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## Atrial Dysfunction in Patients With Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation

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### Abstract

**BACKGROUND**—Paroxysmal and permanent atrial fibrillation (AF) are common in heart failure with preserved ejection fraction (HFpEF).

**OBJECTIVES**—The study sought to determine the implications of left atrial (LA) myopathy and dysrhythmia across the spectrum of AF burden in HFpEF.

**METHODS**—Consecutive patients with HFpEF (n = 285) and control subjects (n = 146) underwent invasive exercise testing and echocardiographic assessment of cardiac structure, function, and pericardial restraint.

**RESULTS**—Patients with HFpEF were categorized into stages of AF progression: 181 (65%) had no history of AF, 49 (18%) had paroxysmal AF, and 48 (17%) had permanent AF. Patients with permanent AF stage were more congested with greater pulmonary vascular disease and lower cardiac output. LA volumes increased, while LA compliance, LA reservoir strain, and right ventricular function decreased with increasing AF burden. The presence of permanent AF was characterized by a distinct pathophysiology, with greater total heart volume caused by atrial dilatation, leading to elevated filling pressures through heightened pericardial restraint. Survival decreased with increasing AF burden. Ten-year progression to permanent AF was common, particularly in paroxysmal AF (52%), and the likelihood of AF progression increased with higher AF stage, poorer LA compliance, and lower LA strain.

**CONCLUSIONS**—LA compliance and mechanics progressively decline with increasing AF burden in HFpEF, increasing risk for new onset AF. These changes promote development of a unique phenotype of HFpEF characterized by heightened ventricular interaction, right heart failure, and worsening pulmonary vascular disease. Further study is required to identify therapeutic interventions targeting LA myopathy to improve outcomes in HFpEF.

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**APPENDIX** For expanded Methods and References sections as well as a supplemental table and figures, please see the online version of this paper.

## Keywords

atrial fibrillation; exercise hemodynamics; HFpEF; left atrial strain; pericardial restraint

Atrial fibrillation (AF) is both common and associated with adverse outcomes in heart failure with preserved ejection fraction (HFpEF) (1–4). When AF becomes permanent, afflicted patients display severe atrial dysfunction and abnormal right ventricular (RV)-pulmonary vascular coupling as compared with patients with HFpEF in sinus rhythm (HFpEF<sub>no-AF</sub>) (5–16). These changes develop gradually, just as permanent AF typically evolves insidiously from an earlier stage in which rhythm disturbances are intermittent. When sustained chronically, increasing exposure to both the dysrhythmia itself and the metabolic and inflammatory stresses associated with AF may lead to a unique clinical AF phenotype in HFpEF that differs from other phenotypes.

The optimal approaches for treatment and prevention of AF in HFpEF are unknown (17). The adverse functional and hemodynamic consequences of permanent AF suggest that efforts to restore sinus rhythm might improve clinical status (18,19). However, there is also concern that patients with AF may display atrial remodeling that is less reversible, in which treatment efficacy may become limited, or potentially even detrimental, worsening LA hypertension to even greater extent (20).

To provide greater insight into the pathophysiologic progression across the spectrum of AF burden in HFpEF, we performed a detailed characterization combining direct measures of cardiac structure and function in control subjects free of AF and HFpEF patients with and without AF. We hypothesized that abnormalities in LA structure, function, pericardial restraint, and hemodynamics in HFpEF would progress along a phenotypic continuum related to the exposure to AF burden, and that increasing severity of LA myopathy would identify patients at higher risk for AF progression.

## METHODS

### GROUP DEFINITIONS.

Consecutive outpatient subjects undergoing elective invasive hemodynamic exercise testing at the Mayo Clinic catheterization laboratory for exertional dyspnea between 2000 and 2015 were identified with HFpEF defined by gold standard invasive criteria (Supplemental Appendix). Control subjects were identified as those with normal rest and exercise pulmonary capillary wedge pressure (PCWP), no history of AF, and left ventricular ejection fraction (LVEF)  $\geq$  50%. The Mayo Clinic Institutional Review Board approved the study protocol.

All electrocardiograms were manually reviewed to determine if AF was present at any time, and charts were reviewed in detail to establish any history of AF episodes prior to and following index evaluation. Patients in AF at the time of evaluation were classified as permanent AF (HFpEF<sub>perm-AF</sub>), those in sinus rhythm at the time of evaluation but with a history of documented AF were classified paroxysmal AF (HFpEF<sub>parox-AF</sub>), and patients with HFpEF but no prior AF were classified as no AF (HFpEF<sub>no-AF</sub>). Patients with

persistent AF (duration <1 year) and permanent AF (>1 year) were both included in the permanent AF group for this analysis.

### **ASSESSMENT OF CARDIAC STRUCTURE AND FUNCTION.**

Details of LV and RV assessment are provided in the Supplemental Appendix. LA volume-based indices were calculated as previously described (details in Supplemental Appendix) (6,21). LA strain was calculated as the average of strain in 6 segments in the 4-chamber and 2-chamber views to calculate reservoir, conduit, and contractile strain, taken as the average of 3 beats (Supplemental Figure 1) (8,9). Atrial strain was measured using the QRS interval as fiducial point because of the absence of p waves in AF. We have demonstrated high inter- and intra-observer reproducibility using these methods in our laboratory (9).

### **HEART VOLUMES, VENTRICULAR INTERACTION, AND PERICARDIAL RESTRAINT.**

Total epicardial heart volume (atrial and ventricular volume) was estimated from 2 hemi-ellipsoids containing both atria and ventricles using the apical 4-chamber view. This allowed calculation of not only total epicardial volume, but also its individual components—total atrial volume and total ventricular volume (5). If total heart volume increases out of proportion to pericardial volume, there is increased pericardial restraint and ventricular interaction (22–24). As previously described, an increase in pericardial restraint is connoted by increases in right atrial pressure (RAP), RAP/PCWP ratio, eccentricity index, and ideal-to-actual radius on short-axis echocardiography.

### **CATHETERIZATION PROTOCOL.**

Right heart catheterization was performed as previously described at rest and during exercise to volitional exhaustion (details in the Supplemental Appendix) (24–26). End-expiratory mean PCWP pressure, a-wave, v-wave, and x- and y-descents were manually measured at rest and peak exercise as the average of 3 measurements by a single observer. The rise in PCWP from the x nadir to the v-wave peak represents the pressure change during the LA reservoir phase (reservoir pressure) (Supplemental Figure 1), and difference from the y nadir to peak a-wave represents the rise in pressure with LA contraction (booster pressure). The fall in pressure from the v-wave peak to the y nadir represented the LA pressure change during the conduit phase.

LV transmural pressure (LVTMP), which reflects LV preload independent of pericardial restraint, was estimated as PCWP minus RAP. Details regarding calculation of the LV stiffness constant  $\beta$  (27) and pulmonary vascular load indices (26,28) are provided in the Supplemental Appendix.

### **INTEGRATED ASSESSMENT OF LA FUNCTION.**

Because imaging does not account for pressure loading, LA strain and volumetric measures from echocardiography were combined with invasive pressure measurements to provide an integrated pressure-volume index. LA compliance was calculated from the quotient of LA deformation (strain) or LA volume change indexed to PCWP x-v pressure rise (Supplemental Figure 1).

