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# Association of Atrial Fibrillation on Rest and Exercise Hemodynamics in Heart Failure with Mid-Range and Preserved Ejection Fraction

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Conflicts of Interest: None

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## **ABSTRACT**

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

**Methods and Results:** We invasively measured central hemodynamics at rest and during symptom limited supine bicycle exercise in HFPEF/ HFmrEF patients, 35 in sinus rhythm and 20 in AF with matched LVEF. At rest, AF patients had significantly increased pulmonary capillary wedge pressures, lower cardiac index and reduced left ventricular stroke work index, despite similar resting heart rate. Under resting conditions, the calculated oxygen consumption and systemic 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 oxygen consumption and this was accompanied by a persistently impaired cardiac index and LV stroke work index.

**Conclusions:** The adverse interaction of AF and HFPEF/HFmrEF may be accounted for by an adverse impact on LV systolic function and peripheral oxygen kinetics.

**Key words:** heart failure with preserved ejection fraction; atrial fibrillation; hemodynamics; systolic function

## **Introduction**

Patients with clinical features of heart failure in the setting of HFPEF or HFmrEF are an increasingly common component of the overall burden of HF (1, 2). These patients typically experience a similar degree of functional limitation as those with 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, whilst there is only limited evidence for pharmacologic approaches to reduce hospitalization (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 the signs and symptoms of HF, whilst also influencing echocardiographic parameters and circulating biomarker levels.

A history of prevalent or incident atrial fibrillation is also particularly common in HFPEF (1, 9-11). It is evident that patients with AF and HFPEF experience poorer outcomes than those in 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  $VO_2$  than those in SR, although the hemodynamic 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 remodeling in HFREF, with attendant implications for contractile performance (16). In the current study we hypothesized similar processes might be operative in HFPEF/HFmrEF patients in AF. We therefore compared the central hemodynamic profiles of HFPEF/HFmrEF patients in AF to those in SR, with particular emphasis on the hemodynamic response to exertion.

## **Methods**

### **Study Design and Patient population**

The present study represents a retrospective, post-hoc analysis of the hemodynamic features of a cohort of patients with confirmed HFPEF or HFmrEF. Baseline study data was 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 HF (NYHA class II-IV), a left ventricular ejection fraction >40% and by definition patients had to have an elevated pulmonary capillary wedge pressure (PCWP) at rest (>15mmHg) or during exercise (>25mmHg), 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 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 hemodynamic 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 Watts (W) with 20W increments every 3 minutes 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 oxygen consumption ( $VO_2$ ) with the use of the thermodilution cardiac output and indirect oximetric assessment of the arterial oxygen saturation. Hemodynamic traces were evaluated at an independent core laboratory (PV Loops LLC, NY, USA) for the measurement of right atrial, pulmonary arterial and PCWP at rest and peak exercise. PCWP and pulmonary artery pressure were also recorded at 20W.

### **Hemodynamic 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 ( $VO_2$ ) 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 the cardiac index to heart rate. Left ventricular stroke work index was calculated according to the formula:  $LVS\text{WI} = (\text{MAP}-\text{PCWP}) \times \text{SVI} \times 0.0136$ . Right ventricular stroke work index was calculated according to the formula:  $RVS\text{WI} = (\text{MPAP}-\text{CVP}) \times \text{SVI} \times 0.0136$ . Systemic and pulmonary vascular resistance were calculated according to standard formulae. The systemic arterial elastance ( $E_a$ ) was calculated according to the formula:  $E_a = \text{ESP}/\text{SV}$ , where ESP

was calculated as  $0.9 \times \text{MAP}$ . Pulmonary arterial compliance was calculated as  $\text{PAC} = \text{SV}/(\text{PA}_{\text{sys}} - \text{PA}_{\text{dias}})$ .

### **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). Offline analysis included measurement of left ventricular and left atrial volumes, right atrial and ventricular volumes and the tricuspid annular plane systolic excursion.

