European Journal of Heart Failure (2017) **19**, 1690–1697
doi:10.1002/ejhf.930

RESEARCH ARTICLE

Impact of atrial fibrillation on rest and exercise haemodynamics in heart failure with mid-range and preserved ejection fraction

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Received 12 April 2017; revised 1 June 2017; accepted 4 June 2017; online publish-ahead-of-print 11 October 2017

Aims Heart failure with preserved (HFpEF) and mid-range ejection fraction (HFmrEF) are becoming the most prevalent forms of heart failure. Patients with HFpEF/HFmrEF in atrial fibrillation (AF) have poorer survival and quality of life, but the mechanism underpinning this is unknown. We sought to investigate the influence of AF on the haemodynamic profile of HFpEF/HFmrEF patients at rest and during exercise.

Methods and results We invasively measured central haemodynamics at rest and during symptom-limited supine bicycle exercise in HFpEF/HFmrEF patients, 35 in sinus rhythm and 20 in AF with matched left ventricular ejection fraction. At rest, AF patients had significantly increased pulmonary capillary wedge pressure, lower cardiac index and reduced left ventricular stroke work index, despite similar resting heart rate. Under resting conditions, calculated oxygen consumption and systemic arteriovenous oxygen gradient were not different between the two groups. During supine cycling at similar levels of workload, AF patients exhibited a reduced capacity to increase their oxygen consumption and this was accompanied by a persistently impaired cardiac index and left ventricular stroke work index.

Conclusions The adverse interaction of AF and HFpEF/HFmrEF may be accounted for by an adverse impact on left ventricular systolic function and peripheral oxygen kinetics.

Keywords Heart failure with preserved ejection fraction • Atrial fibrillation • Haemodynamics • Systolic function

Introduction

Patients with clinical features of heart failure with preserved (HFpEF) or mid-range ejection fraction (HFmrEF) are an increasingly common component of the overall burden of heart failure.[1,2] These patients typically experience a similar degree of functional limitation as those with heart failure with reduced ejection fraction (HFrEF).[3,4] Furthermore, mortality rates and the requirement for hospitalization are roughly similarly for HFpEF and HFrEF patients. Despite the clear need for effective therapy, only modest progress has been made in regard to the development of proven therapies in HFpEF or the recently defined HFmrEF. Specifically, no treatment to date has been shown to improve survival, and there is only limited evidence for pharmacological approaches to reduce hospitalizations.[5,6]

One potential explanation for the lack of success in HFpEF trials is the considerable variability in the clinical features of HFpEF patients and in their co-morbidities.[7,8] In particular, patients tend to be older, more overweight, diabetic and have a history of hypertension and renal disease. Each of these factors may modify

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the signs and symptoms of heart failure, whilst also influencing echocardiographic parameters and circulating biomarker levels.

A history of prevalent or incident atrial fibrillation (AF) is also particularly common in HFpEF.[1,9–11] It is evident that patients with AF and HFpEF experience poorer outcomes than those in sinus rhythm (SR).[12,13] Whilst the presence of an adverse effect of AF has also been reported in HFrEF, it appears that the modifying effect is even greater in HFpEF.[12,13] It has been previously shown that patients with HFpEF and AF are more symptomatic and have a lower peak oxygen consumption (VO_2) than those in SR, although the haemodynamic basis has not been determined during physical activity.[14,15] Despite this important observation, the precise mechanism for the adverse relationship between AF and HFpEF remains unknown. Previously, we demonstrated that an irregular rhythm *per se* was associated with adverse myocardial molecular remodelling in HFrEF, with attendant implications for contractile performance.[16] In the current study, we hypothesized that similar processes might be operative in HFpEF/HFmrEF patients in AF. We therefore compared the central haemodynamic profiles of HFpEF/HFmrEF patients in AF to those in SR, with particular emphasis on the haemodynamic response to exertion.