## OUTCOMES.

Patient follow-up was initiated on the day of cardiac catheterization. Vital status was determined from manual review of the electronic medical records, the Mayo Clinic registration database, and the Rochester Epidemiology Project death database, which uses data ascertained from other medical records, death certificates, obituaries, and notices of death in local newspapers. Data on all Minnesota deaths were obtained from the State of Minnesota annually. Progression of AF stage was ascertained by detailed review of all medical records following cardiac catheterization assessment, including all patient encounters at Mayo Clinic as well as other facilities as part of the “Care Everywhere” application in the Epic electronic health record platform (Epic Systems, Verona, Wisconsin). AF progression was defined as any worsening of AF grade: specifically development of permanent AF for patients with HFpEF<sub>parox-AF</sub>, or the development of any AF in control subjects and patients with HFpEF<sub>no-AF</sub>. Censoring was performed at last date of known follow-up for vital status and AF progression.

## STATISTICAL ANALYSIS.

Data are reported as mean  $\pm$  SD, median and interquartile range, or number (%). Between-group differences were compared by analysis of variance, Kruskal-Wallis test, or chi-square test, as appropriate. The Tukey honestly significant difference test or Steel-Dwass test was used to adjust for multiple testing between subgroups. Linear regression and Pearson’s correlation were used to assess associations between variables. For non-normally distributed variables entered into regression models, the assumption of normally distributed residuals was verified by quantile plots. Mortality and risk of progressive AF burden were compared using the log-rank test to account for censoring and varying time of follow-up. All tests were 2-sided, with a p value  $<0.05$  considered significant. Given the mechanistic basis of this analyses, and to minimize risk of type II error, correction for multiple hypothesis testing was not performed. All analyses were performed by JMP 13.0.0 (SAS Institute, Cary, North Carolina).

## RESULTS

The study cohort includes 146 control subjects with no history of AF and 285 HFpEF patients, of whom 181 (65%) were HFpEF<sub>no-AF</sub>, 49 (18%) were HFpEF<sub>parox-AF</sub>, and 48 (17%) were HFpEF<sub>perm-AF</sub>. As compared with other groups, AF patients were older, and patients with permanent AF displayed lower body mass index than others (Table 1). HFpEF<sub>perm-AF</sub> patients displayed greater congestion than other groups, evidenced by more radiographic cardiomegaly and pulmonary edema, higher N-terminal pro-B-type natriuretic peptide levels and E/e’ ratio, lower hemoglobin, and the greatest LA volumes (Tables 1 and 2).

## BIVENTRICULAR STRUCTURE AND FUNCTION.

Compared with control subjects, HFpEF patients displayed greater LV mass and worse LV diastolic dysfunction, with higher estimated LV diastolic stiffness ( $\beta$ ) (Table 2). However, within the HFpEF groups, there were no differences in LV chamber stiffness or mass when stratifying by AF (Table 2). In contrast, systolic function in both ventricles decreased in a

graded fashion with increasing AF burden (evidenced by lower LVEF and global longitudinal strain, increased RV size, and lower tricuspid annular plane systolic excursion), RV fractional area change, and RV  $s'$  velocities with increasing AF status (Table 2).

### HEART VOLUMES AND PERICARDIAL RESTRAINT.

HFpEF<sub>perm-AF</sub> patients displayed the largest total heart volume of all patient groups, both qualitatively by chest roentgenogram and quantitatively by echocardiography (Table 2, Figure 1). Cardiomegaly in HFpEF<sub>perm-AF</sub> was exclusively caused by atrial dilation: biventricular volumes were equivalent, but there were 2-fold greater atrial volumes in HFpEF<sub>perm-AF</sub> than the other HFpEF groups, and 4-fold greater atrial volumes than in control subjects (Figure 1).

The increases in heart volume in HFpEF<sub>perm-AF</sub> were coupled with findings indicating greater ventricular interdependence and pericardial restraint, as demonstrated by higher eccentricity index and ideal-to-actual radius index, and higher RA pressure and RA/PCWP ratios (Table 2, Figure 1). Notably, heart volumes were not significantly different comparing HFpEF<sub>no-AF</sub> patients with HFpEF<sub>parox-AF</sub> patients, indicating that this change was more specific to HFpEF<sub>perm-AF</sub> patients.

### INVASIVE HEMODYNAMICS.

HFpEF<sub>perm-AF</sub> patients displayed the highest biventricular filling pressures at rest, with lowest CO and stroke volume (Figure 2, Table 3). The pressures at the v-wave peak and y nadir were both highest in HFpEF<sub>perm-AF</sub> patients, consistent with LA reservoir dysfunction and reduced operating LA compliance. There were no differences in systemic arterial load at rest, but patients with HFpEF<sub>perm-AF</sub> displayed more severe pulmonary vascular disease, with higher pulmonary vascular resistance, lower pulmonary arterial (PA) compliance, higher PA elastance, and the most severe pulmonary hypertension (Table 3, Figure 2, Supplemental Table 1).

During exercise, patients with HFpEF displayed lower peak oxygen consumption compared with control subjects (Table 4). Exercise CO reserve was lowest in HFpEF<sub>perm-AF</sub> patients, with a blunted increase in CO relative to oxygen consumption (Figure 2). Similar to resting values, pulmonary vascular resistance and elastance were highest and PA compliance the lowest during exercise in HFpEF<sub>perm-AF</sub> patients (Table 4).

PCWP increased markedly during exercise in all HFpEF groups, reaching similar peak values (Table 4), but the mechanisms by which this occurred differed. In HFpEF<sub>no-AF</sub> and HFpEF<sub>parox-AF</sub> patients, LVTMP increased by over 200% compared with baseline, in keeping with a marked increase in LV preload (Figure 1, Table 4) in the setting of a stiff ventricle. However, in the HFpEF<sub>perm-AF</sub> group, LVTMP failed to increase, meaning that the increase in PCWP during exercise in HFpEF<sub>perm-AF</sub> patients was exclusively related to increases in pericardial restraint, estimated by the greater elevation in RA pressure. Consistent with this, the ratio of RAP/PCWP increased more dramatically with exercise in the HFpEF<sub>perm-AF</sub> group as compared with all others. The increase in RA pressure with exercise was directly correlated with biatrial volume measured at rest (Figure 1).

## INTEGRATED ASSESSMENT OF LA FUNCTION USING PRESSURE, VOLUME, AND STRAIN.

LA maximum, pre A, and minimum LA volume showed a progressive increase with increasing AF severity (Table 5). Absolute LA filling volume (reservoir volume) was not significantly different in the 4 groups, but because HFpEF<sub>perm-AF</sub> patients displayed the largest minimum LA volume (starting volume), they displayed the lowest LA expansion index. The increase in PCWP pressure during LA reservoir filling (x-v wave height) was highest in the HFpEF<sub>perm-AF</sub> group (Table 5). LA reservoir strain progressively worsened across all groups, with the lowest values in HFpEF<sub>perm-AF</sub> patients. Together with the higher x-v wave pressure height, this led to a progressive reduction in LA compliance with increasing AF stage (Figure 3). The height of the v-wave correlated with abnormal PA vascular load both at rest and with exercise, but the relationship was stronger between measures reflecting pulsatile load and LA pressure (PA elastance) ( $r = 0.53$ ,  $p < 0.0001$ ) (Figure 3) compared with non-pulsatile load (pulmonary vascular resistance) ( $r = 0.26$ ,  $p < 0.0001$ ).