### **Statistical Analysis**

Data are presented as mean  $\pm$  standard error of the mean, median (25<sup>th</sup>-75<sup>th</sup> 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 where appropriate. Differential responses to exercise between groups were investigated by repeated measures ANOVA, including an evaluation of the exercise  $\times$  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, Illinois).

### **Results**

The current study compared the demographic, echocardiographic and hemodynamic 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, BMI, gender distribution and left ventricular end diastolic volume and LVEF (Table 2). The left atrial volume index was considerably larger in AF patients (AF vs SR:  $43 \pm 3$  vs  $30 \pm 3$  ml/m<sup>2</sup>,  $p=0.005$ ), as was the right atrial volume index (AF vs SR:  $42 \pm 4$  vs  $32 \pm 3$  ml,  $p=0.03$ ), as shown in Table 2. Right ventricular function as reflected by the tricuspid annular plane systolic excursion was lower in AF patients (AF vs SR:  $17 \pm 1$  vs  $21 \pm 1$  mm,  $p=0.004$ ). 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 Hemodynamics and Metabolism*

At rest, the heart rate and systemic blood pressure were similar in SR and AF patients (Table 3). By contrast, the resting pulmonary PCWP and mean PA pressures were significantly higher in patients with AF. In conjunction, the resting cardiac index was lower in patients with AF as compared to SR patients (AF vs SR:  $2.5 \pm 0.1$  vs  $2.9 \pm 0.1$  ml,  $p=0.038$ ). This difference was accounted for by a

significantly lower stroke volume index in patients in AF. Accordingly the LVSWI was lower at rest in AF patients (Table 3). At rest the arterial and mixed venous oxygen content were similar, and the calculated  $\text{VO}_2$  was similar between AF and SR patients at rest (AF vs SR:  $3.0 \pm 0.1$  vs  $3.0 \pm 0.1$  mL/kg/min).

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, the systemic vascular resistance in AF was similar to SR ( $18.8 \pm 1.3$  vs  $16.4 \pm 0.8$  dyne.cm.sec<sup>-5</sup>) and the arterial elastance was also similar between patients groups (AF vs SR:  $1.9 \pm 0.1$  vs  $1.6 \pm 0.1$  mmHg/mL, p=ns). The resting pulmonary vascular compliance was lower in AF patients, consistent with a stiffer pulmonary circulation (SR vs AF:  $3.7 \pm 0.3$  vs  $5.1 \pm 0.4$  mL/mmHg, p=0.002). The pulmonary vascular resistance tended to be higher in AF patients ( $1.5 \pm 0.1$  vs  $1.1 \pm 0.1$  mmHg.min/L), p=0.05).

#### *Effect of Rhythm on Exercise Capacity and Hemodynamics*

At symptom limited peak exercise the calculated  $\text{VO}_2$  was significantly lower in AF patients compared to SR patients (AF vs SR:  $6.2 \pm 0.7$  vs  $9.7 \pm 0.6$  mL/kg/min, p=0.003, Table 4). Furthermore, whilst as expected exercise significantly increased  $\text{VO}_2$  across the entire cohort, the  $\text{VO}_2$  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 artery and pulmonary capillary wedge pressures all rose significantly (p<0.001). At peak exercise the 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, left ventricular stroke work index (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  $\text{AVO}_2$  difference increased with exercise, the magnitude was significantly less in AF patients.

Given that TAPSE was lower in AF patients we also evaluated hemodynamic measures of RV performance. RVSWI was not different between SR and AF at rest (Table 3), whilst 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 are no differences between the TAPSE groups in hemodynamic or metabolic parameters at rest (Supplementary Table 3). During exercise there were no differences in the exercise time or peak workload. There were no significant differences between the groups with respect to stroke volume

index or cardiac index during exercise (Supplementary Table 4), whilst the right atrial pressure was significantly greater in the low TAPSE group ( $20\pm 1$  vs  $17\pm 1$ ,  $p=0.046$ ) and the calculated VO<sub>2</sub> was somewhat lower ( $7.3\pm 0.7$  vs  $9.1\pm 0.8$  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 hemodynamic 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 comorbidities 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 left ventricular stroke work index, despite similar resting heart rate. AF patients also had significantly greater left and right atrial volumes compared to SR patients. NT-proBNP levels were significantly higher in AF patients. Under resting conditions, the calculated oxygen consumption 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 oxygen consumption and this was accompanied by a persistently impaired cardiac index and LV stroke work index.

