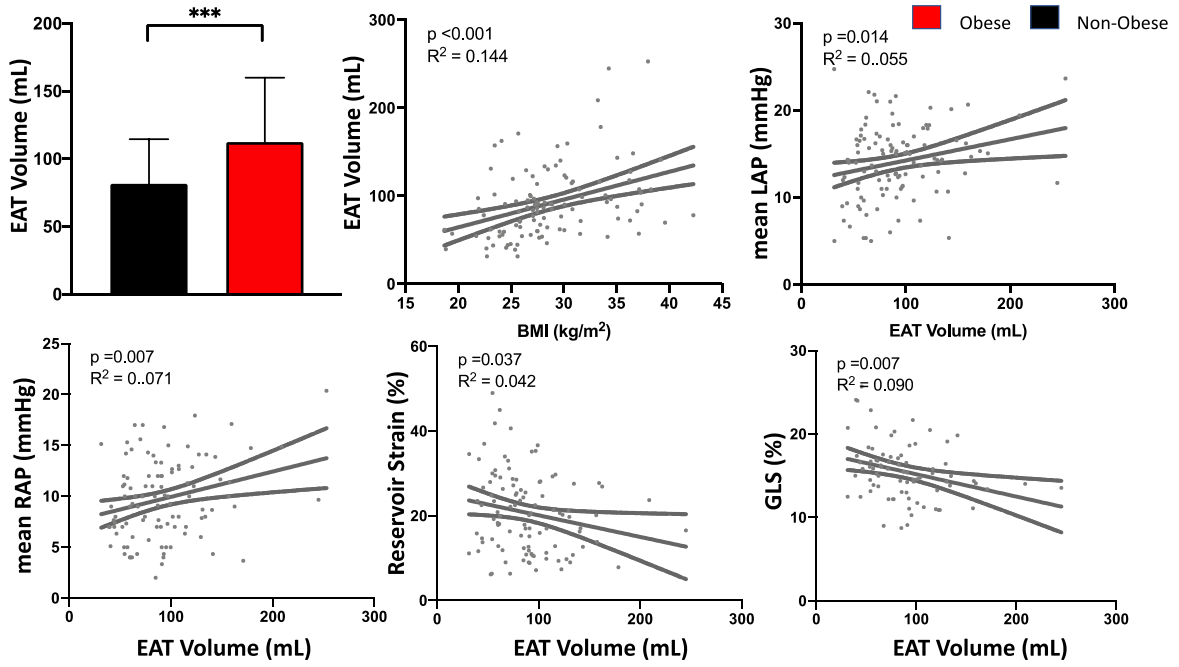
Invasive Haemodynamics. Patients with obesity were associated with A) greater mLAPs, B) greater mRAP and C) greater RA:LA pressure ratios. As a continuous variable, increasing BMI was also associated with D) increasing mLAPs, E) increasing RA pressures and F) increasing RA:LA pressure ratios. Abbreviations: LAP – left atrial pressure, RAP – right atrial pressure, RA:LA ratio – right atrial to left atrial pressure ratio, BMI – body mass index.



ns – not significant, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Figure 3

Relatonship between EAT Volume, invasive haemodynamics and myocardial strain. A) EAT volume was significantly higher in obese individuals and B) increasing BMI correlated significantly with increasing EAT volume. Increasing EAT volume was associated with C) higher mLAP, D) higher mRAP, E) lower LA reservoir strain and F) lower global longitudinal LV strain.



ns – not significant, *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Abbreviations: EAT – epicardial adipose tissue, BMI – body mass index, LAP – left atrial pressure, RAP – right atrial pressure, GLS – global longitudinal strain.

CHAPTER 4 Influence of Cardiorespiratory Fitness on LA Remodeling, Cardiomyopathy and HFpEF

4.1 INTRODUCTION

Reduced cardiorespiratory fitness (CRF) represents an important risk factor and prognostic marker in AF. Reduced CRF has been shown to be associated with increased risk of incident AF[324] as well as higher risk of all-cause mortality, cardiovascular mortality and morbidity in patients with AF.[289,325] In addition, improvements in CRF through exercise training have been shown to be associated with reduced AF burden, improved symptoms and improved quality of life in patients with AF[206]. However, the mechanisms by which CRF exerts this influence on outcomes in AF have yet to be fully elucidated.

Heart failure with preserved ejection fraction (HFpEF) commonly exists in patients with AF. The influence of CRF in patients with HFpEF has been more extensively studied. Reduced CRF is associated with increased risk of all-cause mortality[326] in addition to worse symptoms and quality of life.[327,328] Evidence suggests that reduced CRF in HFpEF is associated with greater left ventricular (LV) remodelling, associated with worse LV diastolic function and reduced LV strain.[329,330] In addition, exercise training to improve CRF has been shown to reduce this remodelling by decreasing LV stiffness.[331]

As shown in **Chapter 2**, HFpEF in AF is characterised by a more advanced LA cardiomyopathy. We hypothesise that reduced CRF may exert its influence on AF through HFpEF, LA remodeling and cardiomyopathy. The aim of this study, therefore, was to assess the relationship between CRF and LA remodelling through comprehensive invasive and non-invasive assessment of LA structure, mechanical function and electrical function.

4.2 METHODS

4.2.1 Study Design

This two-centre prospective clinical study was undertaken at the University of Adelaide. All participants provided written informed consent to the study protocol that was reviewed and approved by the Human Research Ethics Committee of The Central Adelaide Local Health Network and the University of Adelaide. The study was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12620000639921).

4.2.2 Study Population

Consecutive patients with symptomatic paroxysmal or persistent AF scheduled to undergo catheter ablation of AF were enrolled. Patients were excluded if they had: 1) reduced resting left ventricular ejection fraction (<50%); 2) previous diagnosis of cardiomyopathy; 3) moderate-to-severe valvulopathy; 4) previous diagnosis of pulmonary hypertension; 5) active malignancy; 6) severe chronic obstructive airways disease; 7) inability to exercise; or 8) inability to provide written informed consent.

4.2.3 Cardiopulmonary exercise testing and classification

Cardiorespiratory fitness was objectively assessed using cardiopulmonary exercise testing (CPET). CPET was performed using an upright cycle ergometer. Pulmonary gas exchange was measured continuously using a metabolic cart (Vyntus CPX, Vyaire Medical) and 12-lead ECG was monitored throughout. Participants began cycling at a power of 20 Watts, incrementally increasing by 10 Watts per minute. Peak exercise was defined as the point at which the participant felt the need to stop due to symptoms or fatigue. Oxygen consumption (VO_2) and carbon dioxide (VCO_2) production were averaged over 20 second intervals with subsequent calculation of the ventilatory equivalent for CO_2 (VE/VCO_2) and the respiratory exchange ratio

(RER=VCO_2/VO_2). A maximal effort was defined as a RER >1.05 and participants who were unable to achieve RER>1.05 were excluded from further analysis. Peak VO_2 (VO_{2peak}) was identified as the highest attained VO_2 during exercise. Chronotropic response was calculated as the difference between the resting heart rate prior to exercise and the maximum heart rate achieved at peak exercise.

Participants were classified according to VO_{2peak} achieved during the CPET according to the Weber classification system commonly used to classify chronic heart failure patients.[332] VO_{2peak} of less than 20ml/kg/min represents at least mild disease severity and this was the cutoff used to classify patients into 'Low CRF' and 'High CRF' groups.

4.2.4 Invasive Procedures

LA stiffness and electrical evaluation were assessed invasively at the AF ablation procedure. Functional assessment of the LA was further performed non-invasively at the pre-ablation TTE.

4.2.4.1 Patient Preparation

All invasive procedures were undertaken in the fasted state under general anaesthesia. Anticoagulation was uninterrupted. Heparin was administered as a bolus of 100 IU/kg with repeated boluses used to maintain the Activated Clotting Time above 350 seconds. Anaesthetic agents used for induction and maintenance of anaesthesia were standardized across all cases. Anti-arrhythmic medications were withheld for ≥5 half-lives prior to the procedure.

All patients underwent transesophageal echocardiography (TOE) at the start of the procedure to ensure there was no atrial thrombus. Access was obtained via the right femoral vein with ultrasound guidance. A decapolar catheter was placed in the coronary sinus with the proximal electrode positioned at the coronary sinus ostium in best septal LAO position.

Transseptal puncture (TSP) was performed using a SLO sheath and BRK1 needle (Abbott, Minneapolis, MN) under TOE guidance allowing access to the LA. Following TSP, an Agilis sheath (Abbott, Minneapolis, MN) was placed in the LA for LA pressure monitoring. The LA catheter was attached to a pressure transducer and zeroed at the level of the mid-thorax, allowing the recording of LA pressures. Pressures were recorded (240 Hz) on the WorkMate Claris™ Electrophysiology System (Abbott, Minneapolis, MN) and analysed offline.

4.2.4.2 Invasive LA Stiffness Assessment

LA pressure measurements were performed only after confirming hemodynamic stability for a 10-minute period. All inotropic and vasopressor medications were withheld during hemodynamic testing. Pressures were measured at end-expiration and averaged over 3 cardiac cycles. From the LA pressure waveform peak v-wave pressure was measured. Following the recording of baseline pressures, a body mass-adjusted volume (15mls/kg) of normal saline was infused directly into the LA via the Agilis sheath over an 8-minute period. This dose of saline infusion has been used previously for investigation of left ventricular stiffness.[333] The LA and arterial pressures were recorded and stored continuously and evaluated at 2-minute intervals throughout the infusion period.

At the same time, the TOE probe was used to monitor anteroposterior LA diameter. The 120-degree mid-esophageal view was chosen for this analysis due to its minimal underestimation of LA size and using the aortic valve as a landmark to ensure consistency of measurements.[278] This view was maintained throughout the infusion protocol and images were recorded at the same time intervals as the pressure measurements (0, 2, 4, 6 and 8 minutes). LA diameter was measured at end-ventricular systole and averaged over 3 cardiac cycles at each infusion time-point. LA dilatation was calculated as the increase in LA diameter over the course of the infusion in millimetres. All measurements were verified by a second independent

reviewer. All measurements were undertaken by investigators blinded to the clinical characteristics and non-invasive evaluations. LA stiffness was calculated as:

LA Stiffness = ΔPeak LA Pressure/ΔLA Diameter

4.2.4.3 Electroanatomical Mapping

In all cases, three-dimensional electroanatomical mapping (EAM) of the LA was performed prior to ablation in sinus rhythm using the HD-32 Grid Catheter (Abbott, Minneapolis, MN) and the Ensite™ Precision EAM Cardiac Mapping System (Abbott, Minneapolis, MN). Participants were excluded from the LA electrical analysis if they had previously undergone LA ablation or were in AF at the time of mapping. High-density voltage and activation maps were created during pacing at 600ms cycle length from the coronary sinus. Automated collection of points was performed; points were only acquired if they met the internal and external projection criteria of 5mm with 5mm interpolation. Additional electrogram analysis was meticulously performed offline to exclude ectopic beats and noise. The LA was divided into posterior, anterior, roof, inferior, septal and lateral segments, as previously described.[334] The following LA electroanatomical parameters were evaluated:

A) Regional bipolar peak-to-peak voltages were defined as the amplitude between the peak positive and peak negative deflections of the electrogram. Regional voltages were analysed offline using a custom-made validated software, as previously described.[279] An index of heterogeneity of the bipolar voltage amplitude was determined by calculating the coefficient of variation of the different regions in each chamber.

B) Regional conduction velocities were analysed using isochronal activation maps. Conduction velocities (CV) were determined in the direction of wavefront propagation (least isochronal crowding) and calculated as the distance between two

points divided by the difference in local activation times. Mean CV was determined by averaging the CV over 5 pairs of points, as previously described.[183] An index of heterogeneity of the conduction velocity was determined by calculating the coefficient of variation of the different regions in each chamber.

Global electrical parameters were calculated by combining the data from all 6 regions**.**

4.2.5 Non-Invasive Procedures

All participants underwent transthoracic echocardiography within a 4-week period pre-ablation for assessment of LA functional parameters. Transthoracic echocardiographic imaging involved parasternal and apical views. Left ventricular ejection fraction (LVEF) was measured by the Simpson's biplane method. Flow Doppler and tissue Doppler imaging were used to calculate E/e'. Focussed images of the LA were taken for assessment of LA function. Maximum (LA_{max}) and minimum LA (LA_{min}) volumes were obtained using the biplane area-length method and indexed to body surface area. LA emptying fraction (LAEF) was calculated using the formula:

$$LAEF = (LA_{max} - LA_{min})/LA_{max} \times 100.$$

LA strain was performed using a previously validated software.[280] For patients presenting in AF, LA booster strain was not evaluated but LAEF and reservoir strain were assessed as these functions do not depend on LA contractile function. All measurements were obtained according to the American Society for Echocardiography guidelines.[281,282] Measurements were averaged over 3 cardiac cycles in sinus rhythm and over 6 cycles in AF.

4.2.6 Statistical Analysis

Normality of each continuous variable was assessed using the Shapiro-Wilk test. Continuous variables were reported as means ± standard deviation for normally distributed data or median and interquartile range for non-normally distributed data. Categorical variables were reported as frequencies and percentages. Continuous variables were compared between groups using independent-samples Student t-tests or Mann Whitney U tests depending on normality. Categorical variables were compared across the three groups and each pair of groups using the chi-square test or Fisher's exact test (when cell size was less than 5). Linear regression analyses were used to assess LA pressure increases according to volume of saline infused (saline-pressure slopes). Univariable and multivariable predictors of HFpEF were investigated using simple linear regression analyses. P-values of ≤0.05 were considered statistically significant. Linear regression models were used to examine the relationship between exercise capacity (VO_{2peak}) and LA and RA variables. Model 1 was unadjusted whilst model 2 was adjusted for age and gender and model 3 was adjusted for age, gender, hypertension, diabetes, obstructive sleep apnoea, smoking history and history of alcohol excess. P-values of ≤0.05 were considered statistically significant. All statistical analysis was performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

4.3 RESULTS

4.3.1 Participant Recruitment

From 172 consecutive AF ablation patients, 39 were considered ineligible for pre-specified exclusion criteria. A further 33 were not included in the final analysis as they declined participation (n=13) or were unable to satisfactorily complete the CPET (n=20). In total, therefore, 100 participants were included in the final study cohort (Figure 1).

4.3.2 Cardiopulmonary Exercise Testing and Classification According to VO_{2peak}

All 100 participants satisfactorily completed CPET reaching a respiratory exchange ratio of at least 1.05 and volitional exhaustion. There were no major cardiac events or sustained arrhythmias during CPET. The mean VO_{2peak} of the cohort was 21.1±7.4ml/kg/min or 91.9±24.5% of predicted VO_{2peak}. A total of 57 (57%) participants demonstrated a VO_{2peak} of greater than 20ml/kg/min and were therefore classified as "High CRF" whilst 43 (43%) had a VO_{2peak} less than 20ml/kg/min and were classified as "Low CRF". Mean Vo_{2peak} in the High CRF group was 26.0±5.4ml/kg/min compared to 15.6±3.7 ml/kg/min in the Low CRF group ($p<0.001$). The Low CRF group also demonstrated reduced chronotropic response, with significantly lower percent of predicted peak heart rate achieved (80.5±15.2 vs 92.3±16.1, $p=0.006$) and lower heart rate increase with exercise (50.4±23.4 vs 72.5±27.4, $p<0.001$).

4.3.3 Baseline Characteristics

Baseline characteristics of the study cohort are shown in **Table 1**. The low CRF group was older (67.0±11.4 vs 61.3±9.9, $p=0.010$) and consisted of a lower proportion of males (53.5 vs 93%, $p<0.001$). In addition, the Low CRF group demonstrated higher BMI (30.3±5.3 vs 27.8±4.5kg/m^2, $p=0.016$) and higher prevalence of both hypertension (79.1% vs 56.1%, $p=0.029$) and diabetes (23.3% vs 5.3%, $p=0.019$). Overall $CHADS_2Vasc$ scores were significantly higher in the Low CRF group (2 [2-4] vs 1[1-2]).

4.3.4 Invasive Haemodynamic Assessment

Table 2 provides data for the association between VO_{2peak} and LA functional and electrical parameters. Invasively assessed LA stiffness was significantly higher in the Low CRF group (5.2±3.5 vs 3.8±2.9mmHg/mm, $p=0.004$, Figure 2A) and reduced VO_{2peak} was significantly associated with increasing LA stiffness when assessed continuously ($R^2=0.124$, $p<0.001$,

Figure 2B and 2C). Peak LA pressure was significantly higher in the Low CRF group at every stage of the infusion protocol (Figure 2D) and overall LA pressure increase was higher in the Low CRF group (15.5±6.7 vs 13.0±5.7, p=0.048, Figure 2E). Similarly, Low CRF was associated with reduced LA dilatation with saline infusion (3.8±1.8 vs 4.6±2.4, p=0.043, Figure 2F).

4.3.5 Non-Invasive LA Functional Assessment

Despite no differences in LVEF between CRF groups (57.3±6.2 vs 57.7±5.6%, p=0.746), Low CRF was associated with reduced LAEF (34.7±12.8 vs 41.6±12.4%, p=0.009, Figure 3A), underpinned by significantly reduced LA_{Min} (24.3±9.6 vs 18.9±6.7ml/m^2, p=0.003) but no significant difference in LA_{Max} (36.4±12.4 vs 32.1±7.6 ml/m^2, p=0.052). Similarly, Low CRF was associated with reduced LA reservoir strain (16.6±7.6 vs 24.1±10.3%, p<0.001, Figure 3B) in the entire cohort and reduced booster (8.9±4.6 vs 12.2±6.2, p=0.012, Figure 3C) and conduit strain (10.9±3.6 vs 14.6±6.1, p=0.003, Figure 3D) amongst patients presenting in sinus rhythm (n=70).

4.3.6 LA Electrical Assessment

In total, 42 patients were included in the LA electrical assessment after exclusion of those presenting in AF (n=23) and those who had undergone previous LA ablation (n=35). Patients with Low CRF demonstrated reduced LA voltage (3.0±1.4 vs 3.8±1.0mV, p=0.039, Figure 4A) and greaterLA voltage heterogeneity (1.4±0.4 vs 1.1±0.2, p=0.027, Figure 4B). Similarly, Low CRF was associated with reduced LA conduction velocities (0.9±0.2 vs 1.0±0.2, p=0.039, Figure 4C) and greater LA conduction heterogeneity (2.3±1.0 vs 1.7±0.5, p=0.048, Figure 4D).

4.3.7 Linear Regression Models

Table 3 shows the results of the unadjusted and adjusted linear regression analyses investigating the relationship between VO_{2peak} and LA functional and electrical parameters. In unadjusted analyses, VO_{2peak} demonstrated significant associations with LA stiffness ($p<0.001$), LAEF ($p<0.001$) and reservoir ($p<0.001$), booster ($p<0.001$) and conduit strain ($p<0.001$). In addition, VO_{2peak} was also associated with LA voltage ($p=0.013$) and LA conduction velocities ($p<0.001$). Associations remained significant after adjustment for age and gender in Model 2, whilst LA stiffness ($p=0.003$), LAEF ($p<0.001$), reservoir strain ($p<0.001$), booster strain ($p=0.039$) and conduction velocity ($p=0.037$) also remained significant in Model 3, adjusted for age, gender, hypertension, diabetes, obstructive sleep apnoea, alcohol excess and history of smoking.

4.4 DISCUSSION

4.4.1 Major Findings

In this prospective clinical study, we provide novel evidence on the association between reduced cardiorespiratory fitness and the underlying atrial disease amongst patients with symptomatic AF. Using multi-modality techniques, we demonstrate that reduced CRF is independently associated with significant functional and electrical remodelling of the LA, including increased LA stiffness, reduced LA strain and emptying fraction, and reduced LA voltages and conduction velocities. Taken together, our data identifies key features of the atrial disease that are associated with reduced CRF.

4.4.2 Cardiovascular Risk Factors and Atrial Dysfunction

It is well-established that several modifiable and non-modifiable cardiovascular risk factors are associated with atrial remodelling underlying AF.[335] Experimental and clinical studies have

identified electrophysiological and structural atrial remodelling in ageing,[146] hypertension,[124,160] obesity,[183] obstructive sleep apnoea,[126] heart failure[132] and alcohol excess.[336] The mechanisms linking these cardiovascular risk factors with the development of an atrial substrate are numerous and include atrial fibrosis, haemodynamic changes, microvascular dysfunction, systemic inflammation and epicardial adiposity.[28]

In this study we provide novel evidence on the atrial functional abnormalities amongst symptomatic AF patients with reduced CRF. Using a novel invasive method for the assessment of LA stiffness, we show that reduced CRF is associated with increased LA stiffness coupled with reduced LA strain and emptying fraction despite no differences in LV function. The more advanced atrial disease observed in this cohort potentially underpins the association between CRF and outcomes including the development, maintenance, and recurrence of AF. Importantly, we show that these associations occur independently of key non-modifiable risk factors including age and gender and other modifiable risk factors including hypertension, diabetes and obstructive sleep apnoea. Reduced CRF frequently coexists with several other modifiable risk factors including hypertension and obesity.[337] As has previously been shown in other studies of CRF and cardiovascular disease, it is impossible to extricate the effects of reduced CRF from the modulating effects of other coexisting cardiovascular risk factors such as hypertension and obesity.[338] Regardless, our data highlights the fact that CRF plays an important role in the development of an atrial substrate and has the potential to be a target for intervention to improve outcomes in patients with AF.

4.4.3 Cardiorespiratory Fitness and Atrial Electrical Remodelling

In addition to functional remodelling of the atria, AF is also characterised by electrophysiological remodelling. In comparison to patients without AF, paroxysmal AF patients demonstrate larger left atrial volumes coupled with lower bipolar atrial voltages,

reduced atrial conduction velocities and a greater proportion of fractionated electrograms.[339] Moreover, patients with persistent AF have been shown to exhibit an atrial substrate which is even more advanced than seen with paroxysmal AF,[56] whilst those with AF recurrence after AF ablation procedures are also characterised by a greater electrical remodelling.[340,341] These data highlight the key role that atrial substrate plays in the progression of AF. In this study, we show that patients with poor CRF demonstrate a more advanced atrial substrate, independent of age, gender and other AF risk factors, suggesting that AF progression and outcomes may be worse in patients with lower CRF. Our data therefore provides mechanistic evidence to support previous clinical studies identifying reduced CRF as an independent predictor of AF recurrence and progression.[206]

4.4.4 Cardiorespiratory Fitness as a Therapeutic Target in AF

Growing evidence suggests that the atrial substrate underlying AF may be reversible, through treatment of the underlying risk factors associated with its development. In hypertensive sheep, blood pressure reduction with beta-blockers or calcium-channel blockers resulted in faster conduction velocities and reduced conduction heterogeneity.[342] Similarly, in obese sheep, weight loss was associated with improved atrial conduction and reductions in atrial fibrosis and inflammation.[125] In clinical studies of overweight and obese patients, weight reduction through both dietary restrictions and bariatric surgery have been shown to promote the reversal of the natural progression of AF; both strategies are associated with increased chance of reversal from persistent to paroxysmal AF and reverse remodelling of the LA.[254,343] These data suggest that reversal of the underlying substrate in AF is possible through risk factor modification. In this context, our findings that reduced CRF is also associated with a more advanced atrial substrate suggests that improving CRF may improve the underlying atrial substrate and therefore improve outcomes for these patients.[344] Indeed, a recent clinical trial

evaluating exercise as a treatment of patients with paroxysmal or persistent AF showed that a supervised exercise programme resulted in significant improvements in CRF and a reduction in AF recurrence after 12 months.[345] Future work should investigate the direct impact of improvements in CRF on the underlying atrial substrate.

4.4.5 Gender Differences

Of note, there was a significantly lower proportion of females in the 'High CRF' group compared to the 'Low CRF' group. This is consistent with previous studies investigating the influence of gender on maximal aerobic capacity.[346,347] Potential factors underpinning this association include the fact that women tend to have smaller left ventricular chamber size,[348] lower diastolic compliance,[349] lower haemoglobin levels,[350] higher prevalence of obesity and lower lean mass compared to men.[351] Our data suggests that poorer LA function and deranged intracardiac haemodynamics may also contribute to the lower exercise capacity seen in women with AF.

4.5 LIMITATIONS

This study is a cross-sectional study which provides clinical associations but is unable to determine causality. The associations identified in this study may be confounded by other baseline characteristics and risk factors but we did correct for the most important non-modifiable risk factors. Our study cohort was limited by the fact that it only included patients undergoing AF ablation and females were underrepresented, meaning our findings may not be generalisable to the entire population of patients with AF. Invasive haemodynamic measurements were undertaken in an experimental setting in a cardiac catheterisation laboratory under general anaesthetic, as opposed to invasive cardiopulmonary exercise testing. However, this is the only safe way of obtaining direct LA pressure to investigate LA stiffness,

which was a central component of this study. In addition, the electroanatomical mapping component of the study incorporated only a subset of the entire cohort, limiting its power to identify significant differences.

4.6 CONCLUSIONS

Reduced CRF is associated with a more advanced atrial cardiomyopathy characterised by both functional and electrical remodelling of the atria. In this study we have shown that reduced CRF is associated with increased LA stiffness, reduced LA strain, lower bipolar voltages and slower conduction velocities. These associations of reduced CRF occur independently of age, gender and several other AF risk factors including hypertension, diabetes and obstructive sleep apnoea. Taken together our data provides evidence that CRF is an independent marker of underlying atrial substrate in patients with AF and highlights the potential to improve atrial substrate through improving CRF.

4.7 TABLES AND FIGURES

Table 1

Baseline Cohort Characteristics. Patient demographics, clinical characteristics and patient reported physical activity levels compared between the two CRF groups.

	Low CRF (43)	High CRF (57)	p-value
Age, yrs	67.0±11.4	61.3±9.9	0.010
Male Sex, n (%)	23 (53.5)	53 (93.0)	<0.001
BMI (kg/m^2)	30.3±5.3	27.8±4.5	0.016
Weight (kg)	91.8±21.8	90.4±17.3	0.722
Hypertension, n (%)	34 (79.1)	32 (56.1)	0.029
Diabetes, n (%)	10 (23.3)	3 (5.3)	0.019
OSA n (%)	15 (34.9)	16 (28.1)	0.609
Alcohol Excess (>30g/week), n (%)	18 (41.9)	27 (47.4)	0.730
Smoking History, n (%)	8 (18.6)	11 (19.3)	1
CAD, n (%)	4 (9.3)	4 (7.0)	0.738
Stroke, n (%)	3 (7.0)	4 (7.0)	1
CHA_2DS_2-Vasc Score, median (IQR)	2 (2-4)	1(1-2)	<0.001
Persistent AF, n (%)	22 (51.2)	32 (56.1)	0.770
Previous AF ablation, n (%)	16 (37.2)	19 (33.3)	0.849
Duration of AF (mths)	66 (27-157)	57 (19-136)	0.579

Abbreviations: CRF – cardiorespiratory fitness, BMI – body mass index, OSA – obstructive sleep apnoea, CAD – coronary artery disease, AF – atrial fibrillation

Table 2

Functional and Electrical LA Parameters according to CRF group. Results of LA functional and electrical assessment according to CRF group. Low CRF associated with increased LA stiffness, reduced LA function on TTE and electrical remodelling on electroanatomical mapping.

	Low CRF (43)	High CRF (57)	p-value
Invasive Stiffness	5.2±3.5	3.8±2.9	0.004
Increase LA Pressure	15.5±6.7	13.0±5.7	0.048
Change LA Diameter	3.8±1.8	4.6±2.4	0.043
LAEF (%)	34.7±12.8	41.6±12.4	0.009
LA_{Max} (mL/m^2)	36.4±12.4	32.1±7.6	0.052
LA_{Min} (mL/m^2)	24.2±9.6	18.9±6.7	0.003
Reservoir Strain (%)	16.6±7.6	24.1±10.3	<0.001
Booster Strain (%)	8.9±4.6	12.2±6.2	0.013
Conduit Strain (%)	10.9±3.6	14.6±6.1	0.003
Voltage (mV)	3.8±1.0	3.0±1.4	0.039
Voltage Heterogeneity	1.4±0.4	1.1±0.2	0.027
Conduction Velocity (m/s)	0.9 to 0.2	1.0±0.2	0.039
Conduction Heterogeneity	2.2 (1.5 to 2.8)	1.5 (1.2 to 2.0)	0.048

Abbreviations: LA – left atrial, LAEF – left atrial emptying fraction, mV – millivolts, m/s – metres per second.

Table 3

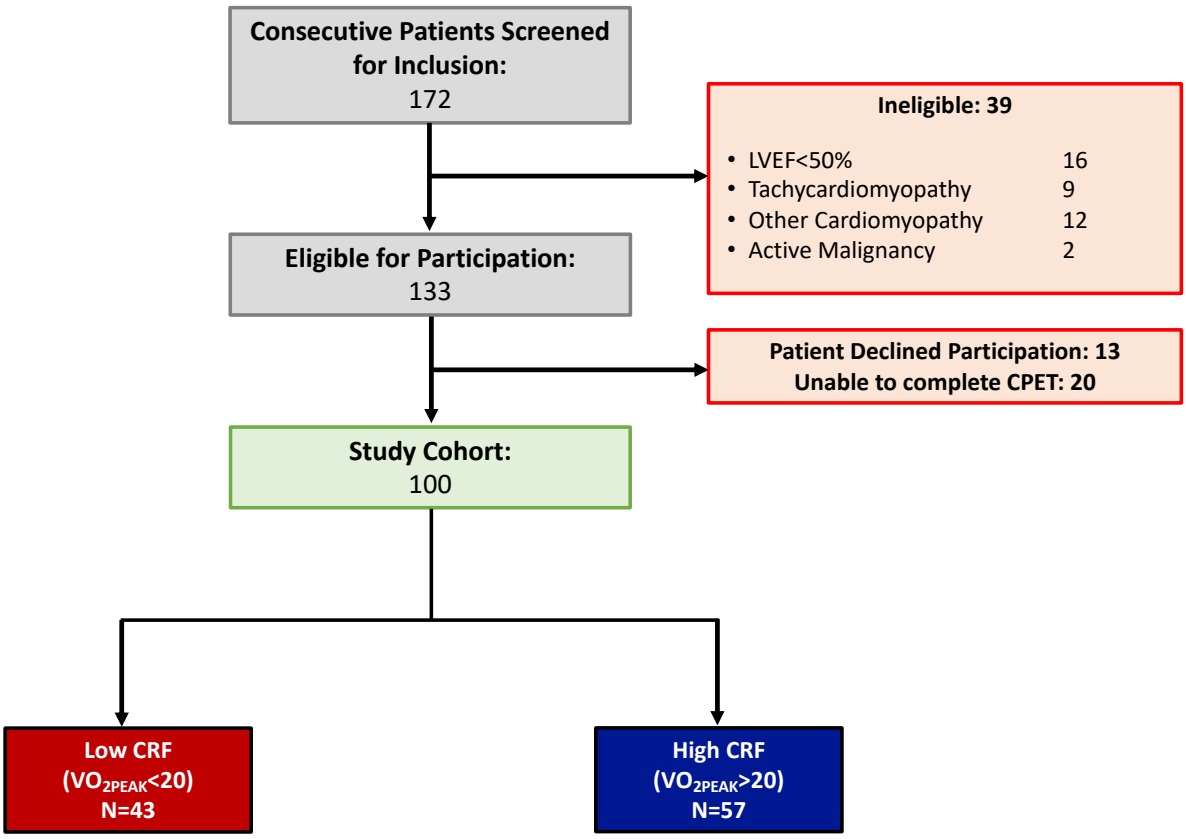
Association between VO_{2peak} and LA functional and electrical parameters. Unadjusted and adjusted linear regression models to assess the relationship between LA size and function and exercise capacity. Model 1 – unadjusted, model 2 – adjusted for age and gender, model 3 – adjusted for age, gender, hypertension, diabetes, obstructive sleep apnoea, history of alcohol excess and history of smoking.