Methods

Study design and patient population

The present study represents a retrospective, post-hoc analysis of the haemodynamic features of a cohort of patients with confirmed HFpEF or HFmrEF. Baseline study data were obtained from subjects who were participating in a trial of a novel inter-atrial septal device, described elsewhere in detail.[17,18] In brief, study inclusion criteria included a history of chronic symptomatic heart failure (NYHA class II–IV), a left ventricular ejection fraction (LVEF) >40% and by definition patients had to have an elevated pulmonary capillary wedge pressure (PCWP) at rest (>15 mmHg) or during exercise (>25 mmHg), as described below. Natriuretic peptide levels were not used as an entry criteria. Subjects had to be able to perform supine cycle ergometry as described below. For the current study, we included patients with resting LVEF within the range of 40–60% to avoid the potential confounding effects of significant between-group differences in LVEF. Data included in the current study comprise the baseline data collected prior to device implantation. All subjects gave written informed consent and the study was approved by relevant institutional ethics committees.

Right heart catheterization

After meeting non-invasive inclusion criteria, patients underwent right heart catheterization for the measurement of cardiac output and haemodynamic pressures at rest and during supine bicycle exercise. After the completion of baseline measurements, patients were instructed to perform symptom-limited exercise commencing at 20 W with 20 W increments every 3 min until symptom-limiting maximal effort was reached. Mixed venous blood gas samples were collected at rest and at peak exercise for the calculation of arteriovenous oxygen difference and VO_2 with the use of the thermodilution cardiac output and indirect oximetric assessment of the arterial oxygen saturation. Haemodynamic traces were evaluated at an independent core laboratory (PV Loops LLC, New York, NY, USA) for the measurement of right atrial, pulmonary arterial and pulmonary capillary wedge pressures at rest and peak exercise. Pulmonary capillary wedge pressure and pulmonary arterial pressure were also recorded at 20 W.

Haemodynamic and metabolic calculations

Systemic and mixed venous oxygen content was determined according to standard formulae and the arteriovenous oxygen content difference was subsequently calculated. Oxygen consumption was calculated as the product of the average cardiac output (measured by thermodilution method) and the arteriovenous oxygen difference at rest and exercise, respectively. We did not perform concurrent expiratory gas analysis for direct Fick analysis of cardiac output. Stroke volume index (SVI) was calculated from the ratio of cardiac index to heart rate. Left ventricular stroke work index (LVSWI) was calculated according to the formula: LVSWI = (MAP-PCWP) x SVI x 0.0136, where MAP is mean arterial pressure. Right ventricular stroke work index (RVSWI) was calculated according to the formula: RVSWI = (MPAP−CVP) x SVI x 0.0136, where MPAP is mean pulmonary arterial pressure and CVP is central venous pressure. Systemic and pulmonary vascular resistance were calculated according to standard formulae. The systemic arterial elastance (Ea) was calculated according to the formula: Ea = ESP/SV, where ESP is end-systolic pressure and was calculated as 0.9 x MAP, and SV is stroke volume. Pulmonary arterial compliance (PAC) was calculated as PAC = SV/(PASP−PADP), where PASP is pulmonary artery systolic pressure and PADP is pulmonary artery diastolic pressure.

Echocardiography

Echocardiographic images were obtained by trained research echocardiographers at each study site, and the analysis was performed at an independent core laboratory located at the University of Pennsylvania (PA, USA). Echocardiographic measurements were made according to published guidelines.[19] Off-line analysis included measurement of left ventricular and left atrial volumes, right atrial and ventricular volumes and the tricuspid annular plane systolic excursion (TAPSE).

Statistical analysis

Data are presented as mean ± standard error of the mean, median (25th–75th percentile range), or as count, according to the distribution of the variable. Between-group analyses were conducted using *t*-test, chi-square test, or Wilcoxon rank-sum test, as appropriate. Differential responses to exercise between groups were investigated by repeated measures ANOVA, including an evaluation of the exercise x rhythm interaction term. A *P*-value of <0.05 was considered to be statistically significant. Statistical analysis was performed using a commercially available software package (IBM SPSS Statistics, version 22; SPSS Inc., Chicago, IL, USA).