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 (MRI) (23-25). In the context of the current study, MRI 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 the pulmonary capillary wedge pressure. It is possible that between group differences could have been missed given the limitations of PCWP measurement to estimated LVEDP during exercise. Additionally, we did not measure LV diastolic volumes during exercise thus precluding the possibility that differences in LV 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 ischemia 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), however the effect of AF on titin phosphorylation is unclear.

In the current study, LA enlargement was evident in AF patients consistent with prior reports (31). The precise contribution of LA contractility to cardiac output is not known in HFPEF, although it has been estimated that the LAEF 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 LV stroke volume during exercise was similar in both groups suggesting that the LA 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 LA pressure during exercise is a reflection of atrial compliance together with ventricular diastolic function.

Despite similar, or greater LV 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 LV 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 LV 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 RV dysfunction in HFPEF is well described (41) and has been shown to be associated with poorer outcome. RV 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 RV systolic function in a similar manner to the LV. Consistent with this, there were significant correlations between RV and LVSWI at rest and during exercise. Interestingly TAPSE per se did not distinguish for the presence of greater degrees of LV or RV dysfunction.

The 33% reduction in peak O<sub>2</sub> consumption, 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 AVO<sub>2</sub> difference. At rest the AVO<sub>2</sub> 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 the cardiac output in AF patients was lower during exertion, which would be expected to result in a lower mixed venous oxygen content. The AVO<sub>2</sub> difference principally reflects net effect of peripheral O<sub>2</sub> consumption 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. AF patients 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. AF patients were slightly older, but otherwise had similar mean blood pressure and BMI. 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 hemodynamic 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 (ref). We observed a modest inverse correlation with cardiac output, however 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 LV systolic wall stress (45). The effect 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 eGFR and BMI 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-BNP levels <100pg/mL. To account for this as a potential confounder we conducted a further comparison of rest and exercise hemodynamics when excluding patients with low NT-BNP levels. As shown in Supplementary Tables 1 and 2, the blunted VO<sub>2</sub>, 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

hemodynamic 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 hemodynamics in the AF group, and as such the present data provide evidence for an association between AF and hemodynamic 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 hemodynamic 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 physiologic and molecular studies may provide further insights into the effect of AF on myocardial biology.

#### **FIGURE LEGENDS:**

Figure 1: Graph representing the differential capacity to increase oxygen consumption during exercise in HFPEF patients in SR vs AF.

Figure 2. Graphs comparing rest and exercise values together with the magnitude of the exercise induced changes for A,B cardiac index; C,D stroke volume index; E,F left ventricular stroke work index; and G,H arterio-venous oxygen difference in SR vs AF patients. \*  $p < 0.05$ , \*\* $p < 0.01$ .

