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A prospective **ST**udy using inv**A**sive haemodynamic measurements fo**LL**owing catheter ablation for **AF** and early **HFpEF**: STALL AF-HFpEF.

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Abstract

Aims: The impact of atrial fibrillation (AF) ablation in early heart failure with preserved ejection fraction (HFpEF) is unknown. Our aim was to determine the impact of AF ablation on symptoms and exercise hemodynamic parameters of early HFpEF.

Methods: Symptomatic AF patients referred for index AF ablation with EF≥50% underwent baseline QOL questionnaires, echocardiography, cardiac magnetic resonance imaging, exercise right heart catheterisation (exRHC), and BNP testing. HFpEF was defined by resting pulmonary capillary wedge pressure (PCWP) ≥15mmHg or peak exercise PCWP ≥25 mmHg. Patients with HFpEF were offered AF ablation and follow-up exRHC ≥ 6 months post-ablation.

Results: Of 54 patients undergoing baseline evaluation, 35(65%) had HFpEF identified by exRHC. HFpEF patients were older (64 ± 10 vs 54 ±13 years, p<0.01), and more frequently female (54% vs 16%, p<0.01), hypertensive (63% vs 16%, p<0.001), and suffering persistent AF (66% vs 11%, p<0.001), compared to those without HFpEF. Twenty HFpEF patients underwent AF ablation and follow-up exRHC 12 ± 6 months post-ablation. Nine (45%) patients no longer fulfilled exRHC criteria for HFpEF at follow-up. Patients remaining arrhythmia free (n=9, 45%) showed significant improvements in peak exercise PCWP (29±4 to 23±2 mmHg, p<0.01) and MLHF score (55±27 to 22±1, p<0.01) while the remainder did not (PCWP 31±5 to 30.0±4 mmHg, p=ns; MLHF score 55±23 to 25±20, p=ns).

Conclusion: HFpEF frequently coexists in patients with symptomatic AF and preserved EF. Restoration and maintenance of sinus rhythm in patients with comorbid AF and HFpEF, improves haemodynamic parameters, BNP and symptoms associated with HFpEF (Graphical abstract).

Key words: Atrial fibrillation, HFpEF, Improvement, exercise wedge pressure, PCWP, sinus rhythm, reversal

Introduction

Heart failure with preserved ejection fraction (HFpEF) is recognised as a major form of heart failure[1]. HFpEF and AF frequently coexist[2] and their comorbidity is associated with poorer prognosis[1]. Despite this, HFpEF is under-recognised in patients with AF[1] and the best treatment approach is unclear.

The diagnosis of HFpEF requires symptoms or signs of heart failure and preserved left ventricular ejection fraction (LVEF ≥50%), combined with additional parameters including natriuretic peptide levels, echocardiographic features of diastolic impairment and the use of invasive exercise hemodynamic measurements where necessary[3]. In patients with AF, the diagnosis of HFpEF is challenging. Symptoms may be attributed solely to AF or may be unrecognised having developed insidiously. AF is thought to directly influence parameters such as BNP and echocardiographic parameters required to diagnose HFpEF[4]. The HFA-PEFF diagnostic algorithm proposes different echocardiographic and natriuretic peptide cut-off values for diagnosing HFpEF in the setting of AF[3], but remains to be validated in this population. The prevalence of HFpEF in patients being considered for catheter ablation with AF suspected as the predominant cause of their symptoms is unknown.

Catheter ablation for AF is considered safe and effective in patients with HFpEF[5] and restoration of sinus is shown to improves quality of life (QOL)[6] and exercise capacity[7]. However, the impact of maintaining sinus rhythm in this population on hemodynamic parameters such as pulmonary capillary wedge pressure (PCWP) and cardiac output (CO) is unknown.

We evaluated the prevalence of HFpEF among patients with preserved LVEF referred for AF ablation at our centre using invasive exercise hemodynamic measurements at baseline and post-ablation to determine the impact of restoring and maintaining sinus rhythm with AF ablation.

Methods

Subjects

This prospective observational study was conducted at The Alfred Hospital in Melbourne, Australia, from April 2017 to Sept 2019 with approval by the institution's ethics review committee. The investigation conforms with the principles outlined in the *Declaration of Helsinki*. All participants provided written informed consent to be in included in the study.

All patients aged 18-80 years with LVEF ≥50% referred to our centre for AF ablation regardless of type of symptoms were evaluated for HFpEF and offered AF ablation based on guideline recommendations[8]. Patients identified as having HFpEF on exRHC criteria (detailed below) were offered AF ablation according to usual institutional practice with additional follow-up evaluation including exRHC ≥6 months post ablation. Patients with persistent AF were required to have had recurrent AF despite at least one attempt at electrical cardioversion on anti-arrhythmic therapy (AAD) therapy.

Exclusion criteria were prior AF ablation, prior cardiac surgery, significant valvular heart disease, obstructive coronary artery disease, prior LV systolic impairment, uncontrolled hypertension (resting systolic blood pressure ≥160mmHg), poorly controlled resting heart rate

in AF (>100 beats per minute), prior cardiac pacemaker or cardioverter-defibrillator implant, or inability to complete exRHC.

Baseline measurements

The following baseline data were collected: New York Heart Association(NYHA) heart failure functional class, the Minnesota living with heart failure quality of life questionnaire (MLHF) score, AF Effect on QualiTy of life survey questionnaire (AFEQT) score, Canadian cardiovascular society severity of AF questionnaire (CCS-SAF) score, 24-h Holter monitoring, transthoracic echocardiography (TTE) measurements, contrast-enhanced cardiac magnetic resonance imaging (CMR) measurements with T1 mapping, exRHC hemodynamic measurements, and resting brain natriuretic peptide (BNP).

Echocardiographic assessment of LA strain

All strain parameters were assessed using speckle-tracking imaging by an external third-party software program (TomTec Imaging Arena, Munich, Germany). After manual tracing, the dedicated software automatically tracked the LA throughout the cardiac cycle. All tracking was reviewed to ensure that it was appropriate and represented LA motion. LA reservoir strain was averaged from the apical four-chamber and two-chamber views[9, 10]. The reference point for image analysis was taken at the onset of the QRS complex (R-R gating)[9, 10].

Exercise Right Heart Catheterisation

Our exRHC protocol has been published previously[11]. Thermodilution technique was used to derive CO. Measurements were performed at rest (supine) and during supine bicycle exercise via the right brachial or jugular vein using a balloon-tipped catheter. After baseline measurements, symptom-limited exercise commenced at a workload of 0.3Watts(W)/kilogram

(kg) with 0.3W/kg increments every 3 minutes until 6 minutes and increased to 1.0W/kg until 9 mins. Beyond 9 minutes, a maximum of 1.5W/kg was used until maximum effort (defined by exercise limiting fatigue or dyspnoea) was reached. Mean PCWP and pressures were measured at end expiration averaged over 2-3 respiratory cycles. Cases with prominent v waves had repeat measures taken from alternate locations to exclude an inadequate wedge. Traces were examined for appropriate timing compared with pulmonary arterial trace, and in cases in which equipoise remained, oximetry was performed from the wedge position to confirm arterialisation. PCWP indexed to workload (PCWL, mmHg/W/kg) is the ratio of PCWP to workload normalised to body weight. Blood samples were taken at the time of peripheral cannulation for BNP analysis, prior to exercise. In this study, diagnosis of HFpEF required demonstration of resting PCWP ≥15mmHg or peak exercise PCWP ≥25 mmHg during exRHC[12] which is in accordance with the current consensus recommendations of the European Society of Cardiology[3].

AF ablation and follow-up

Catheter ablation was pursued once secondary risk factors such as obesity[13, 14], alcohol excess[15] and sleep apnoea[16] were adequately addressed. Ablation generally involved wide antral circumferential ablation technique to achieve electrical isolation of the pulmonary veins, using a 3-dimensional mapping system and contact force capable 3.5mm irrigated-tipped catheter, with additional ablation at operator discretion. Two separate transseptal punctures were performed with transoesophageal echocardiographic guidance with a 8Fr and an 8.5Fr sheath for the mapping and ablation catheter respectively. AAD therapy was discontinued immediately following paroxysmal AF ablation or after 3 months following persistent AF ablation. Recurrence was defined as documented atrial arrhythmia including AF, atrial flutter and focal atrial tachycardia lasting >30 s occurring beyond a 3-month blanking period. Follow-

up evaluation involved scheduled (3-monthly) clinic visits with electrocardiogram (ECG) and 6 monthly Holter monitor. In addition, symptom guided emergent clinic visits with ECG and 24-hour Holter monitoring were performed. BNP measurement, TTE and exRHC were repeated at ≥6 months post-ablation.