Similar to LA reservoir strain, LA conduit strain was impaired in HFpEF, with lower passive EF in the HFpEF<sub>parox-AF</sub> as a result of a higher maximum LA volume prior to mitral valve opening (Table 5). LA booster function was impaired in HFpEF<sub>parox-AF</sub> patients, as evidenced by a smaller LA active EF and LA booster strain compared with control subjects and HFpEF<sub>no-AF</sub> patients.

## OUTCOMES.

Ten-year survival was lower in HFpEF<sub>perm-AF</sub> patients (38%) than in HFpEF<sub>parox-AF</sub> patients (62%), HFpEF<sub>no-AF</sub> patients (73%), and control subjects (94%) ( $p < 0.001$  by log-rank test; hazard ratio [HR]: 1.95; 95% confidence interval [CI]: 1.56 to 2.45 per increase in AF stage). Ten-year progression from paroxysmal to permanent AF was common in HFpEF<sub>parox-AF</sub> patients (52%), and a higher AF stage was associated with an increased risk for progression to greater AF stages over 10 years (31% in HFpEF<sub>no-AF</sub> patients vs. 1% sinus control subjects) ( $p < 0.001$  by log-rank test; HR: 4.95; 95% CI: 3.07 to 8.20 per increasing AF stage). Progression of AF stage was also associated with impaired LA reservoir strain (HR: 6.8; 95% CI: 3.3 to 14.1;  $p < 0.0001$ ), poorer LA compliance (HR: 6.0; 95% CI: 2.9 to 12.7;  $p < 0.0001$ ), and greater elevation in PCWP at baseline (HR: 5.3; 95% CI: 2.8 to 10.3;  $p < 0.0001$ ) (Figure 4, Supplemental Figure 2).

## DISCUSSION

In this study, we present a comprehensive analysis of atrial and ventricular structure, function, and hemodynamics utilizing a combination of invasive and noninvasive assessments across the spectrum of AF burden, in patients with and without HFpEF. We observed that LA remodeling, compliance, and contractile function progressively worsen as AF burden increases, while LV diastolic stiffness was similarly abnormal in all HFpEF groups. The presence of AF, particularly permanent AF, was associated with more biventricular systolic dysfunction, the poorest cardiac output reserve, higher filling pressures, more severe pulmonary vascular disease, reduced LA reservoir function, and

increased LA stiffness. Although most functional and hemodynamic abnormalities worsened across the AF stages, there were important differences between paroxysmal and permanent AF. Patients with permanent AF demonstrated greater cardiomegaly because of atrial dilatation, such that a greater proportion of LA hypertension was driven by ventricular interdependence and pericardial restraint. Increasing AF burden was associated with graded increases in mortality. Progression to permanent AF was common in patients with paroxysmal AF, and risk was greater in patients with more severe reductions in LA strain and compliance. These data identify important and unique pathophysiologic mechanisms by which AF contributes to morbidity and mortality in HFpEF, emphasizing the relevance of a distinct atrial fibrillation or LA myopathy phenotype, as well as the central role of LA reservoir function in progression of AF in HFpEF (Central Illustration). Further study of interventions to mitigate or prevent progression of LA myopathy in patients with HFpEF is urgently required, particularly in patients with paroxysmal AF.

The prevalence of permanent AF in this study was lower than other series, likely related to the fact that the patient population was ambulatory not hospitalized. Community-based studies have shown that two-thirds of patients with HFpEF develop AF at some point during their lifespan (1). Compared with HFpEF<sub>no-AF</sub> patients, HFpEF<sub>perm-AF</sub> patients display poorer exercise capacity, greater burden of RV dysfunction, and increased risk of death (1–16). The findings from the current study, the largest and most comprehensive to date, confirm and importantly extend multiple studies from smaller cohorts focused on permanent AF, extending understandings to include patients across the entire AF or LA phenotypic spectrum in a graded spectrum, including paroxysmal AF. Ventricular systolic function as well as LA systolic and diastolic performance progressively worsened across HFpEF patients as AF burden worsened. These data point to the presence of progressive underlying cardiomyopathic process as AF burden worsens in HFpEF, especially in the atrium, and may help in staging HFpEF patients for targeted LA-specific interventions.

### **IMPLICATIONS FOR TREATMENT.**

The vast majority of abnormalities in atrial function and hemodynamics identified were found to exist along a continuous spectrum mirroring the burden of AF. Therefore, interventions targeting LA myopathy such as unloading the LA may also be useful to mitigate progression. One such therapy is atrial septostomy, which lowers LA pressure and may elicit reverse remodeling of the LA (29,30), and improve pulmonary vascular function in HFpEF (28), consistent with the observed relationship between the height of the LA v-wave (an indicator of LA stiffness) and PA elastance in the present study (Figure 1). Therapies targeting LA myopathy and AF incidence such as sodium-glucose cotransporter-2 inhibitors (31) and risk factor interventions may have a role in these patients, particularly in patients with paroxysmal AF in whom progression rates to permanent AF are very high (32).

### **ROLE OF PERICARDIAL RESTRAINT IN PERMANENT AF.**

Although PCWP was highest in the permanent AF cohort, LV mass, diastolic function, and chamber stiffness were similar across HFpEF groups regardless of rhythm status, suggesting that the higher PCWP in HFpEF<sub>perm-AF</sub> is not caused by differences in LV diastolic properties. Left heart filling pressure is determined by the vector sum of the chamber

distending pressure (LVTMP) and the external pressure applied by the right heart and pericardium, which is estimated by the RA pressure (22,23). Using multiple separate indices, we found that this component related to extrinsic restraint was increased and explained the higher pulmonary capillary pressures in permanent AF (Figure 1).

In animal preparations, slight increases in atrial volume induced by loss of atrial contraction acutely shift the ventricular diastolic pressure-volume relationship upward (33). This effect is completely abrogated by pericardiectomy, proving that the effect is due to extrinsic restraint from atrial enlargement rather than due to LV properties. In the present study, LVTMP was similar in HFpEF<sub>perm-AF</sub> patients at rest but did not increase during exercise nearly as much in the permanent AF group as in others, even as PCWP was equally elevated during stress (Figure 1). This indicates that the increase in PCWP during exercise in HFpEF<sub>perm-AF</sub> was strongly related to extrinsic restraint during the volume loading induced by exercise, rather than to an isolated increase in LV distending pressures resulting from LV myocardial pathology, similar to an animal study (33). HFpEF<sub>perm-AF</sub> patients displayed greater increases in RA pressure at rest and during exercise, which promotes greater pulmonary congestion (34), as noted radiographically in the HFpEF<sub>perm-AF</sub> group in the present study. Increased pericardial constraint also promotes underdistention of the LV, contributing to the observed limitations in cardiac output at rest and during exercise, in part through impaired Frank-Starling reserve (Figure 2) (35). Novel therapies are being developed to release pericardial restraint in HFpEF (22,36,37), and the current data suggest that patients with permanent AF may particularly stand to benefit from this intervention.

#### **AF AS AN INDICATOR OF LA MYOPATHY.**

With reductions in LA compliance, there is an increase in the LA v-wave out of proportion to mean LA pressure, which increases the pulmonary capillary pressure out of proportion to the increase in LV end-diastolic pressure (38). This may explain the stronger association between pulmonary capillary pressure and outcome in HFpEF, as compared with LV end-diastolic pressure (39). In the present study, increases in PCWP and impairments in LA strain and compliance were all strongly associated with increased risk for development of AF. This strongly supports the importance of LA myopathy as a risk factor for AF and important therapeutic target.