## REFERENCES

1. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *New England Journal of Medicine* 2006; 355(3):251-259.
2. Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. *New England Journal of Medicine* 2006; 355(3):260-269.
3. Sweitzer NK, Lopatin M, Yancy CW, Mills RM, Stevenson LW. Comparison of clinical features and outcomes of patients hospitalized with heart failure and normal ejection fraction (> or =55%) versus those with mildly reduced (40% to 55%) and moderately to severely reduced (<40%) fractions. *Am J Cardiol* 2008; 101(8):1151-1156.
4. Dhakal BP, Malhotra R, Murphy RM, Pappagianopoulos PP, Baggish AL, Weiner RB, Houstis NE, Eisman AS, Hough SS, Lewis GD. Mechanisms of exercise intolerance in heart failure with preserved ejection fraction: the role of abnormal peripheral oxygen extraction. *Circ Heart Fail* 2015; 8(2):286-294.
5. Kelly JP, Mentz RJ, Mebazaa A, Voors AA, Butler J, Roessig L, Fiuzat M, Zannad F, Pitt B, O'Connor CM, Lam CS. Patient selection in heart failure with preserved ejection fraction clinical trials. *J Am Coll Cardiol* 2015; 65(16):1668-1682.
6. Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, Shah SJ, Ahmed A, Bonow RO, Cleland JG, Cody RJ, Chioncel O, Collins SP, Dunnmon P, Filippatos G, Lefkowitz MP, Marti CN, McMurray JJ, Misselwitz F, Nodari S, O'Connor C, Pfeffer MA, Pieske B, Pitt B, Rosano G, Sabbah HN, Senni M, Solomon SD, Stockbridge N, Teerlink JR, Georgiopoulou VV, Gheorghiade M. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. *JACC Heart failure* 2014; 2(2):97-112.
7. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. *Circulation* 2016; 134(1):73-90.
8. Nanayakkara S, Kaye DM. Targets for heart failure with preserved ejection fraction. *Clin Pharmacol Ther* 2017.
9. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, Hernandez AF, Fonarow GC, Get With the Guidelines Scientific Advisory C, Investigators. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. *Circulation* 2012; 126(1):65-75.
10. Reddy YN, Borlaug BA. Heart Failure With Preserved Ejection Fraction. *Curr Probl Cardiol* 2016; 41(4):145-188.
11. Kotecha D, Lam CS, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation: Vicious Twins. *J Am Coll Cardiol* 2016; 68(20):2217-2228.
12. Olsson LG, Swedberg K, Ducharme A, Granger CB, Michelson EL, McMurray JJ, Puu M, Yusuf S, Pfeffer MA, Investigators C. Atrial fibrillation and risk of clinical events in chronic heart failure with and without left ventricular systolic dysfunction: results from the Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) program. *J Am Coll Cardiol* 2006; 47(10):1997-2004.
13. Linssen GC, Rienstra M, Jaarsma T, Voors AA, van Gelder IC, Hillege HL, van Veldhuisen DJ. Clinical and prognostic effects of atrial fibrillation in heart failure patients with reduced and preserved left ventricular ejection fraction. *Eur J Heart Fail* 2011; 13(10):1111-1120.
14. Zakeri R, Borlaug BA, McNulty SE, Mohammed SF, Lewis GD, Semigran MJ, Deswal A, LeWinter M, Hernandez AF, Braunwald E, Redfield MM. Impact of atrial fibrillation on exercise capacity in heart failure with preserved ejection fraction: a RELAX trial ancillary study. *Circ Heart Fail* 2014; 7(1):123-130.
15. Lam CS, Rienstra M, Tay WT, Liu LC, Hummel YM, van der Meer P, de Boer RA, Van Gelder IC, van Veldhuisen DJ, Voors AA, Hoendermis ES. Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction: Association With Exercise Capacity, Left Ventricular Filling Pressures, Natriuretic Peptides, and Left Atrial Volume. *JACC Heart failure* 2017; 5(2):92-98.
16. Ling LH, Khammy O, Byrne M, Amirahmadi F, Foster A, Li G, Zhang L, dos Remedios C, Chen C, Kaye DM. Irregular rhythm adversely influences calcium handling in ventricular myocardium: implications for the interaction between heart failure and atrial fibrillation. *Circ Heart Fail* 2012; 5(6):786-793.