Statistical analysis

Categorical variables were compared using Fisher exact test or the $\chi 2$ test as appropriate and expressed as number and percentage. Continuous parametric variables were compared using Student's t-test and expressed as mean ± standard deviation (SD). Continuous nonparametric variables were compared using Wilcoxon signed ranked test. Paired tests were used compare means from baseline to follow-up. A p-value of ≤ 0.05 was considered statistically significant and p-values were reported categorically as NS (not significant, $p > 0.05$), 0.05, <0.05, <0.01 and < 0.001. Analysis was performed using SPSS version 24 (IBM SPSS statistics, IBM Corporation, Armonk, New York).

Results

Of 252 patients referred for AF ablation during the study period, 121 (48.0%) patients did not meet our inclusion / exclusion criteria. Sixty-six (54.5%) were excluded due to history of cardiomyopathy, 35 (28.9%) due to prior AF ablation, 18 (14.9%) due to valvular / structural heart disease, 2 (1.7%) due to the presence of a pacemaker / defibrillator. Of the remaining eligible patients, 65 (49.6%) consented to participation, with 11 (16.9%) subsequently excluded due to a subsequent fall in LVEF to <50% (10) or due to uncontrolled hypertension (1), leaving a total of 54 study subjects (Figure 1).

General baseline characteristics

Baseline characteristics are presented in Table 1 and 2. Patients scheduled for AF ablation were aged 60.5 ± 11.8 years; 22 (41.0%) were female, history of AF for 3.7 ± 3.5 years and 25 (46.3%) had persistent AF diagnosed 2.5 ± 3.6 years prior to their ablation procedure. Overall, patients had a mean BMI of 30.4 ± 4.3 kg/m^2, a diagnosis of hypertension in 25 (46.3%), and a CHA_2DS_2-VASc score of 2.4 ± 1.8. TTE and CMR findings are detailed in Table 2. Patients had a mean LVEF of 60.7 ± 4.3%, LA volume index (LAVI) of 43.5 ± 11.6mL/m^2, average E/e' ratio of 9.7 ± 3.4, and mitral deceleration time of 203.5 ± 58.5 ms.

Baseline characteristics of patients with and without HFpEF

Thirty-five (64.8%) patients met diagnostic criteria for HFpEF with 9 (25.7%) having HFpEF at rest (PCWP ≥ 15mmHg at rest) and 26 (74.3%) having early/exercise induced HFpEF (PCWP <15mmHg at rest but PCWP ≥25mmHg with exercise). HFpEF was more prevalent in persistent AF compared with paroxysmal AF patients (92.0% vs 41.4%, p<0.001). Patients with HFpEF, compared to those without, were older (64.2 ± 9.5 vs 53.7 ± 12.9, p <0.01), more frequently female (54.3% vs 15.8% p<0.01), and were more likely to have a history of hypertension (62.9 vs 15.8 % p <0.001) with a higher CHA_2DS_2-VASc score (3.3 ± 1.4 vs 0.6 ± 1.0 p <0.001) (Table 1). HFpEF patients were more frequently on an ACE-inhibitor or ARB (57.1% vs 15.8%, p<0.01), spironolactone (11.4% vs 0%, p<0.05), and anticoagulation (88.6% vs 52.6%, p<0.05). HFpEF patients also had higher NYHA functional class (2.4 ± 0.8 vs 1.6 ± 0.6 p <0.01), MLHF (51.9 ± 22.3 vs 34.6 ± 24.1 p <0.05) and AFEQT (84.4 ± 25.5 vs 69.1 ± 21.1 p = <0.05) scores.

HFpEF patients had higher E/e' (11.0 ± 3.4 vs 7.2 ± 1.6 p <0.001), lower TAPSE (2.1 ± 0.4 vs 2.4 ± 0.4cm, p<0.05) and lower LA reservoir strain (18.9 ± 8.4 vs 29.4 ± 10.9 p < 0.01) on TTE

compared to patients without HFpEF (see Table 2). On CMR, there were no significant differences in right ventricular function or myocardial T1 time between patients with and without HFpEF.

ExRHC findings (Table 3) for patients with vs without HFpEF included higher resting PCWP (13.4 ± 3.9 vs 9.0 ± 2.8 p <0.001), lower peak exercise work load (85.5 ± 46.2 vs 113.9 ± 38.2 p<0.05), higher peak exercise PCWL (44.8 ± 29.4 vs 16.2 ± 8.3, p<0.001), lower resting CO (5.1 ± 1.0 vs 6.6 ± 1.5 p <0.001) and lower peak exercise CO (9.2 ± 2.8 vs 13.2 ± 3.8 p <0.001). Twenty (57.1%) HFpEF patients and 3 (15.9%) patients without HFpEF were in AF at the time of exRHC. BNP (129.3 ± 95.0 vs 45.0 ± 41.8 p <0.001) and logarithmic BNP (3.4 ± 0.9 vs 4.6 ± 0.7 p <0.001) were significantly higher in HFpEF patients compared with patients without HFpEF (Figure 2).

Procedure characteristics

A total of 44 (81.5%) study patients underwent AF ablation procedure, with the remainder maintained on ongoing medical therapy during the study period with lifestyle interventions such as weight loss and alcohol reduction targets. Pulmonary vein isolation was achieved in all patients with posterior wall isolation completed in 9 (20.5%). Among those with HFpEF who underwent repeat exRHC, 6 (30.0%) had attempted posterior wall isolation in addition to pulmonary vein isolation. Posterior wall isolation strategy was used in 3 (33.3%) patients in the arrhythmia free group and in 3 (27.3%) patients in the arrhythmia recurrence group. Ablation procedure duration was 181.4 ± 43.6 minutes with fluoroscopy time of 12.5 ± 4.7minutes and radiofrequency ablation time of 38.3 ± 10.3 minutes. There was one procedure related complication, a retained arterial line cannula requiring vascular surgery.

Follow-up measurements

Of the 26 HFpEF patients undergoing AF ablation, 6 declined follow-up investigations, and 20 returned for repeat exRHC ≥6 months post index AF ablation. At follow-up of 12 ± 6 months, 9 (45.0%) patients no longer fulfilled criteria for HFpEF (Graphical abstract). Overall, there was a significant decrease in resting PCWP (12.8 ± 4.3 to 10.0 ± 3.4 mm Hg, $p < 0.05$) and peak exercise PCWP (30.3 ± 4.2 vs 26.8 ± 4.7 mmHg, $p < 0.01$) following AF ablation (figure 3A). The time interval between the two exRHC was 10.7 ± 5.7 months with no correlation between time to follow-up exRHC and change in PCWP (Pearson correlation 0.169 p=0.48 & $R^2 = 0.029$). MLHF (figure 3B), AFEQT, and CSS-SAF scores also improved significantly. There was no evidence of left to right shunt across the atrial septum at rest on follow up TTE.

Outcomes for patients based on arrhythmia recurrence status are presented below. There were no differences in baseline characteristics between these 2 groups.

Arrhythmia free group

A total of 9 (45.0%) patients were arrhythmia free at follow up. In this group, peak exercise PCWP decreased from 29.2 ± 3.7 to 22.9 ± 2.0 mmHg ($p < 0.01$, figure 4A) and peak exercise PCWL from 46.2 ± 29.9 to 25.5 ± 17.4 mmHg/W/kg ($p<0.05$, figure 4B). MLHF, AFEQT, and CCS-SAF scores also improved at follow up. There was a trend toward increased resting CO (4.7 ± 0.7 vs 5.4 ± 1.2 L/m, $p < 0.1$) and peak exercise CO (10.3 ± 3.0 vs 13.0 ± 3.6 L/m, $p < 0.1$) representing a 15% and 26% increase respectively. Following successful AF ablation, resting BNP decreased from 94.6 ± 101.6 to 38.0 ± 34.0 pg/ml ($p<0.05$). Eight (88.9%) patients in this group no longer met exRHC criteria for HFpEF (Graphical abstract).

Arrhythmia recurrence group

Eleven patients (55%) had arrhythmia recurrence during follow up. These patients did not demonstrate a significant change in their peak exercise PCWP (31.2 ± 4.5 to 30.0 ± 3.8 p = ns) or peak exercise PCWL (39.5 ± 26.0 to 34.8 ± 23.8 mmHg/W/Kg, p=ns). AFEQT and CCS-AF scores, but not the MLHF score, improved significantly. BNP levels decreased from 142.5 ± 106.7 to 75.1 ± 80.6 pg/ml (p <0.01). One (9.1%) patient in this group no longer met exRHC criteria for HFpEF (Graphical abstract).