	Model 1		**Model 2**		**Model 3**	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**	**Coefficient (95% CI)**	**p-value**
Inv LA Stiffness	-0.81 (-1.25 to -0.37)	<0.001	-0.67 (-1.06 to -0.27)	<0.001	-0.61 (-1.00 to -0.22)	0.003
LAEF	0.26 (0.16 to 0.37)	<0.001	0.19 (0.08 to 0.29)	<0.001	0.18 (0.08 to 0.28)	<0.001
Reservoir Strain	0.39 (0.25 to 0.52)	<0.001	0.32 (0.19 to 0.45)	<0.001	0.32 (0.19 to 0.45)	<0.001
Booster Strain	0.58 (0.28 to 0.88)	<0.001	0.32 (0.03 to 0.60)	0.029	0.31 (0.02 to 0.60)	0.039
Conduit Strain	0.56 (0.24 to 0.87)	<0.001	0.33 (0.02 to 0.64)	0.036	0.30 (-0.02 to 0.62)	0.063
Voltage	14.9 (0.55 to 4.38)	0.013	2.18 (0.31 to 4.06)	0.024	1.84 (-0.30 to 3.97)	0.089
Conduction Velocity	23.09 (9.96 to 36.2)	<0.001	19.82 (5.61 to 34.02)	0.007	5.61 (1.21 to 37.64)	0.037

Abbreviations: LA – left atrial, LAEF – left atrial emptying fraction.

Figure 1

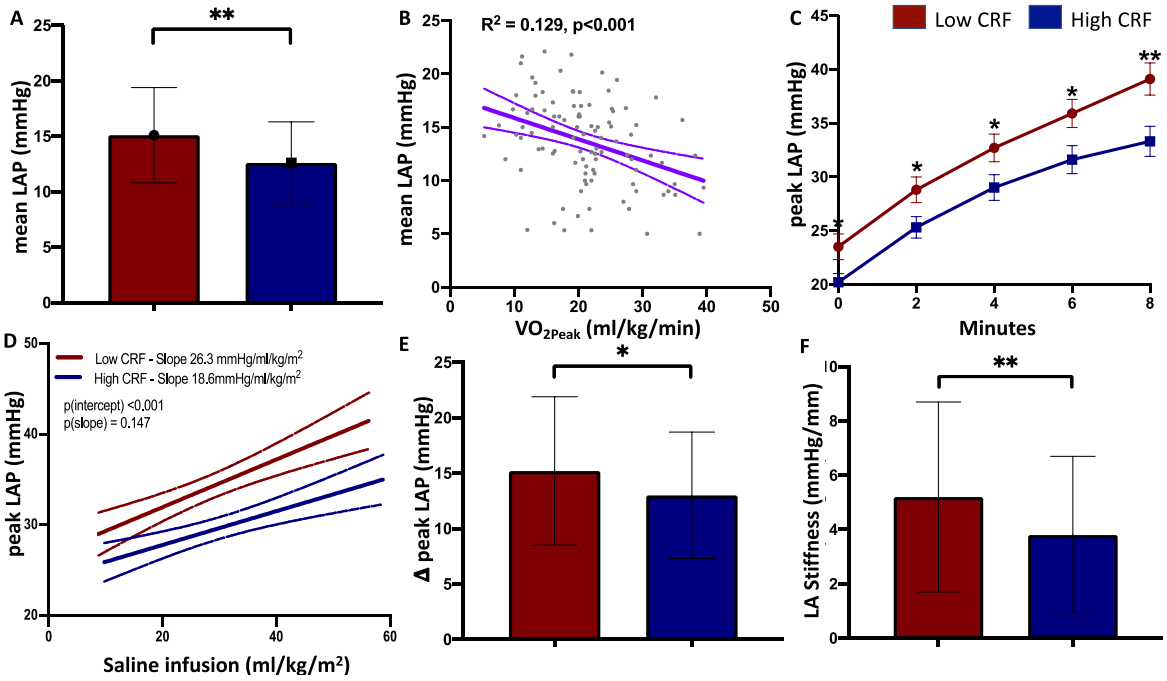
CONSORT diagram. Of 172 patients screened for inclusion, 39 were deemed ineligible for pre-specified exclusion criteria. Of the remaining 133 patients, 13 declined participation and a further 20 were unable to satisfactorily complete the CPET protocol. In total, therefore, 100 patients were included in the study cohort.



Abbreviations: HCM – Hypertrophic cardiomyopathy, LVEF – left ventricular emptying fraction.

Figure 2

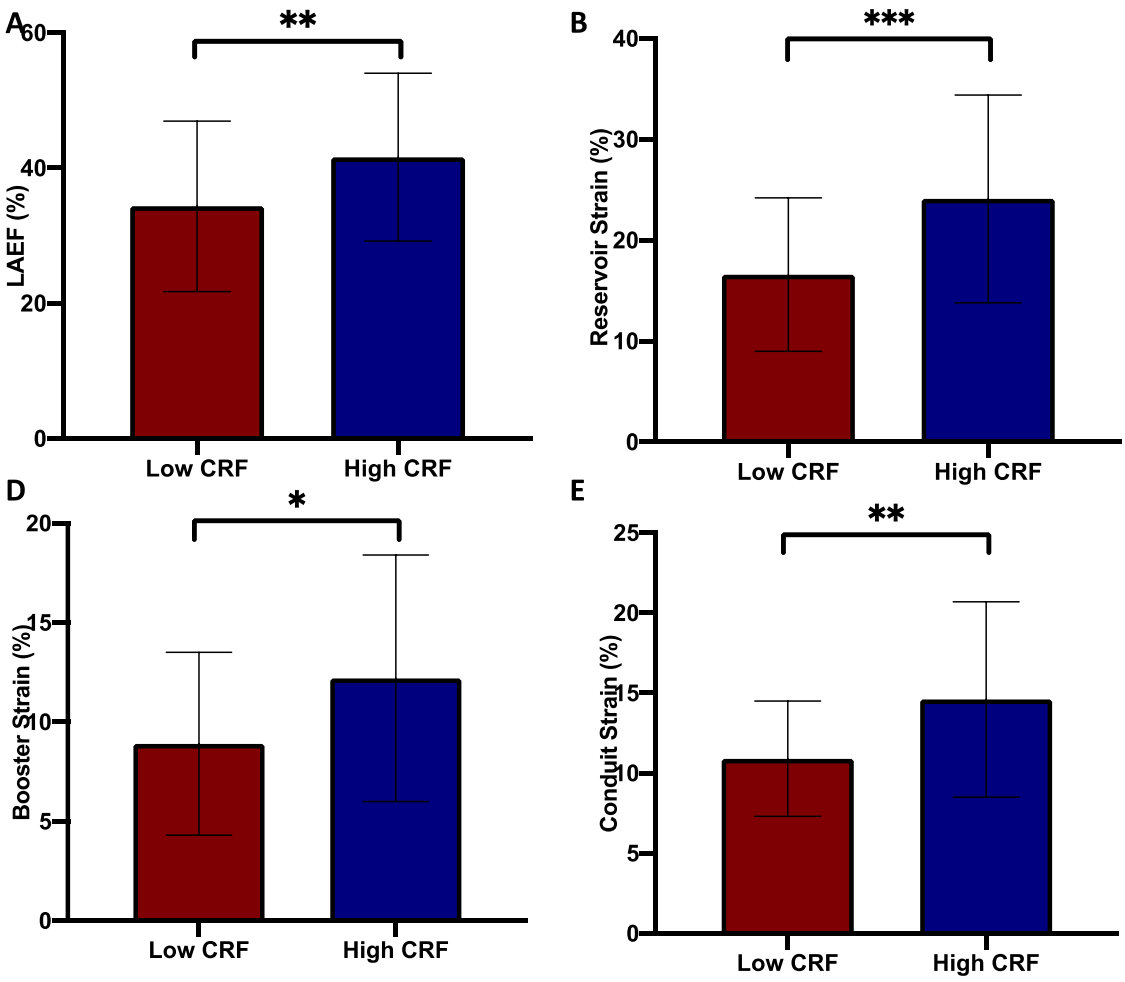
Relationship Between CRF and LA Invasive Functional Parameters. A) Low CRF is associated with increased mLAP. B) Reduced VO_{2peak} as a continuous variable was also significantly associated with increased mLAP. C) The Low CRF group demonstrated higher peak LA pressures at each 2-minute infusion timepoint and D) greater peak LA pressures according to volume of saline infused. E) Overall LA pressure increase with infusion was significantly higher in the Low CRF group resulting in F) increased LA stiffness in the Low CRF group.



Abbreviations: CRF – cardiorespiratory fitness, LA left atrial, VO_{2peak} – maximal oxygen consumption, LAP – left atrial pressure.

Figure 3

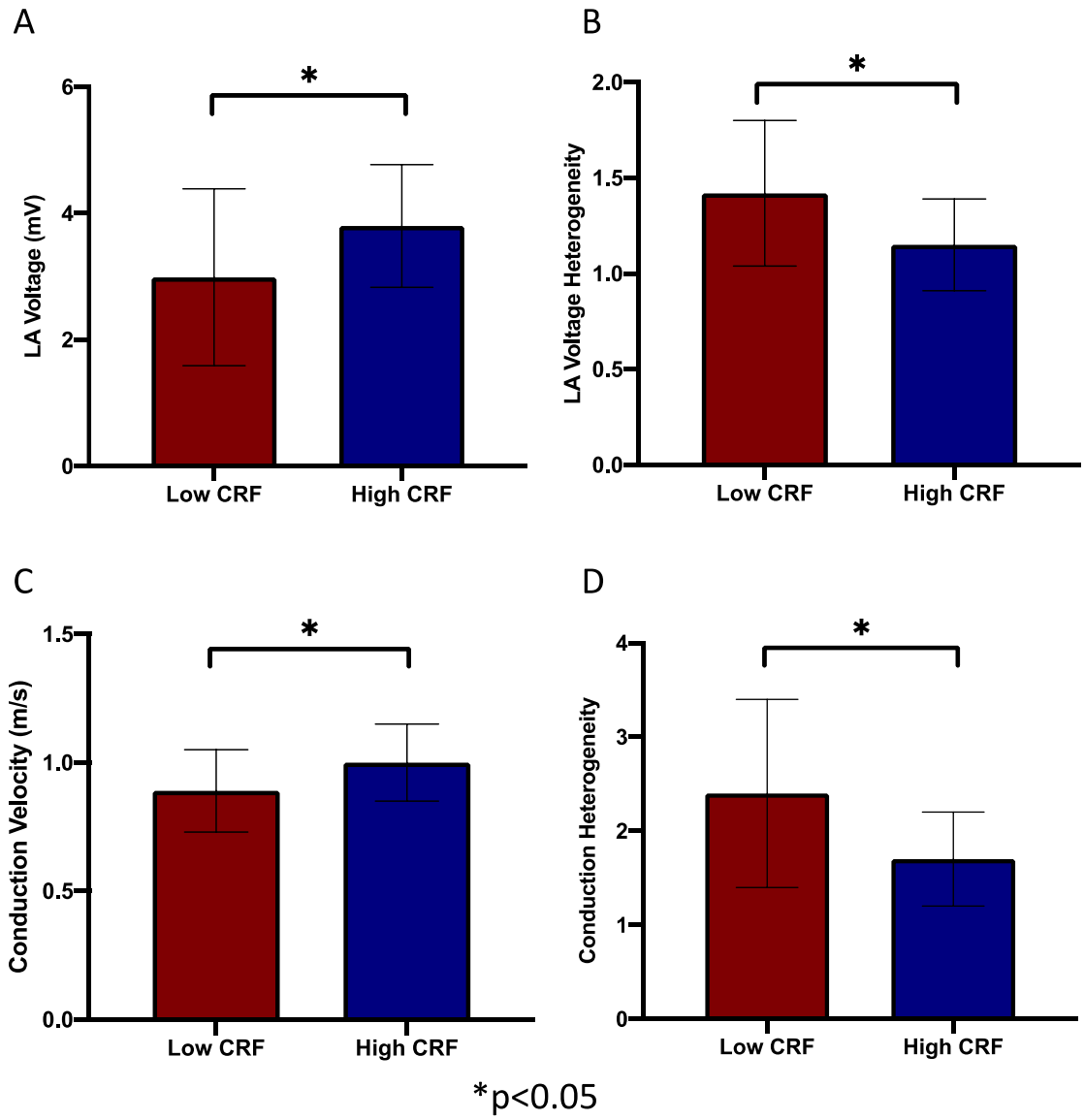
Relationship Between CRF and LA Non-Invasive Functional Parameters. The Low CRF group demonstrated A) reduced LAEF, B) reduced LA reservoir strain, C) reduced LA booster strain and D) reduced LA conduit strain. LAEF – left atrial emptying fraction.



Abbreviations: CRF – cardiorespiratory fitness, LAEF – left atrial emptying fraction.

Figure 4

Relationship Between CRF and LA Electrical Parameters. Relationship Between CRF and LA Electrical Parameters. Bar charts demonstrating that Low CRF was associated with A) reduced global LA voltages, B) increased LA voltage heterogeneity, C) reduced LA conduction velocities and D) increased LA conduction heterogeneity compared to High CRF.



Abbreviations: CRF – cardiorespiratory fitness.

CHAPTER 5 Utility and Validity of the HFA-PEFF and H2FPEF Scores for Diagnosis of HFpEF in Patients with Atrial Fibrillation

5.1 INTRODUCTION

Heart failure (HF) afflicts 64 million people worldwide,[352] representing around 3% of people over the age of 18.[353] Heart failure with preserved ejection fraction (HFpEF) accounts for 50% of these cases,[354,355] with comparable outcomes to HF with reduced ejection fraction (HFrEF).[356] It is increasingly recognised that HFpEF is common in patients with atrial fibrillation (AF).[28] In **Chapter 2**, we show that HFpEF is present in up to 73% of patients with symptomatic AF presenting for AF ablation procedures and is associated with worse symptoms and poorer exercise capacity. However, accurate diagnosis of HFpEF in patients with AF remains a significant clinical challenge due to overlapping signs and symptoms.[28,209] In addition, many of the non-invasive diagnostic tools used for HFpEF, including left ventricular diastolic function and levels of NT-pro BNP, are significantly affected by the presence of atrial fibrillation, making diagnosis even more difficult in this cohort of patients.[207]

In recent years, two novel scoring tools have been developed to assist the non-invasive diagnosis of HFpEF.[208,209] An expert consensus guideline from the European Society of Cardiology provided the HFA-PEFF score,[209] whilst the H_2FPEF score is a weighted composite score based on characteristics of patients with confirmed HFpEF following gold-standard invasive diagnosis of HFpEF.[208] Whilst these tools have been validated in patients with confirmed HFpEF,[357,358] they have not yet been assessed in patients with symptomatic AF. The aim of this study was to assess the utility and accuracy of these non-invasive diagnostic tools for the diagnosis of HFpEF in a cohort of patients with symptomatic AF.

5.2 METHODS

5.2.1 Study Design

This was a prospective clinical study undertaken at the Centre for Heart Rhythm Disorders at the University of Adelaide. All patients provided written informed consent. The study protocol was approved by the Human Research Ethics Committee of the Central Adelaide Local Health Network and the University of Adelaide. The study was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12620000639921).

5.2.2 Study Population

Consecutive individuals with symptomatic paroxysmal or persistent AF due to undergo an AF ablation were eligible to participate. Patients were excluded if they had: 1) reduced left ventricular ejection fraction (<50%); 2) previous diagnosis of cardiomyopathy; 3) moderate-to-severe valvulopathy; 4) previous diagnosis of pulmonary hypertension; 5) active malignancy; 6) severe chronic obstructive airways disease; 7) inability to exercise; or 8) inability to provide written informed consent.

5.2.3 Non-Invasive Diagnosis of HFpEF

All participants underwent non-invasive assessment for the diagnosis of HFpEF based on two established HFpEF scoring tools: 1) the HFA-PEFF score and 2) the H_2FPEF score. Full details of these scoring systems for diagnosis of HFpEF are provided in **Table 1.**

5.2.3.1 HFA-PEFF Score for Diagnosis of HFpEF

The HFA-PEFF diagnostic algorithm is a consensus recommendation from the Heart Failure Association of the European Society of Cardiology for the diagnosis of HFpEF.[209] The algorithm involves a four step process, involving 1) a pretest clinical assessment, 2)

establishing the HFA-PEFF score based on non-invasive diagnostics, 3) performing a diastolic stress test (non-invasive or invasive) for those with intermediate HFpEF probability and 4) investigating for specific HFpEF aetiology. For the purposes of this study, all participants were presumed to meet the step 1 pre-test probability of HFpEF due to the presence of symptomatic AF. All participants were therefore classified according to HFpEF probability based on the (HFA) – PEFF scoring system.

The HFA-PEFF score for each participant was based on 1) resting echocardiography, 2) NT-pro BNP and 3) diastolic stress testing in the form of exercise echocardiography. Resting echocardiography was performed according to a study specific protocol by an experienced sonographer blinded to patient heart failure group. Images obtained included parasternal and apical views. Echocardiographic parameters used for the HFA-PEFF scoring system included E', E/E', TR velocity, LV global longitudinal strain, indexed LA maximum volumes (LAVI), left ventricular mass index and relative wall thickness. Left ventricular ejection fraction (LVEF) was measured by the Simpson's biplane method. Global left ventricular strain was performed using dedicated LV strain software. Left ventricular mass (LVM) was calculated using the following formula:

$$LVM =. 0.8 \times 1.04 \times [(IVS + LVIDD + PWT)^3 - LVIDD^3] + 0.6.$$

Relative wall thickness (RWT) was calculated using the following formula:

$$RWT = (IVS + LVPW)/LVIDD.$$

Left atrial function was assessed by left atrial emptying fraction (LAEF) and LA strain. Maximum (LA_{max}) and minimum LA (LA_{min}) volumes were obtained using the biplane area-length and indexed to body surface area. LAEF was calculated using the formula: $LAEF = (LA_{max} - LA_{min})/LA_{max} \times 100$. Flow Doppler and tissue Doppler imaging were used to calculate E/E'. LA strain was performed using a previously validated software.[280] All measurements

were obtained according to the American Society for Echocardiography guidelines.[281,282] Measurements were averaged over 3 cardiac cycles in sinus rhythm and over 6 cycles in AF.

Blood sampling for analysis of NT-pro BNP levels was undertaken at rest in the fasting state. Scoring for cardiac biomarkers depended not only on the NT-pro BNP level but also on the cardiac rhythm at the time of blood sampling.

The points from the resting echocardiogram and NT-pro BNP result were tallied to provide a total score out of six for each patient. A score of 5 or 6 represents high probability of HFpEF, whilst a score of 0 or 1 represents low probability. Participants scoring 2-4 were considered intermediate risk for HFpEF. For participants in the intermediate group, participants underwent exercise echocardiography for diastolic stress testing.

Exercise echocardiography was performed using a dedicated supine bicycle ergometer. Exercise echocardiography was performed using a dedicated supine bicycle ergometer allowing echocardiographic imaging during exercise. Exercise protocol involved cycling at a workload of 20W, increasing by 20W every 2-minutes. Focussed TTE images were obtained during every second stage. Exercise was stopped at a heart rate of 110 bpm or when symptoms limited further exercise. TR velocity and E/E' measurements were obtained from the exercise echocardiogram using Doppler flow and tissue Doppler techniques. If E/e' during exercise rose to greater than 15, participants scored an extra 2 points. If this change was accompanied by an increase in TR Vmax to above 2.8m/s during exercise, participants scored an additional 3 points.

5.2.3.2 H_2FPEF Score for Diagnosis of HFpEF

Participants were also classified according to the H_2FPEF scoring system. The H_2FPEF scoring system was developed following investigation of 414 dyspneoic patients with confirmed HFpEF and a further 147 dyspnoeic patients without HFpEF.[208] Using independent predictors

for the presence of HFpEF, a weighted composite scoring system was developed, incorporating selected cardiovascular risk factors and resting echocardiographic parameters. Specifically, the parameters used for this system are: elevated BMI >30kg/m^2 (2 points), hypertension (1 point), E/e'>9 (1 point), a history of AF (3 points), pulmonary artery systolic pressure >35mmHg (1 point) and age >60 (1 point) The points from these criteria were tallied to provide a total score out of nine for each patient. A score of ≥6 represents high probability of HFpEF, whilst a score of 3-6 represents intermediate probability. The minimum H_2FPEF score for participants in this study was 3 given that all participants had a history of AF.

5.2.4 Gold-Standard Invasive Diagnosis of HFpEF

Invasive haemodynamic assessment of LV filling pressures remains the gold-standard method for the diagnosis of HFpEF and was used in this study to assess the validity of the non-invasive diagnostic scoring systems. Invasive haemodynamic assessment was undertaken for all participants at the AF ablation procedure. Specific details regarding participant preparation for invasive assessment have been previously described.[359]

Haemodynamic measurements were taken following transseptal puncture. An Agilis sheath (Abbott, Minneapolis, MN) was placed in the left atrium and this was attached to a pressure transducer and zeroed at the level of the mid-thorax, allowing the accurate recording of LA pressures. Pressures were recorded (240 Hz) on the WorkMate Claris™ Electrophysiology System (Abbott, Minneapolis, MN) and analysed offline. Pressures were measured at end-expiration and averaged over 3 cardiac cycles.

Mean LAP provided a direct measure of LV end-diastolic pressure. Mean LAP (mLAP) was taken at the start of the C-wave. In the absence of a visible C wave, mLAP was taken midway between the peak and trough of the A-wave in those with sinus rhythm or 130-160ms after the onset of the QRS in those in AF.[275] Participants were classified into three groups

according to mLAP at rest and with provocation, as defined by a Science Advisory from the American Heart Association.[360] Patients were labelled as 'HFpEF' group if mLAP at baseline was greater than 15mmHg or if mLAP was less than 15mmHg at baseline but rose to above 15mmHg following infusion of 500mls of saline (early HFpEF). All other patients were placed in the 'No HFpEF' group.

5.2.5 Statistical Analysis

Continuous variables were reported as means ± standard deviation for normally distributed data or median and interquartile range for non-normally distributed data. Categorical variables were reported as frequencies and percentages. Continuous variables were compared between each HFpEF group using independent-samples Student t-tests or Mann Whitney U tests as appropriate. Categorical variables were compared across each HFpEF group using the chi-square test or Fisher's exact test. Sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) of high-probability HFpEF scores were calculated to predict invasive HFpEF diagnosis. Receiver Operating Characteristic (ROC) curves and area under the curve (AUC) were computed to compare the diagnostic accuracy of the HFA-PEFF and H2FPEF scores. Odds ratios and 95% confidence intervals were calculated to assess risk of being a false negative compared to true positive. We also performed a sensitivity analysis to assess the performance of these scores if 'early HFpEF' was diagnosed if mLAP rose to above 18mmHg, rather than 15mmHg, with fluid challenge as has been previously described.[361-363] P-values of ≤ 0.05 were considered statistically significant. All statistical analysis was performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

5.3 RESULTS

5.3.1 Participant Recruitment and Invasive HFpEF Classification

Of 172 patients screened for inclusion, we included 120 patients in our final study cohort (Figure 1), all of whom completed invasive assessment at the AF ablation procedure. 57 (47.5%) participants had HFpEF according to a mLAP >15mmHg at baseline. After infusion of 500mls saline a further 31 (25.8%) demonstrated LA pressure >15mmHg and were diagnosed with early HFpEF. In total, therefore, 88 (73.3%) participants displayed haemodynamic evidence of HFpEF, whilst 32 (26.7%) had no HFpEF according to invasive haemodynamic criteria (**Figure 2A**).

5.3.2 HFA-PEFF Classification

Figure 2B shows the results of the HFpEF classification according to the HFA-PEFF scoring system. Of the 120 participants, 33 scored ≥5 and were therefore classified as HFpEF, whilst 13 scored ≤1 and were therefore classified as no HFpEF. The remaining 74 participants were classified as intermediate risk for HFpEF. As per the HFA-PEFF scoring system, these intermediate risk patients went on to undergo stress echocardiography. Five patients demonstrated E/E'>15 during exercise and therefore moved into the HFpEF group, whilst the remaining 69 patients remained classified as intermediate probability of HFpEF. In total, 38 (31.7%) had high probability of HFpEF and 82 (68.3%) had low or intermediate probability of HFpEF according to the non-invasive HFA-PEFF scoring system.

Table 2 shows the baseline characteristics, echocardiographic features and invasive haemodynamic measurements of participants according to HFA-PEFF classification. High probability of HFpEF according to the HFA-PEFF scoring system was associated with older age ($p<0.001$), female sex ($p=0.039$) and lower prevalence of alcohol excess ($p=0.018$). High probability of HFpEF was also associated with higher mLAP. On echocardiography, high

probability of HFpEF was associated with significant structural and functional abnormalities of the LA, including increased indexed LA maximum and minimum volumes, reduced LA emptying fraction and reduced LA reservoir, booster and conduit strain. In addition, high probability of HFpEF according to the HFA-PEFF system was associated with structural and functional abnormalities of the left ventricle, involving smaller left ventricular end diastolic volumes, reduced left ventricular mass index, reduced left ventricular longitudinal strain and reduced E/e'.

5.3.3 H_2FPEF Classification

Figure 2C shows the results of the HFpEF classification according to the non-invasive component of the H_2FPEF scoring system. Of the 120 participants, 72 (60%) scored six or more and were therefore classified as high probability of HFpEF, whilst 48 (40%) scored less than six and were therefore classified as intermediate probability of HFpEF.

Table 2 shows the baseline characteristics of the cohort according to each scoring classification system. High probability of HFpEF according to the H_2FPEF score was associated with higher BMI ($p<0.001$) and higher prevalence of several modifiable risk factors including hypertension ($p<0.001$), diabetes ($p=0.008$) and obesity ($p<0.001$). In addition, higher probability of HFpEF was associated with lower prevalence of early HFpEF compared to those with intermediate probability ($p=0.009$). High probability of HFpEF according to the H_2FPEF scoring system was associated only with reduced E/e' and reduced LA reservoir strain on echocardiography. There was no difference in NT-pro BNP between the two H_2FPEF groups.

5.3.4 Sensitivity, Specificity and Accuracy of Non-Invasive Scoring Systems

Figure 3 shows the results of the sensitivity and specificity analyses for the HFA-PEFF system (**Figure 3A**) and the H_2FPEF system (**Figure 3B**). High probability of HFpEF as diagnosed by a score of ≥5 on the HFA-PEFF scoring system had a sensitivity of 39.8% and specificity of 90.6%. The positive predictive value was 92.1% whilst the negative predictive value was 35.3%. High probability of HFpEF as diagnosed by a score of ≥6 on the H_2FPEF scoring system had a sensitivity of 69.3% and specificity of 65.6%, whilst the positive predictive value was 84.7% and the negative predictive value was 43.8%. Overall performance of the two scoring systems on the ROC analysis showed AUC of 66.3% for the HFA-PEFF system and 70.7% for the H2FPEF system (**Figure 3C**). There was no statistically significant difference between the performance of both scores based on the ROC analysis (p=0.636).

5.3.5 Characteristics of False Negatives

Of patients with invasively confirmed HFpEF, a high proportion of participants were incorrectly identified as low or intermediate risk using both scoring systems (60.2% for HFA-PEFF and 30.7% for H2FPEF). **Figure 4** shows the odds of being identified as a false negative or true positive based on individual baseline characteristics. For the HFA-PEFF scoring system, age <60 years (OR 0.041 [0.005-0.326]) and male sex (OR 0.349 [0.136-0.896]) were associated with increased odds of being a false negative rather than a true positive (**Figure 4A**). For the H_2FPEF scoring system, obesity (OR 9.429 [2.565-34.651]) and hypertension (OR 19.040 [5.718-63.399]) were associated with increased odds of being a true positive whilst an invasive diagnosis of early HFpEF (OR 0.103 [0.037-0.292]) was associated with increased odds of being a false negative (**Figure 4B**).

5.3.6 Sensitivity Analysis

In the sensitivity analysis using 18mmHg, rather than 15mmHg, as the diagnostic cutoff for 'early HFpEF' following 500mls saline infusion, 23 'early HFpEF' participants were reclassified as 'no HFpEF'. In total therefore, 65 patients were classified as 'HFpEF' and 55 as 'no HFpEF' according to these altered criteria.

As a result of this change in classification, high probability of HFpEF as diagnosed by a score of ≥5 on the HFA-PEFF scoring system displayed a modestly improved sensitivity of 43.1% and significantly reduced specificity of 81.8% with an overall slightly reduced AUC of 64.2%. Similarly, the H_2FPEF score demonstrated improved sensitivity of 78.5% but reduced specificity of 60% and a slight improvement in overall performance of the score with an AUC of 73.1% (**Figure 5**).

5.4 DISCUSSION

5.4.1 Major Findings

This is the first study to investigate the utility and accuracy of the non-invasive components of the HFA-PEFF and H2FPEF tools for diagnosis of HFpEF in a cohort of patients with symptomatic AF. The study has identified the following important findings:

a) The HFA-PEFF score demonstrates good specificity (91%) but poor sensitivity (40%) and moderate AUC (0.663) for the accurate identification of AF patients with HFpEF, with younger, obese males less likely to be identified using this score.
b) The H_2FPEF score demonstrates better sensitivity (66%), worse specificity (69%) and similarly moderate AUC (0.707) for identification of HFpEF in AF, with early HFpEF patients more likely to be missed by this scoring system
c) Both scoring tools identify a large proportion of AF patients with intermediate probability of HFpEF and would therefore require further invasive testing according to the algorithms,.

Our findings highlight the fact that these scoring tools are limited in their ability to accurately identify patients with HFpEF in the absence of invasive haemodynamic testing in patients with symptomatic AF.

5.4.2 HFA-PEFF Score

The HFA-PEFF score identified 38 patients with high-probability HFpEF after baseline scoring and diastolic stress testing, demonstrating low sensitivity (40%) but high specificity (91%) in this cohort of patients with symptomatic AF. The patients identified as high-probability in this cohort were older and more commonly female. On echocardiography, these patients demonstrated global cardiac structural and functional abnormalities involving increased LV mass coupled with smaller LV cavity size, larger LA volumes and reduced LA function.

Our data suggests that the HFA-PEFF score was highly effective in identifying older female patients with coexistent HFpEF. This is an important strength of the scoring system, as epidemiological studies have shown that older women represent a large proportion of patients with HFpEF.[364] However, there was a large number of false negative results associated with this scoring system, even after utilising exercise echocardiography to identify those with low scores at baseline but abnormal diastolic responses to exercise. These false negatives were commonly younger males. Younger males in this cohort were more likely to be obese. Obesity represents another important risk factor for the development of HFpEF and has been shown to be associated with a unique phenotype of HFpEF, involving reduced NT-proBNP levels, heightened pericardial restriction due to increased epicardial fat and increased ventricular interdependence.[66] Due to use of both NT-pro BNP levels and LA volumes indexed to body surface area, the HFA-PEFF scoring system is less likely to identify these patients, thereby limiting its utility in a cohort of patients with symptomatic AF who commonly exhibit obesity (over one third of this cohort had obesity).