17. Hasenfuss G, Gustafsson F, Kaye D, Shah SJ, Burkhoff D, Reymond MC, Komtebedde J, Hunlich M, Reduce LAPHFTI. Rationale and Design of the Reduce Elevated Left Atrial Pressure in Patients With Heart Failure (Reduce LAP-HF) Trial. *J Card Fail* 2015; 21(7):594-600.
18. Hasenfuss G, Hayward C, Burkhoff D, Silvestry FE, McKenzie S, Gustafsson F, Malek F, Van der Heyden J, Lang I, Petrie MC, Cleland JG, Leon M, Kaye DM, investigators RL-Hs. A transcatheter intracardiac shunt device for heart failure with preserved ejection fraction (REDUCE LAP-HF): a multicentre, open-label, single-arm, phase 1 trial. *Lancet* 2016; 387(10025):1298-1304.
19. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W, Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015; 28(1):1-39 e14.
20. Maeder MT, Ammann P, Rickli H. The diagnosis of heart failure with normal ejection fraction--a demanding task! *Swiss Med Wkly* 2010; 140(21-22):323; author reply 324.
21. Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J* 2011; 32(6):670-679.
22. van Empel VP, Kaye DM, Borlaug BA. Effects of healthy aging on the cardiopulmonary hemodynamic response to exercise. *Am J Cardiol* 2014; 114(1):131-135.
23. Sinning D, Kasner M, Westermann D, Schulze K, Schultheiss HP, Tschope C. Increased left ventricular stiffness impairs exercise capacity in patients with heart failure symptoms despite normal left ventricular ejection fraction. *Cardiology research and practice* 2011; 2011:692862.
24. Van Heerebeek L, Borbély A, Niessen HWM, Bronzwaer JGF, Van Der Velden J, Stienen GJM, Linke WA, Laarman GJ, Paulus WJ. Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation* 2006; 113(16):1966-1973.
25. Mascherbauer J, Marzluf BA, Tufaro C, Pfaffenberger S, Graf A, Wexberg P, Panzenbock A, Jakowitsch J, Bangert C, Laimer D, Schreiber C, Karakus G, Hulsmann M, Pacher R, Lang IM, Maurer G, Bonderman D. Cardiac magnetic resonance postcontrast T1 time is associated with outcome in patients with heart failure and preserved ejection fraction. *Circ Cardiovasc Imaging* 2013; 6(6):1056-1065.
26. Ling LH, Kistler PM, Ellims AH, Iles LM, Lee G, Hughes GL, Kalman JM, Kaye DM, Taylor AJ. Diffuse ventricular fibrosis in atrial fibrillation: noninvasive evaluation and relationships with aging and systolic dysfunction. *J Am Coll Cardiol* 2012; 60(23):2402-2408.
27. Montgomery JA, Abdallah W, Yoneda ZT, Brittain E, Aznaurov SG, Parvez B, Adkins K, Whalen SP, Estrada JC, Shen S, Crossley GH, Kanagasundram A, Saavedra P, Ellis CR, Lawson M, Darbar D, Shoemaker MB. Measurement of diffuse ventricular fibrosis with myocardial T1 in patients with atrial fibrillation. *J Arrhythm* 2016; 32(1):51-56.
28. Gillebert TC, Leite-Moreira AF, De Hert SG. Load dependent diastolic dysfunction in heart failure. *Heart Fail Rev* 2000; 5(4):345-355.
29. Hamdani N, Franssen C, Lourenço A, Falcao Pires I, Fontoura D, Leite S, Plettig L, Lopez B, Ottenheijm CA, Becher PM, Gonzalez A, Tschope C, Diez J, Linke WA, Leite-Moreira AF, Paulus WJ. Myocardial titin hypophosphorylation importantly contributes to heart failure with preserved ejection fraction in a rat metabolic risk model. *Circulation: Heart Failure* 2013; 6(6):1239-1249.
30. Gladden JD, Linke WA, Redfield MM. Heart failure with preserved ejection fraction. *Pflugers Arch* 2014; 466(6):1037-1053.
31. Melenovsky V, Borlaug BA, Rosen B, Hay I, Ferruci L, Morell CH, Lakatta EG, Najjar SS, Kass DA. Cardiovascular features of heart failure with preserved ejection fraction versus nonfailing hypertensive left ventricular hypertrophy in the urban Baltimore community: the role of atrial remodeling/dysfunction. *J Am Coll Cardiol* 2007; 49(2):198-207.
32. Melenovsky V, Hwang SJ, Redfield MM, Zakeri R, Lin G, Borlaug BA. Left atrial remodeling and function in advanced heart failure with preserved or reduced ejection fraction. *Circ Heart Fail* 2015; 8(2):295-303.
33. Donal E, Raud-Raynier P, De Place C, Gervais R, Rosier A, Roulaud M, Ingels A, Carre F, Daubert JC, Denjean A. Resting Echocardiographic Assessments of Left Atrial Function and Filling Pressure Interest in the Understanding of Exercise Capacity in Patients with Chronic Congestive Heart Failure. *Journal of the American Society of Echocardiography* 2008; 21(6):703-710.
34. Shah AM, Claggett B, Sweitzer NK, Shah SJ, Anand IS, Liu L, Pitt B, Pfeffer MA, Solomon SD. Prognostic Importance of Impaired Systolic Function in Heart Failure With Preserved Ejection Fraction and the Impact of Spironolactone. *Circulation* 2015; 132(5):402-414.