Discussion

To our knowledge, this is the first study to utilise invasive hemodynamic measurement to demonstrate improvement in haemodynamic parameters following AF ablation in patients with comorbid AF and HFpEF.

We demonstrated that there is a high prevalence (65%) of HFpEF among symptomatic AF patients with preserved EF referred for consideration of catheter ablation at our centre. In addition, AF patients with HFpEF were more likely to be older, female, multimorbid, and suffering persistent AF. Restoration and maintenance of sinus rhythm with AF ablation reverses the symptoms and adverse hemodynamic changes of HFpEF in a significant proportion of patients with comorbid AF and HFPEF.

Diagnosis of HFpEF in patients with AF

HFpEF and AF share overlapping symptoms of fatigue, breathlessness, and exercise intolerance. Among patients with pre-existing AF and preserved EF, a diagnosis of HFpEF may be overlooked where their common symptoms are attributed solely to AF. Diagnostic criteria for HFpEF include parameters which are influenced by AF, including natriuretic peptide levels[17] and echocardiographic measurements of diastolic function[4]. Two prior studies

have evaluated HFpEF invasively among AF patients by measuring LA pressure at rest and during arm exercises [18-20]. Meluzin et al diagnosed HFpEF in 39% of paroxysmal AF patients based on an LA pressure > 15 mmHg at rest or ≥ 25mmHg with exercise (n=100, age 59±10 years, 69% male)[19]. In their study population, 64.1% of patients were diagnosed with early HFpEF that was inducible with exercise. Given the overlap between persistent AF and HFpEF, the exclusion of patients with persistent atrial fibrillation is likely to account the higher proportion of patients with HFpEF in our study population. Sramko et al identified HFpEF in 34% of patients scheduled for AF ablation based on an LA pressure >15 mm Hg at rest or on exercise (n=240, age 60±10 years, 67% male, 62% paroxysmal AF)[18]. Inclusion of patients with EF between 40-50% is likely to have contributed to the higher proportion of patients with HFpEF at rest compared with our study. Unlike the difference in cut-off values and direct LA pressure measurements used in the other studies, we used a standardised approach to invasive hemodynamic testing that makes our study and results widely applicable.

Invasive haemodynamic testing serves as a gold standard for diagnosis in patients with comorbid AF. Borlaug recently proposed an integrated diagnostic approach[21] to allow rational application of exercise testing based on an evidence-based study[22]. In addition, an expert consensus recommendation used a scoring system (HFA-PEFF) based on symptoms and baseline investigations to determine which patients requires invasive testing for diagnosis of HFpEF[3]. Both these approaches have a high positive predictive value but exRHC was still required in majority of patients with intermediate scores. However, widespread use of exRHC is limited by cost, expertise, and its invasive nature. Therefore, a high level of clinical suspicion for HFpEF should be applied to all patients with AF and preserved EF.

The HFA-PEFF score incorporates natriuretic peptide and echocardiographic measures to make a diagnosis of HFpEF. Elevation of BNP or N-terminal (NT)-pro hormone BNP (NT-pro-BNP) level is a key criterion in current guidelines[17] but cut-off levels specific to AF lack prospective validation. Our data demonstrates a large overlap in natriuretic peptide levels across HFpEF and non-HFpEF patients with AF, as observed also by others[23]. In our cohort, a high probability HFA-PEFF score (5-6) identified only 11% of HFpEF patients with 100% specificity. Two thirds of the cohort had an intermediate probability score, and among those with a low probability score, 3 of 11 met invasive criteria for HFpEF. Average BNP in our cohort was 129pg/mL which is well below the 240pg/mL cut off used by the HFA-PEFF score. Whether the lower BNP levels seen in our cohort reflects early HFpEF or relates to the burden of AF requires further evaluation.

Arrhythmia outcome following AF ablation in HFpEF

Catheter ablation for drug-refractory AF remains the cornerstone of AF management[8] and it can be safely performed in patients with comorbid AF and HFpEF[24, 25]. Success rates range from 27% to 84%[5, 24] depending on follow-up duration, number of procedures, and AAD use. Our single procedure success rate off antiarrhythmic drug therapy was 45% at 6 months. The high recurrence rate likely reflects advanced atrial remodelling in a population with heart failure and high prevalence of persistent AF. We have used the 30 seconds cut-off for arrhythmia recurrence consistent with current reporting practice[26]. However, many patients have significant decrease in their AF burden following ablation despite being classified as having had recurrence[27]. AF and HFpEF[3] are both independently associated with BNP elevation. Hence, reduction in AF burden following catheter ablation is one possible explanation for the decrease seen in our population despite having arrhythmia recurrence.

Whether this reduction in BNP seen in our population correlates with clinical outcome requires further evaluation.

Improvement in HFpEF haemodynamic parameters

Following AF ablation, 45% of HFpEF patients no longer fulfilled exRHC criteria for HFpEF at follow-up with improvement in symptom scores, functional status, and BNP levels. Atrial dysfunction is an important component of HFpEF[28], with reduced LA atrial compliance and distensibility identified as key pathophysiologic mechanism(s)[29]. Impaired contractility and booster function, as well as atrial natriuretic peptide depletion or resistance have also been implicated[29]. LA strain is used to measure atrial function and has been closely linked to clinical outcomes with prior studies demonstrating markedly reduced LA reservoir and pump functions in patients with HFpEF[30]. The atrial pump function augments the decreased passive early trans mitral diastolic flow in early HFpEF[31] and is an important determinant of LV filling and normal cardiac performance especially under physical stress. AF results in loss of pump function and together with increased pressure and volume associated with HFpEF, there is progressive remodelling of the LA that results in loss of distensibility and decrease in LA reservoir strain[28, 30, 32]. Restoration of normal atrial contractile / pump function in sinus rhythm can potentially reverse the negative haemodynamic effects on LA reservoir function. This is likely to play an important role in the improved outcomes seen in our patient population.

In addition, prior echocardiographic studies have demonstrated reversal of resting LV diastolic dysfunction following successful AF ablation in patients with preserved LVEF[33, 34]. This is supported by CMR studies that identified LV fibrotic remodelling with reduction in diffuse fibrosis following ablation in the presence of preserved LV function[35]. Together, these data raise the possibility that AF can precipitate HFpEF in a subset of the greater HFpEF population

and may have a similar "chicken-and-egg" relationship with HFpEF as it does with heart failure with reduced ejection fraction.

The deleterious effect of irregular electromechanical activity on ventricular myocytes has been described previously[36]. Irregular contraction can result in downregulation of sarco(endo)plasmic reticulum ATPase 2a pump (SERCA)[36] and diastolic impairment has been reported to result from reduced SERCA activity due to delayed elimination of cytosolic contraction[37]. Whether the calcium haemostasis and expression of SERCA improves following restoration and maintenance of sinus rhythm is currently unknown.

It is possible that iatrogenic atrial septal defects (iASD) following catheter ablation can result in a left to right shunt which can improve follow up PCWP[38]. Although iASD is a well-documented consequence of transseptal cardiac interventions[39], the strongest predictor of developing a persistent iASD was the size of the sheath or guiding catheter. The incidence of iASD following mitral valve intervention (20F) was estimated at 23.1% compared with 2.2% for 8F access[39]. At our centre, 2 separate transseptal punctures were performed under trans oesophageal echocardiographic guidance using a 8Fr and a 8.5Fr sheaths that is likely to explain the low incidence of persistent iASD following intervention.

Quality of life outcome

Our baseline MLHF score was slightly higher compared to the REDUCE LAP-HF[38] study reflecting the comorbid condition of AF and HFpEF and the vicious interplay[40] between these conditions. With only a modest drop in PCWP in their population from 34mmHg to 32mmHg, there was a significant decrease in MLHF score from 49 to 36. However, only 36% of the patients included in the REDUCE LAP-HF study had AF. The impact of reduced AF burden

following AF ablation has not been evaluated in the HFpEF population using MLHF questionnaire. It is possible that the combined effect of reduced PCWP and reduced AF burden could have resulted in an improved sense of well-being seen in our patient cohort. The CABANA[6] trial demonstrated significant improvement in quality of life scores following AF ablation associated with reduction in AF burden. The Mayo AF-Specific Symptom Inventory (MAFSI) questionnaire score decreased by over 50% at 12 months follow up supporting the dramatic improvement in quality of life scores following AF ablation. The MAFSI questionnaire included 10 questions with a substantial overlap with MLHF including 'shortness of breath', tired / lack of energy', 'weakness' and 'unable to exercise'. Further studies are needed to assess the impact of AF ablation on MLHF specific scores.

