Cardiorespiratory fitness, obesity and left atrial function in patients with atrial fibrillation

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ABSTRACT

Background: Low cardiorespiratory fitness (CRF) and obesity are related to the development and maintenance of atrial fibrillation (AF). The aim of this study was to determine the association between CRF, obesity and left atrial (LA) mechanical parameters in patients with AF.

Methods: A cohort of 154 consecutive paroxysmal and persistent AF patients (Age: 62 ± 10, 26% female) referred for exercise stress testing and transthoracic echocardiography were included. We included patients in sinus rhythm with preserved left ventricular ejection fraction who were able to complete a maximal exercise test. Left atrial strain in the reservoir (LASr), booster (LASb) and conduit (LASc) phases were assessed using dedicated software. LA stiffness, emptying fraction (LAEF) and LA to LV ratio were calculated using previously described formulas.

Results: CRF was positively associated with LAEF (β = 1.3, 95% CI 0.1–2.3, p = 0.02), reservoir (β = 1.5, 95% CI 0.9–2.1, p < 0.001), booster (β = 0.8, 95% CI 0.4–1.2, p < 0.001) and conduit strain (β = 0.7, 95% CI 0.3–1.1, p = 0.001). We observed an inverse association between CRF and both LA stiffness index (β = −0.02, 95% CI (−0.03)−(−0.01), p < 0.001) and LA to LV ratio (β = −0.03, 95% CI (−0.04)−(−0.01), p < 0.001). Obese patients had significantly higher indexed LA volumes compared to overweight and normal BMI patients. The association between obesity and measures of LA function and stiffness did not reach statistical significance.

Conclusion: Among AF patients, higher CRF was independently associated with greater LA function and compliance. Obesity was associated with higher LA volumes yet preserved mechanical function.

1. Introduction

Atrial fibrillation (AF) is the most common supraventricular arrhythmia and ranks among the leading causes of mortality and morbidity worldwide [1,2]. The development and progression of AF is associated with a complex process of atrial remodelling that includes left atrial (LA) dilation, fibrosis and inflammation leading to atrial myopathy, promoted in large part by the presence of modifiable cardiovascular risk factors [3].

Structural LA abnormalities observed in AF patients are associated with electrical remodelling as well as mechanical dysfunction. Mechanical dysfunction appears to precede AF onset [4] and may be accentuated amongst those with comorbid conditions [5]. LA strain (LAS) has emerged as a novel and reliable tool to assess LA structural remodelling and mechanical function [6–9]. Amongst patients with AF, LA strain independently predicts outcomes including maintenance of sinus rhythm after cardioversion [10], catheter ablation success [11,12], and stroke [13].

Modifiable risk factors, such as obesity and hypertension, have been shown to promote structural and electrical remodelling resulting in the development of AF. In both animal models and in humans, sustained obesity is associated with LA fatty infiltration, LA enlargement, conduction abnormalities and electrogram fractionation [14]. Furthermore, observational evidence highlights a strong association between higher cardiorespiratory fitness (CRF) and the maintenance of sinus rhythm amongst patients with AF [15,16]. However, the mechanism by which preserving CRF is associated with improved AF outcomes, remains unclear.

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Exercise training leads to notable physiologic adaptations, including atrial and ventricular dilatation in association with improved diastolic function and reduced LV stiffness [17,18]. In this study, we sought to investigate whether atrial function and stiffness, assessed using trans-thoracic echocardiography, was associated with CRF amongst patients with AF. In addition, we examined whether obesity influenced these parameters in the same population. We hypothesised that preserved CRF and normal body mass would be associated with enhanced function and reduced stiffness of the LA.

2. Methods

This study was approved by the Human Research Ethics Committee at the University of Adelaide (Ethics approval number H-2021–076) and adhered to the guidelines for human research set out in the Helsinki Declaration. All participants provide written informed consent.