One finding of caution from this study is the demonstration that atrial reservoir function was poor at baseline in HFpEF and worsened with greater AF burden. The reduction in atrial distensibility with AF likely contributed in an important way to the elevation in pulmonary capillary pressures observed. Given the potential for catheter ablation to further reduce LA compliance through scar formation (20), catheter ablation must be performed with careful attention to minimizing atrial injury, especially because the benefit of more extensive ablation remains uncertain (40). In addition to considering paroxysmal versus permanent AF, the current data suggest that consideration of LA reservoir strain may also be important in clinical trials to identify patients in whom ablation may be safer and more effective.



## STUDY LIMITATIONS.

Echocardiography was not performed simultaneously with catheterization, and was only obtained during rest. However, this limitation applies similarly to all patient groups, so this does not affect the internal validity of the results, as this variability would similarly apply to all patient groups. The pressure-volume relationships for LA filling were assumed to be linear but actually represent a curvilinear pressure-volume relationship. However, the linear approximation avoids the complexities of curvilinear estimates of atrial pressure-volume relationships and represents a reasonable assumption of atrial operating compliance. The control group were not truly normal healthy volunteers, but had dyspnea of noncardiac origin, but this would only be expected to bias our results toward the null. The control group was also younger, which may have contributed to differences in hemodynamics compared with the HFpEF groups. Assignment of paroxysmal AF was based on meticulous review of clinical charts and prior electrocardiograms, but despite this, it is possible that some of the patients in the HFpEF<sub>no-AF</sub> group might have had an episode of AF at some time point prior to evaluation. However, this too would only be expected only to bias our results toward the null. A number of baseline differences were present between patient groups, and these were not adjusted for in multivariable analyses. Given the multiple hypotheses tested, this does increase the risk for type I error, and further validation of our results is needed. However, the differences in atrial mechanics and function persisted independent of the use of either echocardiographic or catheterization based methodologies, supporting the robustness of our findings

## CONCLUSIONS

Left atrial myopathy in HFpEF progressively worsens with increasing burden of atrial fibrillation and is strongly associated with hemodynamic abnormalities that contribute to morbidity and mortality. HFpEF<sub>perm-AF</sub> patients display more pulmonary vascular dysfunction and right heart failure, with increases in pericardial restraint because of atrial dilation that adversely impacts exertional cardiac output and filling pressures. These unique pathophysiologic differences suggest that patients with permanent AF may respond differently to treatment and ought to be considered as a separate phenotype. Progression to permanent AF is strongly associated with baseline LA myopathy and compliance, suggesting that therapies targeting LA function may have a role in preventing this transition.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## ABBREVIATIONS AND ACRONYMS

<b>AF</b>	atrial fibrillation
<b>CI</b>	confidence interval
<b>EF</b>	ejection fraction
<b>HFpEF</b>	heart failure with preserved ejection fraction
<b>HFpEF<sub>no-AF</sub></b>	heart failure with preserved ejection fraction with no atrial fibrillation
<b>HFpEF<sub>parox-AF</sub></b>	heart failure with preserved ejection fraction with paroxysmal atrial fibrillation
<b>HFpEF<sub>perm-AF</sub></b>	heart failure with preserved ejection fraction with permanent atrial fibrillation
<b>HR</b>	hazard ratio
<b>LA</b>	left atrium/atrial
<b>LV</b>	left ventricular
<b>LVTMP</b>	left ventricular transmural pressure
<b>PA</b>	pulmonary arterial
<b>PCWP</b>	pulmonary capillary wedge pressure
<b>RAP</b>	right atrial pressure
<b>RV</b>	right ventricular

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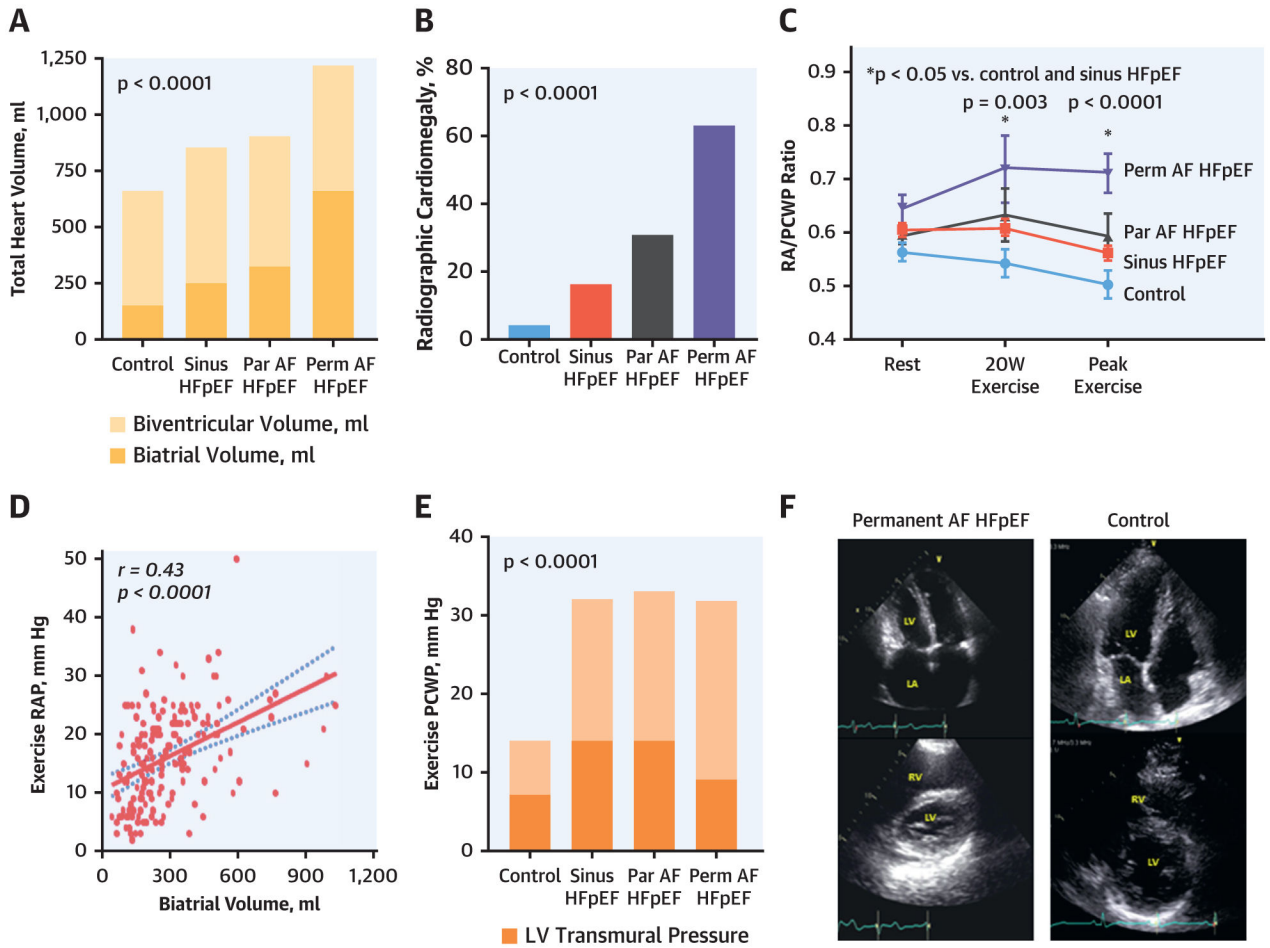
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**PERSPECTIVES****COMPETENCY IN MEDICAL KNOWLEDGE:**