35. Wang TJ, Larson MG, Levy D, Vasan RS, Leip EP, Wolf PA, D'Agostino RB, Murabito JM, Kannel WB, Benjamin EJ. Temporal relations of atrial fibrillation and congestive heart failure and their joint influence on mortality: the Framingham Heart Study. *Circulation* 2003; 107(23):2920-2925.
36. Dries DL, Exner DV, Gersh BJ, Domanski MJ, Waclawiw MA, Stevenson LW. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. *Studies of Left Ventricular Dysfunction. Journal of the American College of Cardiology* 1998; 32(3):695-703.
37. Middlekauff HR, Stevenson WG, Stevenson LW. Prognostic significance of atrial fibrillation in advanced heart failure: a study of 390 patients. *Circulation* 1991; 84:40-48.
38. Hsu LF, Jais P, Sanders P, Garrigue S, Hocini M, Sacher F, Takahashi Y, Rotter M, Pasquie JL, Scavee C, Bordachar P, Clementy J, Haissaguerre M. Catheter ablation for atrial fibrillation in congestive heart failure. *N Engl J Med* 2004; 351(23):2373-2383.
39. Gentlesk PJ, Sauer WH, Gerstenfeld EP, Lin D, Dixit S, Zado E, Callans D, Marchlinski FE. Reversal of left ventricular dysfunction following ablation of atrial fibrillation. *J Cardiovasc Electrophysiol* 2007; 18(1):9-14.
40. Rienstra M, Smit MD, Nieuwland W, Tan ES, Wiesfeld AC, Anthonio RL, Van den Berg MP, Van Veldhuisen DJ, Van Gelder IC. Persistent atrial fibrillation is associated with appropriate shocks and heart failure in patients with left ventricular dysfunction treated with an implantable cardioverter defibrillator. *Am Heart J* 2007; 153(1):120-126.
41. Andersen MJ, Hwang SJ, Kane GC, Melenovsky V, Olson TP, Fetterly K, Borlaug BA. Enhanced pulmonary vasodilator reserve and abnormal right ventricular: pulmonary artery coupling in heart failure with preserved ejection fraction. *Circ Heart Fail* 2015; 8(3):542-550.
42. Hoendermis ES, Liu LC, Hummel YM, van der Meer P, de Boer RA, Berger RM, van Veldhuisen DJ, Voors AA. Effects of sildenafil on invasive haemodynamics and exercise capacity in heart failure patients with preserved ejection fraction and pulmonary hypertension: a randomized controlled trial. *Eur Heart J* 2015; 36(38):2565-2573.
43. Borlaug BA, Lewis GD, McNulty SE, Semigran MJ, LeWinter M, Chen H, Lin G, Deswal A, Margulies KB, Redfield MM. Effects of sildenafil on ventricular and vascular function in heart failure with preserved ejection fraction. *Circ Heart Fail* 2015; 8(3):533-541.
44. Haykowsky MJ, Tomczak CR, Scott JM, Paterson DI, Kitzman DW. Determinants of exercise intolerance in patients with heart failure and reduced or preserved ejection fraction. *J Appl Physiol (1985)* 2015; 119(6):739-744.
45. Maeder MT, Kaye DM. Transcardiac gradients of B-type natriuretic peptides are increased in human pulmonary arterial hypertension. *Int J Cardiol* 2011; 151(1):117-119.
46. Obokata M, Kane GC, Reddy YN, Olson TP, Melenovsky V, Borlaug BA. The Role of Diastolic Stress Testing in the Evaluation for HFpEF: A Simultaneous Invasive-Echocardiographic Study. *Circulation* 2016.
47. Zakeri R, Chamberlain AM, Roger VL, Redfield MM. Temporal relationship and prognostic significance of atrial fibrillation in heart failure patients with preserved ejection fraction: a community-based study. *Circulation* 2013; 128(10):1085-1093.