2.1. Study population

Consecutive patients with AF referred for clinical assessment including both transthoracic echocardiogram (TTE) and treadmill exercise stress test (EST) at the Centre for Heart Rhythm Disorders from March 2020 until January 2021 were screened for inclusion. Exclusion criteria were a) active malignancy, b) AF at presentation, c) moderate to severe valvular disease, LVEF < 50% or low-quality images impeding LAS analysis, d) EST stopped due to musculoskeletal problems or arrhythmia. Patients with history of persistent AF were required to have been in sinus rhythm for the 4 weeks prior to assessment. Anthropometric measurements were obtained by trained technicians and BMI was calculated. Clinical characteristics were obtained from patient review. Body mass and height were recorded, and body mass index computed immediately prior to EST. Patients were classified as obese, overweight and normal body mass according to their BMI (≥30, 25 to < 30 and < 25 kg/m², respectively).

2.2. Cardiorespiratory fitness

Cardiorespiratory fitness (CRF) was assessed with a symptom-limited EST using the standard Bruce protocol. CRF was determined based on final speed and grade and calculated in metabolic equivalents (METs). Patients were continuously monitored with a 12-lead ECG and blood pressure was measured manually at every stage of the Bruce protocol.

2.3. Transthoracic echocardiography

Comprehensive TTE was performed by experienced sonographers, blinded to EST performance, using commercially available ultrasound machines (General Electrics Vivid 9 and Vivid 7 Dimension). Two dimensional (2D) and Doppler images were acquired with the patients in two-chamber views and divided by body surface area (BSA). LA minimal volume (LAmin) was calculated at ventricular end-diastole. LA emptying fraction (LAEF) was calculated as \( \frac{LA_{\text{max}} - LA_{\text{min}}}{LA_{\text{max}}} \times 100 \). Left ventricular ejection fraction (LVEF) was calculated using the Simpson’s biplane method. LA to left ventricular (LV) ratio was calculated with the formula LAmax/LV end diastolic volume as previously described [20] to assess disproportionate LA remodelling compared to LV remodelling.

Doppler measurements were obtained as per international recommendations [21]. Briefly, peak E velocity and peak A velocity were obtained with pulsed wave doppler from apical four chamber view, and mitral valve E/A ratio was calculated with the formula peak E velocity/peak A velocity. Tissue doppler imaging was used to acquire septal e’ and lateral e’. Peak E velocity was divided by septal e’ and lateral e’ to obtain septal E/e’ and lateral E/e’, respectively.

LA strain (LAS) measurements were performed as previously described [20]. Briefly, LA endocardial borders were manually traced in four and two chamber views and region of interest was adjusted for the LA wall. After that, the dedicated LA strain software automatically divided the atrium into six segments (Fig. 1); the tracking quality for each segment was automatically assessed, and tracing was repeated when the software rejected more than 1 segment. Peak LAS reservoir (LASr) and booster (LASb) were obtained using R-R wave gating. LASr was used to calculate LA stiffness index using the formula (mean E/e’)/LASr [20].

2.4. Statistical analysis

Continuous variables are summarized using mean ± SD. Categorical variables are presented as count and percentages. Clinical and echocardiographic variables were compared across BMI categories using ANOVA test for continuous variables and Chi² test for categorical variables. Linear regression models were used to examine the relationship between a) exercise capacity in METs or BMI as the predictor variables and b) LAmax, LAmin, LA to LV ratio, LASr, LASb, LASc, LA stiffness index and LAEIF as dependent variables. Models were adjusted for age, sex and BMI or METs, respectively. Analysis was conducted using RStudio version 1.3.1093 (R Foundation for Statistical Computing, Vienna, Austria) and p-values < 0.05 were considered significant.

3. Results

Between March 2020 and January 2021, a total of 203 patients with a history of AF were referred for treadmill EST and transthoracic echocardiography at the Centre for Heart Rhythm Disorders. After exclusion of 49 who met pre-defined exclusion criteria, 154 were included in the final analysis (Fig. 2).