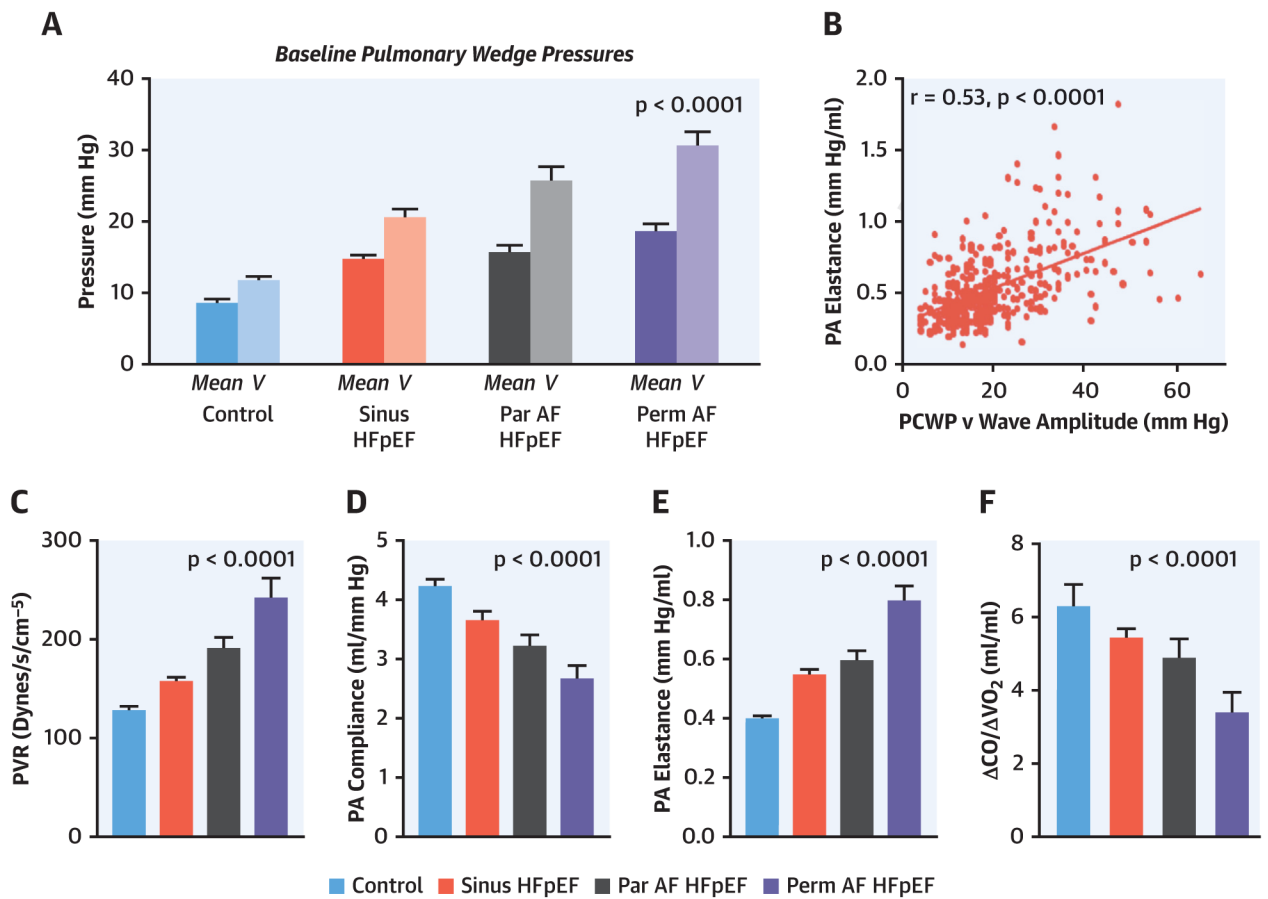
In patients with HFpEF, LA compliance and mechanics worsen as the burden of AF increases, leading to LA enlargement and often to permanent AF.

**TRANSLATIONAL OUTLOOK:**

Additional research is needed to develop strategies that prevent adverse atrial remodeling in patients with HFpEF and AF.

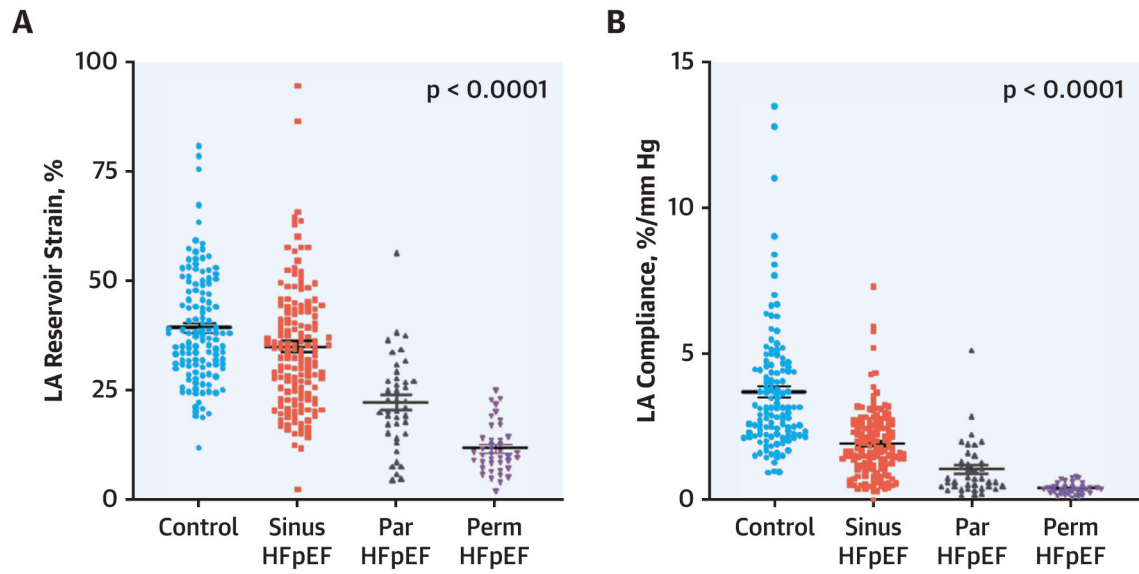


**FIGURE 1. Pericardial and Atrial Size Interaction Across the Spectrum of AF Risk in HFpEF** (A, B) Increasing total heart volume by both echocardiography and chest radiography was driven by atrial enlargement with increasing atrial fibrillation (AF) burden in heart failure with preserved ejection fraction (HFpEF). (C to F) Patients with greater AF burden displayed increased pericardial restraint with a higher exertional right atrial pressure (RAP), RAP/pulmonary capillary wedge pressure (PCWP) ratio, and lower left ventricular (LV) transmural pressure and enhanced diastolic ventricular interaction in the permanent AF HFpEF group. Par = paroxysmal; Perm = permanent.