5.4.3 The H_2FPEF Score

The H_2FPEF scoring system identified a much larger cohort of patients with HFpEF and therefore demonstrated improved sensitivity (69.3%) for the diagnosis of HFpEF compared with the HFA-PEFF tool. However, this scoring system also demonstrated a reduced specificity, reaching only 65.6%. The incorporation of a relatively low age limit (60 years) and obesity into this scoring system meant that there were significantly fewer younger patients with obesity who were missed by this scoring system. Indeed, patients with a high-probability of HFpEF were characterised by increased BMI and a higher prevalence of obesity as well as higher prevalence of other risk factors including hypertension and diabetes. Although the sensitivity of this tool was improved, there remained a relatively high number of false negatives. These were more commonly patients with early HFpEF, with normal haemodynamics at baseline but abnormal responses to saline infusion. This may be unsurprising given that the scoring system was developed using invasive exercise testing rather than saline infusion for the diagnosis of early HFpEF.[208]

5.4.4 Invasive Diagnosis of HFpEF

Our data suggests that invasive assessment should remain the gold-standard method to diagnose HFpEF in patients with AF. However, access to invasive haemodynamic testing with appropriate provocative testing continues to remain a challenge in the day-to-day clinical management of patients with AF. Typical invasive testing for diagnosis of HFpEF involves right heart catheterisation with simultaneous bicycle ergometry providing the provocation to identify those with early HFpEF. The nature of this invasive testing means that it is generally restricted to super-specialised centres which are not easily accessible to the majority of patients.

In this study, we show that appropriate invasive testing with provocation can be done in the cardiac electrophysiology laboratory with fluid infusion used as an alternative to exercise

during AF ablation procedures. This has the potential, therefore, to significantly broaden access to invasive haemodynamic testing for HFpEF diagnosis to all those undergoing such procedures. Given the fact that AF ablation requires pressure-guided transeptal access to the left heart, obtaining LA pressures in these circumstances is relatively straightforward and would not be associated with any increased procedural risk. In addition, the use of fluid infusion rather than exercise allows the procedure to be carried out under general anaesthetic. Whilst there is some evidence to suggest that fluid infusion for the diagnosis of early HFpEF may have inferior sensitivity compared to exercise right heart catheterisation,[361] it has been shown to exhibit excellent specificity, therefore limiting the proportion of patients who would be incorrectly diagnosed with HFpEF.[365] We therefore describe a straightforward protocol for the invasive diagnosis of HFpEF in patients undergoing AF ablation procedures which has the potential to be used across all EP centres worldwide.

5.4.5 Clinical Implications

The overall AUCs for the two scoring systems suggest that these non-invasive tools may be of only limited value for the accurate diagnosis of HFpEF in patients with symptomatic AF. Indeed, in well-phenotyped independent cohorts of patients with suspected HFpEF, both scoring systems have been found to have significantly higher AUCs than those computed in this study, suggesting that scoring systems may require additional refinement in patients with AF.[357,358] It should be noted, of course, that both scoring systems advocate the use of additional invasive testing in cases where non-invasive testing is either inconclusive or suggestive of intermediate probability of HFpEF. In our cohort, a large proportion of patients had intermediate probability of HFpEF and would require additional invasive testing, highlighting the difficulty of diagnosing HFpEF non-invasively in patients with AF. Derivation of novel

scoring systems specific for patients with AF may be possible in larger cohorts of patients in the future.

Although these scoring tools may not be helpful for accurately diagnosing HFpEF, our data suggests that these tools may be helpful to identify AF patients with subclinical abnormalities associated with worse prognostic outcomes. High-probability of HFpEF was associated with elevated LA pressures and reduced LA function. These characteristics have been shown to be associated with mortality, morbidity and increased AF recurrence following AF ablation.[211,286,366] In a similar analysis in patients with pre-clinical HFpEF and largely without AF, high-probability of HFpEF was found to be associated with left atrial dilatation, left ventricular hypertrophy and more severe diastolic dysfunction.[367] These scoring systems may therefore be useful as an additional **tool to** identify patients at increased risk of poor clinical outcomes.

5.5 CONCLUSIONS

In a cohort of patients with symptomatic AF and a high prevalence of haemodynamic HFpEF, the HFA-PEFF and H_2FPEF scoring systems were of moderate accuracy for diagnosing HFpEF. The HFA-PEFF system demonstrated good specificity but poor sensitivity, frequently omitting younger male patients with obesity phenotype HFpEF. The H_2FPEF displayed better sensitivity but worse specificity and commonly omitted patients with normal haemodynamics at rest but abnormal haemodynamics with saline infusion (early HFpEF). However, high-probability of HFpEF according to both scoring systems was associated with important prognostic characteristics including elevated LA pressures and reduced LA function. Taken together this data highlights the fact that invasive haemodynamic diagnosis of HFpEF remains the optimum method to diagnose HFpEF in patients with AF and that non-invasive scoring tools should be used with caution in this cohort of patients.

5.6 TABLES AND FIGURES

Table 1

HFA-PEFF and H2FPEF scoring systems. Breakdown of the two scoring systems detailing points allocated for each baseline or clinical characteristic.

HFA-PEFF Score			**H_2FPEF Score**	
Functional	• Septal e'<7cm/s OR • Lateral e' <10cm/s OR • Average E/e' ≥ 15 OR • TR Velocity >2.8m/s	2	**Hypertension**	1
	• Average E/e' 9-14 OR • GLS <16%	1	**Heavy (BMI>30kg/m^2)**	2
Morphological	• LAVI >34ml/m^2 OR • LVMI >149/122 g/m^2 (m/w) and RWT >0.42	2	**Filling Pressures (E/e'≥9)**	1
	• LAVI 29-34ml/m^2 OR • LVMI?115/95g/m^2 (m/w) OR • RWT>0.42 OR • LV wall thickness ≥12mm	1	**Pulmonary Hypertension (PASP>35)**	1
Biomarker	• NT-proBNP >220pg/ml (in SR) OR • NT-proBNP>660pg/ml (in AF)	2	**Elderly (Age>60)**	1
	• NT-proBNP >125-220 pg/ml (in SR) OR • NT-proBNP 365-660pg/ml (in AF)	1	**Atrial Fibrillation**	3
Total Score	• 0-1 = Low • 2-4 = Intermediate • 5-6 = High		• 0-2 = Low • 3-5 = Intermediate • 6-9 = High	

Abbreviations: TR – Tricuspic regurgitation, GLS – global longitudinal strain, LAVI – left atrial volume indexed, LVMI – left ventricular mass index, RWT – relative wall thickness, LV – left ventricular, PASP – pulmonary artery systolic pressure.

Table 2

Baseline characteristics and transthoracic echocardiographic parameters according to high or low probability of HFpEF using the HFA-PEFF scoring system.

	HFA-PEFF Score		
	<5 (n=82)	**≥5 (n=38)**	**p-value**
Baseline Characteristics			
Age, y	60.0±11.0	72.0±5.8	<0.001
Male Gender, n (%)	64 (78.0)	22 (57.9)	0.039
BMI (kg/m^2)	29.1±4.9	28.3±4.5	0.404
Early HFpEF, n (%)	20 (24.4)	11 (28.9)	0.759
Persistent AF, n (%)	40 (48.8)	21 (55.3)	0.642
Redo Ablation, n (%)	35 (42.7)	12 (31.6)	0.338
Cardiovascular Risk Factors			
Hypertension, n (%)	55 (67.1)	29 (76.3)	0.416
Diabetes, n (%)	6 (7.3)	8 (21.1)	0.062
Obesity, n (%)	32 (39.0)	11 (28.9)	0.386
Stroke, n (%)	6 (7.3)	3 (7.9)	>0.999
CAD, n (%)	4 (4.9)	6 (15.8)	0.796
OSA, n (%)	23 (28.0)	11 (28.9)	>0.999
Alcohol Excess, n (%)	41 (50)	10 (26.3)	0.018
Non-Invasive Diagnostics			
Nt-pro BNP, pg/mL	130 (61-269)	513 (262-1081)	<0.001
MLAP, mmHg	13.4±4.4	15.4±3.6	0.010
LVEF, %	57.5±5.7	57.2±5.9	0.799
LVEDV, mm	99.3±31.4	84.3±27.5	0.023
LVMI, g/m^2	79.5±19.6	92.1±25.7	0.012
LVS, %	16.2±3.7	14.3±2.5	0.011
E/E'	8.3±2.6	11.7±3.2	<0.001
LAMax, mL	31.4±9.0	38.7±9.9	<0.001
LAMin, mL	18.7±7.3	26.8±8.1	<0.001
LAEF, %	41.1±13.4	31.2±9.3	<0.001
LA Reservoir Strain, %	23.2±9.8	15.3±5.9	<0.001
LA Booster Strain, %	12.2±5.9	7.7±3.3	<0.001
LA Conduit Strain, %	14.1±5.6	10.2±3.2	<0.001

Abbreviations: BMI – body mass index, HFpEF – heart failure with preserved ejection fraction, AF – atrial fibrillation, CAD – coronary artery disease, OSA – obstructive sleep apnoea, NT-pro BNP – N-terminal pro b-type natriuretic peptide, LVEF – left ventricular ejection fraction, LVEDV – left ventricular end diastolic volume, LVMI – left ventricular mass index, LA – left atrium, LAEF – left atrial emptying fraction.

Table 3

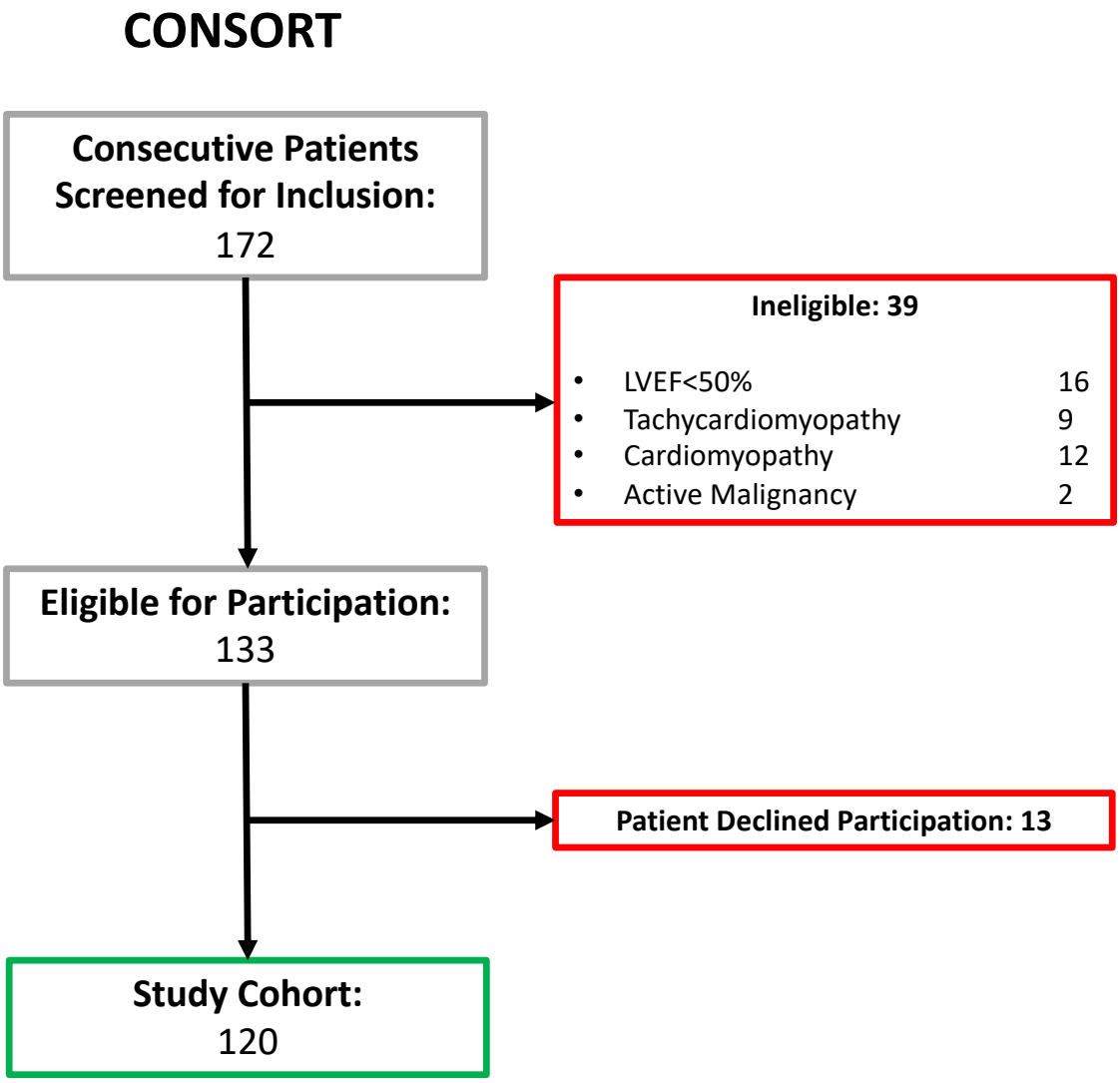
Baseline characteristics and transthoracic echocardiographic parameters according to high or low probability of HFpEF using the H_2FPEF scoring system.

	H2FPEF Score		
	<6 (n=48)	**≥6 (n=72)**	**p-value**
Baseline Characteristics			
Age, y	61.5±10.7	65.3±11.2	0.059
Male Gender, n (%)	39 (81.3)	47 (65.3)	0.089
BMI (kg/m^2)	26.2±3.4	30.7±4.8	<0.001
Early HFpEF, n (%)	19 (39.6)	12 (16.7)	0.009
Persistent AF, n (%)	23 (47.9)	38 (52.8)	0.737
Redo Ablation, n (%)	18 (37.5)	29 (40.3)	0.909
Cardiovascular Risk Factors			
Hypertension, n (%)	18 (37.5)	66 (91.7)	<0.001
Diabetes, n (%)	1 (2.1)	13 (18.1)	0.008
Obesity, n (%)	4 (8.3)	39 (54.2)	<0.001
Stroke, n (%)	6 (12.5)	3 (4.2)	0.154
CAD, n (%)	3 (6.3)	7 (9.7)	0.738
OSA, n (%)	11 (22.9)	23 (31.9)	0.309
Alcohol Excess, n (%)	25 (52.1)	26 (36.1)	0.093
Non-Invasive Diagnostics			
Nt-pro BNP, pg/mL	237 (100-479)	223 (93-552)	0.725
MLAP, mmHg	11.8±3.2	15.5±4.2	<0.001
LVEF, %	58.1±6.0	57.0±5.5	0.382
LVEDV, mm	101.2±31.6	90.5±30.0	0.105
LVMI, g/m^2	79.6±19.9	86.1±23.7	0.118
LVS, %	16.5±3.8	15.0±3.1	0.068
E/E'	7.5±2.1	10.7±3.2	<0.001
LAMax, mL	32.8±9.0	34.4±10.5	0.404
LAMin, mL	19.6±7.4	22.4±8.9	0.078
LAEF, %	40.7±12.5	36.1±13.2	0.074
LA Reservoir Strain, %	23.9±10.1	18.7±8.6	0.007
LA Booster Strain, %	12.0±6.0	10.2±5.4	0.158
LA Conduit Strain, %	14.2±6.1	12.1±4.6	0.099

Abbreviations: BMI – body mass index, HFpEF – heart failure with preserved ejection fraction, AF – atrial fibrillation, CAD – coronary artery disease, OSA – obstructive sleep apnoea, NT-pro BNP – N-terminal pro b-type natriuretic peptide, LVEF – left ventricular ejection fraction, LVEDV – left ventricular end diastolic volume, LVMI – left ventricular mass index, LA – left atrium, LAEF – left atrial emptying fraction.

Figure 1

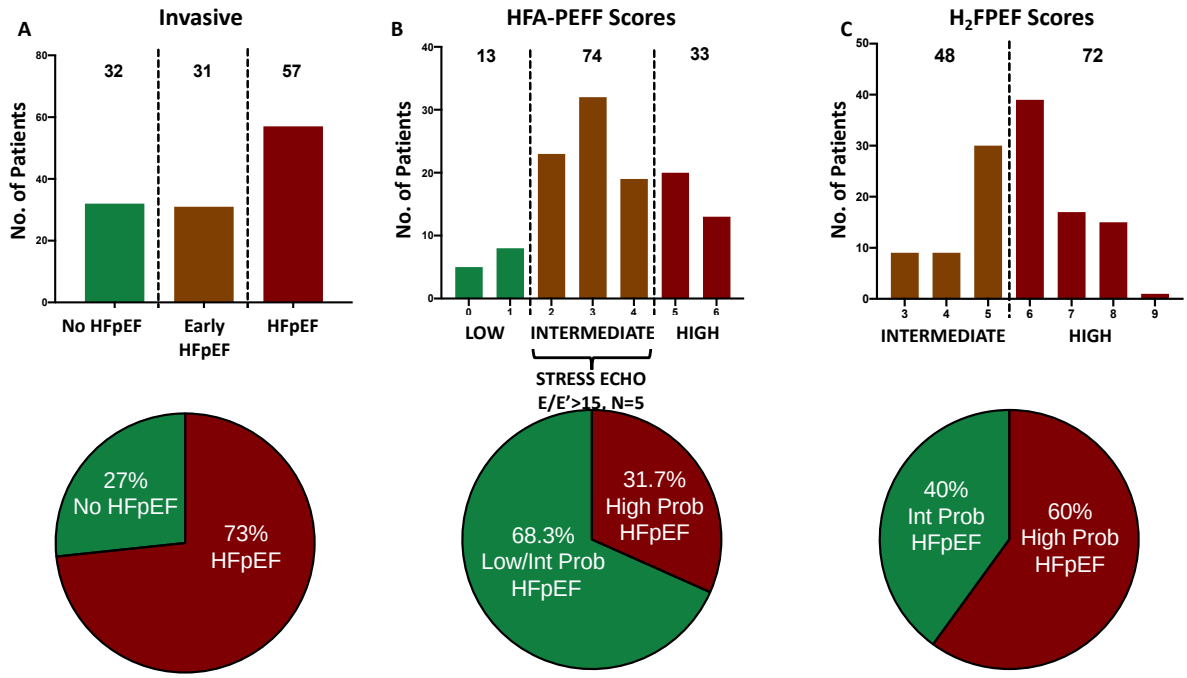
Study CONSORT diagram. Of 172 patients screened for inclusion, 39 were excluded for prespecified exclusion criteria. An additional 13 chose not to participate meaning in total 120 patients were included in the study. LVEF – left ventricular emptying fraction.



Abbreviation: LVEF – left ventricular emptying fraction.

Figure 2

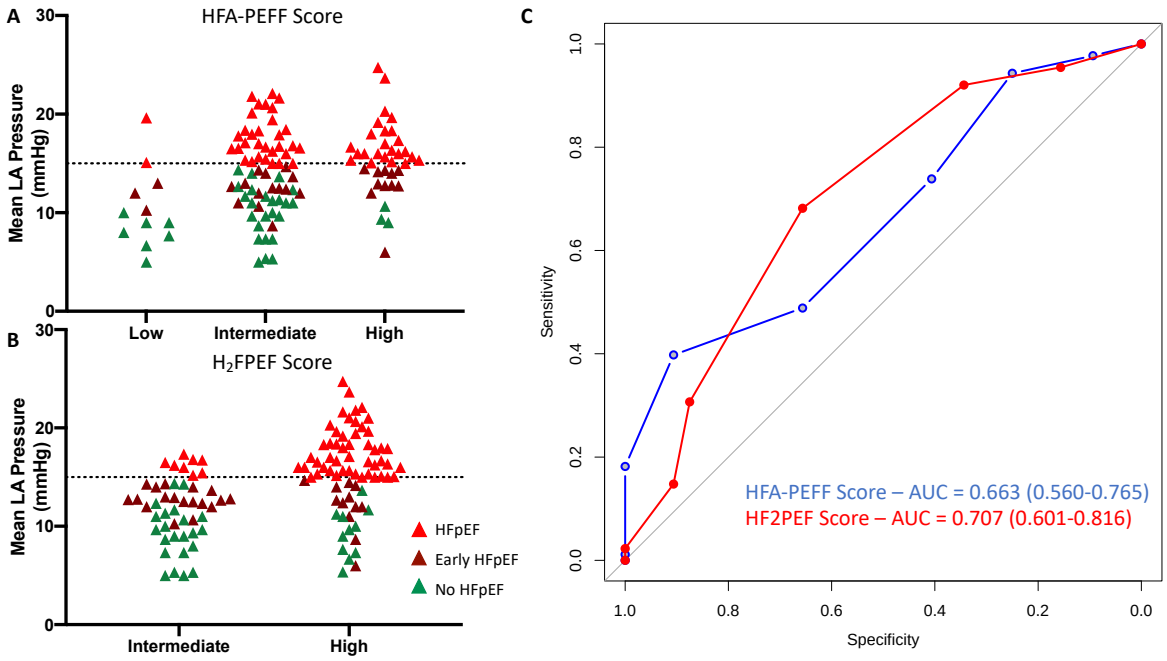
Scoring algorithm outcomes. A) Invasive diagnosis identified 57 HFpEF and 31 early HFpEF patients meaning a total of 88 HFpEF patients altogether. B) The HFA-PEFF score identified 13 low probability, 74 intermediate probability and 33 high probability cases. Of the intermediate cases, an additional 5 moved into the high probability group after exercise echocardiography.C) The H2FPEF score identified 72 high probability of HFpEF patients and 48 patients with intermediate probability of HFpEF.



Abbreviation: HFpEF – heart failure with preserved ejection fraction

Figure 3

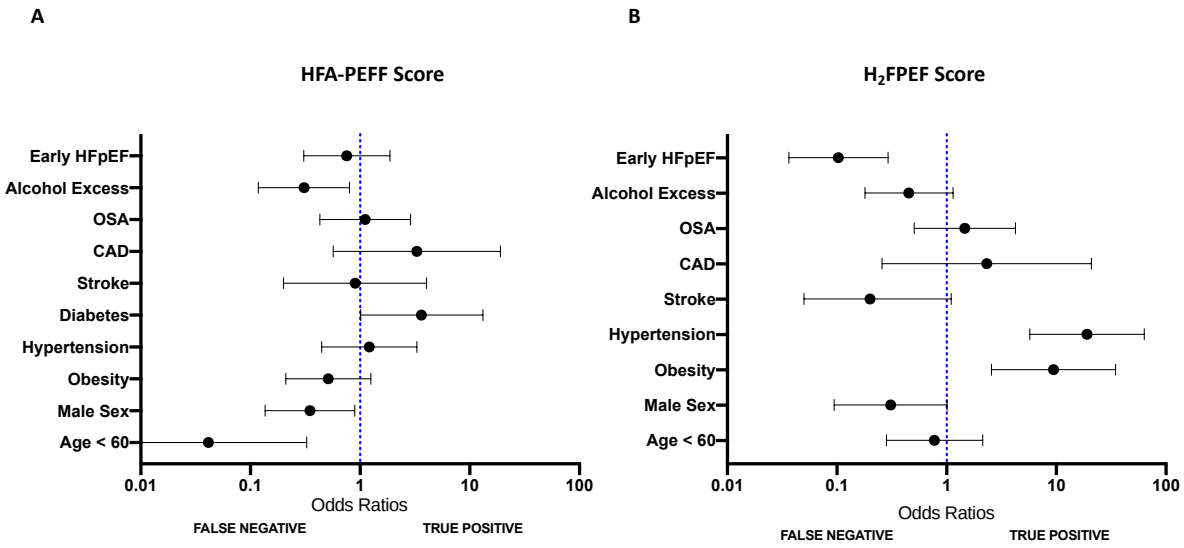
Sensitivity and specificity analysis. A) The HFA-PEFF score identified a large number of patients with HFpEF as low or intermediate risk of HFpEF. B) The H_2FPEF score also identified a significant proportion of false negatives which were mainly patients with early HFpEF (mLAP rising above 15mmHg with fluid infusion). C) Overall performance of the scores is demonstrated in the ROC curves with moderate AUCs for both scoring tools.



Abbreviations: HFpEF – heart failure with preserved ejection fraction, AUC – area under the curve, LA. – left atrium.

Figure 4

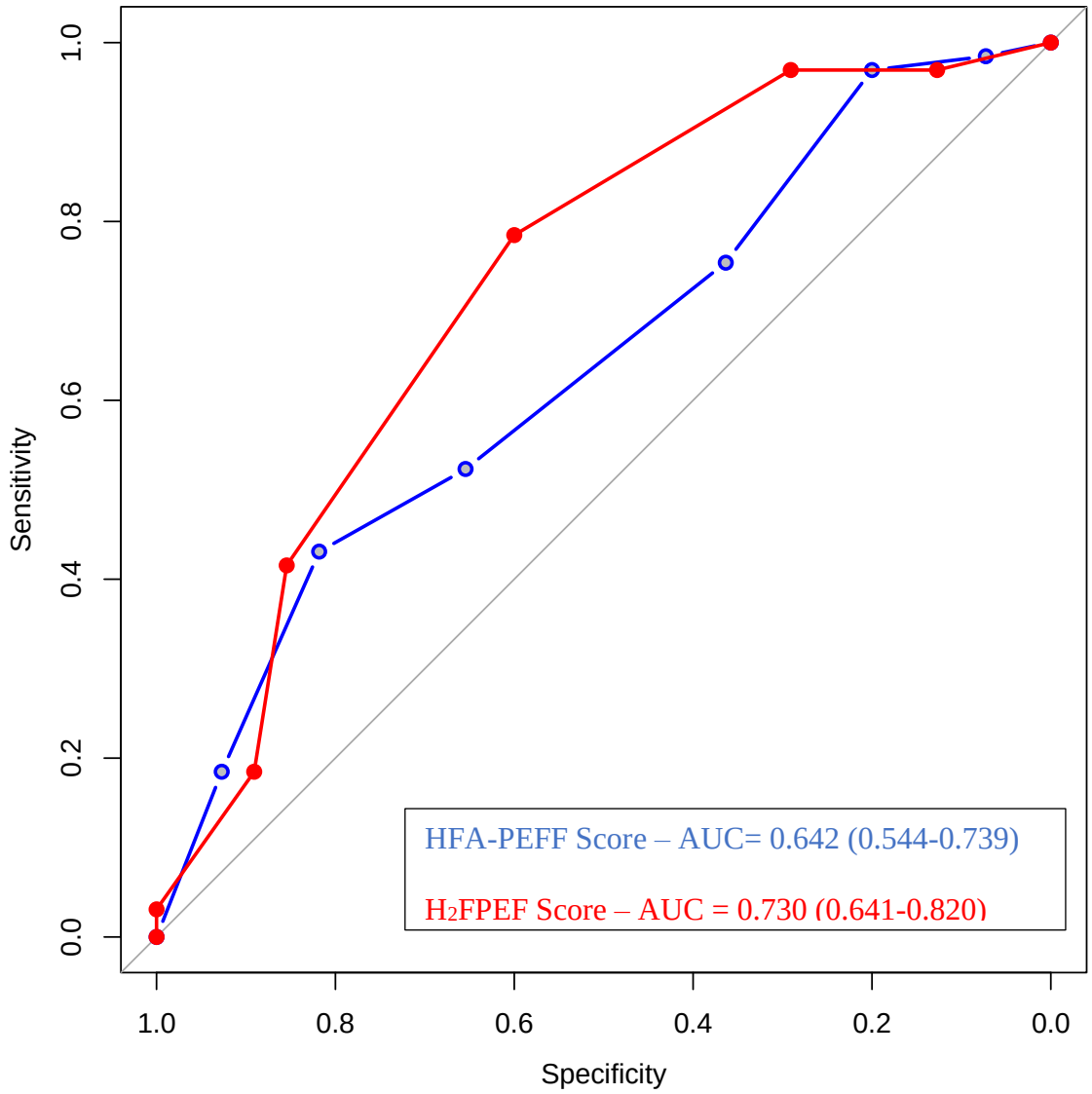
Characteristics of the false negatives using both scoring tools. A) Characteristics at increased risk of being incorrectly identified as 'no HFpEF' using the HFA-PEFF score were age<60 years, male sex, and a history of alcohol excess. B) Using the H_2FPEF score, the only characteristic at increased risk of being a false negative was a diagnosis of early HFpEF on invasive testing.



Abbreviations: HFpEF – heart failure with preserved ejection fraction, OSA – obstructive sleep apnoea, CAD – coronary artery disease.

Figure 5

ROC Curves for Sensitivity Analysis in which early HFpEF diagnosed when mLAP rises above 18mmHg following 500 mls fluid infusion.



CHAPTER 6 Exercise Echocardiography to Assess the Influence of Left Atrial Function on Exercise Intolerance in Patients with Symptomatic AF

6.1 INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia with an estimated worldwide prevalence of 53 million.[368] There is increased risk of mortality[369] as well as significant morbidity and reduced quality of life amongst patients with AF; 62% of patients with AF demonstrate symptoms with 16.5% experiencing severe or disabling symptoms.[31] Whilst palpitations are the most frequently reported symptom of AF, dyspnoea with exertion and exercise intolerance are highly prevalent and contribute significantly to reduced quality of life.[31]

The mechanisms of exercise intolerance in AF remain poorly understood, particularly in patients with preserved left ventricular ejection fraction (LVEF).[218] The loss of atrial systole during AF results in lower cardiac output and exercise tolerance. However, the atrial contribution to left ventricular (LV) filling during AF continues through its reservoir and conduit capacities. Left atrial (LA) reservoir function and emptying volumes are typically reduced in the presence of atrial disease and are associated with impaired exercise tolerance.[370,371] Similarly, in patients with heart failure (HF), LA mechanical dysfunction at rest is associated with low exercise tolerance.[226] However, the data on how the LA responds to exercise during sinus rhythm and AF is limited.

Our aims were twofold; (i) evaluate the LA response during exercise amongst patients in SR and AF at the time of assessment, and (ii) amongst patients in SR, to evaluate the association between LA function during exercise and exercise tolerance. We hypothesised that

reduced LA function with exercise correlates with reduced exercise capacity in patients with AF and preserved LVEF.

6.2 METHODS

6.2.1 Study Design

This prospective clinical study was undertaken at the Centre for Heart Rhythm Disorders (CHRD), University of Adelaide. The study protocol was reviewed and approved by the Human Research Ethics Committees of the Central Adelaide Local Health Network and the University of Adelaide. The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12620000639921).

6.2.2 Study Population

We prospectively recruited consecutive adult patients (>18 years) with symptomatic paroxysmal or persistent AF due to undergo an AF ablation procedure. Patients were excluded from participation for the following reasons: 1) reduced LV function (ejection fraction <50%), 2) prior diagnosis of a cardiomyopathy, 3) moderate-to-severe valvulopathy, 4) inability to perform cardiopulmonary exercise testing to completion, 5) inability to consent, 6) uncontrolled resting heart rate and 7) poor transthoracic echocardiography (TTE) imaging either at rest or during exercise.