Regardless of mechanism, restoration of sinus rhythm is widely reported to improve exercise capacity[41], improve QOL[6], increase cerebral perfusion [42] and reduced HFpEF hospitalisations[43] following AF ablation. In our prospective study, we observed substantial improvement in symptoms and exercise haemodynamics in approximately half our HFpEF patients, supporting AF ablation as a potentially effective therapy in patients with comorbid AF and HFpEF.

Patient selection:

Our study was performed in a preselected population of patients without overt clinical manifestation of HFpEF and moderate elevation in BNP reflecting early HFpEF. The spectrum of HFpEF is broad and the importance of early diagnosis and impact of restoring and maintaining sinus rhythm even in the early stages of HFpEF appear to have positive benefits.

Beyond symptoms, PCWP during exercise predicts mortality in HFpEF[44]. AF has also been associated with increased mortality in patients with HFpEF[2, 45]. Hence, restoration and

maintenance of sinus rhythm with AF ablation could therefore influence mortality in selected HFpEF patients, and further randomised study is required to investigate this hypothesis.

Given the paucity of effective therapies in the management of HFpEF and the large proportion of HFpEF patients affected by AF, our findings have important clinical implications and warrant further confirmation.

Limitations

This was a prospective observational study in a select group of patients considered suitable for AF ablation. Specifically, majority of the patients had early HFpEF without overt clinical manifestations and moderate BNP elevation. The results may not be applicable to the wider HFpEF population with AF, particularly those aged over 75 years who are generally not considered for AF ablation. The invasive nature of exRHC and its availability currently limit its' widespread application. We used PCWP in our study which may not reflect left ventricular end diastolic pressure (LVEDP) in the presence of AF[46]. Hence, assessment of PCWP in AF could have amplified the decrease in PCWP in the small number of patients who were subsequently reassessed in sinus rhythm. This was an observational study and did not include a medical / control group for comparison and 6 patients did not consent to having follow up exRHC. This study was not adequately powered to demonstrate differences in ECV on CMR at baseline or E/e' and other parameters of diastolic function at follow up. Consistent with real world practice, rhythm monitoring was limited to scheduled and emergent reviews using ECGs and 24-hour Holter monitoring. Our reported arrhythmia recurrence rate may have differed with use of a more rigorous monitoring strategy such as implantable loop recorder. Finally, follow-up duration post-ablation was limited, and long-term outcomes are unknown.

Conclusion

There is a high prevalence of HFpEF among symptomatic AF patients with preserved EF considered suitable for AF ablation, particularly in those aged over 65 years. Successful AF ablation reverses the symptoms and adverse hemodynamic changes of HFpEF. Larger randomised studies are required to examine the long-term outcomes of AF ablation in HFpEF.

Figure 1: Study profile. CONSORT diagram illustrating the recruitment for this study. AF = Atrial Fibrillation. LVEF = Left ventricular ejection fraction. exRHC = exercise right heart Catheterisation. HFpEF = Heart failure with preserved ejection fraction. SR = Sinus rhythm.

Figure 2: BNP (log) distribution in patients with AF based on HFpEF status. BNP = Brain natriuretic peptide. HFpEF = Heart failure with preserved ejection fraction. AF = Atrial Fibrillation.

Figure 3A&B: Pre and post ablation peak PCWP and MLHF questionnaire score
MLHF – Minnesota living with heart failure questionnaire score. PCWP = Pulmonary capillary wedge pressure.

Figure 4A&B: Pre and post ablation peak PCWP and PCWL (PCWP indexed to workload) based on arrhythmia recurrence in people with AF and comorbid HFpEF.
PCWP = Peak exercise pulmonary capillary wedge pressure.

Graphical abstract: Overview of the study illustrating the proportion of patients referred for consideration of AF ablation who met the criteria for HFpEF in panel A. Three-dimensional reconstruction of the left atrium with radiofrequency lesions used to achieved pulmonary vein electrical isolation at the time of AF ablation in panel B and results of the follow up exercise right heart catheterisation at ≥ 6 months following AF ablation based on arrhythmia recurrence status in panel C. Panel D illustrates the potential interaction between AF and HFpEF. AF = Atrial Fibrillation. HFpEF = Heart failure with preserved ejection fraction. PCWP = Pulmonary capillary wedge pressure. LSPV = Left superior pulmonary vein. LIPV

= Left inferior pulmonary vein. RSPV = Right superior pulmonary vein. RIPV = Right inferior pulmonary vein. LAPW = Left atrial posterior wall. BNP = Brain natriuretic peptide. QoL = Quality of life.

Table 1: Baseline clinical characteristics of patients scheduled for AF ablation with and without HFpEF

	Total	AF with HFpEF	AF without HFpEF	P value
Total Patients	54	35 (64.8)	19 (35.2)	NA
General characteristics				
Age, years	60.5 ± 11.8	64.2 ± 9.5	53.7 ± 12.9	<0.01
Female	22 (41.0)	19 (54.3)	3 (15.8)	<0.01
Persistent AF	25 (46.3)	23 (65.7)	2 (10.5)	<0.001
Duration of AF, years	3.7 ± 3.5	3.8 ± 3.7	3.5 ± 3.2	NS
Body Mass Index, kg/m^2	30.4 ± 4.3	31.2 ± 4.2	28.9 ± 4.1	NS
Hypertension	25 (46.3)	22 (62.9)	3 (15.8)	<0.001
Diabetes	4 (7.4)	3 (8.6)	1 (5.3)	NS
Stroke / TIA	3 (5.6)	3 (8.6)	0 (0.0)	NS
CHA_2DS_2-VASc score	2.4 ± 1.8	3.3 ± 1.4	0.6 ± 1.0	<0.001
Medications				
ACE inhibitor or ARB	23 (45.6)	20 (57.1)	3 (15.8)	<0.01
Spironolactone	4 (7.4)	4 (11.4)	0 (0.0)	<0.05
Anticoagulation	41 (75.9)	31 (88.6)	10 (52.6)	<0.01
Symptom scores				
NYHA	2.1 ± 0.8	2.4 ± 0.8	1.6 ± 0.6	<0.01
MLHF Total	45.6 ± 24.2	51.9 ± 22.3	34.6 ± 24.1	<0.05
AFEQT Total	79.0 ± 24.9	84.4 ± 25.5	69.1 ± 21.1	<0.05
CCS-SAF	2.9 ± 0.8	3.1 ± 0.7	2.6 ± 1.0	NS

Data expressed as mean ± SD or n (%) unless otherwise specified. CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category. ACE = Angiotensin-Converting Enzyme, ARB = Angiotensin II Receptor Blocker. AFEQT = The Atrial Fibrillation Effect on QualiTy-of-Life questionnaire. MLHF = Minnesota Living with Heart Failure questionnaire. NYHA = New York Heart Association classification. The Canadian Cardiovascular Society Severity in Atrial Fibrillation scale. AF = Atrial Fibrillation.

Table 2: Echocardiographic and cardiac magnetic resonance findings of AF patients with and without HFpEF

	Total	**AF with HFpEF**	**AF without HFpEF**	**P value**
Total Patients	54	35 (64.8)	19 (35.2)	NA
Echocardiography				
LVEF, %	60.7 ± 4.3	60.1 ± 4.8	61.6 ± 3.1	NS
LV end-diastolic diameter, mm	48.4 ± 4.6	48.0 ± 4.3	49.1 ± 5.2	NS
LV end systolic diameter, mm	31.8 ± 4.8	31.2 ± 3.9	32.9 ± 6.1	NS
LA area, cm^2	25.7 ± 5.7	27.0 ± 6.2	23.3 ± 3.4	<0.05
LAVI, mL/m^2	43.5 ± 11.6	45.8 ± 11.8	38.9 ± 10.0	NS
LA reservoir strain (%)	22.4 ± 10.6	18.9 ± 8.4	29.4 ± 10.9	<0.01
RA area, cm^2	20.0 ± 4.2	20.8 ± 4.1	18.7 ± 4.2	NS
E/e'	9.7 ± 3.4	11.0 ± 3.4	7.2 ± 1.6	<0.001
Mitral deceleration time, ms	203.5 ± 58.5	199.5 ± 56.6	212.3 ± 63.9	NS
TAPSE, cm	2.2 ± 0.4	2.1 ± 0.4	2.4 ± 0.4	<0.05
CMR				
LV mass index	54.3 ± 11.5	50.8 ± 9.5	59.7 ± 12.5	<0.05
LV Stroke Volume, mL	87.1 ± 28.8	80.9 ± 17.7	96.3 ± 39.4	NS
RV dimension, mm	44.6 ± 5.5	44.1 ± 4.7	45.8 ± 7.5	NS
RV Fractional area change, %	41.7 ± 7.2	42.2 ± 8.6	40.9 ± 4.7	NS
Native Pre contrast T1	1221.2 ± 105.1	1226.9 ± 96.1	12141 ± 120.1	NS
Post contrast T1	524.7 ± 147.4	508.4 ± 167.6	545.5 ± 121.6	NS
ECV	0.2 ± 0.1	0.2 ± .01	0.2 ± 0.1	NS

LAVI = Left Atrial Volume Index. TAPSE = Tricuspid annular plane systolic excursion. LV = Left Ventricular. LVEF = LV Ejection Fraction. RV = Right ventricular. CMR = Cardiac magnetic resonance imaging. T1 = CMR determined longitudinal relaxation time. ECV = CMR derived extracellular volume.