**FIGURE 2. Left Heart Filling Pressures, Pulmonary Vascular Load, and Cardiac Output Reserve Across AF Grades in HFpEF**

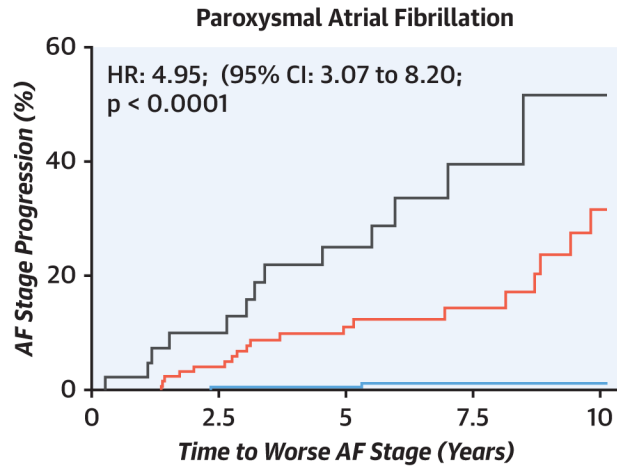
Baseline (resting) PCWP was highest in the permanent AF HFpEF group, and the corresponding PCWP v-wave height (A) increased progressively across groups and (B) was associated with worse pulmonary arterial (PA) elastance. (C to E) There was progressive worsening of pulmonary vascular load measured at rest with increasing AF stages along with (F) decreased cardiac output (CO) reserve during exercise. PVR = pulmonary vascular resistance;  $\text{Vo}_2$  = oxygen consumption; other abbreviations as in Figure 1.



**FIGURE 3. LA Reservoir Dysfunction With Increasing AF Burden in HFpEF**  
Progressive impairment in (A) LA reservoir strain and (B) LA compliance with worsening AF stage. Abbreviations as in Figure 1.

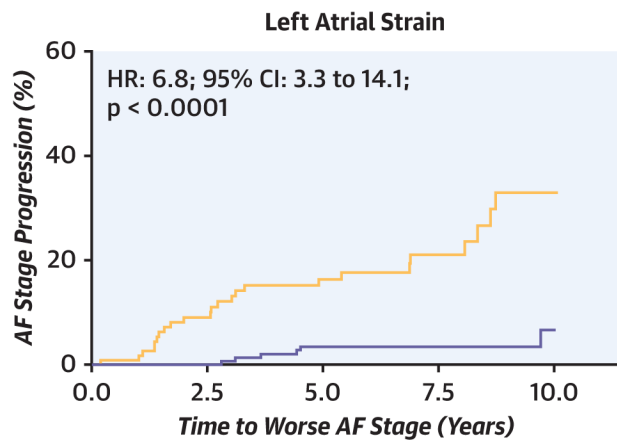


**A**

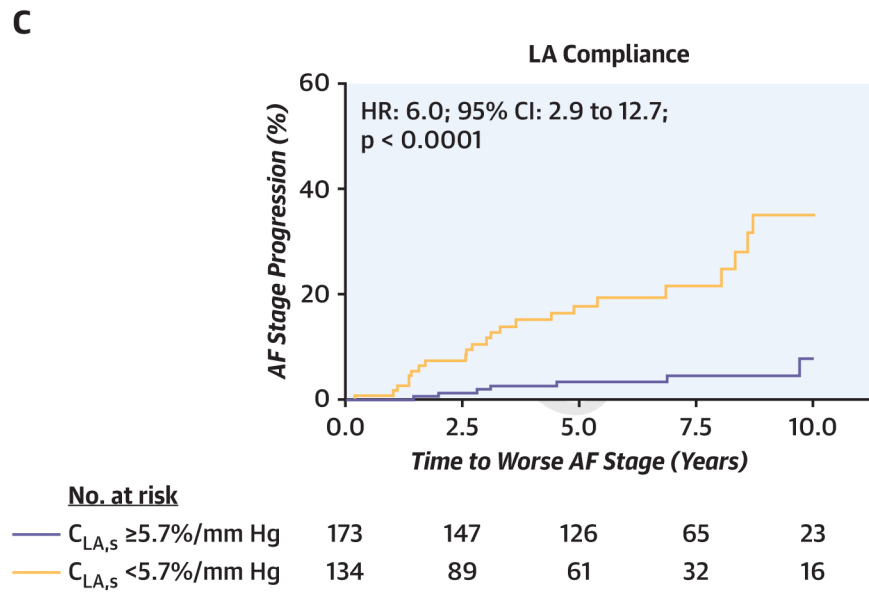


<b>No. at risk</b>						
—	Control	146	142	130	68	29
—	Sinus HFpEF	181	109	77	39	15
—	Paroxysmal AF HFpEF	49	32	21	10	2

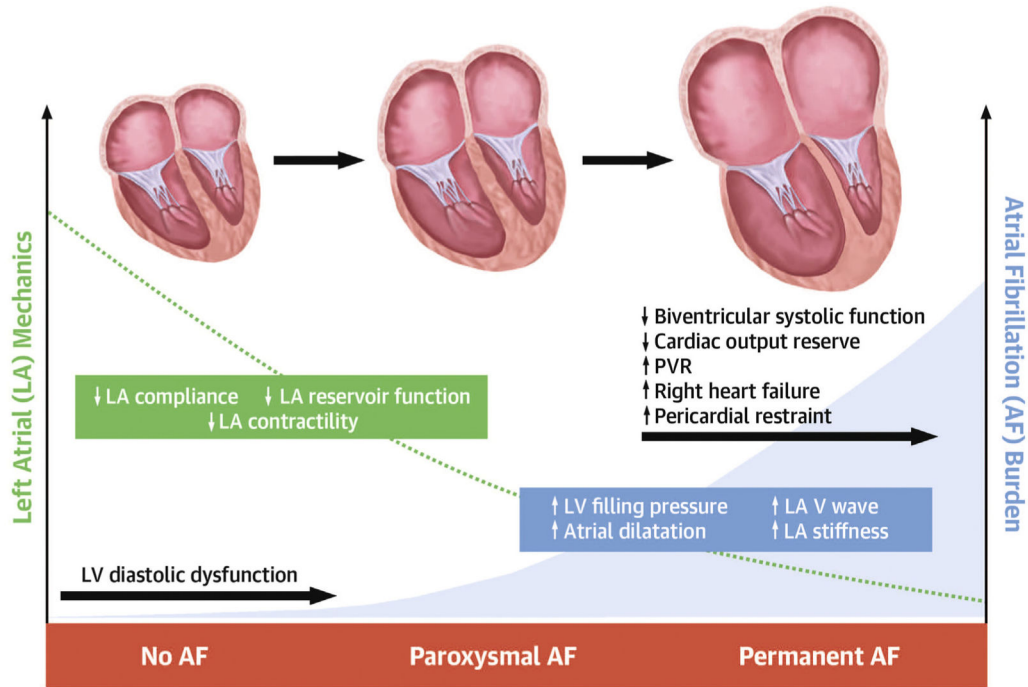
**B**



<b>No. at risk</b>						
—	LA Strain ≥31.5%	179	149	122	60	22
—	LA Strain <31.5%	135	93	71	39	18



**FIGURE 4. Risk of Progression of AF Stratified by Baseline AF Burden**  
 The risk of progressing to higher AF stage increased (A) with higher AF burden at index assessment and (B, C) in patients with more severe LA myopathy as evidenced by lower LA reservoir strain and compliance. For panels B and C, results are presented stratified by median LA reservoir strain and compliance. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.