Results

The current study compared the demographic, echocardiographic and haemodynamic features of a cohort of HFpEF patients dichotomized according to the presence of SR or AF. As shown in *Table 1*, HFpEF patients in SR ($n = 35$) were similar to those in AF ($n = 20$) with regard to age, body mass index, gender distribution, left ventricular end-diastolic volume and LVEF (*Table 2*).

Table 1 Baseline clinical and biochemical characteristics

Parameter	Sinus rhythm ($n=35$)	Atrial fibrillation ($n=20$)	*P*-value
Age, years	70 ± 2	69 ± 1	NS
BMI, kg/m^2	33 ± 1	31 ± 1	NS
NYHA class II/III, *n*	10/25	5/15	NS
eGFR, mL/min/1.73 m^2	64 ± 4	57 ± 4	NS
Medications (%)			
Diuretics	83	100	NS
ACEIs/ARBs	83	70	NS
Beta-blockers	63	65	NS
MRAs	43	45	NS
Digoxin	3	35	<0.01
Co-morbidities (%)			
COPD	6	10	NS
Diabetes	31	20	NS
Chronic kidney disease*	34	40	NS
Hypertension	77	85	NS
Myocardial infarction	11	10	NS
NT-proBNP (pg/mL)**	272 (103–518)	1250 (719–1703)	<0.001

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association.
*Chronic kidney disease defined as eGFR <60 mL/min/1.73 m^2.
**Median (25th–75th percentile).

Table 2 Baseline echocardiographic characteristics

Parameter	Sinus rhythm ($n=35$)	Atrial fibrillation ($n=20$)	*P*-value
LVEF, %	48 ± 1	46 ± 1	NS
LVEDVI, mL	134 ± 4	137 ± 6	NS
LAVI, mL/m^2	30 ± 3	43 ± 3	0.005
RAVI, mL/m^2	32 ± 3	42 ± 4	0.03
TAPSE, mm	21 ± 1	17 ± 1	0.004

LAVI, left atrial volume index; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; RAVI, right atrial volume index; TAPSE, tricuspid annular plane systolic excursion.

Table 3 Resting haemodynamic and metabolic characteristics

Parameter	Sinus rhythm ($n=35$)	Atrial fibrillation ($n=20$)	*P*-value
HR, b.p.m.	67 ± 2	72 ± 4	NS
MAP, mmHg	95 ± 2	98 ± 3	NS
SBP, mmHg	143 ± 4	143 ± 5	NS
RAP, mmHg	9 ± 1	10 ± 1	NS
MPAP, mmHg	22 ± 1	27 ± 1	0.015
PASP, mmHg	35 ± 2	41 ± 2	NS
PCWP, mmHg	16 ± 1	20 ± 1	0.013
TPG, mmHg	6 ± 1	7 ± 1	NS
CI, L/min/m^2	2.9 ± 0.1	2.5 ± 0.1	0.038
SVI, mL/m^2	44 ± 2	36 ± 2	0.014
PVR, mmHg.min/L	1.1 ± 0.1	1.5 ± 0.1	0.05
PA compliance, mL/mmHg	5.1 ± 0.4	3.7 ± 0.3	0.002
LVSWI, kg-m/min/m^2	46 ± 2	38 ± 3	0.03
RVSWI, kg-m/min/m^2	8.4 ± 0.9	8.7 ± 0.8	NS
CaO_2, mL/100 mL	17.0 ± 0.4	17.3 ± 0.5	NS
CvO_2, mL/100 mL	12.1 ± 0.4	12.1 ± 0.5	NS
Ca–vO_2, mL/100 mL	4.8 ± 0.2	5.2 ± 0.2	NS
VO_2, mL/kg/min	3.0 ± 0.1	3.0 ± 0.1	NS

CaO_2, arterial oxygen content; CI, cardiac index; CvO_2, venous oxygen content; HR heart rate; LVSWI, left ventricular stroke work index; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; SBP, systolic blood pressure; SVI, stroke volume index; TPG, transpulmonary gradient; VO_2, oxygen consumption.