Table 3: ExRHC and Resting BNP findings in AF patients with and without HFpEF

	Total	AF with HFpEF	AF without HFpEF	P value
Total Patients	54	35 (64.8)	19 (35.2)	NA
Rest and exercise RHC				
Resting SBP, mmHg	139.5 ± 19.2	140.3 ± 21.2	138.1 ± 15.3	NS
Resting DBP, mmHg	83.9 ± 18.5	85.9 ± 21.1	80.0 ± 12.0	NS
Peak exercise SBP, mmHg	170.2 ± 33.4	163.5 ± 31.9	181.8 ± 33.25	NS
Peak exercise DBP, mmHg	93.3 ± 11.4	93.8 ± 11.9	92.3 ± 10.9	NS
Resting heart rate, bpm	68.5 ± 15.0	69.2 ± 16.3	67.3 ± 12.7	NS
Peak exercise heart rate, bpm	110.9 ± 23.2	107.6 ± 22.7	117.0 ± 23.8	NS
Resting PCWP, mmHg	11.9 ± 4.1	13.4 ± 3.9	9.0 ± 2.8	<0.001
3 Min PCWP, mmHg	23.1 ± 7.7	27.4 ± 5.1	14.9 ± 4.5	<0.001
3 min PCWL, mmHg/W/kg	75.7 ± 27.4	91.2 ± 17.1	47.2 ± 18.4	<0.001
Peak exercise PCWP, mmHg	26.1 ± 7.3	30.3 ± 4.6	18.4 ± 4.4	<0.001
Peak exercise PCWL, mm Hg/W/kg	34.8 ± 27.7	44.8 ± 29.4	16.2 ± 8.3	<0.001
Peak exercise workload, Watts	95.5 ± 45.3	85.5 ± 46.2	113.9 ± 38.2	<0.05
Resting CO, L/min	5.6 ± 1.4	5.1 ± 1.0	6.6 ± 1.5	<0.001
Peak exercise CO, L/min	10.6 ± 3.7	9.2 ± 2.8	13.2 ± 3.8	<0.001
Total exercise time, seconds	485.9 ± 193.0	419.7 ± 176.9	604.5 ± 164.7	<0.001
AF at exRHC	23 (42.6)	20 (57.1)	3 (15.8)	<0.01
BNP				
Resting BNP, pg/ml	101.2 ± 90.2	129.3 ± 95.0	45.0 ± 41.8	<0.001

PCWP = Pulmonary capillary wedge pressure. SBP = Systolic blood pressure. DBP = Diastolic blood pressure. bpm = beats per minute. CO = cardiac output. BNP = Brain natriuretic peptide. NS = not significant.

Table 4: Paired analysis of symptoms, exercise hemodynamic and echocardiographic parameters before and after ablation based on arrhythmia status at follow up.

	Overall (20)			Arrhythmia free (9)			Arrhythmia recurrence (11)		
	Baseline	**Post Ablation**	**p Value**	**Baseline**	**Post Ablation**	**p Value**	**Baseline**	**Post Ablation**	**p Value**
General characteristics									
Age, years	65.1 ± 8.8			67.2 ± 7.6			63.3 ± 9.7		
Female	9 (45.0)			5 (55.6)			4 (36.4)		
Persistent AF	14 (70.0)			6 (66.7)			8 (72.7)		
BMI	31.4 ± 4.3	31.0 ± 4.6	NS	31.1 ± 5.0	30.1 ± 4.6	NS	31.5 ± 3.9	31.8 ± 4.7	NS
Symptom scores									
NYHA	2.4 ± 0.7	2.0 ± 0.8	NS	2.3 ± 0.9	1.8 ± 1.0	NS	2.5 ± 0.5	2.3 ± 0.5	NS
MLHF	53.4 ± 24.3	26.1 ± 25.8	<0.001	55.0 ± 29.6	22.3 ± 29.8	<0.01	53.8 ± 22.5	29.9 ± 22.9	NS
AFEQT	90.9 ± 24.5	47.5 ± 27.8	<0.001	91.7 ± 28.9	47.8 ± 26.5	<0.01	90.1 ± 20.2	47.1 ± 31.1	<0.01
CCS-SAF	3.2 ± 0.6	1.3 ± 1.3	<0.001	3.1 ± 0.6	0.8 ± 1.1	<0.001	3.3 ± 0.5	2.0 ± 1.4	<0.05
Echocardiographic findings									
LA area	27.3 ± 5.7	24.5 ± 5.1	<0.05	24.0 ± 4.0	21.3 ± 3.7	NS	30.1 ± 5.2	27.3 ± 4.7	NS
LAVI, mL/m^2	51.3 ± 14.9	42.1 ± 14.3	NS	43.2 ± 14.2	36.2 ± 10.5	NS	61.5 ± 8.5	49.5 ± 16.4	NS
RA area, cm^2	22.3 ± 5.3	19.8 ± 8.2	NS	18.5 ± 2.9	15.0 ± 2.9	NS	26.0 ± 4.5	24.5 ± 9.4	NS
E/e'	9.9 ± 3.5	11.1 ± 5.9	NS	10.4 ± 4.7	12.4 ± 8.1	NS	9.4 ± 2.0	9.7 ± 2.0	NS
MV -DT	198.1 ± 54.1	193.1 ± 33.7	NS	216.0 ± 65.5	200.9 ± 38.6	NS	180.1 ± 36.1	185.3 ± 28.8	NS
TAPSE, cm	1.8 ± 0.5	2.1 ± 0.4	NS	1.9 ± 0.7	2.0 ± 0.4	NS	1.8 ± 0.4	2.1 ± 0.4	NS
Rest and exercise RHC findings									
Rest PCWP, mmHg	12.8 ± 4.3	10.0 ± 3.4	<0.05	12.2 ± 6.0	7.8 ± 2.3	NS	13.2 ± 2.6	11.7 ± 3.1	NS
3 min PCWP, mmHg	27.5 ± 5.1	24.5 ± 5.7	<0.05	24.4 ± 4.6	20.3 ± 3.5	<0.05	29.8 ± 4.2	27.6 ± 5.0	NS
3 min PCWL, mmHg/W/kg	91.3 ± 16.5	77.7 ± 26.1	<0.05	81.5 ± 14.3	60.0 ± 8.3	<0.05	99.4 ± 14.0	92.1 ± 16.8	NS
Peak PCWP, mmHg	30.3 ± 4.2	26.8 ± 4.7	<0.01	29.2 ± 3.7	22.9 ± 2.0	<0.01	31.2 ± 4.5	30.0 ± 3.8	NS

Peak PCWL, mmHg/W/Kg	42.5 ± 27.3	30.6 ± 21.2	NS	46.2 ± 29.9	25.5 ± 17.4	<0.05	39.5 ± 26.0	34.8 ± 23.8	NS
Peak exercise Watts, W	90.2 ± 48.8	99.7 ± 39.7	NS	81.6 ± 54.0	98.8 ± 44.7	NS	97.8 ± 45.0	100.6 ± 37.1	NS
CO rest, L/min	5.1 ± 1.1	5.6 ± 1.2	NS	4.7 ± 0.7	5.4 ± 1.2	NS	5.4 ± 1.2	5.7 ± 1.2	NS
CO Peak, L/min	9.6 ± 2.9	11.1 ± 3.8	<0.05	10.3 ± 3.0	12.1 ± 4.0	NS	9.1 ± 2.9	10.5 ± 3.7	NS
Exercise time, seconds	431.6 ± 173.4	516.3 ± 177.8	NS	448.4 ± 196.5	507.1 ± 162.6	NS	418.2 ± 162.3	523.6 ± 197.6	NS
AF at exRHC	13 (65.0)	3 (15.0)	<0.001	4 (44.4)	0 (0.0)	<0.05	9 (81.8)	3 (27.3)	<0.01
BNP									
Resting BNP, pg/ml	142.5 ± 106.7	75.1 ± 80.6	<0.01	94.6 ± 101.6	38.0 ± 34.0	<0.05	181.6 ± 98.2	105.5 ± 98.8	<0.05