**Table 1. Baseline Clinical and Biochemical Characteristics**

<b>Parameter</b>	<b>Sinus Rhythm (n=35)</b>	<b>Atrial Fibrillation (n=20)</b>	<b>p value</b>
Age (years)	70±2	69±1	ns
BMI (kg/m <sup>2</sup> )	33±1	31±1	ns
NYHA (II/III)	10/25	5/15	ns
eGFR (ml/min/1.73m <sup>2</sup> )	64±4	57±4	ns
<b>Medications (%)</b>			
Diuretics	83	100	ns
ACEI/ARB	83	70	ns
Beta blockers	63	65	ns
MR antagonists	43	45	ns
Digoxin	3	35	<0.01
<b>Co-Morbidities (%)</b>			
COPD	6	10	ns
Diabetes	31	20	ns
Chronic Kidney Disease	34	40	ns
Hypertension	77	85	ns
Myocardial Infarction	11	10	ns
NT-BNP (pg/mL)*	272 (103-518)	1250 (719-1703)	<0.001

Abbreviations/Definitions: ACEI/ARB- angiotensin converting enzyme inhibitor/angiotensin receptor blocker; MR mineralocorticoid receptor; COPD – chronic obstructive pulmonary disease; Chronic Kidney Disease defined as eGFR <60ml/min/1.73m<sup>2</sup>.

\*Median (25<sup>th</sup>-75<sup>th</sup> percentile)

**Table 2. Baseline Echocardiographic Characteristics**

<b>Parameter</b>	<b>Sinus Rhythm (n=35)</b>	<b>Atrial Fibrillation (n=20)</b>	<b>p value</b>
LVEF (%)	48±1	46±1	ns
LVEDVI (mL)	134±4	137±6	ns
LAVI (mL/m <sup>2</sup> )	30±3	43±3	0.005
RAVI (mL/m <sup>2</sup> )	32±3	42±4	0.03
TAPSE (mm)	2.1±0.1	1.7±0.1	0.004

Abbreviations: LVEDVI left ventricular end diastolic volume index; LAVI left atrial volume index  
RAVI right atrial volume index; TAPSE tricuspid annular plane excursion.

\*Median (25<sup>th</sup>-75<sup>th</sup> percentile)

**Table 3. Resting hemodynamic and metabolic characteristics**

Parameter	Sinus Rhythm (n=41)	Atrial Fibrillation (n=23)	p value
HR (bpm)	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
PA <sub>m</sub> (mmHg)	22±1	27±1	0.015
PA <sub>sys</sub> (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 <sup>2</sup> )	2.9±0.1	2.5±0.1	0.038
SVI (ml/m <sup>2</sup> )	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	0.01
LVSWI (kg-m.min <sup>-1</sup> .m <sup>-2</sup> )	46±2	38±3	0.03
RVSWI (kg-m.min <sup>-1</sup> .m <sup>-2</sup> )	8.4±0.9	8.7±0.8	ns
CaO <sub>2</sub> (mL/100mL)	17.0±0.4	17.3±0.5	ns
CvO <sub>2</sub> (mL/100mL)	12.1±0.4	12.1±0.5	ns
C(a-v)O <sub>2</sub> (mL/100mL)	4.8±0.2	5.2±0.2	ns
VO <sub>2</sub> (mL/min/kg)	3.0±0.1	3.0±0.1	ns