3.1. Baseline characteristics

Baseline clinical characteristics for the whole sample are presented in Table 1. For the whole sample, the average age was 62 ± 10 years, and the percentage of females was 26%. The mean BMI was 27.3 ± 4 kg/m² and the METs achieved was 10.3 ± 3. The number of patients in the normal, overweight and obese range was 41, 88 and 25 respectively. The obese group had a greater proportion of patients with persistent AF, previous ablation, hypertension and obstructive sleep apnoea. Echocardiographic parameters, stratified by BMI group, are presented in Table 2. The mean LVEF was 65 ± 5% and the mean LAmax was 32 ± 10 mL/m².

4. Cardiorespiratory fitness and LA volume

In unadjusted models, CRF was not significantly associated with LAmax (\( \beta = -0.5, 95\%\ CI \ -1.1 \ -0.1, p < 0.09 \)) but it was inversely associated with LAmin (\( \beta = -0.7, 95\%\ CI \ -1.2 \ -0.2, p < 0.009 \)) and LA to LV ratio (\( \beta = -0.03, 95\%\ CI \ -0.04 \ -0.01, p < 0.001 \)) in Table 2). In age, sex and BMI adjusted models, the association between CRF and LAmax (\( \beta = -0.8, 95\%\ CI \ -1.6 \ -0.02, p < 0.04 \)), LAmin (\( \beta = -1.5, 95\%\ CI \ -2.1 \ -0.8, p < 0.001 \)) and LA to LV ratio (\( \beta = -0.03, 95\%\ CI \ -0.04 \ -0.01, p < 0.004 \)) was statistically significant (Table 2).

4.1. Obesity and LA volume

The obese group had significantly higher indexed LAmax (38.9 ±
14.6 mL/m$^2$) and LA$_{\text{min}}$ (23.3 ± 11.9 mL/m$^2$) compared to overweight (30.3 ± 7.2 and 17.0 ± 7.1 mL/m$^2$) and normal BMI groups (31.6 ± 9.0 and 18.3 ± 8.2 mL/m$^2$) (p < 0.001 and p = 0.004, respectively). LA to LV ratio was higher in the obese (0.71 ± 0.31) compared to overweight (0.57 ± 0.19) (p = 0.02) with no significant difference compared to normal BMI (0.61 ± 0.23, p = 0.3) (Table 3). In both unadjusted and adjusted linear regression models, BMI was not associated with LAmax, LA min or LA to LV ratio (Supplemental Table 1).

### 4.2. Cardiorespiratory fitness and LA function parameters

CRF showed a significant association with LA functional parameters (Table 2, Fig. 3). In unadjusted models, CRF was positively associated with LA strain in the reservoir ($\beta = 1.5$, 95% CI 0.9–2.1, p < 0.001), conduit ($\beta = 0.7$, 95% CI 0.3–1.1, p = 0.001), and booster phases ($\beta = 0.8$, 95% CI 0.4–1.2, p < 0.001). Likewise, there was a positive association between CRF and LAEF ($\beta = 1.3$, 95% CI 0.1–2.3, p = 0.02). LA stiffness index was inversely associated with CRF ($\beta = -0.02$, 95% CI (-0.03) – (-0.01), p < 0.001). When adjusted for age, sex and BMI, associations between CRF and LA function parameters remained significant (Table 2, Fig. 3).
4.3. Obesity and LA function parameters

LA strain measurements (LASr, LASc and LASb) were not significantly different among the obese (25.8 ± 9.5%, 12.8 ± 6.5% and 13.2 ± 5.4%, respectively) compared to the overweight (30.6 ± 11.1%, 13.8 ± 6.6% and 16.7 ± 7.0%) and normal BMI (30.2 ± 8.5, 14.2 ± 5.9 and 16.0 ± 6.0) groups (P for trend = 0.1, 0.7 and 0.07, respectively) (Table 3, Fig. 4A, B and C). LA stiffness index (0.35 ± 0.18, 0.32 ± 0.17 and 0.32 ± 0.14, respectively) and LAEF (40.1 ± 18.8%, 44.5 ± 16.5% and 42.6 ± 18.2%, respectively) did not differ between normal, overweight and obese BMI groups (P for trend = 0.6 and 0.5, respectively) (Table 3, Fig. 4D and E). In both unadjusted and adjusted linear regression models, only LAS showed a significant inverse relationship with BMI in unadjusted model (β = −0.2, 95% CI [−0.4] −[−0.006], p = 0.04) which was not significant after adjustment for age, sex and METs (β = −0.2, 95% CI [−0.4] −0.09, p = 0.2) (Supplemental table 1, Supplemental Fig. 1).