Data expressed as mean ± SD or n (%) unless otherwise specified. exRHC = Exercise right heart catheter. AFEQT = The Atrial Fibrillation Effect on QualiTy-of-Life questionnaire. MLHF = Minnesota Living with Heart Failure questionnaire. NYHA = New York Heart Association classification. The Canadian Cardiovascular Society Severity in Atrial Fibrillation scale. AF = Atrial Fibrillation. LAVI = Left Atrial Volume Index. TAPSE = Tricuspid annular plane systolic excursion. LV = Left Ventricular. LVEF = LV Ejection Fraction. RV = Right ventricular. CMR = Cardiac magnetic resonance imaging. T1 = CMR determined longitudinal relaxation time. ECV = CMR derived extracellular volume. PCWP = Pulmonary capillary wedge pressure. PCWL = peak PCWP indexed to workload. CO = cardiac output. BNP = Brain natriuretic peptide.

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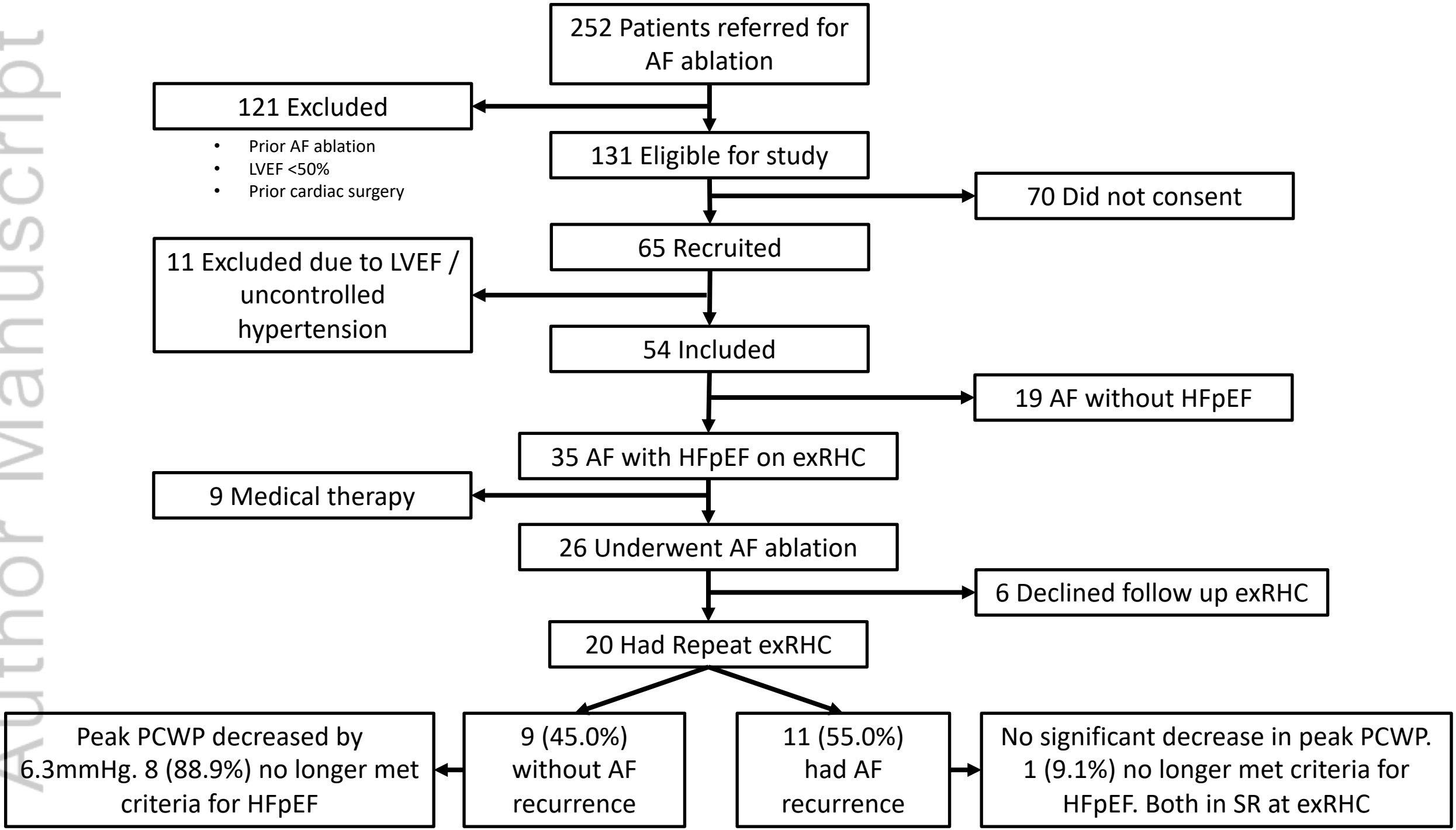
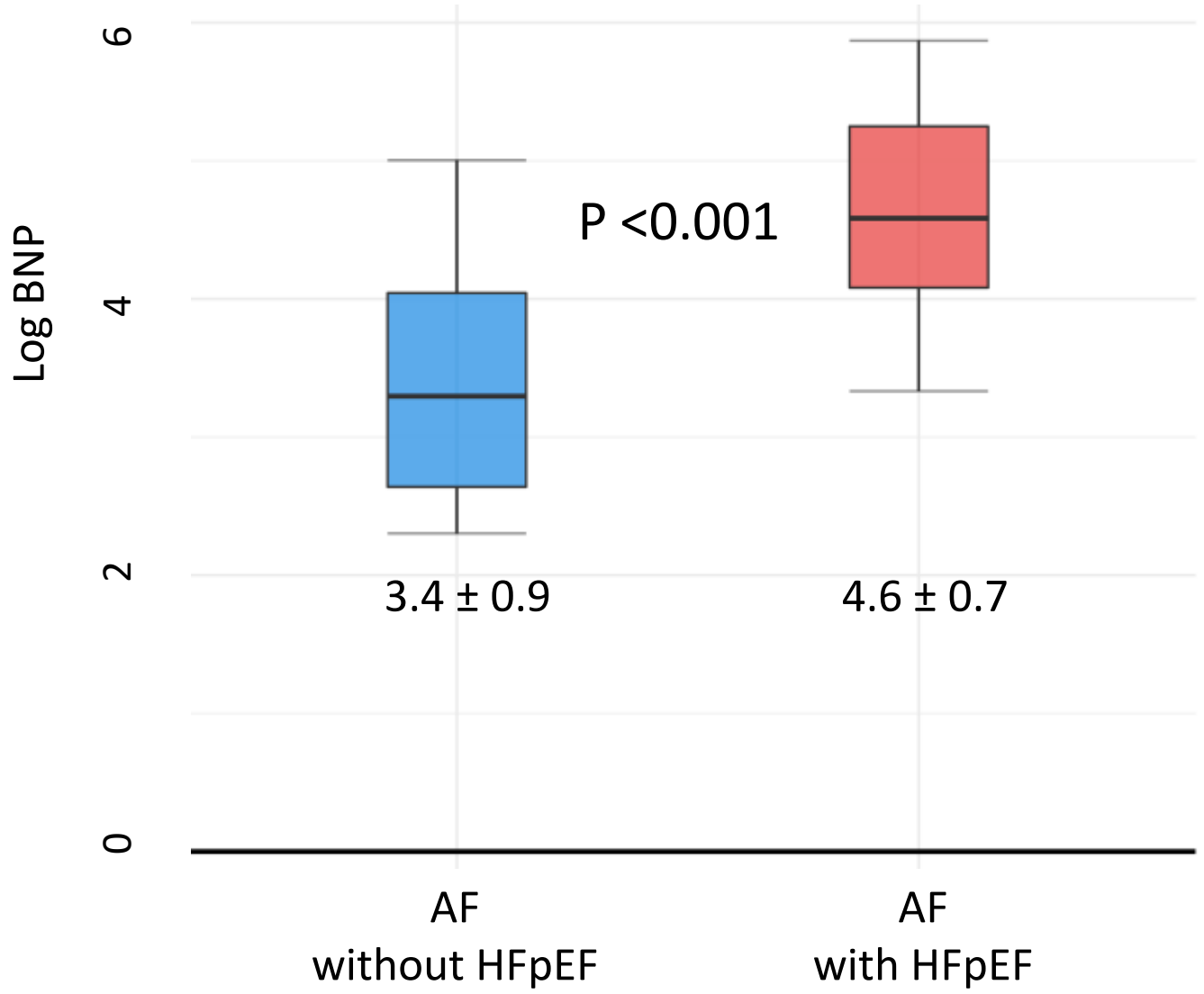
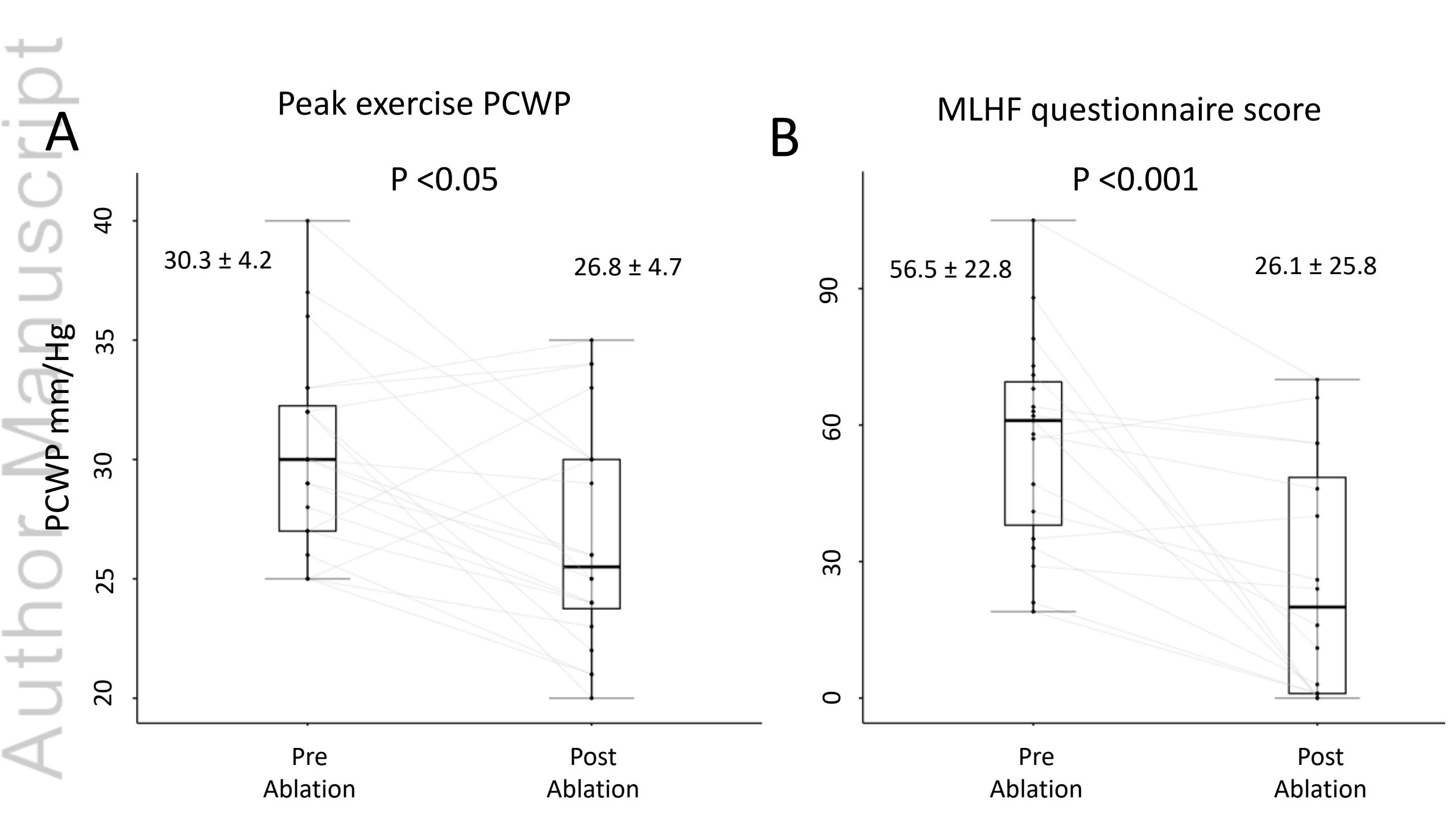
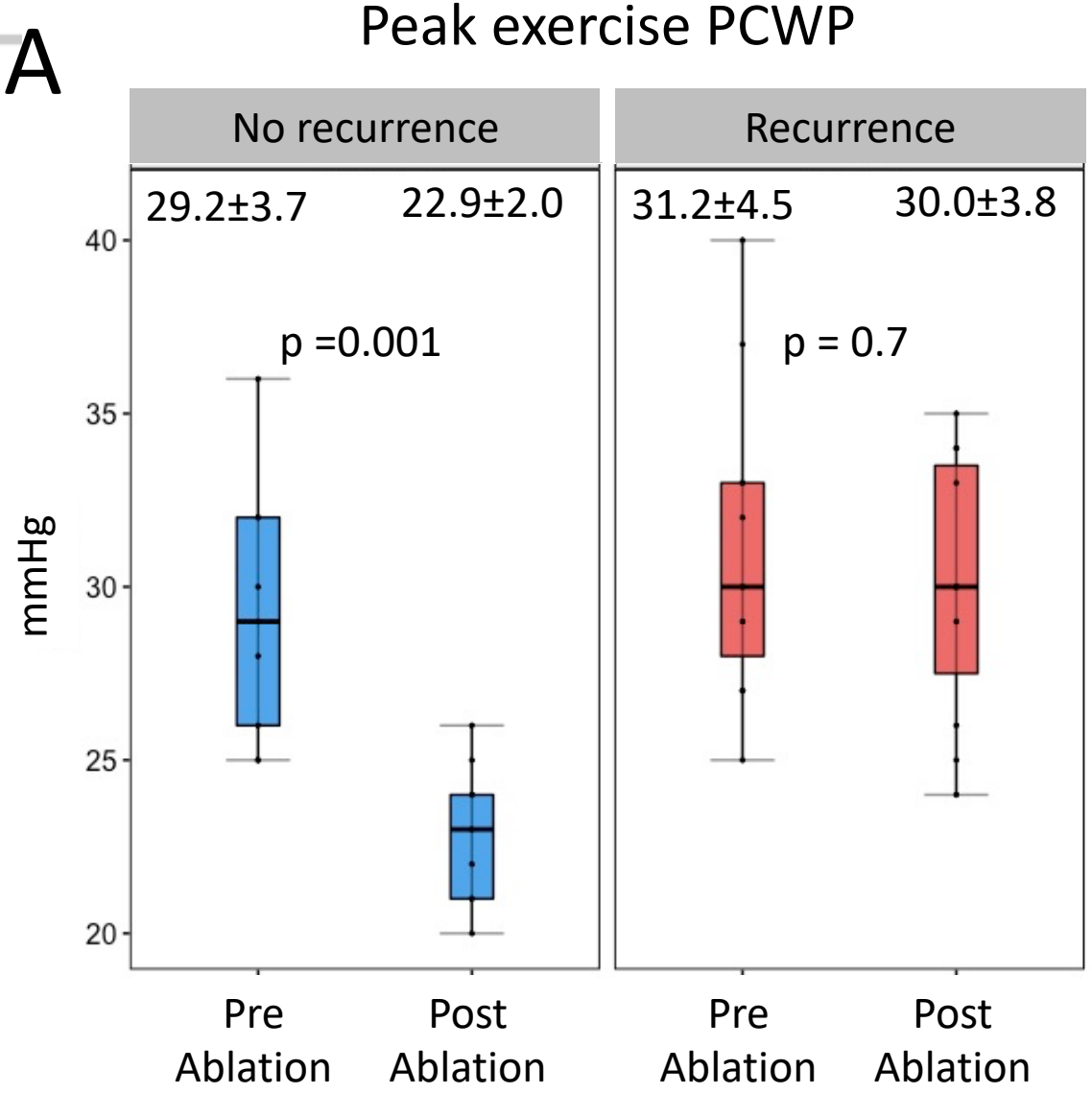