6.2.3 Study Protocol

Participants underwent cardiopulmonary exercise testing (CPET) for objective assessment of exercise capacity in addition to exercise echocardiography. Patients presented for CPET and exercise echocardiography on the same day. Exercise testing was performed in a fasting state and off rate-controlling and anti-arrhythmic medications (withheld for 48 hours). Exercise

echocardiography was performed first, followed by CPET. In order to assess the influence of cardiac rhythm on exercise capacity, participants were grouped according to the rhythm they presented with on the day of exercise testing (AF vs SR).

6.2.4 Resting and Exercise TTE

Resting and exercise TTE were performed on a dedicated supine cycle ergometer in the left lateral decubitus position. TTE was performed according to a study specific protocol by an experienced sonographer. Images obtained included apical 4- and 2-chamber views and focussed on LV and LA structure and function. LV systolic function (LVSF) was measured by the Simpson's biplane method for calculation of ejection fraction (LVEF). Maximum (LA_{max}) and minimum (LA_{min}) LA volumes were obtained using the biplane area-length method and were indexed according to body surface area. Left atrial emptying fraction (LAEF) was calculated using the formula: $(LA_{max} - LA_{min})/LA_{max}$ x 100. Early LV filling velocities (E) using flow Doppler imaging and early diastolic mitral annular velocities (e') using tissue Doppler imaging were measured. Average E/e' was calculated as the mean of septal and lateral E/e'. Left atrial strain measurements using speckle tracking echocardiography were obtained offline using dedicated software (AFI LA, GE EchoPAC) according to standardised guidelines[372].

The exercise protocol involved cycling at a constant pedal speed of 60 revolutions per minute with incremental increases in power of 10 Watts/minute. Focussed LA and LV TTE images were obtained at peak exercise defined as the point of fusion of the E and A waves. LVEF, E/e', TR V_{max}, LV global longitudinal strain (LV GLS), LAEF and reservoir strain measurements were obtained at peak exercise. Booster and conduit strain were not assessed due to fusion of reservoir and booster components at peak exercise. All measurements were

averaged over 3 cardiac cycles in sinus rhythm and 6 cycles in AF and verified by a second experienced and independent reviewer.

6.2.5 Cardiopulmonary Exercise Testing

Symptom-limited CPET was performed on a dedicated upright cycle ergometer. Twelve (12) lead ECG was attached and monitored throughout to assess heart rate and rhythm. Pulmonary gas exchange was measured continuously using a metabolic cart (Vyntus CPX, Vyaire Medical). Oxygen consumption (VO_2) and carbon dioxide (VCO_2) production were averaged over 20 second intervals and adjusted to body mass (ml/kg/min). Prior to exercise, participants underwent a 5-minute rest period to obtain baseline values. Participants were then asked to begin cycling at a power of 20 Watts. Power was incrementally increased by 10 Watts per minute. Peak exercise was defined as the point at which the participant felt the need to stop due to symptoms or fatigue. A maximal effort was defined as having reached a respiratory exchange ratio >1.05. Peak oxygen consumption (VO_{2peak}) was identified as the highest attained VO_2 during exercise. A VO_{2peak} <20ml/kg/min (Weber Class B) was considered objective evidence of reduced exercise capacity as previously described.[373]

6.2.6 Statistical Analyses

Continuous variables were reported as means ± standard deviation for normally distributed data or median and interquartile range for non-normally distributed data. Categorical variables were reported as frequencies and percentages. Continuous variables were compared between groups using independent-samples Student t-tests or Mann Whitney U tests as appropriate. Categorical variables were compared between groups using the chi-square test or Fisher's exact test. Comparisons between resting and exercise TTE parameters were made using paired-samples Student t-tests. Test and retest reliability for LA and LV volumes measured during

exercise was assessed using Pearson Correlation Coeeficient. Associations between VO_{2peak} and exercise echocardiography parameters were assessed using adjusted linear regression models. Model 1 adjusted for age and gender, whilst model 2 adjusted for age, gender and resting LVEF. P-values of ≤0.05 were considered statistically significant. All statistical analysis was performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

6.3 RESULTS

6.3.1 Participant Recruitment

Of 177 consecutive symptomatic AF patients, 39 were excluded for pre-specified exclusion criteria and a further 13 declined to participate. The remaining 125 patients consented to undertake the protocol and presented for exercise testing. However, a further 20 patients were excluded from the analysis, due to inability to complete CPET. In total, therefore, 105 patients were included in the analysis with 74 presenting in SR and 31 presenting in AF (**Figure 1**).

6.3.2 Baseline Characteristics

Table 1 compares the patient demographics and baseline characteristics of patients presenting in SR and AF. Patients in AF were more likely to have persistent AF and take loop diuretics. There were no other significant differences in demographics, risk factors or medications taken between the 2 groups.

6.3.3 Cardiopulmonary Exercise Testing

All 105 participants included in the final analysis satisfactorily completed the CPET protocol achieving maximal effort defined as an RER>1.05 and volitional exhaustion. There were no major cardiac events or sustained ventricular arrhythmias during CPET. Overall, mean VO_{2peak}

in the entire cohort was 21.3±7.4ml/kg/min with 45 (42.9%) meeting objective criteria for reduced exercise tolerance (VO_{2peak}<20ml/kg/min).

Comparing AF with SR, participants presenting in AF had significantly lower cardiopulmonary reserve, demonstrating reduced VO_{2peak} (18.4±5.6 vs 22.5±7.7mL/Kg/min, p=0.003, **Figure 2A**) and percent of predicted VO_2 (82.7±18.7 vs 96.4±25.5%, p=0.003). Of patients presenting in AF, 17 (54.8%) demonstrated reduced exercise tolerance whilst 28 (37.8%) of patients in SR had reduced exercise tolerance (p=0.165). Patients in AF had higher resting heart rates (83.8±15.2 vs 64.4±12.1bpm, p<0.001) but there was no difference in maximal heart rate achieved during CPET (139.5±35.0 vs 133.2±26.2bpm, p=0.390) or overall chronotropic response (59.4±33.3 vs 66.4±26.6bpm, p=0.34).

6.3.4 Resting and Exercise LA Function

Table 2 shows the resting and exercise echocardiography results according to presenting rhythm. At rest, patients in AF demonstrated reduced LAEF and reservoir strain. With exercise, LAEF failed to augment amongst those in AF but significantly increased in those presenting in SR (**Figure 2B**). Overall LAEF reserve (change in LAEF with exercise) was significantly higher with SR compared with AF (+6.9±9.0 vs +0.7±10.0, p=0.009). Volumetric LA analysis revealed that participants in AF had larger LA volumes at rest but there were no significant differences in LA_{MAX} or LA_{MIN} with exercise. Participants in SR, on the other hand, demonstrated significant LA_{MAX} dilatation but no difference in LA_{MIN} with exercise (**Figure 2C**). Similarly, LA reservoir strain was significantly reduced at rest in patients with AF and failed to augment with exercise (**Figure 2D**) with LA reservoir strain reserve (change in reservoir strain with exercise) significantly higher in the SR group (+4.1±7.3 vs -0.6±4.6%, p=0.002).

6.3.5 Resting and Exercise LV Function

Compared to patients in SR, patients in AF demonstrated significantly reduced LVEF and GLS at rest. During exercise, neither LVEF nor GLS augmented amongst patients in AF but there was significant augmentation amongst patients in SR (**Figure 2E and 2F**). Underpinning these differences in LV function with exercise was a reduction in LVESV during exercise amongst patients in SR that was not observed amongst those in AF. In terms of diastolic LV function, E/e' was no different between AF and SR and we did not observe any statistically significant differences in E/e' between rest and exercise in either group.

6.3.6 Association between LA function and exercise capacity

Of the 74 patients presenting in SR, 28 (38.7%) demonstrated objective evidence of reduced exercise capacity (VO_{2peak} <20ml/kg/min). Table 3 shows the association between resting and exercise LA parameters and VO_{2peak} in the 74 patients presenting in SR. Whilst there was no relationship between VO_{2peak} and LA volumes, VO_{2peak} demonstrated significant associations with resting LAEF, reservoir strain and booster strain in model 1. VO_{2peak} was also significantly associated with LAEF and reservoir strain during exercise in model 1. In model 2, VO_{2peak} remained significantly associated with resting LAEF (**Figure 3A**) and reservoir strain (**Figure 3B**) in addition to reservoir strain during exercise (**Figure 3C**).

6.3.7 Test-Retest Reliabilty

The test-retest correlation coefficient for LA_{MAX} during exercise was 0.84. These measures therefore demonstrated good reliability. Similarly, the correlation coefficient for LVEDV during exercise was 0.85, also demonstrating good reliability.

6.4 DISCUSSION

6.4.1 Major Findings

This prospective clinical study utilised exercise echocardiography and CPET to investigate LA function during exercise and its association with exercise intolerance in patients with symptomatic AF. The study has identified several novel findings:

1. Amongst AF patients in SR, the LA response to exercise is characterised by an augmentation of LA emptying fraction, primarily through an increase in LA filling and a concomitant increase in LA reservoir strain.
2. In contrast, patients in AF demonstrate reduced LA and LV function at rest and a failure to augment LA emptying and LV function with exercise. These differences are observed in parallel with reduced exercise capacity on CPET.
3. A high proportion (37.8%) of AF patients presenting in SR exhibit objective evidence of reduced exercise capacity. Reduced exercise capacity in AF patients maintaining SR is associated with reduced resting and exercise LAEF and reservoir strain, independent of LV function.

6.4.2 Atrial Response to Exercise in Sinus Rhythm

The influence of AF on LA mechanical function at rest has been well described using transthoracic echocardiography and cardiac magnetic resonance imaging. Our study extends on previous findings by using exercise echocardiography to evaluate the LA response to exercise, which has not been well described during exercise, AF patients in SR demonstrate a capacity to increase LAEF, primarily due to an increase in LA_{max}, with stable LA_{min}. The increase in LAEF is frequently observed during exercise amongst healthy individuals. However, there is limited data on the atrial response to exercise in AF patients. This study demonstrates that, despite the presence of underlying atrial disease promoting arrhythmia, AF

patients in SR retain the capacity to increase the atrial contribution to LV filling during exercise. Notably, our data show that LAEF is enhanced through an increase in LA_{max} in the absence of a reduction in LA_{min}. This pattern of response is consistent with that shown in healthy participants without AF.[374] In addition to increased LAEF, we also demonstrated an LA strain reserve during exercise in patients who were in SR, consistent with that observed elsewhere in the presence of HF[375].

6.4.3 Atrial Response to Exercise in AF

With the loss of atrial systole during AF, the atrial contribution to the cardiac response during exertion is frequently overlooked. We provide novel information on the atrial contribution to LV filling amongst patients in AF at the time of assessment. As expected, patients in AF had larger LA size at rest and reduced LA function, both on volumetric and strain measures. In contrast to patients in SR, those in AF showed little ability to augment LAEF or LA strain with exercise. The limited ability to dilate the LA with the onset of exercise may contribute to the lower exercise tolerance observed with AF, in addition to the loss of LA contraction. We also demonstrated a limited LV response to exercise with a blunted LVEF response and GLS reserve. We speculate that the absence of LA contraction may limit LV filling and preload, subsequently limiting stroke volume.[376-380]. However, it may also be that reduced LV contraction limits the apical movement of the atrio-ventricular plane, limiting the aspiration of blood from the pulmonary veins into the LA. Overall, we show that patients presenting in AF rhythm demonstrate significantly reduced exercise capacity on CPET compared to those presenting in SR, despite no difference in exercise heart rate or underlying risk factors. Based on this data, we attribute this limited exercise capacity, in part, due to restricted augmentation of LA filling, in addition to the absence of atrial contraction. Our data therefore highlights the influence AF rhythm independent of rate control on cardiac function during exercise and

overall exercise capacity. We also provide further mechanistic evidence to support previous findings that exercise capacity may be improved through rhythm control strategies including DC cardioversion,[381-383] antiarrhythmic drugs[217] and AF ablation.[384,385]

6.4.4 LA Function and Exercise Capacity in Sinus Rhythm

Of those presenting in SR, we found that more than one third demonstrated objective evidence of reduced exercise capacity according to the Weber Classification System.[373] This finding highlights the fact that for many AF patients, exercise intolerance is related to factors beyond rhythm control, as has previously been described.[218] Our linear regression analysis suggests that LA function at rest and during exercise are strongly associated with exercise capacity in these patients.

The healthy LA contributes 15-30% of overall LV stroke volume[23] and it is known that the loss of atrial activity characterised by the rhythm of AF results in reduced cardiac output during exercise.[24] However, exercise intolerance is frequently reported in patients who maintain SR and may be the consequence of underlying atrial disease mechanisms. In this study, we demonstrate that reduced LA reservoir and emptying function in SR is associated with reduced exercise capacity, independent of LV function. This findings mirrors that from patients HF across a broad range of ejection fraction.[226,375] It is well-established that AF patients demonstrate impaired LA function and LA strain in SR and these changes have been shown to be associated with important prognostic effects including mortality and stroke.[366,386] However, the relationship between LA function and exercise capacity in patients with AF has not been established. Furthermore, to our knowledge, this is the first study to correlate LA function during exercise with objective assessment of exercise capacity. Importantly, we show that impaired LA function during exercise also correlates closely with reduced exercise

capacity, confirming the likely contribution of LA function to overall cardiac output during exercise.

6.4.5 Atrial Dysfunction and the Interaction Between AF and HF

Whilst LA mechanical dysfunction is an established hallmark of AF, it is increasingly recognised as an important feature of heart failure with preserved ejection fraction (HFpEF). Growing evidence suggests that AF and HFpEF are closely related and commonly coexist due to the presence of atrial dysfunction.[13,28] In heart failure (including reduced and preserved ejection fraction), it has been shown that impaired LA function is associated with reduced stroke volume and cardiac output at peak exercise.[387] Our findings that LA dysfunction is closely related to exercise intolerance in patients with AF and preserved LVEF strengthens the likelihood that 'early' HFpEF may be an underlying feature of exercise intolerance in symptomatic AF. It therefore follows that treatment of underlying HFpEF may result in improvements in exercise capacity for these patients. Interestingly, a recent small randomised trial suggested that AF ablation for patients with AF and haemodynamically confirmed HFpEF resulted in significant improvements in invasive haemodynamics compared to medical therapy and this was associated with improvements in maximal exercise capacity.[293] In addition, there is evidence that exercise training can improve LA function resulting in exercise capacity gains in heart failure with mid-range ejection fraction patients.[388] There is further promise in the development of SGLT2-inhibitors as a treatment for HFpEF[257,258]; future work should investigate the effect of lifestyle changes and medications on cardiac function and exercise tolerance in patients with AF.

6.5 LIMITATIONS

We recognise several limitations that should be considered when interpreting this study. We used 2D transthoracic echocardiography, which may not provide the accuracy of exercise cardiac magnetic resonance imaging (CMR). Validation of these findings with exercise CMR should be considered. The absence of direct assessment of stroke volume or invasive haemodynamic limits our interpretation of the response to exercise. Studies in which simultaneous assessment of invasive pressures and imaging would be an advantage in this setting. We did not compare patients in AF after reversion to sinus rhythm. Therefore, these findings do not provide evidence that restoration of sinus rhythm would restore LA function during exercise. Likewise, we did not assess other features of atrial disease, such as fibrosis or electroanatomical remodelling between groups, which may influence the atrial response to exercise. Our sample size was relatively small, which may open the possibility for type II error in comparing between and within-groups. In addition we did not compare the atrial response to exercise with non-AF control subjects, However, the atrial response to exercise in peoplewithout AF has been described previously. [374,387]

6.6 CONCLUSIONS

In patients with symptomatic AF, the maintenance of sinus rhythm is associated with preserved capacity to augment LA filling and function during exercise. In contrast, LA reservoir function is limited at rest and during exercise amongst patients in AF at the time of assessment. These divergent responses parallel a reduced VO_{2peak} amongst patients in AF. Amongst patients who are in SR, exercise intolerance was observed in 39% of patients. Exercise intolerance amongst AF patients maintaining SR is associated with reduced LA reservoir strain and emptying fraction at rest and during exercise, independent of resting or exercise LV function. Taken together our data highlight the potential role of LA function in contributing to maximal exercise

capacity in patients with AF. Future research investigating the influence of novel therapies for AF on LA function at rest and during exertion may improve our understanding of the effect of these therapies on patient symptoms and functional capacity.

6.7 TABLES AND FIGURE

Table 1

Baseline Characteristics. Baseline Characteristics. Patient characteristics, comorbidities and medications across each presenting rhythm group (AF versus SR).

Baseline Characteristics	Sinus Rhythm (n=74)	Atrial Fibrillation (n=31)	p-value
Age, (yrs)	62.5±11.5	66.0±10.5	0.129
Male Sex, n (%)	56 (82.3)	25 (80.6)	0.683
Persistent AF, n (%)	31 (45.6)	26 (83.9)	<0.001
Previous AF Ablation, n (%)	28 (37.3)	8 (25.8)	0.361
AF duration (months)	63 (20-140)	52 (31-132)	0.799
Cardiovascular Risk Factors			
BMI (kg/m^2)	28.7±5.3	29.2±4.2	0.627
Weight (kg)	92.8±17.9	90.2±20.6	0.518
Hypertension, n (%)	49 (65.3)	20 (64.5)	1
Diabetes, n (%)	9 (12)	4 (12.9)	1
Previous Stroke, n (%)	5 (6.7)	4 (12.9)	0.443
Coronary Artery Disease, n (%)	5 (6.7)	3 (9.7)	0.670
Obstructive Sleep Apnoea, n (%)	25 (33.3)	7 (22.6)	0.461
Current smoker, n (%) **Previous smoker, n (%)**	5 (6.7%) 11 (14.9%)	2 (6.5%) 2 (6.5%)	0.999 0.336
Alcohol Excess (>30g/week), n (%)	34 (45.3)	12 (38.7)	0.681
CHA_2DS_2-Vasc Score	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.227
Medications			
ACEi/ARB	42 (56.0)	14 (58.1)	1
Beta-blocker	33 (44.0)	11 (35.5)	0.553
MRA	7 (9.3)	2 (6.5)	1
Antiarrhythmic	57 (76.0)	23 (74.2)	1
Loop diuretics	1 (1.5)	5 (16.1)	0.007

Abbreviations: AF atrial fibrillation, BMI body mass index, ACEi angiotensin converting enzyme inhibitor, ARB angiotensin receptor blocker.

Table 2

Resting and Exercise Echocardiographic Parameters. Left atrial and left ventricular size and function at baseline and peak exercise in patients in AF and SR at the time of exercise.

	Resting Echocardiography			Exercise Echocardiography		
	SR (n=74)	**AF (n=31)**	**p-value**	**SR (n=74)**	**AF (n=31)**	**p-value**
LAEF	41.2±13.3	30.8±9.3	<0.001	48.6±12.1[a]	32.4±9.6	<0.001
Reservoir Strain	24.3±9.1	13.3±6.8	<0.001	28.1±11.3[a]	12.9±5.7	<0.001
LA_{MAX}	31.9±8.5	38.1±11.6	0.027	35.4±9.2[a]	36.7±9.8	0.561
LA_{MIN}	19.0±7.3	26.5±8.9	<0.001	18.3±7.0	24.9±8.2	<0.001
LVEF	58.8±5.9	54.5±4.0	<0.001	63.5±7.0[a]	56.6±7.8	0.001
LV GLS	16.7±3.3	13.0±2.8	<0.001	19.0±3.8[a]	14.4±2.4	<0.001
LV_{MAX}	98.5±30.9	84.0±29.7	0.049	98.1±32.3	87.6±25.3	0.183
LV_{MIN}	41.3±14.8	41.4±13.0	0.965	36.3±14.5[a]	40.6±14.4	0.301
E/E'	9.2±3.2	9.9±3.6	0.332	9.4±3.5	11.3±6.7	0.247
[a]p<0.05 vs SR group at rest						

Abbreviations: LA left atrium, LAEF left atrial emptying fraction, LV left ventricle, LVEF left ventricular emptying fraction, GLS global longitudinal strain.

Table 3

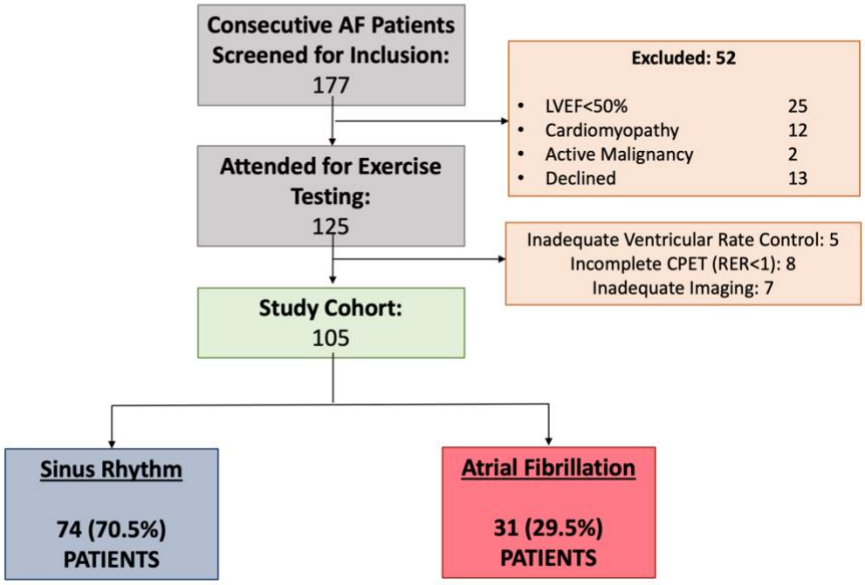
Relationship between LA parameters and VO_{2peak} in patients in SR. Adjusted linear regression models to assess the relationship between LA size and function and exercise capacity.

Variable	Model 1*		Model 2**	
	Coefficient (95% CI)	**p-value**	**Slope (95% CI)**	**p-value**
Resting LA Parameters				
LA_{max} (ml/m^2)	0.04 (-0.15 to 0.23)	0.655	0.09 (-0.13 to 0.31)	0.414
LA_{min} (ml/m^2)	-0.17 (-0.41 to 0.07)	0.169	-0.16 (-0.43 to 0.12)	0.26
LAEF (%)	**0.14 (0.02 to 0.27)**	**0.028**	**0.17 (0.02 to 0.31)**	**0.024**
Reservoir Strain (%)	**0.26 (0.07 to 0.45)**	**0.007**	**0.25 (0.02 to 0.49)**	**0.033**
Booster Strain (%)	**0.34 (0.05 to 0.62)**	**0.021**	0.31 (-0.03 to 0.65)	0.076
Conduit Strain (%)	0.30 (-0.01 to 0.62)	0.056	0.33 (-0.06 to 0.73)	0.098
Exercise LA Parameters				
LA_{max} (ml/m^2)	0.11 (-0.06 to 0.28)	0.211	0.11 (-0.08 to 0.30)	0.245
LA_{min} (ml/m^2)	-0.05 (-0.30 to 0.21)	0.713	-0.04 (-0.31 to 0.23)	0.761
LAEF (%)	**0.16 (0.0006 to 0.32)**	**0.049**	0.15 (-0.02 to 0.32)	0.084
Reservoir Strain (%)	**0.31 (0.11 to 0.51)**	**0.003**	**0.31 (0.08 to 0.54)**	**0.009**
***Model 1 – adjusted for age and sex** ****Model 2 – adjusted for age, sex and resting LVEF**				

Abbreviations: LA left atrium, LAEF left atrial emptying fraction.

Figure 1

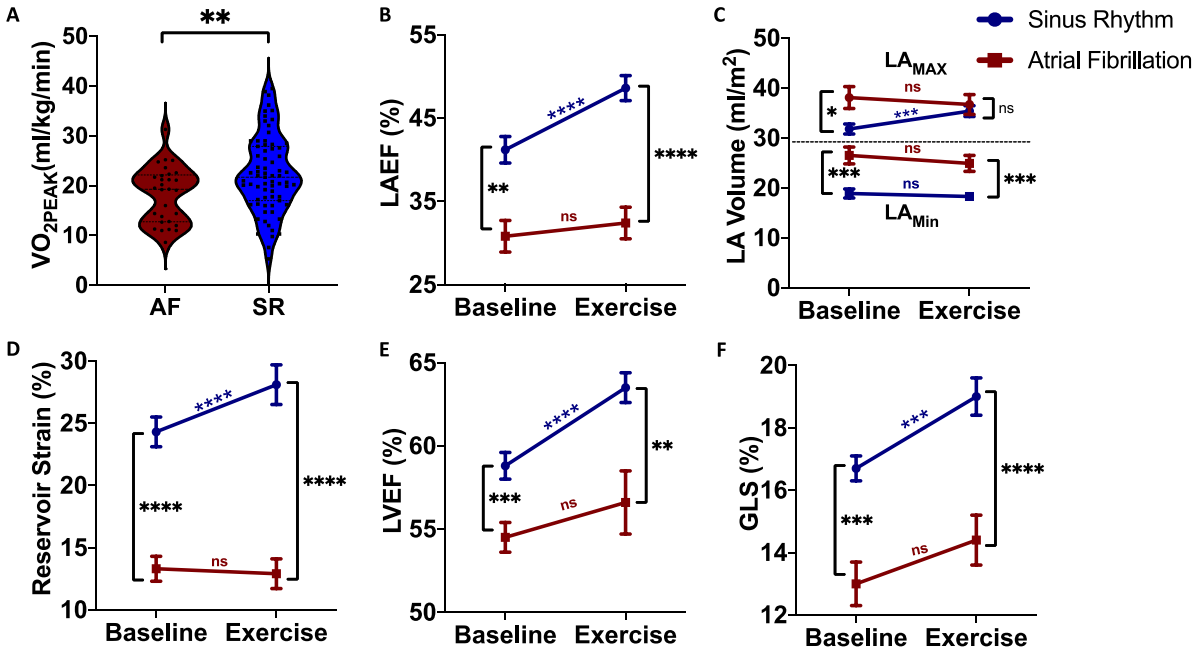
CONSORT diagram. Consort diagram showing patient recruitment and classification including reasons for exclusion.



Abbreviations: LVEF left ventricular ejection fraction, RER respiratory exchange ratio.

Figure 2

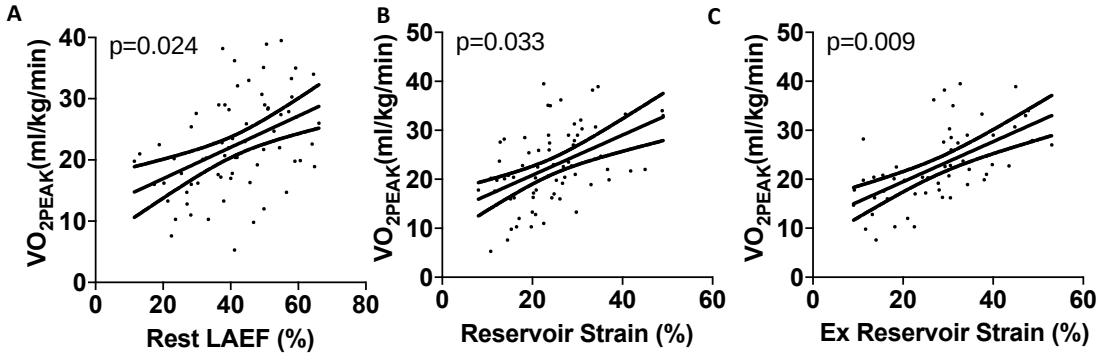
Atrial fibrillation versus sinus rhythm – cardiorespiratory fitness and LA and LV parameters. A) AF rhythm was associated with reduced VO_{2peak} compared to patients in SR. B) LAEF was higher in patients in SR at rest and increased significantly with exercise whereas AF patients did not augment LAEF with exercise. Underpinning these differences in LAEF response was C) reduced LA_{max} dilatation patients in in AF compared to SR. Exercise did not affect LA_{MIN} in either group. D) Patients in SR also demonstrated LA reservoir strain reserve with exercise, which was absent in AF. E) Similarly, LVEF also significantly increased with exercise in patients in SR but not in patients in AF whilst F) LV GLS was reduced in patients in AF at baseline and did not augment with exercise compared to patients in SR.



Abbreviations: LAEF – left atrial emptying fraction, LA – left atrial, LVEF – left ventricular ejection fraction, GLS – global longitudinal strain.

Figure 3

Relationship between LA function and cardiorespiratory fitness in patients in sinus rhythm. A) Higher LAEF is associated with significantly associated with increased VO_{2peak} independent of age, gender and resting left ventricular ejection fraction. Similarly, higher LA reservoir strain was associated with higher VO_{2peak} both B) at rest and C) during exercise independent of age, gender and resting left ventricular ejection fraction.



Abbreviation: LAEF – left atrial emptying fraction, VO_{2peak} – maximal oxygen consumption.

CHAPTER 7 HFpEF in AF is Associated with Structural and Functional Remodelling of the Left Atrial Appendage: Implications for Stroke Risk

7.1 INTRODUCTION

Atrial fibrillation (AF) is associated with a five-fold increased risk of stroke [234]. This elevated risk is attributable to an increased propensity of the left atrium (LA) to develop thrombus in patients with AF, related to morphological and functional LA remodelling, endothelial dysfunction and serum hypercoagulability [237,389]. It has been shown that up to 90% of LA thrombus in non-valvular AF arises in the LA appendage (LAA) [390], an embryonic remnant which forms an accessory outpouching of the LA.

Heart failure (HF) has been shown to be an important predictor of LAA thrombus formation and risk of stroke in patients with AF and contributes to the established CHA_2DS_2-Vasc scoring system for estimating annual stroke risk [391]. However, most data relates to HF with reduced ejection fraction (HFrEF). There is minimal data regarding LAA thrombus and stroke risk in heart failure with preserved ejection fraction (HFpEF), which contributes 50% of all HF cases [392]. In **Chapter 2** we have shown that HFpEF is common in patients with symptomatic AF and associated with LA dysfunction. We hypothesise that AF patients with haemodynamic evidence of HFpEF also demonstrate impaired LAA structure and function compared to those without HFpEF, representing a potential for increased risk of stroke. The aim of this study was to use multimodality imaging techniques to comprehensively assess LAA structure and function in AF patients with haemodynamically confirmed HFpEF.

7.2 METHODS

7.2.1 Study Design

This was a prospective clinical study undertaken at the Centre for Heart Rhythm Disorders (CHRD) at the University of Adelaide. All patients provided written informed consent. The study protocol was approved by the Human Research Ethics Committee of the Central Adelaide Local Health Network and the University of Adelaide. The study was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12620000639921).

7.2.2 Study Population

All patients aged >18 years with symptomatic paroxysmal or persistent AF undergoing invasive AF ablation procedures at the CHRD were eligible to participate. Specific exclusion criteria included: 1) reduced left ventricular ejection fraction (<50%); 2) previous diagnosis of cardiomyopathy; 3) moderate-to-severe valvulopathy; 4) previous diagnosis of pulmonary hypertension; 5) active malignancy; 6) severe chronic obstructive airways disease; 7) previous LAA closure or 7) inability to provide written informed consent.