**CENTRAL ILLUSTRATION. Progressive LA Myopathy and AF Burden in Heart Failure With Preserved Ejection Fraction**

Increasing atrial fibrillation (AF) burden in heart failure with preserved ejection fraction was associated with worsening left atrial (LA) mechanics, LA remodeling, central hemodynamics, right ventricular-pulmonary artery coupling, and pericardial restraint. LV = left ventricular; PVR = pulmonary vascular resistance.

**TABLE 1**

Demographics and Clinical Characteristics

	Control Subjects (n = 146)	HFpEF <sub>non-AF</sub> (n = 181)	HFpEF <sub>parox-AF</sub> (n = 49)	HFpEF <sub>perm-AF</sub> (n = 48)	p Value
Age, yrs	56 ± 15 <sup>*</sup>	66 ± 11 <sup>*</sup>	71 ± 7	75 ± 6	<0.0001
Female	60	62	61	60	0.9
BMI, kg/m <sup>2</sup>	28.3 ± 5.6	33.8 ± 7.4 <sup>‡</sup>	32.9 ± 7.9 <sup>‡</sup>	30.7 ± 5.7	<0.0001
Hemoglobin, g/dl	12.9 ± 1.3 <sup>*</sup>	12.3 ± 1.5	12.2 ± 1.5	11.8 ± 1.6	<0.0001
Diabetes	14	30	35	21	<0.0001
Hypertension	84	94	100	98	0.0001
COPD	8	12	12	10	0.7
Laboratories and chest radiography					
NT-proBNP, pg/ml	69 (31–127) <sup>*</sup>	195 (68–557) <sup>*</sup>	613 (296–1,061) <sup>*</sup>	1,859 (969–3,051) <sup>*</sup>	<0.0001
Creatinine, mg/dl	0.9 ± 0.2 <sup>*</sup>	1.1 ± 0.4	1.2 ± 0.4	1.2 ± 0.4	<0.0001
eGFR, ml/min/1.73 m <sup>2</sup>	73 ± 18 <sup>*</sup>	61 ± 17	58 ± 20	55 ± 20	<0.0001
Cardiomegaly	4	16	31	62	<0.0001
Lung congestion	0	3	4	19	<0.0001
Medication					
Beta-blocker	29	51	47	75	<0.0001
ACE inhibitor or ARB	24	41	39	58	<0.0001
Diuretic	23	43	55	65	<0.0001
MRA	6	10	16	27	0.0008
Digoxin	2		2	23	<0.0001
Anticoagulation	5	7	33	75	<0.0001

Values are mean ± SD, %, or median (interquartile range). Correction for multiple hypothesis testing was not performed.

<sup>\*</sup> p < 0.05 vs. all by Tukey's test.

<sup>‡</sup> p < 0.05 vs. control subjects by Tukey's test.

<sup>‡</sup> p < 0.05 vs. HFpEF<sub>perm-AF</sub> by Tukey's test.

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ACE = angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HFpEF<sub>no-AF</sub> = heart failure with preserved ejection fraction in sinus rhythm; HFpEF<sub>parox-AF</sub> = heart failure with preserved ejection fraction with paroxysmal atrial fibrillation; HFpEF<sub>perm-AF</sub> = heart failure with preserved ejection fraction in permanent atrial fibrillation; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

TABLE 2

## Cardiac Structure and Function

	Control Subjects (n = 146)	HFpEF <sub>no-AF</sub> (n = 181)	HFpEF <sub>parox-AF</sub> (n = 49)	HFpEF <sub>perm-AF</sub> (n = 48)	p Value
LV structure and function					
LA volume index, ml/m <sup>2</sup>	28 ± 8*	33 ± 9*	41 ± 12*	56 ± 15*	<0.0001
LVEDD, mm	48 ± 5	48 ± 5	49 ± 6	49 ± 6	0.2
EF, %	63 ± 5	64 ± 6	62 ± 7	61 ± 6 <sup>†</sup>	0.005
LV mass index, g/m <sup>2</sup>	84 ± 19*	90 ± 21	98 ± 26	97 ± 27	<0.0001
LV GLS, %	16 ± 3	16 ± 3	15 ± 3 <sup>‡</sup>	14 ± 4 <sup>‡‡</sup>	<0.0001
LV stiffness b, mm Hg/ml	0.42 ± 0.11	0.47 ± 0.15 <sup>‡</sup>	0.46 ± 0.14	0.47 ± 0.12 <sup>‡</sup>	0.009
E/e'	9 ± 4*	13 ± 7	14 ± 6	16 ± 6 <sup>‡‡</sup>	<0.0001
Septal a', cm/s	10 ± 2	9 ± 3	7 ± 3*	—	<0.0001
RV structure and function					
RV basal diameter	31 ± 6	32 ± 6	34 ± 6 <sup>‡‡</sup>	35 ± 8 <sup>‡‡</sup>	<0.0001
RV mid diameter	24 ± 5	25 ± 6	26 ± 6	27 ± 7 <sup>‡</sup>	0.02
RV dilation <sup>  </sup>	11	22	30	66	<0.0001
RV diastolic area, cm <sup>2</sup>	13.1 ± 4.1	13.7 ± 4.0	14.8 ± 3.9	15.0 ± 5.3	0.04
RV systolic area, cm <sup>2</sup>	6.3 ± 2.3	6.8 ± 2.7	7.6 ± 3.0	8.9 ± 4.5 <sup>‡‡</sup>	<0.0001
RV FAC, %	53 ± 6	51 ± 8	49 ± 9	43 ± 11*	<0.0001
TAPSE, mm	23 ± 6	23 ± 6	19 ± 7	17 ± 4 <sup>‡‡</sup>	0.0001
TV s', cm/s	14 ± 3	13 ± 3	13 ± 3	11 ± 2 <sup>‡‡</sup>	0.0002
Ventriculoatrial remodeling and interdependence					
Total heart volume, ml	664 ± 216*	857 ± 251	901 ± 235	1212 ± 400*	<0.0001
Biatrial volume, ml	158 ± 72*	255 ± 128	311 ± 125	658 ± 291*	<0.0001
Biventricular volume, ml	506 ± 198	602 ± 190 <sup>‡</sup>	590 ± 223	555 ± 196	0.02
Biatrial volume/total heart volume, %	25 ± 10*	30 ± 10*	35 ± 13*	53 ± 11*	<0.0001
Eccentricity index diastole	0.97 ± 0.09	1.02 ± 0.12 <sup>#</sup>	1.00 ± 0.13	1.03 ± 0.13 <sup>‡</sup>	0.004
Eccentricity index systole	0.97 ± 0.11	1.03 ± 0.12 <sup>#</sup>	1.00 ± 0.09	1.08 ± 0.23 <sup>‡‡</sup>	<0.0001

	Control Subjects (n = 146)	HFpEF <sub>no-AF</sub> (n = 181)	HFpEF <sub>parox-AF</sub> (n = 49)	HFpEF <sub>perm-AF</sub> (n = 48)	p Value
Ideal radius index diastole	1.04 ± 0.24	1.16 ± 0.29 <sup>‡</sup>	1.11 ± 0.22	1.18 ± 0.31 <sup>‡</sup>	0.009
Ideal radius index systole	1.06 ± 0.28	1.14 ± 0.31	1.08 ± 0.22	1.22 ± 0.54 <sup>‡</sup>	0.05

Values are mean ± SD or %. Correction for multiple hypothesis testing was not performed.

\* p < 0.05 vs. all by Tukey's test.

<sup>‡</sup> p < 0.05 vs. HFpEF<sub>no-AF</sub> by Tukey's test.