BNP distribution (log) in patients with AF based on HFpEF status

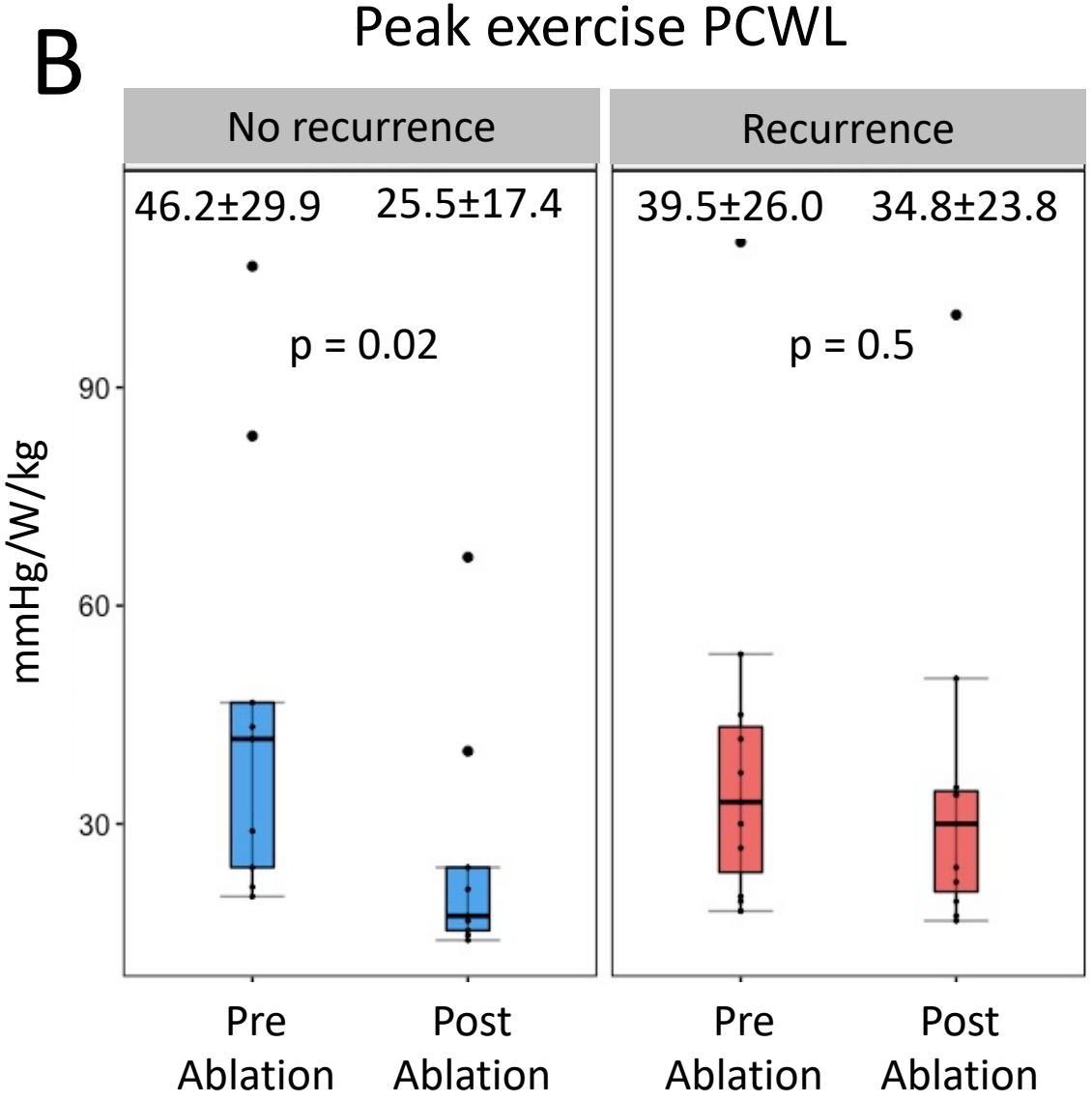




A



B



Impact of catheter ablation on HFpEF in people with comorbid atrial fibrillation and HFpEF using invasive haemodynamic testing.

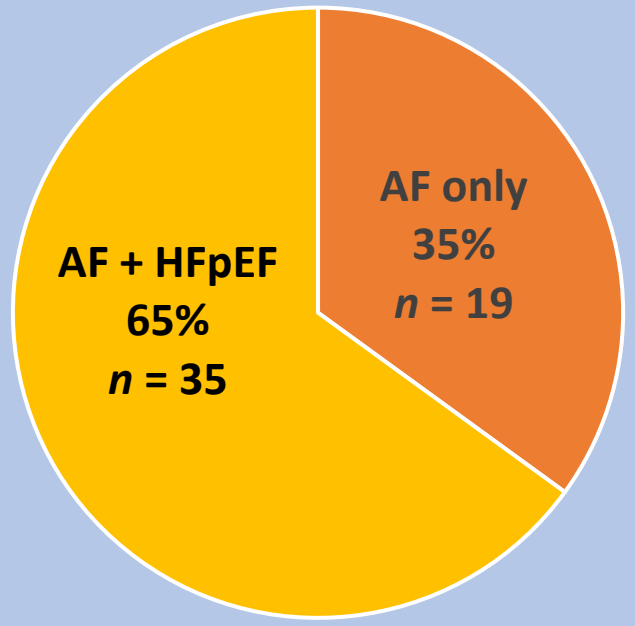
Permission note:

All materials are original to this submission

STALL AF-HFpEF: Prospective study in patients with AF undergoing exercise right heart catheterisation

Patients with AF + HFpEF undergo AF ablation (*n*=26)

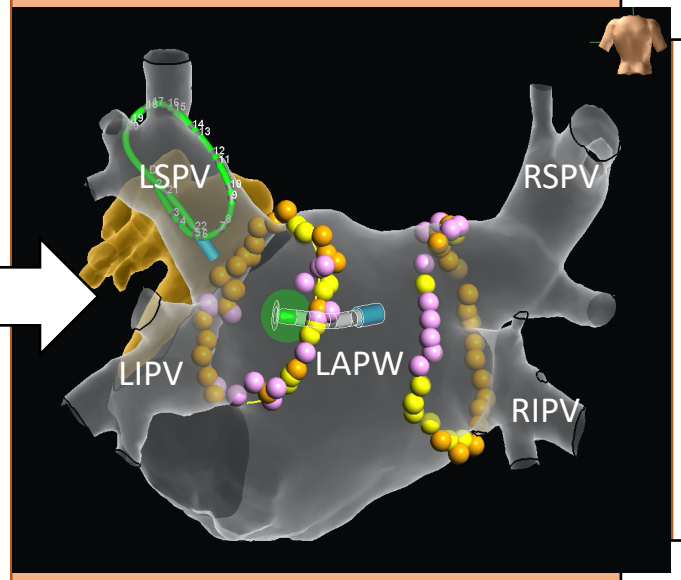
Follow-up exercise right heart catheterisation ≥ 6 months post-ablation



HFpEF defined by:
Resting PCWP ≥ 15 mmHg, or
Peak exercise PCWP ≥ 25 mmHg

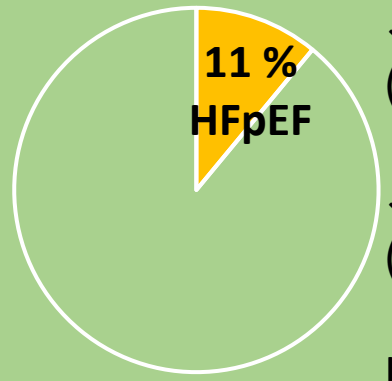
A

6 patients declined follow up exercise right heart catheterisation



B

No arrhythmia recurrence (*n* = 9)



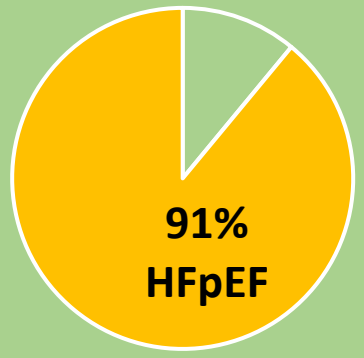
↓ Peak PCWP
(6.3 mmHg , p<0.01)

↓ BNP
(56.6pg/ml, p<0.05)

Improved QoL symptom score

Arrhythmia recurrence (*n* = 11)

↓ Peak PCWP
(1.2 mmHg, p=NS)



↓ BNP,
(76.1pg/ml, p<0.05)

Improved QoL symptom score

C

- Increased volume and pressure overload
- Atrial remodeling

AF ⇄ HFpEF

- Diffuse fibrosis / Atrial dysfunction
- Loss of LA pump function
- Irregular ventricular contraction

D