The left atrial volume index was considerably larger in AF patients than in SR subjects (43 ± 3 vs. 30 ± 3 mL/m^2, $P=0.005$), as was the right atrial volume index (42 ± 4 vs. 32 ± 3 mL/m^2, $P=0.03$) (*Table 2*). Right ventricular function as reflected by TAPSE was lower in AF patients (17 ± 1 vs. 21 ± 1 mm, $P=0.004$). N-terminal pro-brain natriuretic peptide (NT-proBNP) was significantly higher in AF patients. Across the entire cohort, NT-proBNP and log NT-proBNP levels were inversely correlated with cardiac output ($r=-0.31$, $P=0.03$ and $r=-0.34$, $P=0.02$, respectively). By analysis of covariance, natriuretic peptide levels continued to differ significantly between rhythm groups ($P<0.001$).

Baseline haemodynamics and metabolism

At rest, heart rate and systemic blood pressure were similar in SR and AF patients (*Table 3*). By contrast, resting PCWP and mean pulmonary arterial pressure were significantly higher in patients with AF. In conjunction, the resting cardiac index was lower in patients with AF as compared with SR patients (2.5 ± 0.1 vs. 2.9 ± 0.1 L/min/m^2, $P=0.038$). This difference was accounted for by a significantly lower stroke volume index in AF patients. Accordingly, LVSWI was lower at rest in AF patients (*Table 3*). At rest, the arterial and mixed venous oxygen content were similar, and the calculated VO_2 was similar between AF and SR patients at rest (3.0 ± 0.1 vs. 3.0 ± 0.1 mL/kg/min, $P=$ NS).

In addition to differences in cardiac performance and right heart pressures, there was also evidence of differences in baseline vascular function between the two groups. At rest, systemic vascular resistance in AF was similar to SR (18.8 ± 1.3 vs. 16.4 ± 0.8 dyne.cm.sec^{-5}) and the arterial elastance was also similar between groups (1.9 ± 0.1 vs. 1.6 ± 0.1 mmHg/mL, $P=$ NS). Resting pulmonary vascular compliance was lower in AF patients, consistent with a stiffer pulmonary circulation

Table 4 Exercise haemodynamic and metabolic characteristics

Parameter	Sinus rhythm ($n=35$)	Atrial fibrillation ($n=20$)	*P*-value
Peak workload, W	47 ± 3	39 ± 4	NS
Exercise time, min	7.6 ± 0.5	7.1 ± 0.8	NS
HR, b.p.m.	94 ± 2	97 ± 5	NS
MAP, mmHg	116 ± 4	113 ± 4	NS
SBP, mmHg	175 ± 5	166 ± 6	NS
RAP, mmHg	17 ± 1	21 ± 1	0.019
MPAP, mmHg	43 ± 2	47 ± 2	NS
PASP, mmHg	65 ± 2	71 ± 3	NS
PCWP, mmHg	34 ± 1	36 ± 1	NS
TPG, mmHg	9 ± 1	10 ± 1	NS
CI, L/min/m^2	4.7 ± 0.2	3.8 ± 0.2	0.002
SVI, mL/m^2	51 ± 2	39 ± 2	0.001
PVR, mmHg.min/L	1.0 ± 0.1	1.5 ± 0.2	0.03
PA compliance, mL/mmHg	3.3 ± 0.3	2.6 ± 0.4	NS
LVSWI, kg-m/min/m^2	56 ± 3	42 ± 5	0.02
RVSWI, kg-m/min/m^2	17.5 ± 0.9	14.0 ± 1.3	0.03
CaO_2, mL/100 mL	16.6 ± 0.5	17.2 ± 0.5	NS
CvO_2, mL/100 mL	7.7 ± 0.5	9.8 ± 0.7	0.018
Ca−vO_2, mL/100 mL	8.9 ± 0.5	7.4 ± 0.7	NS
Ex-Rest Ca−vO_2, mL/100 mL	4.1 ± 0.6	2.1 ± 0.7	0.03
VO_2, mL/kg/min	9.3 ± 0.6	6.2 ± 0.7	0.003

CaO_2, arterial oxygen content; CI, cardiac index; CvO_2, venous oxygen content; HR heart rate; LVSWI, left ventricular stroke work index; MAP, mean arterial pressure; MPAP, mean pulmonary arterial pressure; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVSWI, right ventricular stroke work index; SBP, systolic blood pressure; SVI, stroke volume index; TPG, transpulmonary gradient; VO_2, oxygen consumption.