5. Discussion

This study of patients with a history of AF in sinus rhythm, demonstrates three important findings; (1) Higher CRF is independently associated with improved LA mechanical function and reduced stiffness after adjustment for age, sex and BMI, (2) higher CRF is associated with reduced LA remodeling and (3) obesity is associated with LA dilatation but preserved LA mechanical function.

Higher CRF is associated with a lower AF incidence, particularly in the obese [22]. Baseline CRF is also associated with a lower arhythmia recurrence and lower mortality after AF ablation [15]. However, there is limited understanding as to the biological mechanisms supporting the association between higher CRF and improved outcomes. This study provides novel insights into the benefits associated with higher CRF in patients with AF; namely, preserved LA systolic function, and lower LA stiffness, both of which may contribute to lower risk of AF recurrence [23].

Although there is a lack of data amongst patients with AF, the association between LA function and CRF is supported by data from other patient groups. In a cohort of 669 patients with suspected heart failure with preserved ejection fraction (HFpEF), Ye et al. [9] reported a linear association between LASr and exercise capacity. Similarly, in a population of 65 patients with heart failure with preserved and mid-range EF, lower LASr, LASb and LASc were associated with impaired peak oxygen consumption [24]. The association of abnormal LAS with reduced exercise capacity has also been demonstrated with cardiac magnetic resonance (CMR) in patients with HFpEF [25].

In our cohort, we demonstrate a moderate association between exercise capacity and LA function through each of the atrial phases, which may have important clinical implications.

That higher CRF is associated with greater LA function may have important implications beyond rhythm control in patients with AF. Lower LA function is associated with risk of cardioembolic stroke, independent of AF episodes [26]. Additionally, LA remodelling is central to the development of HFpEF [5,27]. Therefore, patients with higher CRF may represent a cohort with comparatively lower risk of both AF recurrence and significant comorbidities, including stroke and heart failure. Prospective studies of well phenotyped AF patients will be key in determining whether this is the case.

The assessment of LA stiffness may represent a key measure of the extent of pathophysiological remodelling within the LA. Measures of LA stiffness, derived from simultaneous invasive LA pressure and cardiac MRI measurements, are independently associated with AF recurrence after ablation [23]. In addition, amongst patients undergoing AF ablation, LA stiffness is associated with elevated natriuretic peptides, pro-fibrotic markers, diastolic dysfunction and AF recurrence [28]. More recently, Kishima et al. [29] showed that higher LA stiffness was independently associated with lower LA stiffness and higher LASr, thus suggesting a more compliant LA in this subset of patients.

Although we are unable to establish cause and effect based on these observational findings, our data is consistent with earlier findings that...
exercise training amongst previously sedentary individuals, contributes to improved LAEF and left ventricular stiffness [17,30]. Additionally, higher measures of LA function can be seen in masters endurance athletes [18]. The observational nature of our study does not permit the analysis of whether exercise interventions can further increase LA function in this cohort, although previous studies demonstrate a preservation of atrial function amongst AF patients randomised to exercise training, compared with non-exercise controls [31].