7.2.3 Invasive Diagnosis of HFpEF

7.2.3.1 Patient Preparation

HFpEF was diagnosed invasively at the AF ablation procedure based on established haemodynamic criteria. Haemodynamic assessment was performed in a fasted state under general anaesthesia. Anaesthetic agents used for induction and maintenance of anaesthesia were standardized across all cases. Tidal volumes were set at 7ml/kg, with respiration rates of 10-12 breaths per minute and positive end-expiratory pressure of 5cmH_2O. All anti-arrhythmic drugs were withheld for ≥5 half-lives prior to the procedure. No patients were on chronic

amiodarone treatment. All patients underwent transesophageal echocardiography (TOE) at the start of the procedure to ensure there was no atrial thrombus. In all patients, heparin was administered to maintain the activated clotting time over 350 seconds. Access was via the right femoral vein with ultrasound guidance. Transseptal puncture was performed using a SLO sheath and BRK1 needle (Abbott, Minneapolis, MN) under TOE guidance allowing access to the LA. An Agilis sheath (Abbott, Minneapolis, MN) was placed in the LA and a 6F pigtail catheter in the RA for simultaneous pressure monitoring.

7.2.3.2 Haemodynamic Assessment

All hemodynamic measurements were performed only after confirming hemodynamic stability for a 10-minute period. All inotropic and vasopressor medications were withheld during hemodynamic testing. The LA, right atrial (RA) and arterial catheters were attached to pressure transducers and zeroed at the level of the mid-thorax, allowing the recording of LA, RA and arterial pressures. Pressures were recorded (240 Hz) on the WorkMate Claris™ Electrophysiology System (Abbott, Minneapolis, MN) and analysed offline. Pressures were measured at end-expiration and averaged over 3 cardiac cycles for patients in sinus rhythm (SR) and over 6 cycles for patients in AF.

For the diagnosis of HFpEF mLAP was measured. Mean LAP was taken at the start of the C-wave. In the absence of a visible C wave, mLAP was taken midway between the peak and trough of the A-wave in those with SR or 130-160ms after the onset of the QRS in those in AF.[275] Participants were classified into three groups according to mLAP both at rest and after saline infusion, as defined by a Science Advisory from the American Heart Association.[393] Patients were assigned to the 'HFpEF' group if mLAP at baseline was greater than 15mmHg as per the gold-standard definition of HFpEF.[394] Patients were placed in the 'Early HFpEF' group if mLAP was less than 15mmHg at baseline but rose to above 15mmHg following

infusion of 500mls of saline, as defined previously.[276] All other patients were placed in the 'No HFpEF' group.

7.2.4 LAA Structural and Functional Assessment

7.2.4.1 Contrast-Enhanced Cardiac CT

All participants underwent pre-procedural contrast-enhanced cardiac CT within 2-weeks of invasive assessment. High-pitch CT scans for LA and pulmonary vein anatomy were undertaken at end-expiration using a 64-slice DSCT scanner (2x64x0.6mm collimation, gantry rotation time of 330ms, tube voltage of 120kVp, effective tube current of 158-826mAs). Scans were triggered at 60% R-R interval on ECG in diastole and images were acquired in one heartbeat. Iodinated contrast was infused at a flow rate of 5-6ml/sec with 40mL of normal saline solution at the same rate.

Offline analysis of LAA volume was undertaken offline using the validated post-processing software 3D-slicer (v5.0.3) [301]. Manual segmentation of the LAA was then undertaken slice by slice using a paintbrush tool and an attenuation range of 250-1100 Hounsfield units. On completing the manual segmentation, 3D-slicer calculated and provided the total LAA volume in mililitres (mL).

7.2.4.2 Transesophageal Echocardiography

Transesophageal echocardiography (TOE) was performed pre-procedurally on the day of the AF ablation after administration of general anaesthetic. The LAA was visualized with the probe in the mid-esophageal position at an angle providing the longest apex to orifice length (typically 45-90°). Using a frame rate of 60-90 frames per second, 2D images focussed on the LAA were recorded and stored in addition to pulsed-wave Dopplers obtained from 1cm below the LAA orifice.

All images were recorded to a hard drive and analysis was performed offline using EchoPAC (GE Healthcare). LAA ejection fraction (LAAEF) was calculated in all participants presenting with SR. Maximum and minimum LAA areas were measured using planimetry and LAA ejection fraction was calculated using the formula:

$$LAAEF = (LAA_{Max} - LAA_{Min}) / LAA_{Max} \times 100$$

LAA emptying velocities (LAAEV) and filling velocities (LAAFV) were measured from the pulsed-wave Doppler recordings. Velocities were averaged over three cycles for patients in SR and ten cycles for those in atrial arrhythmia. LAA spontaneous echo (LAASEC) contrast was also assessed from gain-adjusted TOE images and was graded according to a previously validated semiquantitative method.[395,396] Patients scored 0 if there was no visible LAASEC, 1 if there was mild LAASEC (minimal echogenicity located in the LA appendage or sparely distributed in the main cavity of the left atrium; may be detectable only transiently during the cardiac cycle; imperceptible at operating gain settings for two dimensional echocardiographic analysis), 2 for mild-moderate LAASEC (more dense swirling pattern than grade 1+ but with similar distribution; detectable without increased gain settings), 3 for moderate LAASEC (dense swirling pattern in the LAA, generally associated with somewhat lesser intensity in the main cavity; may fluctuate in intensity but detectable constantly throughout the cardiac cycle and 4 for severe LAASEC ((intense echo density and very slow swirling patterns in the LAA, usually with similar density in the main cavity).

7.2.4.3 Electroanatomical Mapping

Three-dimensional electroanatomical mapping (EAM) of the LAA was performed prior to ablation using the HD-32 Grid Catheter (Abbott, Minneapolis, MN) and the Ensite™ Precision EAM Cardiac Mapping System (Abbott, Minneapolis, MN), as previously described in Chapter 2. High-density voltage maps of the LAA were created during pacing at 600ms cycle

length from the coronary sinus. Patients who had undergone previous AF ablation (n=45) and patients in AF at the time of mapping (n=24) were excluded from the electrical analysis. Automated collection of points was performed; points were only acquired if they met the internal and external projection criteria of 5mm with 5mm interpolation. Additional electrogram analysis was meticulously performed offline to exclude ectopic beats and noise. Regional bipolar peak-to-peak voltages were defined as the amplitude between the peak positive and peak negative deflections of the electrogram. Overall LAA voltage was calculated using a previously validated software as the mean of the peak-to-peak bipolar voltages collected within the LAA.[279]

7.2.5 Statistical Analysis

Continuous variables were tested for normality using the Shapiro-Wilk test and reported as means ± standard deviation or median and interquartile range as appropriate. Categorical variables were reported as frequencies and percentages. Continuous variables were compared across the three HFpEF groups using one-way analysis of variance (ANOVA) procedures or Kruskal-Wallis H test as appropriate. Independent-samples Student t-tests or Mann Whitney U tests were performed between each pair of groups. Categorical variables were compared across the three groups and each pair of groups using the chi-square test or Fisher's exact test as appropriate. Univariable and multivariable predictors of LAAEV were investigated using binary logistic regression. P-values of ≤ 0.05 were considered statistically significant. Power analysis determined that a sample size of 93 would be required to identify a HFpEF prevalence of 40% with a desired precision of ±10% at the 95% confidence interval. All statistical analysis was performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

7.3 RESULTS

7.3.1 Recruitment and HFpEF Classification

In total, 112 patients were included in the study cohort after exclusion of 41 patients meeting pre-specified exclusion criteria, 13 patients who declined participation and 6 who had inadequate TOE imaging of the LAA. Of these 112 participants, 53 (47.3%) had baseline mLAP of >15mmHg and were therefore placed in the 'HFpEF' group. A further 29 (25.9%) had baseline mLAP <15mmHg but an increase to greater than 15mmHg following 500mls saline infusion and were classified as 'Early HFpEF'. The remaining 30 (26.8%) participants were classified as 'No HFpEF'. Figure 1 demonstrates the CONSORT diagram from screening, recruitment and classification.

7.3.2 Baseline Characteristics

Table 1 shows the baseline characteristics across the three HFpEF groups. There were no significant differences in age (p=0.178), gender (p=0.599) or type of AF (p=0.992) across the groups. In addition, there was no difference in the proportion of patients with a history of previous AF ablation (p=0.660) or AF duration (p=0.138) between the groups. However, the HFpEF group demonstrated a higher burden of cardiovascular risk factors, with higher BMI (p=0.005) and higher prevalence of hypertension (p=0.014) and diabetes (p=0.008). The HFpEF group demonstrated higher $CHADS_2Vasc$ scores than the early and no HFpEF groups (p=0.007) but the early HFpEF group did not exhibit any other differences in baseline characteristics compared with the no HFpEF group.

7.3.3 LAA Structure

LAA volumes assessed by contrast-enhanced cardiac CT were not significantly different across the three groups (11.2±4.5 vs 10.2±4.7 vs 11.1±4.7mL, p=0.633, Figure 1A). Similarly,

LAA_{Max} measured on TOE was not significantly different between the three groups (2.6±1.2 vs 3.0±1.9 vs 3.3±1.6, p=0.298). There was no significant relationship between mLAP at baseline and LAA volume (p=0.836, R^2=0.0005, Figure 1B) as measured on contrast-enhanced CT scans.

7.3.4 LAA Mechanical Function

Table 2 shows the LAA functional parameters across the three HFpEF groups. Increasing HFpEF group was associated with significantly reduced LAAEV (36.0 [23.0-47.7] vs 52.1 [27.6-61.0] vs 50.6 [38.9-59.5]cm/s, p=0.038, Figure 2A) but no differences in LAAFV (38.0 [25.8-57.2] vs 46.3 [35.7-60.6] vs 50.7 [42.6-61.7]cm/s, p=0.114) or LASEC (1 [0-2] vs 1 [0-2] vs 1 [0-1], p=0.271). In a linear regression model, elevated mLAP at baseline was significantly associated with reduced LAAEV (p=0.001, R^2 = 0.059, Figure 2B). Including only patients in SR at the time of TOE (n=78, 69.6%), LAAEV (41.4±17.8 vs vs 50.8±16.8 vs 52.9±16.7 cm/s, p=0.031, Figure 2C), LAAFV (44.7±18.0 vs 51.9±16.8 vs 59.1±21.3 cm/s, p=0.024, Figure 2D) and LAAEF (41.6±12.8 vs 48.8±15.8 vs 54.1±11.1%, p=0.010, Figure 2E) were all significantly reduced in the HFpEF group compared to no HFpEF. In AF (n=34, 31.4%), we did not detect any statistically significant difference in average LAAEV across the three groups (21.9 [17.6-44.3]vs 27.5 [23.4-43.3] vs 34.0 [22.2-52.1]cm/s, p=0.460) or LAAFV (33.4 [21.0-48.7] vs 32.3 [23.2±41.3] vs 39.5 [20.8-48.2] cm/s, p=0.920).

7.3.5 LAA Bipolar Voltage

LAA bipolar voltages were significantly reduced in the HFpEF group compared to the no HFpEF group (3.0 [2-3-3.9] vs 4.2 [3.5-5.3], p=0.023). In contrast, the early HFpEF group did not demonstrate reduced LAA bipolar voltages compared to the no HFpEF group (3.9 [3.0-5.6] vs 4.2 [3.5-5.3], p=0.792).

7.3.6 Predictors of LAA Function

Univariable predictors of reduced LAAEV in SR were increasing age (p=0.003), female gender (p=0.004), $CHADS_2Vasc$ score (p=0.012) and increasing HFpEF group (p=0.016). When these characteristics were assessed in a multivariable analysis, both female gender (p=0.001) and HFpEF group (p=0.047) remained independent predictors of LAAEV (Table 3).

7.4 DISCUSSION

7.4.1 Major Findings

In this comprehensive, multi-modality assessment of LAA structure and function in symptomatic AF patients with and without invasively confirmed subclinical HFpEF, we have shown that 1) patients with evidence of coexistent HFpEF demonstrate reduced LAA mechanical function and electroanatomical remodelling compared to those with early or no HFpEF , 2) elevated LA pressures at baseline are not associated with dilatation or enlargement of the LAA but are associated with reduced LAA function and 3) the presence of HFpEF is an independent predictor of reduced LAA function. Taken together our data highlights the independent influence of HFpEF on stroke risk in patients with symptomatic AF. Identification of HFpEF through invasive haemodynamic testing may therefore provide a novel tool to identify those at greatest risk of stroke in patients with symptomatic AF.

7.4.2 HFpEF in AF Associated with Reduced LAA Function: Clinical Implications

It is now well-established that LAA function is an important predictor of both the presence of LAA thrombus and stroke in patients with AF. Several studies have shown that reduced LAA emptying velocities are associated with thrombus formation and increased risk of stroke.[249,251] For the first time, we have shown that the presence of haemodynamically confirmed HFpEF is

associated with significantly reduced LAA velocities and ejection fraction in patients with symptomatic AF, suggesting that these patients are at increased risk of future thrombus formation and systemic thromboembolism. We have also shown a continuous inverse relationship between mLAP and LAAEV but no relationship with LAA volume, suggesting that, despite the LAA being a compliant structure, elevated LAP does not dilate the LAA but does impair LAA function, potentially raising stroke risk.

Heart failure represents an important predictor of stroke in patients with symptomatic AF and is included in the $CHADS_2Vasc$ stroke risk stratification scoring tool.[397] However, the specific role of HFpEF on stroke risk in patients with AF remains unclear.[391] Recent data suggests that stroke risk may be highest in AF patients with HFpEF compared to those with HFrEF or HFmrEF.[398] Our data further highlights this important association and provides mechanistic insights into these novel findings, demonstrating the role of LAA dysfunction in patients with HFpEF.

7.4.3 Early HFpEF and LAA Function

We have previously shown that early HFpEF in patients with symptomatic AF is associated with impaired LA haemodynamics, reduced LA mechanical function, electrical remodelling and reduced cardiopulmonary reserve (**Chapter 2**). However, in this study we have shown that early HFpEF diagnosed in the same way is not associated with differences in LAA structure or function. This suggests that LAA dysfunction represents a delayed change in the progression of from early HFpEF to HFpEF and highlights the potential to prevent LAA dysfunction through prompt identification and treatment of patients with early HFpEF. Future research should focus on assessing the impact of treatment of early HFpEF, using proven treatments such as SGLT2 inhibitors and aggressive lifestyle interventions (including calorific restriction and aerobic exercise training),[256,257] on progression of LAA dysfunction.

7.4.4 Electroanatomical Remodelling of the LAA

In addition to the mechanical changes described above we have also demonstrated electroanatomical remodelling of the LAA with significantly reduced bipolar voltages in patients with underlying subclinical HFpEF. Electrical remodelling of the LAA may have a significant influence on the risk of AF. The BELIEF Trial showed that empirical isolation of the LAA in patients with long-standing persistent AF was associated with improved AF-free survival, suggesting that the LAA may be an important source of AF.[399] Our data on electrical function of the LAA in AF highlights the global deterioration of LAA function associated with HFpEF and may provide evidence to suggest that the LAA may be a particularly arrhythmogenic structure in patients with HFpEF and AF.

7.4.5 Gender Differences in LAA Function

In the multivariate analysis, female gender was shown to be a significant independent predictor of reduced LAAEV. This data confirms the findings of previous studies showing that females have reduced LAA function compared to males, independent of other risk factors.[400] Previous data suggests that females are also at increased risk of developing HFpEF, further highlghting the close interplay between AF, HFpEF and stroke risk. Stroke risk associated with HFpEF may therefore be particularly relevant in female patients with AF and our findings may explain the increased risk of stroke in both anticoagulated and non-anticoagulated females.[401-403]

7.5 LIMITATIONS

Only patients undergoing AF ablation procedures were included in the study cohort meaning the findings cannot be generalised to the entire AF population. However, patients undergoing AF ablation represent an ever-increasing proportion of patients with AF suggesting that these

findings can be extrapolated to a wider cohort of AF patients. In addition, at the time of investigation, all participants had been fully anticoagulated for at least four weeks; this may explain the lack of difference in LASEC seen on TOE between the three groups. In addition, LASEC was evaluated semi-quantitatively; use of quantitative methods such as integrated backscatter may have improved the accuracy of this analysis.[404] Finally, as this is a cross-sectional study, we have not been able to associate the presence of HFpEF with any major cardiac outcomes including stroke or systemic thromboembolism. However, appendage velocities have been shown to be closely related to LAA thrombus and stroke[251] and represent an adequate marker of stroke risk for this study.

7.6 CONCLUSIONS

Using invasive haemodynamic assessment and multimodality imaging techniques, we show that HFpEF in patients with symptomatic AF is associated with reduced LAA function despite the absence of increased LAA volume. Our data suggests that AF patients with HFpEF are at increased risk of stroke. Invasive diagnosis of HFpEF may provide a novel strategy to identify AF patients with elevated risk of stroke. Future work should investigate the clinical outcomes associated with underlying HFpEF in patients with AF and explore the potential to reverse LAA remodelling by targeting treatment of HFpEF.

7.7 Tables and Figures

Table 1

Baseline Characteristics. Baseline and clinical characteristics across the three HFpEF groups.

Baseline Characteristics	No HFpEF (n=30)	Early HFpEF (n=29)	HFpEF (n=53)	p-value
Age, (yrs)	61.0±11.3	64.2±9.5	65.8±12.0	0.178
Male Sex, n (%)	22 (73.3)	22 (75.9)	35 (66.0)	0.599
Paroxysmal AF, n (%)	16 (53.3)	15 (51.7)	28 (52.8)	0.992
Persistent AF, n (%)	14 (46.7)	14 (48.3)	25 (47.2)	0.992
Previous AF Ablation, n (%)	10 (33.3)	12 (41.4)	23 (43.4)	0.660
AF duration (months)	77.2±72.8	77.6±77.3	107.9±84.8	0.138
Cardiovascular Risk Factors				
BMI (kg/m^2)	27.5±4.7	27.6±4.3	30.5±4.8[ab]	0.005
Weight (kg)	89.5±17.5	84.8±15.8	93.7±21.3	0.131
Hypertension, n (%)	17 (56.7)	17 (58.6)	44 (83.0)[ab]	0.014
Diabetes, n (%)	1 (3.3)	1 (3.4)	11 (20.8)	0.008
Previous Stroke, n (%)	1 (3.3)	4 (13.8)	3 (5.7)	0.318
Coronary Artery Disease, n (%)	4 (13.3)	0 (0)	6 (11.3)	0.120
Obstructive Sleep Apnea, n (%)	10 (33.3)	9 (31.0)	14 (26.4)	0.784
History of Smoking, n (%)	6 (20.0)	6 (20.7)	14 (26.4)	0.747
Alcohol Excess (>30g/week), n (%)	17 (56.7)	11 (37.9)	21 (39.6)	0.247
CHA_2DS_2-Vasc Score	2 (1,2)	2 (1,3)	2 (1,4)[ab]	0.007
Medications				
ACEi/ARB	12 (40.0)	13 (44.8)	38 (71.7)[ab]	0.007
Beta-blocker	12 (40.0)	12 (41.4)	23 (43.4)	0.953
MRA	0 (0)	6 (20.7)[a]	4 (7.5)	0.018
Antiarrhythmic	20 (66.7)	24 (82.7)	39 (73.6)	0.367
[a]p<0.05 compared to No HFpEF group [b]p<0.05 compared to Early HFpEF group				

Abbreviations: HFpEF – Heart failure with preserved ejection fraction, HFpEF – Heart failure with preserved ejection fraction, AF – Atrial fibrillation, BMI – body mass index, ACEi – angiotensin converting enzyme inhibitor, ARB – angiotensin receptor blocker, MRA - mineralocorticoid receptor blocker.

Table 2

LAA structural and functional parameters. LAA structure and function across the three HFpEF groups and according to presenting rhythm.

ENTIRE COHORT (n=112)				
	No HFpEF (n=30)	**Early HFpEF (n=29)**	**HFpEF (n=53)**	**p-value**
LAA Volume (ml)	11.3±4.7	10.2±4.8	11.3±4.7	0.634
LAA Emptying Velocity (cm/s)	50.6 (38.9-59.5)	52.1 (27.6-61)	36.0 (23.0-47.7)[a]	0.038
LAA Filling Velocity (cm/s)	50.7 (42.6-61.7)	46.3 (35.7-60.6)	38.0 (25.8-57.2)	0.114
LAA Spontaneous Echo Contrast)	1(0-1)	1(0-2)	1(0-2)	0.271
SINUS RHYTHM (n=78)				
	No HFpEF (n=20)	**Early HFpEF (n=21)**	**HFpEF (n=37)**	**p-value**
LAA Volume (ml)	10.3±5.1	10.6±5.4	10.5±5.0	0.984
LAA Emptying Velocity (cm/s)	52.9±16.7	50.8±16.8	41.4±17.8[a]	0.031
LAA Filling Velocity (cm/s)	59.1±21.3	51.9±16.8	44.7±18.0[a]	0.024
LAA Ejection Fraction (%)	54.1±11.1	48.8±15.8	41.6±12.8[a]	0.010
LAA Spontaneous Echo Contrast	0.5(0-1)	1(0-2)	1(0-2)	0.630
LAA Bipolar Voltage (mV)	4.2±1.1	4.3±1.5	3.3±1.1[a]	0.041
ATRIAL FIBRILLATION (n=34)				
	No HFpEF (n=10)	**Early HFpEF (n=8)**	**HFpEF (n=16)**	**p-value**
LAA Volume (ml)	13.0±3.6	8.7±1.9[ac]	13.2±3.1	0.030
LAA Emptying Velocity (cm/s)	33.95 (22.2-52.1)	27.5 (23.4-43.3)	21.9 (17.6-44.3)	0.460
LAA Filling Velocity (cm/s)	39.5 (20.8-48.2)	32.3 (23.2±41.3)	33.4 (21.0-48.7)	0.920
LAA Spontaneous Echo Contrast	1(0.75-1)	2(2-2)	1(1-2)	0.141
[a]p<0.05 compared to No HFpEF group [b]p<0.05 compared to Early HFpEF group [c]p<0.05 compared to HFpEF group				

Table 3

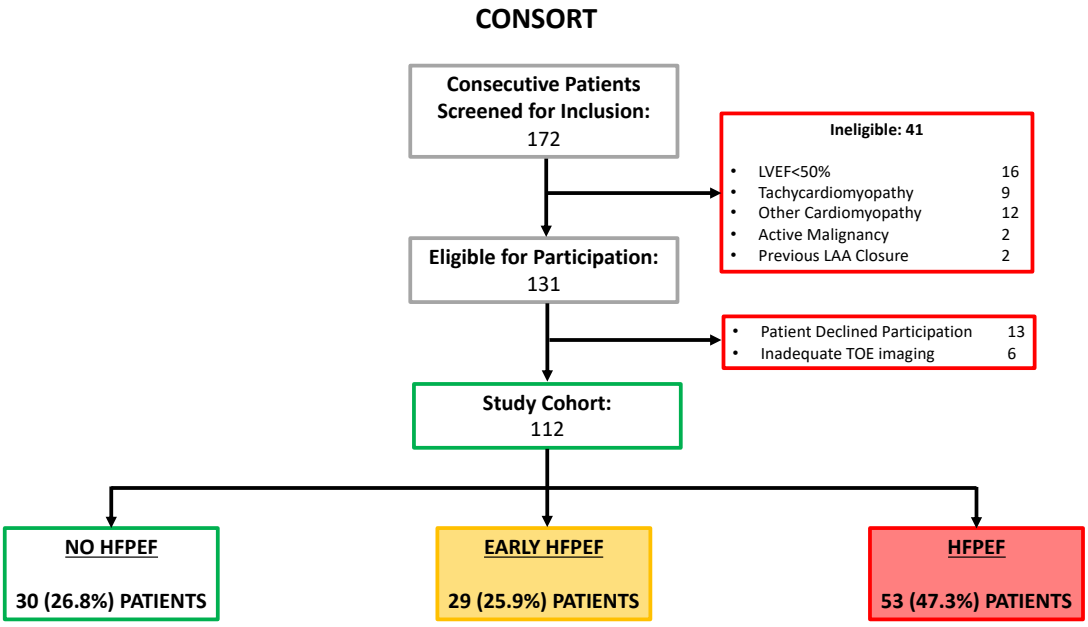
Predictors of LAA Emptying Velocities. Univariable and multivariable predictors of LAAEV using linear regression models.

Variable	Univariable Regression Analysis		Multivariable Regression Analysis	
	Coefficient (95% CI)	**p-value**	**Coefficient (95% CI)**	**p-value**
HFpEF Group	**-5.46 (-9.89 to -1.04)**	**0.016**	**-4.41 (-8.77 to -0.05)**	**0.047**
Age	**-0.50 (-0.82 to -0.17)**	**0.003**	-0.36 (-0.78 to 0.07)	0.099
Male Gender	**11.83 (3.80 to 19.85)**	**0.004**	**14.96 (6.25 to 23.68)**	**0.001**
BMI	-0.17 (-0.95 to 0.61)	0.662		
Hypertension	-3.06 (-11.93 to 4.52)	0.374		
Diabetes	-5.12 (-16.55 to 6.32)	0.377		
Alcohol	4.36 (-3.25 to 11.96)	0.259		
Smoking	4.35 (-4.60 to 13.30)	0.338		
$CHADS_2Vasc$	**-4.28 (-6.83 to -1.73)**	**0.012**	0.36 (-3.49 to 4.20)	0.853
Paroxysmal AF	7.15 (-0.34 to 14.63)	0.061		
Previous ablation	-1.20 (-5.35 to 2.95)	0.568		
Duration of AF	-0.02 (-0.07 to 0.03)	0.399		

Abbreviations: HFpEF – heart failure with preserved ejection fraction, BMI – body mass index, AF – atrial fibrillation, CI – confidence intervals.

Figure 1

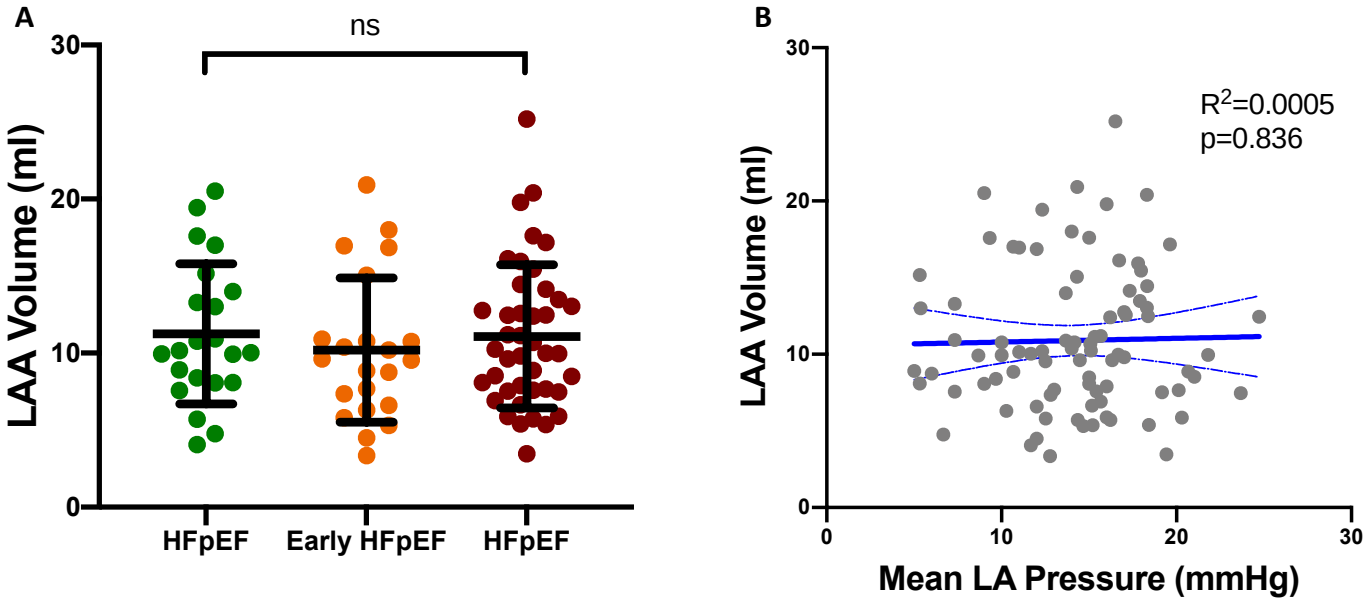
Consort diagram. Consort diagram. Of 172 patients screened for inclusion, 112 patients were included with 41 exclusions and an additional 13 patients who declined participation and 6 patients who had inadequate appendage visualisation on TOE imaging.



HFPEF – heart failure with preserved ejection fraction, LVEF – left ventricular emptying fraction.

Figure 2

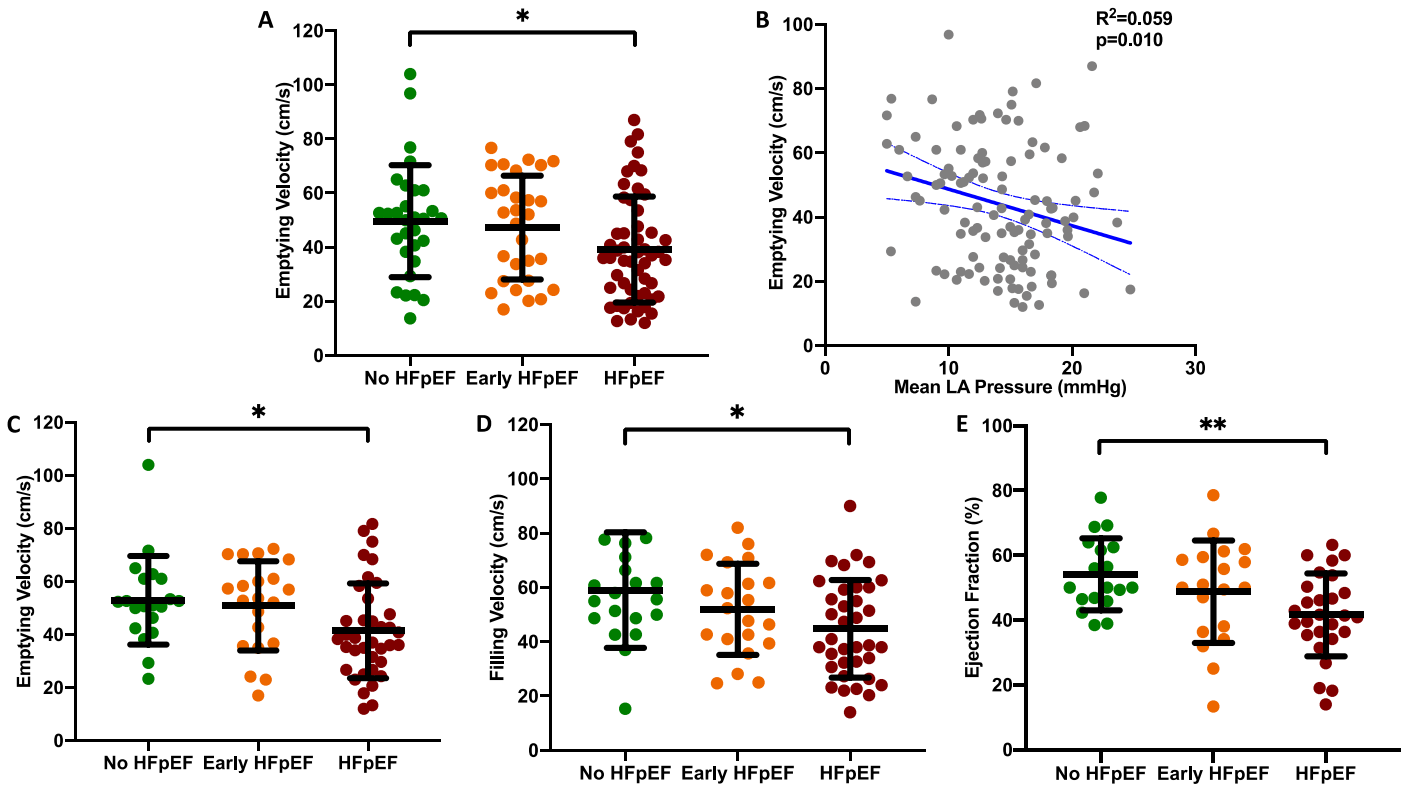
Association between LAA volume measured on contrast-enhanced cardiac CT scans and invasive haemdynamics. A) There was no difference in LAA volume across the three HFpEF groups. B) Similarly, there was no association between mLAP and LAA volumes.