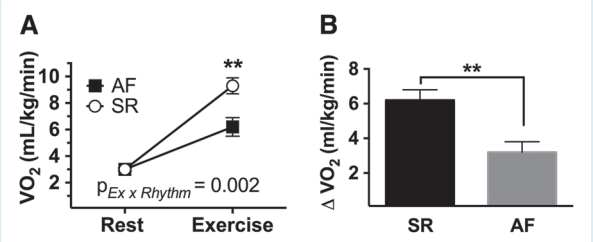

Figure 1 Differential capacity to increase oxygen consumption (VO_2) during exercise in heart failure with preserved ejection fraction patients in sinus rhythm (SR) vs. atrial fibrillation (AF). $^{**}P < 0.01$.

(3.7 ± 0.3 vs. 5.1 ± 0.4 mL/mmHg, $P = 0.002$). Pulmonary vascular resistance tended to be higher in AF patients (1.5 ± 0.1 vs. 1.1 ± 0.1 mmHg.min/L, $P = 0.05$).

Effect of rhythm on exercise capacity and haemodynamics

At symptom-limited peak exercise, the calculated VO_2 was significantly lower in AF patients compared to SR patients (6.2 ± 0.7 vs 9.3 ± 0.6 mL/min/kg, $P = 0.003$) (*Table 4*). Furthermore, whilst as expected exercise significantly increased VO_2 across the entire cohort, the VO_2 response to exercise was significantly blunted in AF patients as demonstrated in *Figure 1*, despite a similar heart rate and systemic blood pressure response. Right atrial, pulmonary arterial and pulmonary capillary wedge pressures all rose significantly ($P < 0.001$). At peak exercise, right atrial pressure was significantly higher in AF patients.

During exercise, cardiac index rose significantly in both SR and AF groups (both $P < 0.001$); however, the magnitude of the rise in cardiac index during exercise was significantly blunted in AF patients as compared to that in SR (*Figure 2A* and *B*). The lower peak cardiac index in AF patients was principally explained by a significantly lower peak stroke volume index, although the magnitude of the exercise-mediated change did not differ statistically between patient groups (*Figure 2C* and *D*). In keeping with the cardiac index responses, LVSWI was also significantly lower in AF at rest and at peak exercise (*Figure 2E* and *F*). Together with between-group differences in cardiac performance, we also identified a differential oxygen extraction response between groups. As shown in *Figure 2G* and *H*, whilst the arteriovenous oxygen difference increased with exercise, the magnitude was significantly less in AF patients.

Given that TAPSE was lower in AF patients, we also evaluated haemodynamic measures of right ventricular performance. The RVSWI was not different between SR and AF at rest (*Table 3*), whereas it was lower in AF patients during exercise (*Table 4*). At rest, there was a modest correlation between LVSWI and RVSWI ($r = 0.036$, $P = 0.008$) and the correlation was more evident during exercise ($r = 0.54$, $P < 0.001$). There were no differences between the TAPSE groups in haemodynamic or metabolic parameters at rest (Supplementary material online, *Table S1*). During exercise there were no differences in exercise time or peak workload. There were no significant differences between groups with respect to stroke volume index or cardiac index during exercise, whereas right atrial pressure was significantly greater in the low TAPSE group (20 ± 1 vs. 17 ± 1, $P = 0.046$) and the calculated VO_2 was somewhat lower (7.3 ± 0.7 vs. 9.1 ± 0.8 mL/kg/min, $P = 0.018$). Of note, the magnitude of the differences in these parameters was less than that when patients were stratified according to the presence or absence of AF.