In contrast, we found no evidence of an association between LA mechanical dysfunction and BMI status. This finding is in line with the results of Gulel et al. [32] who found no significant differences in LA mechanical function assessed by LAS. More recently, Cichón et al. [33], reported no significant differences in LASr in the 4-chamber view with a significant yet clinically minimal difference in the 2-chamber view. In

Fig. 3. Linear models of left atrial function according to cardiorespiratory fitness (METs). LA = Left atrium.
contrast, Chirinos et al. [34] showed a reduced LASr and LASC with a higher LASb function among overweight and obese middle-age adults. The link between obesity and AF is well established. In both animal models and humans, obesity promotes the development of conduction slowing and heterogeneity, alongside atrial fibrosis and lowering of bipolar voltages within the atria [14,35]. Despite relatively preserved LA function in the context of high BMI, we found significantly higher LA volumes, even when scaled to LV size [36], indicating disproportionate LA remodelling in this group. Of future interest will be whether long-term changes in body mass, modifies LA mechanical function given the dynamic relationship between BMI and AF [37].

This study is not without its limitations. First, this is a cross-sectional single-centre study that is not geared to determine causality. Some patients had to be excluded due to unsatisfactory speckle-tracking with echocardiography. Cardiac magnetic resonance may offer improved capabilities to detect subtle differences in LA function. Importantly, this study relies on indirect measurements of haemodynamic parameters, thus confirmation with invasive measurements is warranted. However,
the pragmatic approach of combining non-invasive imaging with exercise test data provides enhanced clinical translation. We also did not include imaging during exercise, which may reveal different patterns of LA function and its association with CRF. Furthermore, we do not know the duration of AF or whether these patients had paroxysmal episodes prior to testing which may impact these results. The exclusion of patients in AF at the time of assessment and those unable to undertake treadmill exercise testing likely contributed to a relatively healthy AF patient cohort with well-preserved cardiorespiratory fitness. This may limit the extrapolation of these findings to those with significantly reduced exercise tolerance or with persistent AF. Similarly, the relatively few patients falling into the morbid obesity range precludes extrapolation of these findings to that patient cohort. Future studies may include those with a focus on patients at the further extremities of the BMI range. Finally, there is some uncertainty regarding the appropriate indexing of LA size in the context of obesity [38], which may require further investigation.

6. Conclusions

Among patients with AF, CRF was independently associated with a lower LA stiffness as well as a higher LA systolic function while obesity was associated with increased LA volumes with relatively preserved LA mechanical function. These findings highlight potential mechanisms through which higher CRF is associated with improved AF outcomes. Further prospective, randomised studies are warranted to evaluate the effects of lifestyle-based interventions that may concomitantly promote the maintenance of sinus rhythm and improve LA structure and function.

CRediT authorship contribution statement

Ricardo S. Mishima: Conceptualization, Methodology, Formal analysis, Investigation, Visualization, Writing – original draft. Jonathan P. Ariyaratnam: Investigation, Formal analysis, Writing – review & editing. Bradley M. Pitman: Investigation, Formal analysis, Writing – review & editing. Varun Malik: Investigation, Writing – review & editing. Mehrdad Emami: Investigation, Writing – review & editing. Olivia McNamee: Investigation, Formal analysis, Writing – review & editing. Michael B. Stokes: Investigation, Writing – review & editing. Dennis H. Lau: Conceptualization, Methodology, Supervision, Writing – review & editing. Prashanthan Sanders: Conceptualization, Methodology, Supervision, Writing – original draft, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Disclosures

Dr Lau reports that the University of Adelaide has received on his behalf lecture and/or consulting fees from Abbott Medical, Bayer, Biotronik, Boehringer Ingelheim, Medtronic, MicroPort CRM and Pfizer. Dr Sanders reports having served on the advisory board of Biosense-Webster, Boston Scientific, CathRx, Medtronic, and St Jude Medical. Dr Sanders reports that the University of Adelaide has received on his behalf lecture and/or consulting fees from Biosense-Webster, Medtronic, Boston-Scientific, Pfizer and St Jude Medical. Dr Sanders reports that the University of Adelaide has received on his behalf research funding from Medtronic, St Jude Medical, Boston Scientific, Biotronik and Liva Nova. All other authors have no disclosures.

Appendix A. Supplementary material

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