Abbreviations: LAA – left atrial appendage, HFpEF – heart failure with preserved ejection fraction, LA – left atrial.

Figure 3

Association between LAA function assessed on TOE and invasive haemodynamics. A) HFpEF was associated with significantly reduced LAAEV in the entire cohort and B) increasing mLAP at baseline was associated with reducing LAAEV. In patients presenting in SR only (n=78), HFpEF was also associated with C) reduced LAAEV, D) reduced LAAFV and E) reduced LAAEF.



Abbreviations: HFpEF – heart failure with preserved ejection fraction, LA – left atrial.

CHAPTER 8 Conclusions

This thesis investigates the role of heart failure with preserved ejection fraction (HFpEF) in patients with symptomatic atrial fibrillation (AF). Using a consecutive, unselected cohort of patients undergoing AF ablation, it provides novel insights into the prevalence of HFpEF in AF, provides mechanistic insights into the development of HFpEF in AF and highlights the role of cardiovascular risk factors in the pathogenesis of HFpEF within AF. In addition, the thesis highlights the challenges associated with the clinical diagnosis of HFpEF in patients with AF, recognising the value of invasive diagnostic testing above non-invasive diagnostic tools. Importantly, the thesis also defines some of the clinical consequences of HFpEF in AF, including increased AF symptom burden, reduced exercise capacity, poorer quality of life and impaired left atrial appendage (LAA) function indicative of an increased risk of systemic thromboembolism and stroke.

Chapter 2 shows that up to 73% of patients with symptomatic AF undergoing AF ablation demonstrate the haemodynamic features of HFpEF. Patients with features of HFpEF demonstrate a higher burden of AF-related symptoms, poorer exercise capacity and worse quality of life. This high prevalence of HFpEF in AF challenges the notion that rhythm and rate-control of the AF dysrhythmia is sufficient for the effective treatment of AF. A renewed focus on HFpEF and specifically reversal of the LA cardiomyopathy that appears to underlie HFpEF in AF has the potential to significantly improve outcomes for patients with AF.

The thesis goes on to explore two important modifiable risk factors (obesity and cardiorespiratory fitness) underlying AF with a view to understanding their role in the development of HFpEF in AF. In Chapter 3, the influence of obesity and epicardial adipose tissue (EAT) is investigated. Obesity is found to be associated with a higher prevalence of HFpEF in AF, driven largely by pericardial restraint rather than worse LA cardiomyopathy. In addition, EAT is shown to be associated with abnormal haemodynamics as well as reduced LA

and LV strain, suggesting both a direct influence on myocardial function as well as a role in increasing pericardial restraint. In Chapter 4, reduced cardiorespiratory fitness (CRF) is found to be independently associated with features of LA dysfunction, a characteristic feature of HFpEF in AF. Reduced CRF is shown to be associated not only with extensive mechanical dysfunction but also significant electrical dysfunction, providing novel evidence that the underlying atrial substrate in AF is independently influenced by CRF. Data from these two chapters would suggest that reversal of these modifiable risk factors, through weight reduction and improvements in CRF, may have the potential to reduce the influence of HFpEF in AF and therefore improve outcomes for patients with AF.

Chapter 5 investigates the challenges associated with the diagnosis of HFpEF in patients with AF. Diagnosing HFpEF in AF is difficult because of the overlapping symptomatology between the two conditions. In addition, many of the non-invasive diagnostic methods for HFpEF rely on biomarkers (such as NT-pro BNP) which are also abnormal in patients with AF. The development of two non-invasive scoring systems for the diagnosis of HFpEF has increased the potential to diagnose HFpEF in AF but we show that both scoring systems remain significantly limited in their diagnostic ability in comparison to invasive testing which remains the gold-standard. Traditionally, invasive diagnosis has been limited to super-specialist centres with access to invasive cardiopulmonary exercise testing. However, this thesis highlights the ability to perform this relatively straightforward haemodynamic testing during AF ablation procedures, potentially widening access for such testing to greater proportion of AF patients.

Finally, the thesis investigates the clinical consequences of HFpEF in AF. Chapter 6 shows that, regardless of presenting rhythm, LA mechanical dysfunction at rest and during exercise is associated with reduced exercise capacity independent of differences in LV function. This suggests that LA mechanical dysfunction plays an important role in the cardiac

response to exercise, and that the LA dysfunction that is characteristic of HFpEF in AF could be a target for improving exercise intolerance in patients with AF. Chapter 7 shows that HFpEF in AF is associated with significantly reduced LAA function, suggesting that the presence of HFpEF may provide the conditions for thrombus formation within the LAA and thereby increase the risk of stroke and systemic thromboembolism. Exercise intolerance and stroke are two of the most clinically relevant consequences of AF; our findings that HFpEF may underlie both of these consequences highlights the need for further investigation into the potential for HFpEF to be considered as a therapeutic target in patients with AF.

CHAPTER 9 Future Directions

This thesis identifies HFpEF as a highly prevalent coexisting feature in patients with AF influencing symptoms, quality of life and exercise capacity. HFpEF in AF may therefore represent a novel therapeutic target with the potential to significantly improve the lives of patients with AF. The presence and influence of HFpEF in AF is underrecognised amongst clinicians and is not addressed in current guidelines for the management of patients with AF. Future research should further explore the role of HFpEF in AF, specifically investigating its role in mediating hard cardiovascular outcomes in AF and investigating whether treating HFpEF in AF may improve symptoms, quality of life and outcomes in patients with AF.

Current strategies for the treatment of AF focus largely on management of the dysrhythmia. However, many patients do not obtain symptomatic benefit from rhythm or rate control management strategies such as cardioversion, AF ablation or AV node ablation procedures. The reasons for this lack of clinical response remain unclear. This thesis provides evidence that underlying HFpEF may be the cause of ongoing symptoms even after rhythm and rate control treatments. Future research should investigate the role of HFpEF in patients who do not respond to traditional AF treatments. These patients may benefit from HFpEF treatment as an alternative to rhythm management.

Traditionally, management of HFpEF has been limited by an absence of proven efficacious treatments. However, recent years has seen a growth in pharmacological options for the treatment of HFpEF. For example, SGLT-2 inhibitors have been shown to reduce heart failure hospitalisations and mortality in patients with HFpEF. The utility of these medications in AF populations has yet to be established. Our finding that almost 75% of patients undergoing AF ablation procedures exhibit features of HFpEF would suggest that many AF patients may benefit from such treatments. More recent data has identified GLP-1 inhibitors as another important potential therapy in patients specifically with the obesity phenotype of HFpEF,

although more data regarding the impact of these treatments on the relative proportions of fat mass and lean body mass is required to ensure optimal management of HFpEF. Overall, our data suggests that the obesity phenotype is prevalent amongst patients with AF and future clinical trials should therefore investigate potential benefits of these medications in AF populations.

Non-pharmacological therapies are also important in HFpEF and may provide benefits for patients with AF. This thesis has highlighted the role of risk factors in the development of HFpEF in AF. Patients with HFpEF were more likely to be obese and have hypertension. In addition, obesity and reduced cardiorespiratory fitness were associated with more advanced features of HFpEF on invasive testing. Moving forward, investigation into whether improving treating these risk factors through lifestyle interventions can reduce the influence of HFpEF and reverse the LA dysfunction may provide new hope for improving symptoms and quality of life in patients with AF.

We have also shown that exercise intolerance is a key feature of HFpEF in AF and may therefore be an important target for treatment. We have shown that LA cardiomyopathy and deranged haemodynamics are key predictors of exercise intolerance in AF and treatment of these factors may improve exercise capacity. However, LA-LV coupling represents only one feature of the oxygen cascade and other factors including diffusive oxygen conductance may represent novel targets for treatment of exercise intolerance in AF.

Another potential mechanism for the treatment of HFpEF is offloading LA pressure. Previous studies have demonstrated the feasibility of using atrial shunt devices to reduce LA pressures. Whilst these devices have yet to show proven benefit in HFpEF cohorts, they may be of particular interest in AF patients given the predominant LA cardiomyopathy that we have identified is characteristic of HFpEF in AF. Future research should investigate the role of LA offloading in improving symptoms and quality of life in patients with AF and HFpEF.

Finally, research should address the potential to lower major cardiovascular events through treatment of HFpEF in AF. Both rhythm and rate control of AF are associated with important improvements in patient symptoms and quality of life but there continues to be an absence of evidence that these strategies improve long-term hard cardiovascular outcomes including mortality and stroke. This thesis provides evidence to suggest that HFpEF in AF may be associated with increased stroke risk through impaired LA and LAA function. Randomised clinical trials are required to determine whether treatment of HFpEF can result in lower stroke and all-cause mortality risk in the long-term as this has the potential to dismantle current beliefs regarding the optimal management of patients with AF.

CHAPTER 10 References

1. Li H, Song X, Liang Y, et al. Global, regional, and national burden of disease study of atrial fibrillation/flutter, 1990–2019: results from a global burden of disease study, 2019. *BMC Public Health.* 2022;22(1).
2. Dorian P, Jung W, Newman D, et al. The impairment of health-related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. *Journal of the American College of Cardiology.* 2000;36(4):1303-1309.
3. van den Berg MP, Hassink RJ, Tuinenburg AE, et al. Quality of life in patients with paroxysmal atrial fibrillation and its predictors: importance of the autonomic nervous system. *Eur Heart J.* 2001;22(3):247-253.
4. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ.* 2016:i4482.
5. Halmos PB, Patterson GC. Effect of atrial fibrillation on cardiac output. *Br Heart J.* 1965;27(5):719-723.
6. Morris JJ, Entman M, North WC, Kong Y, McIntosh H. The Changes in Cardiac Output with Reversion of Atrial Fibrillation to Sinus Rhythm. *Circulation.* 1965;31(5):670-678.
7. Habibi M, Lima JAC, Khurram IM, et al. Association of Left Atrial Function and Left Atrial Enhancement in Patients With Atrial Fibrillation. *Circulation: Cardiovascular Imaging.* 2015;8(2):e002769-e002769.
8. Shen MJ, Arora R, Jalife J. Atrial Myopathy. *JACC Basic Transl Sci.* 2019;4(5):640-654.

9. Omote K, Borlaug BA. Left Atrial Myopathy in Heart Failure With Preserved Ejection Fraction. *Circulation Journal.* 2023;87(8):1039-1046.

10. Patel RB, Lam CSP, Svedlund S, et al. Disproportionate left atrial myopathy in heart failure with preserved ejection fraction among participants of the PROMIS-HFpEF study. *Scientific Reports.* 2021;11(1).

11. Zile MR, Gottdiener JS, Hetzel SJ, et al. Prevalence and Significance of Alterations in Cardiac Structure and Function in Patients With Heart Failure and a Preserved Ejection Fraction. *Circulation.* 2011;124(23):2491-2501.

12. Melenovsky V, Borlaug BA, Rosen B, et al. Cardiovascular Features of Heart Failure With Preserved Ejection Fraction Versus Nonfailing Hypertensive Left Ventricular Hypertrophy in the Urban Baltimore Community. *Journal of the American College of Cardiology.* 2007;49(2):198-207.

13. Reddy YNV, Obokata M, Verbrugge FH, Lin G, Borlaug BA. Atrial Dysfunction in Patients With Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation. *Journal of the American College of Cardiology.* 2020;76(9):1051-1064.

14. Santhanakrishnan R, Wang N, Larson MG, et al. Atrial Fibrillation Begets Heart Failure and Vice Versa. *Circulation.* 2016;133(5):484-492.

15. Sartipy U, Dahlström U, Fu M, Lund LH. Atrial Fibrillation in Heart Failure With Preserved, Mid-Range, and Reduced Ejection Fraction. *JACC Heart Fail.* 2017;5(8):565-574.

16. Vermond RA, Geelhoed B, Verweij N, et al. Incidence of Atrial Fibrillation and Relationship With Cardiovascular Events, Heart Failure, and Mortality. *Journal of the American College of Cardiology.* 2015;66(9):1000-1007.

17. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal Relationship and Prognostic Significance of Atrial Fibrillation in Heart Failure Patients With Preserved Ejection Fraction. *Circulation.* 2013;128(10):1085-1093.

18. Lippi G, Sanchis-Gomar F, Cervellin G. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge. *Int J Stroke.* 2021;16(2):217-221.

19. Weng LC, Preis SR, Hulme OL, et al. Genetic Predisposition, Clinical Risk Factor Burden, and Lifetime Risk of Atrial Fibrillation. *Circulation.* 2018;137(10):1027-1038.

20. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime Risk for Development of Atrial Fibrillation. *Circulation.* 2004;110(9):1042-1046.

21. Gallagher C, Hendriks JM, Giles L, et al. Increasing trends in hospitalisations due to atrial fibrillation in Australia from 1993 to 2013. *Heart.* 2019;105(17):1358-1363.

22. James SL, Abate D, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The Lancet.* 2018;392(10159):1789-1858.

23. Gurwitz JH, Magid DJ, Smith DH, et al. Contemporary Prevalence and Correlates of Incident Heart Failure with Preserved Ejection Fraction. *The American Journal of Medicine.* 2013;126(5):393-400.

24. Yancy CW, Lopatin M, Stevenson LW, De Marco T, Fonarow GC. Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. *J Am Coll Cardiol.* 2006;47(1):76-84.

25. Tsao CW, Lyass A, Enserro D, et al. Temporal Trends in the Incidence of and Mortality Associated With Heart Failure With Preserved and Reduced Ejection Fraction. *JACC Heart Fail.* 2018;6(8):678-685.

26. Gerber Y, Weston SA, Redfield MM, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med.* 2015;175(6):996-1004.

27. Tromp J, Claggett BL, Liu J, et al. Global Differences in Heart Failure With Preserved Ejection Fraction. *Circulation: Heart Failure.* 2021;14(4).

28. Ariyaratnam JP, Elliott AD, Mishima RS, Gallagher C, Lau DH, Sanders P. Heart failure with preserved ejection fraction: An alternative paradigm to explain the clinical implications of atrial fibrillation. *Heart Rhythm O2.* 2021;2(6):771-783.

29. Pellicori P, Urbinati A, Kaur K, et al. Prevalence and Incidence of Atrial Fibrillation in Ambulatory Patients With Heart Failure. *The American Journal of Cardiology.* 2019;124(10):1554-1560.

30. Zile MR, Baicu CF, S. Ikonomidis J, et al. Myocardial Stiffness in Patients With Heart Failure and a Preserved Ejection Fraction. *Circulation.* 2015;131(14):1247-1259.

31. Freeman JV, Simon DN, Go AS, et al. Association Between Atrial Fibrillation Symptoms, Quality of Life, and Patient Outcomes. *Circulation: Cardiovascular Quality and Outcomes.* 2015;8(4):393-402.

32. Lip GYH, Laroche C, Popescu MI, et al. Heart failure in patients with atrial fibrillation in Europe: a report from the EURObservational Research Programme Pilot survey on Atrial Fibrillation. *European Journal of Heart Failure.* 2015;17(6):570-582.

33. Silva-Cardoso J, Zharinov OJ, Ponikowski P, et al. Heart Failure in Patients With Atrial Fibrillation Is Associated With a High Symptom and Hospitalization Burden: The RealiseAF Survey. *Clinical Cardiology.* 2013;36(12):766-774.

34. Scherf D, Romano FJ, Terranova R. Experimental studies on auricular flutter and auricular fibrillation. *Am Heart J.* 1948;36(2):241-251.

35. Haïssaguerre M, Jaïs P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998;339(10):659-666.

36. Hocini M, Ho SY, Kawara T, et al. Electrical conduction in canine pulmonary veins: electrophysiological and anatomic correlation. *Circulation.* 2002;105(20):2442-2448.

37. de Bakker JM, Ho SY, Hocini M. Basic and clinical electrophysiology of pulmonary vein ectopy. *Cardiovasc Res.* 2002;54(2):287-294.

38. Hamabe A, Okuyama Y, Miyauchi Y, et al. Correlation between anatomy and electrical activation in canine pulmonary veins. *Circulation.* 2003;107(11):1550-1555.

39. Perez-Lugones A, McMahon JT, Ratliff NB, et al. Evidence of specialized conduction cells in human pulmonary veins of patients with atrial fibrillation. *J Cardiovasc Electrophysiol.* 2003;14(8):803-809.

40. Kalifa J, Tanaka K, Zaitsev AV, et al. Mechanisms of wave fractionation at boundaries of high-frequency excitation in the posterior left atrium of the isolated sheep heart during atrial fibrillation. *Circulation.* 2006;113(5):626-633.

41. Tsai CF, Tai CT, Hsieh MH, et al. Initiation of atrial fibrillation by ectopic beats originating from the superior vena cava: electrophysiological characteristics and results of radiofrequency ablation. *Circulation.* 2000;102(1):67-74.

42. Volkmer M, Antz M, Hebe J, Kuck KH. Focal atrial tachycardia originating from the musculature of the coronary sinus. *J Cardiovasc Electrophysiol.* 2002;13(1):68-71.

43. Chauvin M, Shah DC, Haïssaguerre M, Marcellin L, Brechenmacher C. The anatomic basis of connections between the coronary sinus musculature and the left atrium in humans. *Circulation.* 2000;101(6):647-652.

44. Di Biase L, Burkhardt JD, Mohanty P, et al. Left atrial appendage: an underrecognized trigger site of atrial fibrillation. *Circulation.* 2010;122(2):109-118.

45. Lin YJ, Tai CT, Liu TY, et al. Electrophysiological mechanisms and catheter ablation of complex atrial arrhythmias from crista terminalis. *Pacing Clin Electrophysiol.* 2004;27(9):1231-1239.

46. Kistler PM, Sanders P, Hussin A, et al. Focal atrial tachycardia arising from the mitral annulus: electrocardiographic and electrophysiologic characterization. *J Am Coll Cardiol.* 2003;41(12):2212-2219.

47. Della Rocca DG, Di Biase L, Mohanty S, et al. Targeting non-pulmonary vein triggers in persistent atrial fibrillation: results from a prospective, multicentre, observational registry. *Europace.* 2021;23(12):1939-1949.

48. Moe GK, Abildskov JA. Atrial fibrillation as a self-sustaining arrhythmia independent of focal discharge. *Am Heart J.* 1959;58(1):59-70.

49. Moe GK, Rheinboldt WC, Abildskov JA. A COMPUTER MODEL OF ATRIAL FIBRILLATION. *Am Heart J.* 1964;67:200-220.

50. Allessie MA. Experimental evaluation of Moe's multiple wavelet hypothesis of atrial fibrillation. 1985.

51. Naccarelli GV, Wolbrette DL, Khan M, et al. Old and new antiarrhythmic drugs for converting and maintaining sinus rhythm in atrial fibrillation: comparative efficacy and results of trials. *Am J Cardiol.* 2003;91(6a):15d-26d.

52. Cox JL, Boineau JP, Schuessler RB, Kater KM, Lappas DG. Five-year experience with the maze procedure for atrial fibrillation. *Ann Thorac Surg.* 1993;56(4):814-823; discussion 823-814.

53. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. *J Am Coll Cardiol.* 2014;63(22):2335-2345.

54. Qi XY, Yeh YH, Xiao L, et al. Cellular signaling underlying atrial tachycardia remodeling of L-type calcium current. *Circ Res.* 2008;103(8):845-854.

55. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. *Circulation.* 1995;92(7):1954-1968.

56. Teh AW, Kistler PM, Lee G, et al. Electroanatomic Remodeling of the Left Atrium in Paroxysmal and Persistent Atrial Fibrillation Patients Without Structural Heart Disease. *Journal of Cardiovascular Electrophysiology.* 2012;23(3):232-238.

57. Folse R, Braunwald E. Determination of fraction of left ventricular volume ejected per beat and of ventricular end-diastolic and residual volumes. Experimental and clinical observations with a precordial dilution technic. *Circulation.* 1962;25:674-685.

58. Luchi RJ, Snow E, Luchi JM, Nelson CL, Pircher FJ. Left ventricular function in hospitalized geriatric patients. *J Am Geriatr Soc.* 1982;30(11):700-705.

59. Zile MR, Baicu CF, Gaasch WH. Diastolic heart failure--abnormalities in active relaxation and passive stiffness of the left ventricle. *N Engl J Med.* 2004;350(19):1953-1959.

60. Liu YW, Tsai WC, Su CT, Lin CC, Chen JH. Evidence of left ventricular systolic dysfunction detected by automated function imaging in patients with heart failure and preserved left ventricular ejection fraction. *J Card Fail.* 2009;15(9):782-789.

61. Lam CS, Roger VL, Rodeheffer RJ, Borlaug BA, Enders FT, Redfield MM. Pulmonary hypertension in heart failure with preserved ejection fraction: a community-based study. *J Am Coll Cardiol.* 2009;53(13):1119-1126.

62. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. *J Am Coll Cardiol.* 2013;62(4):263-271.

63. Kawaguchi M, Hay I, Fetics B, Kass DA. Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: implications for systolic and diastolic reserve limitations. *Circulation.* 2003;107(5):714-720.

64. Borlaug BA, Melenovsky V, Russell SD, et al. Impaired chronotropic and vasodilator reserves limit exercise capacity in patients with heart failure and a preserved ejection fraction. *Circulation.* 2006;114(20):2138-2147.

65. McHugh K, DeVore Adam D, Wu J, et al. Heart Failure With Preserved Ejection Fraction and Diabetes. *Journal of the American College of Cardiology.* 2019;73(5):602-611.

66. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. *Circulation.* 2017;136(1):6-19.

67. Ter Maaten JM, Damman K, Verhaar MC, et al. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. *Eur J Heart Fail.* 2016;18(6):588-598.

68. Yanaka K, Akahori H, Imanaka T, et al. The impact of peripheral artery disease on left ventricular diastolic function. *J Cardiol.* 2019;73(6):453-458.

69. Kitzman DW, Nicklas B, Kraus WE, et al. Skeletal muscle abnormalities and exercise intolerance in older patients with heart failure and preserved ejection fraction. *Am J Physiol Heart Circ Physiol.* 2014;306(9):H1364-1370.

70. Haykowsky MJ, Brubaker PH, Morgan TM, Kritchevsky S, Eggebeen J, Kitzman DW. Impaired aerobic capacity and physical functional performance in older heart failure patients with preserved ejection fraction: role of lean body mass. *J Gerontol A Biol Sci Med Sci.* 2013;68(8):968-975.

71. Peters AE, Tromp J, Shah SJ, et al. Phenomapping in heart failure with preserved ejection fraction: insights, limitations, and future directions. *Cardiovasc Res.* 2023;118(18):3403-3415.

72. Blume GG, Mcleod CJ, Barnes ME, et al. Left atrial function: physiology, assessment, and clinical implications. *European Journal of Echocardiography.* 2011;12(6):421-430.

73. Patel RB, Shah SJ. Therapeutic Targeting of Left Atrial Myopathy in Atrial Fibrillation and Heart Failure With Preserved Ejection Fraction. *JAMA Cardiol.* 2020;5(5):497-499.

74. Patel RB, Lam CSP, Svedlund S, et al. Disproportionate left atrial myopathy in heart failure with preserved ejection fraction among participants of the PROMIS-HFpEF study. *Scientific Reports.* 2021;11(1):4885.

75. Freed BH, Daruwalla V, Cheng JY, et al. Prognostic Utility and Clinical Significance of Cardiac Mechanics in Heart Failure With Preserved Ejection Fraction: Importance of Left Atrial Strain. *Circ Cardiovasc Imaging.* 2016;9(3).

76. Santos AB, Roca GQ, Claggett B, et al. Prognostic Relevance of Left Atrial Dysfunction in Heart Failure With Preserved Ejection Fraction. *Circ Heart Fail.* 2016;9(4):e002763.

77. Mesquita TRR, Zhang R, De Couto G, et al. Mechanisms of atrial fibrillation in aged rats with heart failure with preserved ejection fraction. *Heart Rhythm.* 2020;17(6):1025-1033.

78. Bode D, Lindner D, Schwarzl M, et al. The role of fibroblast – Cardiomyocyte interaction for atrial dysfunction in HFpEF and hypertensive heart disease. *Journal of Molecular and Cellular Cardiology.* 2019;131:53-65.

79. Duca F, Kammerlander AA, Zotter-Tufaro C, et al. Interstitial Fibrosis, Functional Status, and Outcomes in Heart Failure With Preserved Ejection Fraction. *Circulation: Cardiovascular Imaging.* 2016;9(12):e005277.

80. Zile MR, Gottdiener JS, Hetzel SJ, et al. Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction. *Circulation.* 2011;124(23):2491-2501.

81. Khan MS, Memon MM, Murad MH, et al. Left atrial function in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *Eur J Heart Fail.* 2020;22(3):472-485.

82. Takahashi N, Imataka K, Seki A, Fujii J. Left atrial enlargement in patients with paroxysmal atrial fibrillation. *Jpn Heart J.* 1982;23(5):677-683.

83. Kuppahally SS, Akoum N, Burgon NS, et al. Left Atrial Strain and Strain Rate in Patients With Paroxysmal and Persistent Atrial Fibrillation. *Circulation: Cardiovascular Imaging.* 2010;3(3):231-239.

84. Reddy YNV, Obokata M, Egbe A, et al. Left atrial strain and compliance in the diagnostic evaluation of heart failure with preserved ejection fraction. *European Journal of Heart Failure.* 2019;21(7):891-900.

85. Melenovsky V, Hwang S-J, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left Atrial Remodeling and Function in Advanced Heart Failure With Preserved or Reduced Ejection Fraction. *Circulation: Heart Failure.* 2015;8(2):295-303.

86. Kalogeropoulos A, Georgiopoulou V, Psaty BM, et al. Inflammatory Markers and Incident Heart Failure Risk in Older Adults. *Journal of the American College of Cardiology.* 2010;55(19):2129-2137.

87. Patel RB, Colangelo LA, Bielinski SJ, et al. Circulating Vascular Cell Adhesion Molecule-1 and Incident Heart Failure: The Multi-Ethnic Study of Atherosclerosis (MESA). *Journal of the American Heart Association.* 2020;9(22).

88. Patel RB, Colangelo LA, Reiner AP, et al. Cellular Adhesion Molecules in Young Adulthood and Cardiac Function in Later Life. *Journal of the American College of Cardiology.* 2020;75(17):2156-2165.

89. Wu N, Xu B, Xiang Y, et al. Association of inflammatory factors with occurrence and recurrence of atrial fibrillation: A meta-analysis. *International Journal of Cardiology.* 2013;169(1):62-72.

90. Rienstra M, Sun JX, Magnani JW, et al. White Blood Cell Count and Risk of Incident Atrial Fibrillation (From the Framingham Heart Study). *The American Journal of Cardiology.* 2012;109(4):533-537.

91. Prasada S, Rivera A, Nishtala A, et al. Differential Associations of Chronic Inflammatory Diseases With Incident Heart Failure. *JACC: Heart Failure.* 2020;8(6):489-498.

92. Lindhardsen J, Ahlehoff O, Gislason GH, et al. Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ.* 2012;344(mar08 2):e1257-e1257.

93. Kim YR, Nam G-B, Han S, et al. Effect of Short-Term Steroid Therapy on Early Recurrence During the Blanking Period After Catheter Ablation of Atrial Fibrillation. *Circulation: Arrhythmia and Electrophysiology.* 2015;8(6):1366-1372.

94. Van Osch D, Dieleman JM, Van Dijk D, et al. Dexamethasone for the prevention of postoperative atrial fibrillation. *International Journal of Cardiology.* 2015;182:431-437.

95. Paulus WJ, Zile MR. From Systemic Inflammation to Myocardial Fibrosis. *Circulation Research.* 2021;128(10):1451-1467.

96. Yildiz M, Oktay AA, Stewart MH, Milani RV, Ventura HO, Lavie CJ. Left ventricular hypertrophy and hypertension. *Progress in Cardiovascular Diseases.* 2020;63(1):10-21.

97. Norton GR, Woodiwiss AJ, Gaasch WH, et al. Heart failure in pressure overload hypertrophy. *Journal of the American College of Cardiology.* 2002;39(4):664-671.

98. Vaziri SM, Larson MG, Lauer MS, Benjamin EJ, Levy D. Influence of blood pressure on left atrial size. The Framingham Heart Study. *Hypertension.* 1995;25(6):1155-1160.

99. Lau DH, Shipp NJ, Kelly DJ, et al. Atrial Arrhythmia in Ageing Spontaneously Hypertensive Rats: Unraveling the Substrate in Hypertension and Ageing. *PLoS ONE.* 2013;8(8):e72416.

100. Dandona P, Dhindsa S, Ghanim H, Chaudhuri A. Angiotensin II and inflammation: the effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockade. *Journal of Human Hypertension.* 2007;21(1):20-27.

101. Munger TM, Dong YX, Masaki M, et al. Electrophysiological and hemodynamic characteristics associated with obesity in patients with atrial fibrillation. *J Am Coll Cardiol.* 2012;60(9):851-860.

102. Mahajan R, Lau DH, Brooks AG, et al. Electrophysiological, Electroanatomical, and Structural Remodeling of the Atria as Consequences of Sustained Obesity. *J Am Coll Cardiol.* 2015;66(1):1-11.

103. Turkbey EB, McClelland RL, Kronmal RA, et al. The impact of obesity on the left ventricle: the Multi-Ethnic Study of Atherosclerosis (MESA). *JACC Cardiovascular imaging.* 2010;3(3):266-274.

104. Woodiwiss AJ, Libhaber CD, Majane OH, Libhaber E, Maseko M, Norton GR. Obesity promotes left ventricular concentric rather than eccentric geometric remodeling and hypertrophy independent of blood pressure. *Am J Hypertens.* 2008;21(10):1144-1151.

105. Frank RC, Min J, Abdelghany M, et al. Obesity Is Associated With Pulmonary Hypertension and Modifies Outcomes. *Journal of the American Heart Association.* 2020;9(5).

106. Crea F, Camici PG, Bairey Merz CN. Coronary microvascular dysfunction: an update. *European Heart Journal.* 2014;35(17):1101-1111.

107. Franssen C, Chen S, Unger A, et al. Myocardial Microvascular Inflammatory Endothelial Activation in Heart Failure With Preserved Ejection Fraction. *JACC: Heart Failure.* 2016;4(4):312-324.

108. Shah AM, Claggett B, Sweitzer NK, et al. Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. *Circulation.* 2015;132(5):402-414.