Discussion

We compared the haemodynamic profiles of HFpEF patients in AF to those in SR to understand the basis for the adverse impact of AF on outcomes. Patients were similar in regard to their degree of symptomatic and functional limitation together with their LVEF. In addition, patients were well matched with regard to co-morbidities and concomitant medications, except for digoxin. We demonstrated that at rest, HFpEF patients in AF had evidence of increased filling pressures, lower cardiac index and reduced LVSWI, despite similar resting heart rate. Patients in AF also had significantly greater left and right atrial volumes compared to SR

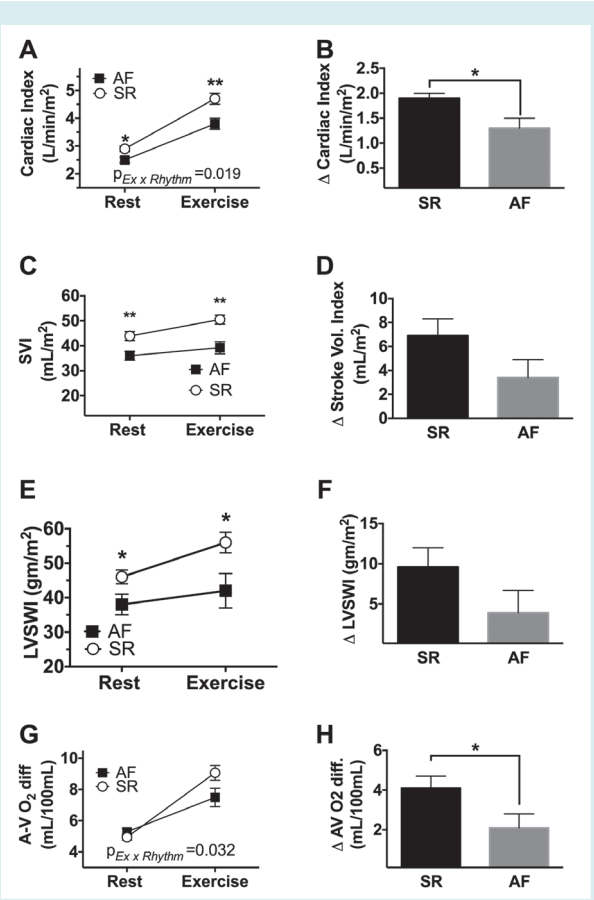

Figure 2 Comparison of rest and exercise values together with the magnitude of exercise-induced changes for cardiac index (*A*, *B*), stroke volume index (SVI) (*C*, *D*), left ventricular stroke work index (LVSWI) (*E*, *F*), and arteriovenous oxygen difference ($A\text{-}VO_2$) (*G*, *H*) in sinus rhythm (SR) vs. atrial fibrillation (AF) patients. $^*P < 0.05$; $^{**}P < 0.01$.

patients. NT-proBNP levels were significantly higher in AF patients. Under resting conditions, the calculated VO_2 and arteriovenous oxygen gradient was not different between the two groups. During supine cycling at similar levels of workload, AF patients exhibited a reduced capacity to increase their VO_2 and this was accompanied by a persistently impaired cardiac index and LVSWI.

Impaired diastolic reserve has been identified as playing an important role in the causation of HFpEF symptoms based upon the demonstration of raised filling pressures, particularly during exertion.[20−22] Mechanistically, myocardial fibrosis has been well documented in HFpEF on the basis of myocardial biopsy and magnetic resonance imaging.[23−25] In the context of the current study, magnetic resonance imaging studies have also demonstrated the presence of increased levels of ventricular fibrosis in patients with AF compared with controls.[26,27] The finding of elevated filling pressures in AF patients with similar left ventricular diastolic volumes would be consistent with more advanced myocardial fibrosis. During exercise, patients reached similar peak filling pressures as measured by PCWP. It is possible that between-group differences could have been missed given the limitations of PCWP measurement to estimated left ventricular end-diastolic pressure during exercise. Additionally, we did not measure left ventricular diastolic volumes during exercise, thus precluding the possibility that differences in left ventricular volumes may have been present.