**Abbreviations:** HR heart rate, MAP mean arterial pressure, SBP systolic blood pressure, RAP right atrial pressure, PA<sub>m</sub> mean pulmonary artery pressure, PA<sub>sys</sub> pulmonary artery systolic pressure, PCWP pulmonary capillary wedge pressure, TPG transpulmonary gradient, PVR pulmonary vascular resistance, CI cardiac index, SVI stroke volume index, LVSWI left ventricular stroke work index, CaO<sub>2</sub>, CvO<sub>2</sub> arterial and mixed venous oxygen content, VO<sub>2</sub> oxygen consumption.

**Table 4. Exercise hemodynamic and metabolic characteristics**

<b>Parameter</b>	<b>Sinus Rhythm (n=41)</b>	<b>Atrial Fibrillation (n=23)</b>	<b>p value</b>
Peak Workload	47±3	39±4	ns
Exercise time (min)	7.6±0.5	7.1±0.8	ns
HR (bpm)	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
PA <sub>m</sub> (mmHg)	43±2	47±2	ns
PA <sub>sys</sub> (mmHg)	65±2	71±3	ns
PCWP (mmHg)	34±1	36±1	ns
TPG (mmHg)	9±1	10±1	ns
CI (L/min/m <sup>2</sup> )	4.7±0.2	3.8±0.2	0.002
SVI (ml/m <sup>2</sup> )	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 <sup>-1</sup> .m <sup>-2</sup> )	56±3	42±5	0.02
RVSWI (kg-m.min <sup>-1</sup> .m <sup>-2</sup> )	17.5±0.9	14.0±1.3	0.03
CaO <sub>2</sub> (mL/100mL)	16.6±0.5	17.2±0.5	ns
CvO <sub>2</sub> (mL/100mL)	7.7±0.5	9.8±0.7	0.018
C(a-v)O <sub>2</sub> (mL/100mL)	8.9±0.5	7.4±0.7	ns
Ex-Rest C(a-v)O <sub>2</sub> (mL/100mL)	4.1±0.6	2.1±0.7	0.03
VO <sub>2</sub> (mL/min/kg)	9.3±0.6	6.2±0.7	0.003

Figure 1

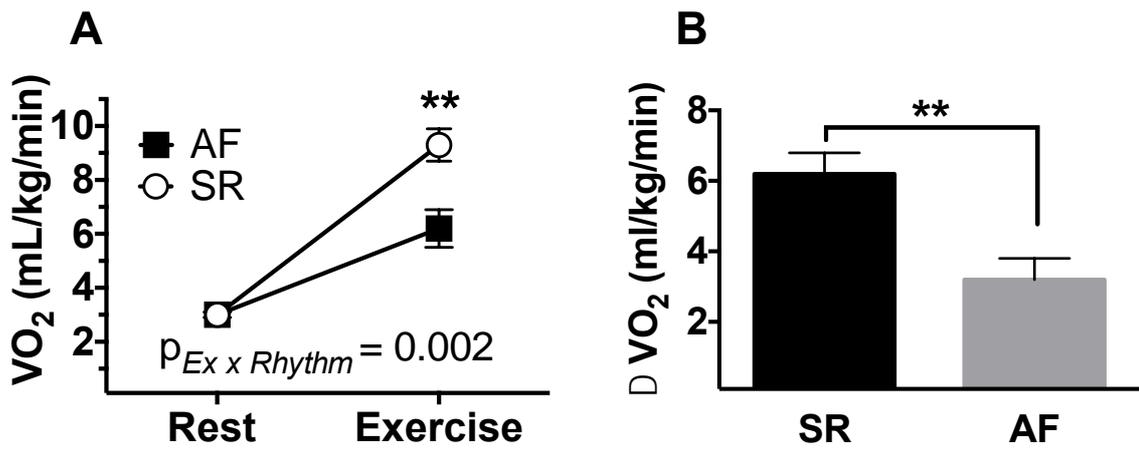


Figure 2