109. Borlaug BA, Lam CSP, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and Ventricular Systolic Stiffening in Hypertensive Heart Disease. *Journal of the American College of Cardiology.* 2009;54(5):410-418.

110. Yip G. Left ventricular long axis function in diastolic heart failure is reduced in both diastole and systole: time for a redefinition? *Heart.* 2002;87(2):121-125.

111. Obokata M, Reddy YNV, Melenovsky V, et al. Myocardial Injury and Cardiac Reserve in Patients With Heart Failure and Preserved Ejection Fraction. *Journal of the American College of Cardiology.* 2018;72(1):29-40.

112. Ahmad A, Corban MT, Toya T, et al. Coronary microvascular dysfunction is associated with exertional haemodynamic abnormalities in patients with heart failure with preserved ejection fraction. *European Journal of Heart Failure.* 2021;23(5):765-772.

113. Shah SJ, Lam CSP, Svedlund S, et al. Prevalence and correlates of coronary microvascular dysfunction in heart failure with preserved ejection fraction: PROMIS-HFpEF. *European Heart Journal.* 2018;39(37):3439-3450.

114. Skalidis EI, Hamilos MI, Karalis IK, Chlouverakis G, Kochiadakis GE, Vardas PE. Isolated Atrial Microvascular Dysfunction in Patients With Lone Recurrent Atrial Fibrillation. *Journal of the American College of Cardiology.* 2008;51(21):2053-2057.

115. Wong CX, Sun MT, Odutayo A, et al. Associations of Epicardial, Abdominal, and Overall Adiposity With Atrial Fibrillation. *Circ Arrhythm Electrophysiol.* 2016;9(12).

116. Van Woerden G, Gorter TM, Westenbrink BD, Willems TP, Van Veldhuisen DJ, Rienstra M. Epicardial fat in heart failure patients with mid-range and preserved ejection fraction. *European Journal of Heart Failure.* 2018;20(11):1559-1566.

117. KankaanpäÄ M, Lehto H-R, PäRkkä JP, et al. Myocardial Triglyceride Content and Epicardial Fat Mass in Human Obesity: Relationship to Left Ventricular Function and Serum Free Fatty Acid Levels. *The Journal of Clinical Endocrinology & Metabolism.* 2006;91(11):4689-4695.

118. Malavazos AE, Di Leo G, Secchi F, et al. Relation of Echocardiographic Epicardial Fat Thickness and Myocardial Fat. *The American Journal of Cardiology.* 2010;105(12):1831-1835.

119. Greulich S, Maxhera B, Vandenplas G, et al. Secretory Products From Epicardial Adipose Tissue of Patients With Type 2 Diabetes Mellitus Induce Cardiomyocyte Dysfunction. *Circulation.* 2012;126(19):2324-2334.

120. Cherian S, Lopaschuk GD, Carvalho E. Cellular cross-talk between epicardial adipose tissue and myocardium in relation to the pathogenesis of cardiovascular disease. *Am J Physiol Endocrinol Metab.* 2012;303(8):E937-949.

121. Koepp KE, Obokata M, Reddy YNV, Olson TP, Borlaug BA. Hemodynamic and Functional Impact of Epicardial Adipose Tissue in Heart Failure With Preserved Ejection Fraction. *JACC: Heart Failure.* 2020;8(8):657-666.

122. Harada M, Nattel S. Implications of Inflammation and Fibrosis in Atrial Fibrillation Pathophysiology. *Card Electrophysiol Clin.* 2021;13(1):25-35.

123. Lau DH, Linz D, Schotten U, Mahajan R, Sanders P, Kalman JM. Pathophysiology of Paroxysmal and Persistent Atrial Fibrillation: Rotors, Foci and Fibrosis. *Heart, Lung and Circulation.* 2017;26(9):887-893.

124. Medi C, Kalman JM, Spence SJ, et al. Atrial Electrical and Structural Changes Associated with Longstanding Hypertension in Humans: Implications for the Substrate for Atrial Fibrillation. *Journal of Cardiovascular Electrophysiology.* 2011;22(12):1317-1324.

125. Mahajan R, Lau DH, Brooks AG, et al. Atrial Fibrillation and Obesity: Reverse Remodeling of Atrial Substrate With Weight Reduction. *JACC Clin Electrophysiol.* 2021;7(5):630-641.

126. Dimitri H, Ng M, Brooks AG, et al. Atrial remodeling in obstructive sleep apnea: Implications for atrial fibrillation. *Heart Rhythm.* 2012;9(3):321-327.

127. Takahashi Y, Yamaguchi T, Otsubo T, et al. Histological validation of atrial structural remodelling in patients with atrial fibrillation. *European Heart Journal.* 2023;44(35):3339-3353.

128. Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary Microvascular Rarefaction and Myocardial Fibrosis in Heart Failure With Preserved Ejection Fraction. *Circulation.* 2015;131(6):550-559.

129. Yamamoto K. Myocardial stiffness is determined by ventricular fibrosis, but not by compensatory or excessive hypertrophy in hypertensive heart. *Cardiovascular Research.* 2002;55(1):76-82.

130. Ariyaratnam JP, Lau DH, Sanders P, Kalman JM. Atrial Fibrillation and Heart Failure: Epidemiology, Pathophysiology, Prognosis, and Management. *Card Electrophysiol Clin.* 2021;13(1):47-62.

131. Solti F, Vecsey T, Kékesi V, Juhász-Nagy A. The effect of atrial dilatation on the genesis of atrial arrhythmias. *Cardiovasc Res.* 1989;23(10):882-886.

132. Sanders P, Morton JB, Davidson NC, et al. Electrical Remodeling of the Atria in Congestive Heart Failure. *Circulation.* 2003;108(12):1461-1468.

133. Kitzman DW. Pathophysiological Characterization of Isolated Diastolic Heart Failure in Comparison to Systolic Heart Failure. *JAMA.* 2002;288(17):2144.

134. Li D, Shinagawa K, Pang L, et al. Effects of Angiotensin-Converting Enzyme Inhibition on the Development of the Atrial Fibrillation Substrate in Dogs With Ventricular Tachypacing–Induced Congestive Heart Failure. *Circulation.* 2001;104(21):2608-2614.

135. Mitchell JH, Gupta DN, Payne RM. Influence of Atrial Systole on Effective Ventricular Stroke Volume. *Circulation Research.* 1965;17(1):11-18.

136. Borlaug BA. Evaluation and management of heart failure with preserved ejection fraction. *Nature Reviews Cardiology.* 2020;17(9):559-573.

137. Ling L-H, Kistler PM, Ellims AH, et al. Diffuse Ventricular Fibrosis in Atrial Fibrillation. *Journal of the American College of Cardiology.* 2012;60(23):2402-2408.

138. Daoud EG, Weiss R, Bahu M, et al. Effect of an irregular ventricular rhythm on cardiac output. *The American Journal of Cardiology.* 1996;78(12):1433-1436.

139. Lloyd-Jones DM, Wang TJ, Leip EP, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation.* 2004;110(9):1042-1046.

140. Ghelani KP, Chen LY, Norby FL, Soliman EZ, Koton S, Alonso A. Thirty-Year Trends in the Incidence of Atrial Fibrillation: The ARIC Study. *Journal of the American Heart Association.* 2022;11(8).

141. Heeringa J, van der Kuip DA, Hofman A, et al. Prevalence, incidence and lifetime risk of atrial fibrillation: the Rotterdam study. *Eur Heart J.* 2006;27(8):949-953.

142. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of Systolic and Diastolic Ventricular Dysfunction in the Community. *JAMA.* 2003;289(2):194.

143. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol.* 1998;82(8a):2n-9n.

144. Lee MP, Glynn RJ, Schneeweiss S, et al. Risk Factors for Heart Failure with Preserved or Reduced Ejection Fraction Among Medicare Beneficiaries: Application of Competing Risks Analysis and Gradient Boosted Model. *Clin Epidemiol.* 2020;12:607-616.

145. Centurión OA, Isomoto S, Shimizu A, et al. The effects of aging on atrial endocardial electrograms in patients with paroxysmal atrial fibrillation. *Clin Cardiol.* 2003;26(9):435-438.

146. Kistler PM, Sanders P, Fynn SP, et al. Electrophysiologic and electroanatomic changes in the human atrium associated with age. *J Am Coll Cardiol.* 2004;44(1):109-116.

147. van der Does WFB, Houck CA, Heida A, et al. Atrial electrophysiological characteristics of aging. *J Cardiovasc Electrophysiol.* 2021;32(4):903-912.

148. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. *Nat Rev Cardiol.* 2018;15(9):505-522.

149. Fujimoto N, Borlaug BA, Lewis GD, et al. Hemodynamic Responses to Rapid Saline Loading. *Circulation.* 2013;127(1):55-62.

150. van de Hoef TP, Echavarria-Pinto M, Meuwissen M, Stegehuis VE, Escaned J, Piek JJ. Contribution of Age-Related Microvascular Dysfunction to Abnormal Coronary: Hemodynamics in Patients With Ischemic Heart Disease. *JACC: Cardiovascular Interventions.* 2020;13(1):20-29.

151. Biernacka A, Frangogiannis NG. Aging and Cardiac Fibrosis. *Aging Dis.* 2011;2(2):158-173.

152. McMurray JJ, Carson PE, Komajda M, et al. Heart failure with preserved ejection fraction: clinical characteristics of 4133 patients enrolled in the I-PRESERVE trial. *Eur J Heart Fail.* 2008;10(2):149-156.

153. Benjamin EJ. Independent Risk Factors for Atrial Fibrillation in a Population-Based Cohort. *JAMA.* 1994;271(11):840.

154. Gong FF, Jelinek MV, Castro JM, et al. Risk factors for incident heart failure with preserved or reduced ejection fraction, and valvular heart failure, in a community-based cohort. *Open Heart.* 2018;5(2):e000782.

155. Lau DH, Shenasa HA, Shenasa M. Hypertension, Prehypertension, Hypertensive Heart Disease, and Atrial Fibrillation. *Card Electrophysiol Clin.* 2021;13(1):37-45.

156. M JS, L YC, Whalen SP, et al. Effect of Intensive Blood Pressure Lowering on Incident Atrial Fibrillation: A Systematic Review and Meta-Analysis. *J Atr Fibrillation.* 2020;13(4):2401.

157. Verdecchia P, Angeli F, Cavallini C, et al. Blood pressure reduction and renin-angiotensin system inhibition for prevention of congestive heart failure: a meta-analysis. *Eur Heart J.* 2009;30(6):679-688.

158. Devereux RB, Pickering TG, Harshfield GA, et al. Left ventricular hypertrophy in patients with hypertension: importance of blood pressure response to regularly recurring stress. *Circulation.* 1983;68(3):470-476.

159. Lau DH, Mackenzie L, Kelly DJ, et al. Hypertension and atrial fibrillation: evidence of progressive atrial remodeling with electrostructural correlate in a conscious chronically instrumented ovine model. *Heart Rhythm.* 2010;7(9):1282-1290.

160. Lau DH, Mackenzie L, Kelly DJ, et al. Short-term hypertension is associated with the development of atrial fibrillation substrate: a study in an ovine hypertensive model. *Heart Rhythm.* 2010;7(3):396-404.

161. Ehrlich JR, Hohnloser SH, Nattel S. Role of angiotensin system and effects of its inhibition in atrial fibrillation: clinical and experimental evidence. *Eur Heart J.* 2006;27(5):512-518.

162. Lau YF, Yiu KH, Siu CW, Tse HF. Hypertension and atrial fibrillation: epidemiology, pathophysiology and therapeutic implications. *Journal of Human Hypertension.* 2012;26(10):563-569.

163. Xiao L, Harrison DG. Inflammation in Hypertension. *Can J Cardiol.* 2020;36(5):635-647.

164. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *Jama.* 1979;241(19):2035-2038.

165. Echouffo-Tcheugui JB, Xu H, DeVore AD, et al. Temporal trends and factors associated with diabetes mellitus among patients hospitalized with heart failure:

Findings from Get With The Guidelines-Heart Failure registry. *Am Heart J.* 2016;182:9-20.

166. Qi W, Zhang N, Korantzopoulos P, et al. Serum glycated hemoglobin level as a predictor of atrial fibrillation: A systematic review with meta-analysis and meta-regression. *PLoS One.* 2017;12(3):e0170955.

167. Gu J, Fan YQ, Zhang JF, Wang CQ. Association of hemoglobin A1c variability and the incidence of heart failure with preserved ejection fraction in patients with type 2 diabetes mellitus and arterial hypertension. *Hellenic J Cardiol.* 2018;59(2):91-97.

168. Lind V, Hammar N, Lundman P, et al. Impaired fasting glucose: a risk factor for atrial fibrillation and heart failure. *Cardiovasc Diabetol.* 2021;20(1):227.

169. Watanabe M, Yokoshiki H, Mitsuyama H, Mizukami K, Ono T, Tsutsui H. Conduction and refractory disorders in the diabetic atrium. *American Journal of Physiology-Heart and Circulatory Physiology.* 2012;303(1):H86-H95.

170. Nakanishi K, Daimon M, Fujiu K, et al. Prevalence of glucose metabolism disorders and its association with left atrial remodelling before and after catheter ablation in patients with atrial fibrillation. *EP Europace.* 2023;25(5).

171. Faria A, Persaud SJ. Cardiac oxidative stress in diabetes: mechanisms and therapeutic potential. *Pharmacology & therapeutics.* 2017;172:50-62.

172. Di Carli Marcelo F, Janisse J, Ager J, Grunberger G. Role of chronic hyperglycemia in the pathogenesis of coronary microvascular dysfunction in diabetes. *Journal of the American College of Cardiology.* 2003;41(8):1387-1393.

173. Li Y, Liu B, Li Y, et al. Epicardial fat tissue in patients with diabetes mellitus: a systematic review and meta-analysis. *Cardiovasc Diabetol.* 2019;18(1):3.

174. Russo I, Frangogiannis NG. Diabetes-associated cardiac fibrosis: cellular effectors, molecular mechanisms and therapeutic opportunities. *Journal of molecular and cellular cardiology.* 2016;90:84-93.

175. Jia G, Whaley-Connell A, Sowers JR. Diabetic cardiomyopathy: a hyperglycaemia-and insulin-resistance-induced heart disease. *Diabetologia.* 2018;61(1):21-28.

176. Wanahita N, Messerli FH, Bangalore S, Gami AS, Somers VK, Steinberg JS. Atrial fibrillation and obesity--results of a meta-analysis. *Am Heart J.* 2008;155(2):310-315.

177. Wang TJ. Obesity and the Risk of New-Onset Atrial Fibrillation. *JAMA.* 2004;292(20):2471.

178. Huxley RR, Lopez FL, Folsom AR, et al. Absolute and Attributable Risks of Atrial Fibrillation in Relation to Optimal and Borderline Risk Factors. *Circulation.* 2011;123(14):1501-1508.

179. Rao VN, Zhao D, Allison MA, et al. Adiposity and Incident Heart Failure and its Subtypes. *JACC: Heart Failure.* 2018;6(12):999-1007.

180. Miller WL, Borlaug BA. Impact of Obesity on Volume Status in Patients With Ambulatory Chronic Heart Failure. *J Card Fail.* 2020;26(2):112-117.

181. Szabo L, McCracken C, Cooper J, et al. The role of obesity-related cardiovascular remodelling in mediating incident cardiovascular outcomes: a population-based observational study. *European Heart Journal - Cardiovascular Imaging.* 2023;24(7):921-929.

182. Nalliah CJ, Sanders P, Kottkamp H, Kalman JM. The role of obesity in atrial fibrillation. *European Heart Journal.* 2015;37(20):1565-1572.

183. Mahajan R, Nelson A, Pathak RK, et al. Electroanatomical Remodeling of the Atria in Obesity. *JACC: Clinical Electrophysiology.* 2018;4(12):1529-1540.

184. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci.* 2017;13(4):851-863.

185. Bajaj Navkaranbir S, Osborne Michael T, Gupta A, et al. Coronary Microvascular Dysfunction and Cardiovascular Risk in Obese Patients. *Journal of the American College of Cardiology.* 2018;72(7):707-717.

186. Mahajan R, Lau DH, Sanders P. Impact of obesity on cardiac metabolism, fibrosis, and function. *Trends in Cardiovascular Medicine.* 2015;25(2):119-126.

187. Kadhim K, Middeldorp ME, Elliott AD, et al. Prevalence and Assessment of Sleep-Disordered Breathing in Patients With Atrial Fibrillation: A Systematic Review and Meta-analysis. *Canadian Journal of Cardiology.* 2021;37(11):1846-1856.

188. Bitter T, Faber L, Hering D, Langer C, Horstkotte D, Oldenburg O. Sleep-disordered breathing in heart failure with normal left ventricular ejection fraction. *Eur J Heart Fail.* 2009;11(6):602-608.

189. Youssef I, Kamran H, Yacoub M, et al. Obstructive Sleep Apnea as a Risk Factor for Atrial Fibrillation: A Meta-Analysis. *J Sleep Disord Ther.* 2018;7(1).

190. Linz D, Woehrle H, Bitter T, et al. The importance of sleep-disordered breathing in cardiovascular disease. *Clin Res Cardiol.* 2015;104(9):705-718.

191. Chaouat A, Weitzenblum E, Krieger J, Oswald M, Kessler R. Pulmonary hemodynamics in the obstructive sleep apnea syndrome. Results in 220 consecutive patients. *Chest.* 1996;109(2):380-386.

192. Arias MA, García-Río F, Alonso-Fernández A, Mediano O, Martínez I, Villamor J. Obstructive sleep apnea syndrome affects left ventricular diastolic function: effects of nasal continuous positive airway pressure in men. *Circulation.* 2005;112(3):375-383.

193. Kohler M, Stradling JR. Mechanisms of vascular damage in obstructive sleep apnea. *Nat Rev Cardiol.* 2010;7(12):677-685.

194. Iwasaki YK, Kato T, Xiong F, et al. Atrial fibrillation promotion with long-term repetitive obstructive sleep apnea in a rat model. *J Am Coll Cardiol.* 2014;64(19):2013-2023.

195. Monahan K, Storfer-Isser A, Mehra R, et al. Triggering of nocturnal arrhythmias by sleep-disordered breathing events. *J Am Coll Cardiol.* 2009;54(19):1797-1804.

196. Linz D, Schotten U, Neuberger HR, Böhm M, Wirth K. Negative tracheal pressure during obstructive respiratory events promotes atrial fibrillation by vagal activation. *Heart Rhythm.* 2011;8(9):1436-1443.

197. Pandey A, Patel KV, Vaduganathan M, et al. Physical Activity, Fitness, and Obesity in Heart Failure With Preserved Ejection Fraction. *JACC Heart Fail.* 2018;6(12):975-982.

198. Pandey A, LaMonte M, Klein L, et al. Relationship Between Physical Activity, Body Mass Index, and Risk of Heart Failure. *J Am Coll Cardiol.* 2017;69(9):1129-1142.

199. Elliott AD, Linz D, Mishima R, et al. Association between physical activity and risk of incident arrhythmias in 402 406 individuals: evidence from the UK Biobank cohort. *European Heart Journal.* 2020;41(15):1479-1486.

200. Pandey A, Patel KV, Bahnson JL, et al. Association of Intensive Lifestyle Intervention, Fitness, and Body Mass Index With Risk of Heart Failure in Overweight or Obese Adults With Type 2 Diabetes Mellitus: An Analysis From the Look AHEAD Trial. *Circulation.* 2020;141(16):1295-1306.

201. Qureshi WT, Alirhayim Z, Blaha MJ, et al. Cardiorespiratory Fitness and Risk of Incident Atrial Fibrillation. *Circulation.* 2015;131(21):1827-1834.

202. Soares-Miranda L, Sattelmair J, Chaves P, et al. Physical activity and heart rate variability in older adults: the Cardiovascular Health Study. *Circulation.* 2014;129(21):2100-2110.

203. Houmard JA, Tanner CJ, Slentz CA, Duscha BD, McCartney JS, Kraus WE. Effect of the volume and intensity of exercise training on insulin sensitivity. *Journal of applied physiology.* 2004;96(1):101-106.

204. Tinken TM, Thijssen DH, Black MA, Cable NT, Green DJ. Time course of change in vasodilator function and capacity in response to exercise training in humans. *The Journal of physiology.* 2008;586(20):5003-5012.

205. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. *Nature reviews immunology.* 2011;11(9):607-615.

206. Pathak RK, Elliott A, Middeldorp ME, et al. Impact of CARDIOrespiratory FITness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation: The CARDIO-FIT Study. *J Am Coll Cardiol.* 2015;66(9):985-996.

207. Lam CSP, Rienstra M, Tay WT, et al. Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction. *JACC: Heart Failure.* 2017;5(2):92-98.

208. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. *Circulation.* 2018;138(9):861-870.

209. Pieske B, Tschöpe C, De Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA–PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). *European Heart Journal.* 2019;40(40):3297-3317.

210. Verbrugge FH, Reddy YNV, Sorimachi H, Omote K, Carter RE, Borlaug BA. Diagnostic scores predict morbidity and mortality in patients hospitalized for heart failure with preserved ejection fraction. *European Journal of Heart Failure.* 2021.

211. Sramko M, Wichterle D, Melenovsky V, et al. Resting and Exercise-Induced Left Atrial Hypertension in Patients With Atrial Fibrillation. *JACC: Clinical Electrophysiology.* 2017;3(5):461-469.

212. Meluzin J, Starek Z, Kulik T, et al. Prevalence and Predictors of Early Heart Failure With Preserved Ejection Fraction in Patients With Paroxysmal Atrial Fibrillation. *Journal of Cardiac Failure.* 2017;23(7):558-562.

213. Sugumar H, Nanayakkara S, Vizi D, et al. A prospective STudy using invAsive haemodynamic measurements foLLowing catheter ablation for AF and early HFpEF : STALL AF-. *European Journal of Heart Failure.* 2021.

214. Reddy YNV, Obokata M, Gersh BJ, Borlaug BA. High Prevalence of Occult Heart Failure With Preserved Ejection Fraction Among Patients With Atrial Fibrillation and Dyspnea. *Circulation.* 2018;137(5):534-535.

215. Berlier C, Saxer S, Lichtblau M, et al. Influence of Upright Versus Supine Position on Resting and Exercise Hemodynamics in Patients Assessed for Pulmonary Hypertension. *J Am Heart Assoc.* 2022;11(4):e023839.

216. Dickinson MG, Lam CS, Rienstra M, et al. Atrial fibrillation modifies the association between pulmonary artery wedge pressure and left ventricular end-diastolic pressure. *European Journal of Heart Failure.* 2017;19(11):1483-1490.

217. Atwood JE, Myers JN, Tang XC, Reda DJ, Singh SN, Singh BN. Exercise capacity in atrial fibrillation: A substudy of the Sotalol-Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T). *American Heart Journal.* 2007;153(4):566-572.

218. Elliott AD, Verdicchio CV, Gallagher C, et al. Factors Contributing to Exercise Intolerance in Patients With Atrial Fibrillation. *Heart, Lung and Circulation.* 2020.

219. Del Buono MG, Arena R, Borlaug BA, et al. Exercise Intolerance in Patients With Heart Failure: JACC State-of-the-Art Review. *Journal of the American College of Cardiology.* 2019;73(17):2209-2225.

220. Haykowsky MJ, Brubaker PH, John JM, Stewart KP, Morgan TM, Kitzman DW. Determinants of Exercise Intolerance in Elderly Heart Failure Patients With Preserved Ejection Fraction. *Journal of the American College of Cardiology.* 2011;58(3):265-274.

221. Abudiab MM, Redfield MM, Melenovsky V, et al. Cardiac output response to exercise in relation to metabolic demand in heart failure with preserved ejection fraction. *European journal of heart failure.* 2013;15(7):776-785.

222. Zweerink A, van der Lingen A-LC, Handoko ML, van Rossum AC, Allaart CP. Chronotropic incompetence in chronic heart failure: a state-of-the-art review. *Circulation: Heart Failure.* 2018;11(8):e004969.

223. Borlaug BA, Jaber WA, Ommen SR, Lam CS, Redfield MM, Nishimura RA. Diastolic relaxation and compliance reserve during dynamic exercise in heart failure with preserved ejection fraction. *Heart.* 2011;97(12):964-969.

224. Obokata M, Reddy YNV, Melenovsky V, et al. Myocardial Injury and Cardiac Reserve in Patients With Heart Failure and Preserved Ejection Fraction. *J Am Coll Cardiol.* 2018;72(1):29-40.

225. Bandera F, Generati G, Pellegrino M, et al. Mitral regurgitation in heart failure: insights from CPET combined with exercise echocardiography. *European Heart Journal-Cardiovascular Imaging.* 2017;18(3):296-303.

226. Maffeis C, Morris DA, Belyavskiy E, et al. Left atrial function and maximal exercise capacity in heart failure with preserved and mid-range ejection fraction. *ESC Heart Failure.* 2021;8(1):116-128.

227. von Roeder M, Rommel KP, Kowallick JT, et al. Influence of Left Atrial Function on Exercise Capacity and Left Ventricular Function in Patients With Heart Failure and Preserved Ejection Fraction. *Circ Cardiovasc Imaging.* 2017;10(4).

228. Singh I, Rahaghi FN, Naeije R, Oliveira RKF, Systrom DM, Waxman AB. Right Ventricular-Arterial Uncoupling During Exercise in Heart Failure With Preserved Ejection Fraction: Role of Pulmonary Vascular Dysfunction. *Chest.* 2019;156(5):933-943.

229. Palau P, Seller J, Domínguez E, et al. Effect of β-Blocker Withdrawal on Functional Capacity in Heart Failure and Preserved Ejection Fraction. *J Am Coll Cardiol.* 2021;78(21):2042-2056.

230. Olson TP, Johnson BD, Borlaug BA. Impaired pulmonary diffusion in heart failure with preserved ejection fraction. *JACC: Heart Failure.* 2016;4(6):490-498.

231. Wong E, Selig S, Hare DL. Respiratory muscle dysfunction and training in chronic heart failure. *Heart, lung and circulation.* 2011;20(5):289-294.

232. Haykowsky MJ, Kouba EJ, Brubaker PH, Nicklas BJ, Eggebeen J, Kitzman DW. Skeletal Muscle Composition and Its Relation to Exercise Intolerance in Older Patients With Heart Failure and Preserved Ejection Fraction. *The American Journal of Cardiology.* 2014;113(7):1211-1216.

233. Scandalis L, Kitzman DW, Nicklas BJ, et al. Skeletal Muscle Mitochondrial Respiration and Exercise Intolerance in Patients With Heart Failure With Preserved Ejection Fraction. *JAMA Cardiology.* 2023;8(6):575.

234. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22(8):983-988.

235. Otite FO, Khandelwal P, Chaturvedi S, Romano JG, Sacco RL, Malik AM. Increasing atrial fibrillation prevalence in acute ischemic stroke and TIA. *Neurology.* 2016;87(19):2034-2042.

236. Henriksson KM, Farahmand B, Åsberg S, Edvardsson N, Terént A. Comparison of cardiovascular risk factors and survival in patients with ischemic or hemorrhagic stroke. *International journal of stroke.* 2012;7(4):276-281.

237. Lim HS, Willoughby SR, Schultz C, et al. Effect of atrial fibrillation on atrial thrombogenesis in humans: impact of rate and rhythm. *J Am Coll Cardiol.* 2013;61(8):852-860.

238. Daoud EG, Glotzer TV, Wyse DG, et al. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. *Heart Rhythm.* 2011;8(9):1416-1423.

239. Brambatti M, Connolly SJ, Gold MR, et al. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation.* 2014;129(21):2094-2099.

240. Camen S, Ojeda FM, Niiranen T, et al. Temporal relations between atrial fibrillation and ischaemic stroke and their prognostic impact on mortality. *Europace.* 2020;22(4):522-529.

241. King JB, Azadani PN, Suksaranjit P, et al. Left Atrial Fibrosis and Risk of Cerebrovascular and Cardiovascular Events in Patients With Atrial Fibrillation. *J Am Coll Cardiol.* 2017;70(11):1311-1321.

242. Leung M, van Rosendael PJ, Abou R, et al. Left atrial function to identify patients with atrial fibrillation at high risk of stroke: new insights from a large registry. *Eur Heart J.* 2018;39(16):1416-1425.

243. Packer DL, Mark DB, Robb RA, et al. Effect of Catheter Ablation vs Antiarrhythmic Drug Therapy on Mortality, Stroke, Bleeding, and Cardiac Arrest Among Patients With Atrial Fibrillation. *JAMA.* 2019;321(13):1261.

244. Barra S, Baran J, Narayanan K, et al. Association of catheter ablation for atrial fibrillation with mortality and stroke: A systematic review and meta-analysis. *Int J Cardiol.* 2018;266:136-142.

245. Singer DE, Ziegler PD, Koehler JL, Sarkar S, Passman RS. Temporal Association Between Episodes of Atrial Fibrillation and Risk of Ischemic Stroke. *JAMA Cardiol.* 2021;6(12):1364-1369.

246. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. *Ann Thorac Surg.* 1996;61(2):755-759.

247. Burrell LD, Horne BD, Anderson JL, Muhlestein JB, Whisenant BK. Usefulness of left atrial appendage volume as a predictor of embolic stroke in patients with atrial fibrillation. *Am J Cardiol.* 2013;112(8):1148-1152.

248. Beinart R, Heist EK, Newell JB, Holmvang G, Ruskin JN, Mansour M. Left atrial appendage dimensions predict the risk of stroke/TIA in patients with atrial fibrillation. *J Cardiovasc Electrophysiol.* 2011;22(1):10-15.

249. Lee JM, Shim J, Uhm JS, et al. Impact of increased orifice size and decreased flow velocity of left atrial appendage on stroke in nonvalvular atrial fibrillation. *Am J Cardiol.* 2014;113(6):963-969.

250. Di Biase L, Santangeli P, Anselmino M, et al. Does the left atrial appendage morphology correlate with the risk of stroke in patients with atrial fibrillation? Results from a multicenter study. *J Am Coll Cardiol.* 2012;60(6):531-538.

251. Goldman ME, Pearce LA, Hart RG, et al. Pathophysiologic correlates of thromboembolism in nonvalvular atrial fibrillation: I. Reduced flow velocity in the left

atrial appendage (The Stroke Prevention in Atrial Fibrillation [SPAF-III] study). *J Am Soc Echocardiogr.* 1999;12(12):1080-1087.

252. Pathak RK, Middeldorp ME, Meredith M, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort. *Journal of the American College of Cardiology.* 2015;65(20):2159-2169.

253. Pathak RK, Middeldorp ME, Lau DH, et al. Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for the Outcome of Ablation. *Journal of the American College of Cardiology.* 2014;64(21):2222-2231.

254. Middeldorp ME, Pathak RK, Meredith M, et al. PREVEntion and regReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation: the REVERSE-AF study. *EP Europace.* 2018;20(12):1929-1935.

255. Middeldorp ME, Ariyaratnam J, Lau D, Sanders P. Lifestyle modifications for treatment of atrial fibrillation. *Heart.* 2020;106(5):325-332.

256. Kitzman DW, Brubaker P, Morgan T, et al. Effect of Caloric Restriction or Aerobic Exercise Training on Peak Oxygen Consumption and Quality of Life in Obese Older Patients With Heart Failure With Preserved Ejection Fraction. *JAMA.* 2016;315(1):36.

257. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *New England Journal of Medicine.* 2021;385(16):1451-1461.

258. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *N Engl J Med.* 2022;387(12):1089-1098.

259. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *New England Journal of Medicine.* 2023.

260. Infeld M, Wahlberg K, Cicero J, et al. Effect of Personalized Accelerated Pacing on Quality of Life, Physical Activity, and Atrial Fibrillation in Patients With Preclinical and Overt Heart Failure With Preserved Ejection Fraction: The myPACE Randomized Clinical Trial. *JAMA Cardiology.* 2023;8(3):213-221.

261. Parameswaran R, Al-Kaisey AM, Kalman JM. Catheter ablation for atrial fibrillation: current indications and evolving technologies. *Nature Reviews Cardiology.* 2021;18(3):210-225.

262. Kirchhof P, Camm AJ, Goette A, et al. Early Rhythm-Control Therapy in Patients with Atrial Fibrillation. *New England Journal of Medicine.* 2020;383(14):1305-1316.

263. Allessie M. Electrical, contractile and structural remodeling during atrial fibrillation. *Cardiovascular Research.* 2002;54(2):230-246.

264. Bunch TJ, May HT, Bair TL, et al. Increasing time between first diagnosis of atrial fibrillation and catheter ablation adversely affects long-term outcomes. *Heart Rhythm.* 2013;10(9):1257-1262.

265. Rettmann ME, Holmes DR, 3rd, Monahan KH, et al. Treatment-Related Changes in Left Atrial Structure in Atrial Fibrillation: Findings From the CABANA Imaging Substudy. *Circ Arrhythm Electrophysiol.* 2021;14(5):e008540.

266. Wylie JV, Peters DC, Essebag V, Manning WJ, Josephson ME, Hauser TH. Left atrial function and scar after catheter ablation of atrial fibrillation. *Heart Rhythm.* 2008;5(5):656-662.

267. Kuppahally SS, Akoum N, Badger TJ, et al. Echocardiographic left atrial reverse remodeling after catheter ablation of atrial fibrillation is predicted by preablation delayed enhancement of left atrium by magnetic resonance imaging. *American Heart Journal.* 2010;160(5):877-884.

268. Xiong B, Li D, Wang J, Gyawali L, Jing J, Su L. The Effect of Catheter Ablation on Left Atrial Size and Function for Patients with Atrial Fibrillation: An Updated Meta-Analysis. *PLOS ONE.* 2015;10(7):e0129274.

269. Jeevanantham V, Ntim W, Navaneethan SD, et al. Meta-analysis of the effect of radiofrequency catheter ablation on left atrial size, volumes and function in patients with atrial fibrillation. *Am J Cardiol.* 2010;105(9):1317-1326.

270. Obokata M, Reddy YNV, Borlaug BA. Diastolic Dysfunction and Heart Failure With Preserved Ejection Fraction. *JACC: Cardiovascular Imaging.* 2020;13(1):245-257.

271. Iwasaki Y-K, Nishida K, Kato T, Nattel S. Atrial Fibrillation Pathophysiology. *Circulation.* 2011;124(20):2264-2274.

272. Khan MS, Memon MM, Murad MH, et al. Left atrial function in heart failure with preserved ejection fraction: a systematic review and meta-analysis. *European Journal of Heart Failure.* 2020;22(3):472-485.

273. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation.* 2022;145(18).

274. Behnoush AH, Khalaji A, Naderi N, Ashraf H, Von Haehling S. ACC/AHA/HFSA 2022 and ESC 2021 guidelines on heart failure comparison. *ESC Heart Failure.* 2023;10(3):1531-1544.

275. Bonno EL, Viray MC, Jackson GR, Houston BA, Tedford RJ. Modern Right Heart Catheterization: Beyond Simple Hemodynamics. *Advances in Pulmonary Hypertension.* 2020;19(1):6-15.

276. Robbins IM, Hemnes AR, Pugh ME, et al. High Prevalence of Occult Pulmonary Venous Hypertension Revealed by Fluid Challenge in Pulmonary Hypertension. *Circulation: Heart Failure.* 2014;7(1):116-122.

277. Fox BD, Shimony A, Langleben D, et al. High prevalence of occult left heart disease in scleroderma-pulmonary hypertension. *European Respiratory Journal.* 2013;42(4):1083-1091.

278. Singh H, Jain AC, Bhumbla DK, Failinger C. Comparison of left atrial dimensions by transesophageal and transthoracic echocardiography. *Echocardiography.* 2005;22(10):789-796.

279. Kuklik P, Szumowski L, Zebrowski JJ, Walczak F. The reconstruction, from a set of points, and analysis of the interior surface of the heart chamber. *Physiol Meas.* 2004;25(3):617-627.

280. Mirea O, Duchenne J, Voigt JU. Comparison between Nondedicated and Novel Dedicated Tracking Tool for Right Ventricular and Left Atrial Strain. *J Am Soc Echocardiogr.* 2021.

281. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for Cardiac Chamber Quantification by Echocardiography in Adults: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography.* 2015;28(1):1-39.e14.

282. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2016;29(4):277-314.

283. Bilbao A, Escobar A, García-Perez L, Navarro G, Quirós R. The Minnesota living with heart failure questionnaire: comparison of different factor structures. *Health and Quality of Life Outcomes.* 2016;14(1).

284. Dorian P, Guerra PG, Kerr CR, et al. Validation of a New Simple Scale to Measure Symptoms in Atrial Fibrillation. *Circulation: Arrhythmia and Electrophysiology.* 2009;2(3):218-224.

285. Borlaug BA, Nishimura RA, Sorajja P, Lam CSP, Redfield MM. Exercise Hemodynamics Enhance Diagnosis of Early Heart Failure With Preserved Ejection Fraction. *Circulation: Heart Failure.* 2010;3(5):588-595.

286. Dorfs S, Zeh W, Hochholzer W, et al. Pulmonary capillary wedge pressure during exercise and long-term mortality in patients with suspected heart failure with preserved ejection fraction. *European Heart Journal.* 2014;35(44):3103-3112.

287. Ewert R, Heine A, Müller-Heinrich A, et al. Exercise and fluid challenge during right heart catheterisation for evaluation of dyspnoea. *Pulmonary Circulation.* 2020;10(3):1-9.

288. Khurram IM, Maqbool F, Berger RD, et al. Association Between Left Atrial Stiffness Index and Atrial Fibrillation Recurrence in Patients Undergoing Left Atrial Ablation. *Circulation: Arrhythmia and Electrophysiology.* 2016;9(3):e003163.

289. Garnvik LE, Malmo V, Janszky I, et al. Physical activity, cardiorespiratory fitness, and cardiovascular outcomes in individuals with atrial fibrillation: the HUNT study. *European Heart Journal.* 2020;41(15):1467-1475.

290. Inciardi RM, Giugliano RP, Claggett B, et al. Left atrial structure and function and the risk of death or heart failure in atrial fibrillation. *Eur J Heart Fail.* 2019;21(12):1571-1579.

291. Habibi M, Zareian M, Ambale Venkatesh B, et al. Left Atrial Mechanical Function and Incident Ischemic Cerebrovascular Events Independent of AF: Insights From the MESA Study. *JACC Cardiovasc Imaging.* 2019;12(12):2417-2427.

292. Daccarett M, Badger TJ, Akoum N, et al. Association of left atrial fibrosis detected by delayed-enhancement magnetic resonance imaging and the risk of stroke in patients with atrial fibrillation. *J Am Coll Cardiol.* 2011;57(7):831-838.

293. Chieng D, Sugumar H, Segan L, et al. Atrial Fibrillation Ablation for Heart Failure With Preserved Ejection Fraction: A Randomized Controlled Trial. *JACC Heart Fail.* 2023.

294. Zylla MM, Leiner J, Rahm A-K, et al. Cryoballoon-ablation of atrial fibrillation in patients with heart failure and preserved ejection fraction. *EP Europace.* 2022;24.

295. Andersen MJ, Olson TP, Melenovsky V, Kane GC, Borlaug BA. Differential hemodynamic effects of exercise and volume expansion in people with and without heart failure. *Circ Heart Fail.* 2015;8(1):41-48.

296. Reddy YNV, El-Sabbagh A, Nishimura RA. Comparing Pulmonary Arterial Wedge Pressure and Left Ventricular End Diastolic Pressure for Assessment of Left-Sided Filling Pressures. *JAMA Cardiology.* 2018;3(6):453.

297. Wang TJ, Parise H, Levy D, et al. Obesity and the risk of new-onset atrial fibrillation. *Jama.* 2004;292(20):2471-2477.

298. Boutari C, Mantzoros CS. A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. *Metabolism.* 2022;133:155217.

299. Stritzke J, Markus MR, Duderstadt S, et al. The aging process of the heart: obesity is the main risk factor for left atrial enlargement during aging the MONICA/KORA

(monitoring of trends and determinations in cardiovascular disease/cooperative research in the region of Augsburg) study. *J Am Coll Cardiol.* 2009;54(21):1982-1989.

300. Wasserman K, Hansen JE, Sue DY, Whipp BJ, Froelicher VF. Principles of exercise testing and interpretation. *Journal of Cardiopulmonary Rehabilitation and Prevention.* 1987;7(4):189.

301. Fedorov A, Beichel R, Kalpathy-Cramer J, et al. 3D Slicer as an image computing platform for the Quantitative Imaging Network. *Magn Reson Imaging.* 2012;30(9):1323-1341.

302. Wong CX, Sullivan T, Sun MT, et al. Obesity and the Risk of Incident, Post-Operative, and Post-Ablation Atrial Fibrillation. *JACC: Clinical Electrophysiology.* 2015;1(3):139-152.

303. Sandhu RK, Ezekowitz J, Andersson U, et al. The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. *Eur Heart J.* 2016;37(38):2869-2878.

304. Sandhu RK, Ezekowitz JA, Hijazi Z, et al. Obesity paradox on outcome in atrial fibrillation maintained even considering the prognostic influence of biomarkers: insights from the ARISTOTLE trial. *Open Heart.* 2018;5(2):e000908.

305. Zhu W, Wan R, Liu F, et al. Relation of Body Mass Index With Adverse Outcomes Among Patients With Atrial Fibrillation: A Meta-Analysis and Systematic Review. *J Am Heart Assoc.* 2016;5(9).

306. Boriani G, Laroche C, Diemberger I, et al. Overweight and obesity in patients with atrial fibrillation: Sex differences in 1-year outcomes in the EORP-AF General Pilot Registry. *J Cardiovasc Electrophysiol.* 2018;29(4):566-572.

307. Bertomeu-Gonzalez V, Moreno-Arribas J, Esteve-Pastor MA, et al. Association of Body Mass Index With Clinical Outcomes in Patients With Atrial Fibrillation: A Report From the FANTASIIA Registry. *Journal of the American Heart Association.* 2020;9(1).

308. Sandhu RK, Ezekowitz J, Andersson U, et al. The 'obesity paradox' in atrial fibrillation: observations from the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial. *European Heart Journal.* 2016;37(38):2869-2878.

309. Balla SRMD, Cyr DDP, Lokhyngina YP, et al. Relation of Risk of Stroke in Patients With Atrial Fibrillation to Body Mass Index (From Patients Treated With Rivaroxaban and Warfarin in the ROCKET AF Trial). *The American journal of cardiology.* 2017;119(12):1989-1996.

310. Vasan RS. Cardiac function and obesity. *Heart.* 2003;89(10):1127-1129.

311. Aurigemma GP, De Simone G, Fitzgibbons TP. Cardiac Remodeling in Obesity. *Circulation: Cardiovascular Imaging.* 2013;6(1):142-152.

312. Tyberg JV, Taichman GC, Smith ER, Douglas NW, Smiseth OA, Keon WJ. The relationship between pericardial pressure and right atrial pressure: an intraoperative study. *Circulation.* 1986;73(3):428-432.

313. McCauley MD, Hong L, Sridhar A, et al. Ion Channel and Structural Remodeling in Obesity-Mediated Atrial Fibrillation. *Circ Arrhythm Electrophysiol.* 2020;13(8):e008296.

314. Hatem SN, Sanders P. Epicardial adipose tissue and atrial fibrillation. *Cardiovasc Res.* 2014;102(2):205-213.

315. Wong CX, Abed HS, Molaee P, et al. Pericardial fat is associated with atrial fibrillation severity and ablation outcome. *J Am Coll Cardiol.* 2011;57(17):1745-1751.

316. Thanassoulis G, Massaro JM, O'Donnell CJ, et al. Pericardial fat is associated with prevalent atrial fibrillation: the Framingham Heart Study. *Circ Arrhythm Electrophysiol.* 2010;3(4):345-350.

317. Pugliese NR, Paneni F, Mazzola M, et al. Impact of epicardial adipose tissue on cardiovascular haemodynamics, metabolic profile, and prognosis in heart failure. *Eur J Heart Fail.* 2021;23(11):1858-1871.

318. Zamani SK, Sarma S, Macnamara JP, et al. Excess Pericardial Fat Is Related to Adverse Cardio-Mechanical Interaction in Heart Failure With Preserved Ejection Fraction. *Circulation.* 2023;148(18):1410-1412.

319. Oduah MT, Sundaram V, Reddy YN. Epicardial Fat in Heart Failure with Preserved Ejection Fraction: Bad Actor or Just Lying Around? *Card Fail Rev.* 2023;9:e06.

320. Min J, Putt ME, Yang W, et al. Association of Pericardial Fat with Cardiac Structure, Function, and Mechanics: The Multi-Ethnic Study of Atherosclerosis. *J Am Soc Echocardiogr.* 2022;35(6):579-587.e575.

321. Mahajan R, Nelson A, Pathak RK, et al. Electroanatomical Remodeling of the Atria in Obesity: Impact of Adjacent Epicardial Fat. *JACC Clin Electrophysiol.* 2018;4(12):1529-1540.

322. Tadros TM, Massaro JM, Rosito GA, et al. Pericardial fat volume correlates with inflammatory markers: the Framingham Heart Study. *Obesity (Silver Spring).* 2010;18(5):1039-1045.

323. Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. *Nat Med.* 2021;27(11):1954-1960.

324. Qureshi WT, Alirhayim Z, Blaha MJ, et al. Cardiorespiratory Fitness and Risk of Incident Atrial Fibrillation: Results From the Henry Ford Exercise Testing (FIT) Project. *Circulation.* 2015;131(21):1827-1834.

325. Proietti M, Boriani G, Laroche C, et al. Self-reported physical activity and major adverse events in patients with atrial fibrillation: a report from the EURObservational Research Programme Pilot Survey on Atrial Fibrillation (EORP-AF) General Registry. *Europace.* 2017;19(4):535-543.

326. Orimoloye OA, Kambhampati S, Hicks AJ, 3rd, et al. Higher cardiorespiratory fitness predicts long-term survival in patients with heart failure and preserved ejection fraction: the Henry Ford Exercise Testing (FIT) Project. *Arch Med Sci.* 2019;15(2):350-358.

327. Reddy YNV, Rikhi A, Obokata M, et al. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. *Eur J Heart Fail.* 2020;22(6):1009-1018.

328. Honigberg MC, Lau ES, Jones AD, et al. Sex Differences in Exercise Capacity and Quality of Life in Heart Failure With Preserved Ejection Fraction: A Secondary Analysis of the RELAX and NEAT-HFpEF Trials. *J Card Fail.* 2020;26(3):276-280.

329. Kondamudi N, Thangada N, Patel KV, et al. Regional adiposity, cardiorespiratory fitness, and left ventricular strain: an analysis from the Dallas Heart Study. *J Cardiovasc Magn Reson.* 2021;23(1):78.

330. Brinker SK, Pandey A, Ayers CR, et al. Association of Cardiorespiratory Fitness With Left Ventricular Remodeling and Diastolic Function. *JACC: Heart Failure.* 2014;2(3):238-246.

331. Howden EJ, Sarma S, Lawley JS, et al. Reversing the Cardiac Effects of Sedentary Aging in Middle Age-A Randomized Controlled Trial: Implications For Heart Failure Prevention. *Circulation.* 2018;137(15):1549-1560.

332. Guazzi M, Adams V, Conraads V, et al. Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. *Circulation.* 2012;126(18):2261-2274.

333. Hieda M, Sarma S, Hearon CM, et al. Increased Myocardial Stiffness in Patients With High-Risk Left Ventricular Hypertrophy. *Circulation.* 2020;141(2):115-123.

334. John B, Stiles MK, Kuklik P, et al. Electrical remodelling of the left and right atria due to rheumatic mitral stenosis. *European Heart Journal.* 2008;29(18):2234-2243.

335. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable Risk Factors and Atrial Fibrillation. *Circulation.* 2017;136(6):583-596.

336. Voskoboinik A, Wong G, Lee G, et al. Moderate alcohol consumption is associated with atrial electrical and structural changes: Insights from high-density left atrial electroanatomic mapping. *Heart Rhythm.* 2019;16(2):251-259.

337. Carnethon MR. Prevalence and Cardiovascular Disease Correlates of Low Cardiorespiratory Fitness in Adolescents and Adults. *JAMA.* 2005;294(23):2981.

338. Erez A, Kivity S, Berkovitch A, et al. The association between cardiorespiratory fitness and cardiovascular risk may be modulated by known cardiovascular risk factors. *Am Heart J.* 2015;169(6):916-923.e911.

339. Stiles MK, John B, Wong CX, et al. Paroxysmal Lone Atrial Fibrillation Is Associated With an Abnormal Atrial Substrate. *Journal of the American College of Cardiology.* 2009;53(14):1182-1191.

340. Masuda M, Fujita M, Iida O, et al. Left atrial low-voltage areas predict atrial fibrillation recurrence after catheter ablation in patients with paroxysmal atrial fibrillation. *Int J Cardiol.* 2018;257:97-101.

341. Marrouche NF, Wilber D, Hindricks G, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. *Jama.* 2014;311(5):498-506.

342. Thanigaimani S, Lau D, Brooks A, et al. Reverse Remodelling of the Atrial Substrate in Hypertensive Ovine Model: Implications of Conventional Anti-hypertensive Drugs. *Heart, Lung and Circulation.* 2013;22:S99.

343. Donnellan E, Wazni OM, Elshazly M, et al. Impact of Bariatric Surgery on Atrial Fibrillation Type. *Circulation: Arrhythmia and Electrophysiology.* 2020;13(2).

344. Elliott AD, Ariyaratnam J, Howden EJ, La Gerche A, Sanders P. Influence of exercise training on the left atrium: implications for atrial fibrillation, heart failure, and stroke. *Am J Physiol Heart Circ Physiol.* 2023;325(4):H822-h836.

345. Elliott AD, Verdicchio CV, Mahajan R, et al. An Exercise and Physical Activity Program in Patients With Atrial Fibrillation: The ACTIVE-AF Randomized Controlled Trial. *JACC Clin Electrophysiol.* 2022.

346. Astrand I. Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand Suppl.* 1960;49(169):1-92.

347. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J.* 1973;85(4):546-562.

348. Beale AL, Meyer P, Marwick TH, Lam CSP, Kaye DM. Sex Differences in Cardiovascular Pathophysiology: Why Women Are Overrepresented in Heart Failure With Preserved Ejection Fraction. *Circulation.* 2018;138(2):198-205.

349. Redfield MM, Jacobsen SJ, Borlaug BA, Rodeheffer RJ, Kass DA. Age- and gender-related ventricular-vascular stiffening: a community-based study. *Circulation.* 2005;112(15):2254-2262.

350. Martens P, Nijst P, Verbrugge FH, Smeets K, Dupont M, Mullens W. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. *Acta Cardiol.* 2018;73(2):115-123.

351. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues - the biology of pear shape. *Biol Sex Differ.* 2012;3(1):13.

352. Savarese G, Becher PM, Lund LH, Seferovic P, Rosano GMC, Coats AJS. Global burden of heart failure: a comprehensive and updated review of epidemiology. *Cardiovasc Res.* 2023;118(17):3272-3287.

353. Heidenreich PA, Albert NM, Allen LA, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. *Circ Heart Fail.* 2013;6(3):606-619.

354. Kittleson MM, Panjrath GS, Amancherla K, et al. 2023 ACC Expert Consensus Decision Pathway on Management of Heart Failure With Preserved Ejection Fraction. *Journal of the American College of Cardiology.* 2023;81(18):1835-1878.

355. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol.* 2017;14(10):591-602.

356. Shah KS, Xu H, Matsouaka RA, et al. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *Journal of the American College of Cardiology.* 2017;70(20):2476-2486.

357. Barandiarán Aizpurua A, Sanders-van Wijk S, Brunner-La Rocca HP, et al. Validation of the HFA-PEFF score for the diagnosis of heart failure with preserved ejection fraction. *Eur J Heart Fail.* 2020;22(3):413-421.

358. Sepehrvand N, Alemayehu W, Dyck GJB, et al. External Validation of the H(2)F-PEF Model in Diagnosing Patients With Heart Failure and Preserved Ejection Fraction. *Circulation.* 2019;139(20):2377-2379.

359. Ariyaratnam JP, Elliott AD, Mishima RS, et al. Identification of Subclinical Heart Failure With Preserved Ejection Fraction in Patients With Symptomatic Atrial Fibrillation. *JACC Heart Fail.* 2023.

360. Brittain EL, Thenappan T, Huston JH, et al. Elucidating the Clinical Implications and Pathophysiology of Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction: A Call to Action: A Science Advisory From the American Heart Association. *Circulation.* 2022.

361. Ewert R, Heine A, Müller-Heinrich A, et al. Exercise and fluid challenge during right heart catheterisation for evaluation of dyspnoea. *Pulmonary Circulation.* 2020;10(3):10.1177_2045894.

362. Vachiéry JL, Tedford RJ, Rosenkranz S, et al. Pulmonary hypertension due to left heart disease. *Eur Respir J.* 2019;53(1).

363. D'Alto M, Badesch D, Bossone E, et al. A Fluid Challenge Test for the Diagnosis of Occult Heart Failure. *Chest.* 2021;159(2):791-797.

364. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. *Nature Reviews Cardiology.* 2017;14(10):591-602.

365. Wernhart S, Goertz A, Hedderich J, et al. Diastolic exercise stress testing in heart failure with preserved ejection fraction: The DEST-HF study. *Eur J Heart Fail.* 2023.

366. Inciardi RM, Giugliano RP, Claggett B, et al. Left atrial structure and function and the risk of death or heart failure in atrial fibrillation. *European Journal of Heart Failure.* 2019;21(12):1571-1579.

367. Koepp KE, Reddy YNV, Obokata M, et al. Identification of patients with preclinical heart failure with preserved ejection fraction using the H2FPEF score. *Nature Cardiovascular Research.* 2022;1(1):59-66.

368. Lindstrom M, Decleene N, Dorsey H, et al. Global Burden of Cardiovascular Diseases and Risks Collaboration, 1990-2021. *Journal of the American College of Cardiology.* 2022;80(25):2372-2425.

369. Odutayo A, Wong CX, Hsiao AJ, Hopewell S, Altman DG, Emdin CA. Atrial fibrillation and risks of cardiovascular disease, renal disease, and death: systematic review and meta-analysis. *BMJ.* 2016:i4482.

370. Mitchell JH, Shapiro W. Atrial function and the hemodynamic consequences of atrial fibrillation in man. *Am J Cardiol.* 1969;23(4):556-567.

371. Mishima RS, Ariyaratnam JP, Pitman BM, et al. Cardiorespiratory fitness, obesity and left atrial function in patients with atrial fibrillation. *IJC Heart & Vasculature.* 2022;42:101083.

372. Badano LP, Kolias TJ, Muraru D, et al. Standardization of left atrial, right ventricular, and right atrial deformation imaging using two-dimensional speckle tracking echocardiography: a consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. *European Heart Journal - Cardiovascular Imaging.* 2018;19(6):591-600.

373. Guazzi M, Adams V, Conraads V, et al. EACPR/AHA Scientific Statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. *Circulation.* 2012;126(18):2261-2274.

374. Wright S, Sasson Z, Gray T, et al. Left atrial phasic function interacts to support left ventricular filling during exercise in healthy athletes. *J Appl Physiol (1985).* 2015;119(4):328-333.

375. Sugimoto T, Barletta M, Bandera F, et al. Central role of left atrial dynamics in limiting exercise cardiac output increase and oxygen uptake in heart failure: insights by cardiopulmonary imaging. *Eur J Heart Fail.* 2020.

376. Ariansena I, Gjesdala K, Abdelnoorb M, Edvardsenc E, Engerd S, Tveitd A. Quality of Life, Exercise Capacity and Comorbidity in Old Patients with Permanent Atrial Fibrillation. *J Atr Fibrillation.* 2008;1(4):136.

377. Elshazly MB, Senn T, Wu Y, et al. Impact of Atrial Fibrillation on Exercise Capacity and Mortality in Heart Failure With Preserved Ejection Fraction: Insights From Cardiopulmonary Stress Testing. *Journal of the American Heart Association.* 2017;6(11).

378. Takano N, Amiya E, Oguri G, et al. Influence of atrial fibrillation on oxygen uptake and exercise tolerance in cardiovascular patients; close association with heart rate response. *Int J Cardiol Heart Vasc.* 2019;22:84-91.

379. Zakeri R, Borlaug BA, McNulty SE, et al. Impact of atrial fibrillation on exercise capacity in heart failure with preserved ejection fraction: a RELAX trial ancillary study. *Circ Heart Fail.* 2014;7(1):123-130.

380. Agostoni P, Emdin M, Corrà U, et al. Permanent atrial fibrillation affects exercise capacity in chronic heart failure patients. *Eur Heart J.* 2008;29(19):2367-2372.

381. Gilbert KA, Hogarth AJ, MacDonald W, Lewis NT, Tan LB, Tayebjee MH. Restoration of sinus rhythm results in early and late improvements in the functional reserve of the heart following direct current cardioversion of persistent AF: FRESH-AF. *Int J Cardiol.* 2015;199:121-125.

382. Atwood JE, Myers J, Sullivan M, et al. The effect of cardioversion on maximal exercise capacity in patients with chronic atrial fibrillation. *Am Heart J.* 1989;118(5 Pt 1):913-918.

383. Gosselink AT, Bijlsma EB, Landsman ML, Crijns HJ, Lie KI. Long-term effect of cardioversion on peak oxygen consumption in chronic atrial fibrillation. A 2-year follow-up. *Eur Heart J.* 1994;15(10):1368-1372.

384. Mujović NM, Marinković MM, Nedeljković I, et al. Improvement of Maximal Exercise Performance After Catheter-Ablation of Atrial Fibrillation and Its Prognostic Significance for Long-Term Rhythm Outcome. *Journal of the American Heart Association.* 2021;10(3).

385. Katayama H, Shibata A, Doi A, et al. Successful catheter ablation improves exercise tolerance in persistent atrial fibrillation patients, especially those with reduced ventricular contraction, preserved atrial function, or a high CHADS2 score. *Journal of Cardiology.* 2020;75(5):529-536.

386. Sachdeva S, Desai R, Andi K, et al. Reduced left atrial strain can predict stroke in atrial fibrillation - A meta-analysis. *Int J Cardiol Heart Vasc.* 2021;36:100859.

387. Sugimoto T, Barletta M, Bandera F, et al. Central role of left atrial dynamics in limiting exercise cardiac output increase and oxygen uptake in heart failure: insights by cardiopulmonary imaging. *Eur J Heart Fail.* 2020;22(7):1186-1198.

388. Caminiti G, Perrone MA, D'Antoni V, et al. The Improvement of Left Atrial Function after Twelve Weeks of Supervised Concurrent Training in Patients with Heart Failure with Mid-Range Ejection Fraction: A Pilot Study. *J Cardiovasc Dev Dis.* 2023;10(7).

389. Ayirala S, Kumar S, O'Sullivan DM, Silverman DI. Echocardiographic predictors of left atrial appendage thrombus formation. *J Am Soc Echocardiogr.* 2011;24(5):499-505.

390. Odell JA, Blackshear JL, Davies E, et al. Thoracoscopic obliteration of the left atrial appendage: potential for stroke reduction? *Ann Thorac Surg.* 1996;61(2):565-569.

391. Mulder BA, Veldhuisen DJ, Rienstra M. What should the C ('congestive heart failure') represent in the CHA 2 DS 2 -VASc score? *European Journal of Heart Failure.* 2020;22(8):1294-1297.

392. Ho JE, Enserro D, Brouwers FP, et al. Predicting Heart Failure With Preserved and Reduced Ejection Fraction. *Circulation: Heart Failure.* 2016;9(6):e003116.

393. Brittain EL, Thenappan T, Huston JH, et al. Elucidating the Clinical Implications and Pathophysiology of Pulmonary Hypertension in Heart Failure With Preserved Ejection Fraction: A Call to Action: A Science Advisory From the American Heart Association. *Circulation.* 2022;146(7).

394. Pfeffer MA, Shah AM, Borlaug BA. Heart Failure With Preserved Ejection Fraction In Perspective. *Circulation Research.* 2019;124(11):1598-1617.

395. Fatkin D, Loupas T, Jacobs N, Feneley MP. Quantification of blood echogenicity: evaluation of a semiquantitative method of grading spontaneous echo contrast. *Ultrasound Med Biol.* 1995;21(9):1191-1198.

396. Sanders P, Morton JB, Kistler PM, Vohra JK, Kalman JM, Sparks PB. Reversal of atrial mechanical dysfunction after cardioversion of atrial fibrillation: implications for the mechanisms of tachycardia-mediated atrial cardiomyopathy. *Circulation.* 2003;108(16):1976-1984.

397. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest.* 2010;137(2):263-272.

398. Uhm JS, Kim J, Yu HT, et al. Stroke and systemic embolism in patients with atrial fibrillation and heart failure according to heart failure type. *ESC Heart Failure.* 2021;8(2):1582-1589.

399. Di Biase L, Burkhardt JD, Mohanty P, et al. Left Atrial Appendage Isolation in Patients With Longstanding Persistent AF Undergoing Catheter Ablation: BELIEF Trial. *J Am Coll Cardiol.* 2016;68(18):1929-1940.

400. Handke M, Harloff A, Hetzel A, Olschewski M, Bode C, Geibel A. Left atrial appendage flow velocity as a quantitative surrogate parameter for thromboembolic risk: determinants and relationship to spontaneous echocontrast and thrombus formation--a transesophageal echocardiographic study in 500 patients with cerebral ischemia. *J Am Soc Echocardiogr.* 2005;18(12):1366-1372.

401. Yoshida K, Obokata M, Kurosawa K, Sorimachi H, Kurabayashi M, Negishi K. Effect of Sex Differences on the Association Between Stroke Risk and Left Atrial Anatomy or Mechanics in Patients With Atrial Fibrillation. *Circulation: Cardiovascular Imaging.* 2016;9(10):e004999.

402. Poli D, Antonucci E, Grifoni E, Abbate R, Gensini GF, Prisco D. Gender differences in stroke risk of atrial fibrillation patients on oral anticoagulant treatment. *Thromb Haemost.* 2009;101(5):938-942.

403. Nielsen PB, Skjøth F, Overvad TF, Larsen TB, Lip GYH. Female Sex Is a Risk Modifier Rather Than a Risk Factor for Stroke in Atrial Fibrillation. *Circulation.* 2018;137(8):832-840.

404. Klein AL, Murray RD, Black IW, et al. Integrated backscatter for quantification of left atrial spontaneous echo contrast. *J Am Coll Cardiol.* 1996;28(1):222-231.