Together with the effects of myocardial fibrosis, diastole performance is also dependent upon early active relaxation and factors that operate throughout diastole. The initial phase of active relaxation can be adversely influenced by ischaemia and increased late systolic afterload. [28] In the current study, AF patients had a somewhat higher arterial elastance at rest, which could possibly have influenced diastolic performance, although this difference was not significant during exertion. Titin and its phosphorylation state is increasingly recognized as a key modifier of diastolic stiffness,[29,30] but the effect of AF on titin phosphorylation is unclear.

In the current study, left atrial enlargement was evident in AF patients consistent with prior reports.[31] The precise contribution of left atrial contractility to cardiac output is not known in HFpEF, although it has been estimated that left atrial ejection fraction is approximately 40%.[32] Under acute conditions, left atrial mechanical function contributes significantly to left ventricular filling and to pulmonary venous and arterial pressures, via its compliance properties and contractility.[33] Impaired atrial function could explain the reduction in resting cardiac output in AF patients; however, interestingly, the degree of augmentation in left ventricular stroke volume during exercise was similar in both groups suggesting that the left atrium may be relatively passive in the exercise cardiac output response. This conclusion is consistent with the data of Melenovsky and colleagues who demonstrated the presence of a relatively flat relationship between atrial preload and stroke volume in HFpEF.[32] Further, this suggests that the rise in left atrial pressure during exercise is a reflection of atrial compliance together with ventricular diastolic function.

Despite similar, or greater left ventricular filling pressures, we found that AF patients had evidence of reduced systolic function as reflected by a lower stroke work index during both rest and exercise. Reduced left ventricular systolic function, assessed by strain imaging, has been demonstrated to be an important prognostic factor in HFpEF.[34] An adverse interaction between AF and HFrEF has also been identified,[35−37] and it has been suggested that irregular cycle length *per se* rather than loss of atrial function or inadequate rate control may be an important factor.[36,38−40] In this context, we showed that patients with advanced HFrEF and AF had reduced ventricular expression of the sarcoplasmic reticulum ATPase (SERCA2a) and a reduction in the extent of phospholamban phosphorylation.[16] Further, we previously showed that isolated cardiomyocytes paced electrically with an irregular drive sequence similarly exhibit reductions in SERCA2a expression and in the degree of phosphorylation of phospholamban.[16] Given the evidence of impaired left ventricular systolic function in the present study, it is possible that molecular changes such as these could occur in HFpEF patients in AF.

In addition to left ventricular systolic dysfunction, AF patients also demonstrated some evidence of right ventricular systolic dysfunction as reflected by the lower resting TAPSE. The presence of right ventricular dysfunction in HFpEF is well described[41] and

has been shown to be associated with poorer outcome. Right ventricular dysfunction in HFpEF is typically considered to be the consequence of exposure to pulmonary hypertension. Recent studies have investigated the potential utility of phosphodiesterase type V inhibitors in HFpEF patients. These agents have not yielded benefit in HFpEF,[42,43] however the studies were not designed to investigate potential utility in subgroups such as those with AF. At rest, in the present study, AF patients did have modest, but significantly higher pulmonary artery pressures together with evidence of elevated pulmonary arterial stiffness. It is also possible that an irregular rhythm contributed to the reduction in right ventricular systolic function in a similar manner to the left ventricle. Consistent with this, there were significant correlations between RVSWI and LVSWI at rest and during exercise. Interestingly, TAPSE *per se* did not distinguish for the presence of greater degrees of left or right ventricular dysfunction.

The 33% reduction in peak VO_2, calculated via the Fick equation, in AF patients was accounted for by a 19% reduction in cardiac output in conjunction with a 17% reduction in the arteriovenous oxygen difference. At rest, the arteriovenous oxygen difference was similar amongst groups, despite a somewhat lower cardiac index. During exercise, at similar albeit low workloads, the mixed venous oxygen content was significantly lower in SR patients, suggesting greater muscle extraction of oxygen. This finding is also somewhat surprising given that cardiac output in AF patients was lower during exertion, which would be expected to result in a lower mixed venous oxygen content. The arteriovenous oxygen difference principally reflects net effect of peripheral VO_2 together with extraction, which is influenced by transit time and the diffusional coefficient.[44] Whilst interpretation of the current data is limited by difficulty in ensuring a true steady state, the data suggest that oxygen delivery to muscle could become limiting in AF patients leading to an inability to increase oxygen extraction. Alternately, a substantial difference in muscle mass could account for the findings, although body weight and work capacity were similar between groups. Abnormal large and small vessel function, ventriculo–vascular coupling and skeletal muscle performance is also a determinant of functional capacity in HFpEF. Patients in AF demonstrated features of increased arterial elastance at rest, indicating the possibility that there was a concomitant abnormality of vascular function. The specific mechanism for abnormal arterial function in AF patients could not be determined from the current study. Atrial fibrillation patients were slightly older, but otherwise had similar mean blood pressure and body mass index. The true direct physiologic effect of AF in comparison to its possible role as a marker of chronicity or severity can only be addressed by repeating the haemodynamic evaluation after reversion to SR.

Our finding of an increased NT-proBNP level in AF patients is consistent with other studies in both HFrEF and HFpEF. We observed a modest inverse correlation with cardiac output, but this did not account for the between-group differences in natriuretic peptide levels. Previously, we demonstrated that myocardial release rates of natriuretic peptides are related to left ventricular systolic wall stress.[45] The effects of varying cycle lengths on local wall stress are not known. Plasma levels of NT-proBNP are also influenced by other factors such as renal function and obesity; however, in the present study estimated glomerular filtration rate and body mass index did not differ significantly between groups. Recent studies have raised questions regarding the sensitivity and specificity of resting measures, including natriuretic peptide levels, for the diagnosis of HFpEF.[46] In the current study, natriuretic peptide levels were not an entry criteria for study inclusion, and 7 patients in the SR group had NT-proBNP levels <100 pg/mL. To account for this as a potential confounder, we conducted a further comparison of rest and exercise haemodynamics when excluding patients with low NT-proBNP levels. As shown in the Supplementary materials online, *Tables S3* and *S4*, the blunted VO_2, cardiac index and stroke volume index remained evident during exertion in AF patients.

The limited success of prior trials in HFpEF has been attributed to a range of issues, including difficulties with the identification of homogeneous sub-populations with sufficient and consistent event rates. As recently reviewed, AF has been identified in between 21% and 34% of HFpEF registry patients and from 4% to 61% of trial patients.[5] Our data indicate that AF patients exhibit haemodynamic differences to SR patients that could respond differently to various interventions. As noted above, AF patients had higher NT-proBNP levels, larger left atrial volumes and a lower peak VO_2, which are all known to be independently associated with a worse outcome in HFpEF.[47] Accordingly, the current data further underscore the need for careful consideration of clinical trial design and the balanced inclusion of AF patients in HFpEF studies.

The current study has some potential limitations. We did not investigate whether reversion to SR improved haemodynamics in the AF group, and as such the present data provide evidence for an association between AF and haemodynamic impairment. For pragmatic and safety reasons, patients performed symptom-limited exercise in the supine position rather than the upright position. It is possible that differences in venous return may result in findings that vary between the supine position and the upright position. Also we did not require patients to work to a pre-determined or estimated peak exercise capacity and we did not perform respiratory gas analysis during the exercise right heart catheter study.

Taken together, this study highlights the presence of important differences in the central haemodynamic and peripheral responses of HFpEF patients in AF during exercise. These observations, particularly in respect of relative impairments in left and right ventricular systolic function in AF could explain previously reported differences in clinical outcome according to rhythm. Detailed physiological and molecular studies may provide further insights into the effect of AF on myocardial biology.

Conflict of interest: none declared.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Influence of TAPSE on resting haemodynamics.

Table S2. Influence of TAPSE on exercise haemodynamics.

Table S3. Resting haemodynamics in patients with NT-proBNP >100 pg/mL.

Table S4. Exercise haemodynamics in patients with NT-proBNP >100 pg/mL.

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