<sup>‡</sup> p < 0.05 vs. control subjects by Tukey's test.

<sup>§</sup> p < 0.05 vs. HFpEF<sub>parox-AF</sub> by Tukey's test.

// Based on qualitative assessment.

a' = ●●●; E/e' = ●●●; FAC = fractional area change; GLS = global longitudinal strain; LA = left atrial; LV = left ventricular; LVEDD = left ventricular end-diastolic dimension; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; s' = ●●●; TV = tricuspid valve; other abbreviations as in Table 1.

TABLE 3

## Resting Hemodynamics

	Control Subjects (n = 146)	HFpEF <sub>no-AF</sub> (n = 181)	HFpEF <sub>parox-AF</sub> (n = 49)	HFpEF <sub>perm-AF</sub> (n = 48)	p Value
Pressure data, mm Hg					
PCWP, mean	9 ± 3*	15 ± 5	16 ± 6	19 ± 6 <sup>†‡</sup>	<0.0001
Peak a-wave	12 ± 4*	19 ± 6	20 ± 6	–	<0.0001
Nadir x-descent	8 ± 3*	14 ± 5*	16 ± 6*	18 ± 5*	<0.0001
Peak v-wave	12 ± 5*	21 ± 10*	26 ± 12*	31 ± 11*	<0.0001
Nadir y-descent	8 ± 3*	14 ± 5*	16 ± 6	18 ± 5 <sup>†‡</sup>	<0.0001
RA mean	5 ± 2*	9 ± 4	10 ± 4	12 ± 5*	<0.0001
PA mean	17 ± 4*	25 ± 7*	28 ± 10	31 ± 9	<0.0001
PA systolic	28 ± 7*	38 ± 11 <sup>§  </sup>	43 ± 15	47 ± 14	<0.0001
LVTMP	4 ± 2*	6 ± 4	7 ± 4	7 ± 4	<0.0001
RA/PCWP	0.57 ± 0.21	0.61 ± 0.20	0.59 ± 0.15	0.64 ± 0.17	0.08
PCWP/LVEDV	0.08 ± 0.04*	0.14 ± 0.06	0.15 ± 0.06	0.17 ± 0.07 <sup>†‡</sup>	<0.0001
LVTMP/LVEDV	0.04 ± 0.03*	0.06 ± 0.04	0.07 ± 0.05	0.06 ± 0.04	<0.0001
O <sub>2</sub> transport					
Vo <sub>2</sub> , ml/min	217 ± 56	229 ± 62	220 ± 55	224 ± 53	0.4
Vo <sub>2</sub> , ml/min/kg	2.7 ± 0.6 <sup>‡§</sup>	2.5 ± 0.6	2.4 ± 0.6	2.6 ± 0.5	0.002
CO, l/min	5.5 ± 1.6	5.4 ± 1.5	4.9 ± 1.2	4.6 ± 1.2 <sup>†‡</sup>	0.0007
HR, beats/min	73 ± 13	70 ± 11	67 ± 11#	71 ± 9	0.003
CI, l/min/m <sup>2</sup>	2.86 ± 0.78 <sup>§  </sup>	2.68 ± 0.66	2.43 ± 0.53	2.30 ± 0.58 <sup>†‡</sup>	<0.0001
SV, ml	76 ± 23	78 ± 25	76 ± 22	65 ± 18 <sup>†‡</sup>	0.005
SVI, ml/m <sup>2</sup>	39 ± 10	39 ± 11	37 ± 10	33 ± 9 <sup>†‡</sup>	0.0008
Afterload					
PVR, dynes/cm <sup>-5</sup>	128 ± 63*	157 ± 82	191 ± 83	241 ± 135*	<0.0001
TPG, mm Hg	8 ± 3*	10 ± 5	11 ± 5	13 ± 6 <sup>†‡</sup>	<0.0001
PAC, ml/mm Hg	4.2 ± 1.6*	3.7 ± 1.9	3.2 ± 1.1	2.7 ± 1.5 <sup>†‡</sup>	<0.0001



	<b>Control Subjects (n = 146)</b>	<b>HFpEF<sub>no-AF</sub> (n = 181)</b>	<b>HFpEF<sub>parox-AF</sub> (n = 49)</b>	<b>HFpEF<sub>perm-AF</sub> (n = 48)</b>	<b>p Value</b>
PA Ea, mm Hg/ml	0.4 ± 0.1 *	0.5 ± 0.2 *	0.6 ± 0.2 §//	0.8 ± 0.3 *	<0.0001

Values are mean ± SD. Correction for multiple hypothesis testing was not performed.

\* p < 0.05 vs. all by Tukey's test.

† p < 0.05 vs. control subjects by Tukey's test.

‡ p < 0.05 vs. sinus HFpEF by Tukey's test.

§ p < 0.05 vs. HFpEF<sub>parox-AF</sub> by Tukey's test.

// p < 0.05 vs. HFpEF<sub>perm-AF</sub> by Tukey's test.

CI = ●●●; CO = ●●●; Ea = elastance; HR = heart rate; LVEDV = left ventricular end-diastolic volume; LVTMP = left ventricular transmural pressure; PA = pulmonary artery; PAC = pulmonary arterial compliance; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RA = right atrial; SV = stroke volume; SVI = stroke volume index; TPG = transpulmonary gradient; V<sub>O2</sub> = oxygen consumption; other abbreviations as in Table 1.

TABLE 4

## Exercise Hemodynamics

	Control Subjects (n = 146)	HFpEF <sub>no-AF</sub> (n = 181)	HFpEF <sub>parox-AF</sub> (n = 49)	HFpEF <sub>perm-AF</sub> (n = 48)	p Value
Pressure data, mm Hg					
PCWP mean	14 ± 5*	32 ± 6	32 ± 6	32 ± 5	<0.0001
Peak a-wave	18 ± 5*	36 ± 9	35 ± 8	—	<0.0001
Nadir x-descent	12 ± 5*	28 ± 8	27 ± 6	29 ± 6	<0.0001
Peak v-wave	21 ± 8*	47 ± 13	51 ± 14	52 ± 13	<0.0001
Nadir y-descent	13 ± 5*	29 ± 8	27 ± 7	28 ± 5	<0.0001
RA mean	7 ± 4*	18 ± 7	19 ± 7	23 ± 9 <sup>†</sup>	<0.0001
PA mean	26 ± 8*	45 ± 11	47 ± 11	48 ± 9	<0.0001
PA systolic	42 ± 13*	63 ± 16	67 ± 17	69 ± 12	<0.0001
RA/PCWP	0.50 ± 0.25	0.56 ± 0.17	0.59 ± 0.22	0.71 ± 0.22 <sup>†‡</sup>	<0.0001
LVTMP	7 ± 4 <sup>†§</sup>	14 ± 6 <sup>†  </sup>	14 ± 8	9 ± 7 <sup>†§</sup>	<0.0001
O <sub>2</sub> transport					
Vo <sub>2</sub> , ml/min	933 ± 323*	819 ± 266	756 ± 233	745 ± 252	0.0006
Vo <sub>2</sub> , ml/min/kg	11.7 ± 4.2*	9.0 ± 3.1	8.3 ± 2.2	8.6 ± 3.1	<0.0001
AVo <sub>2</sub> diff, ml/dl	9.2 ± 2.0	9.3 ± 2.1	10.0 ± 2.2	11.1 ± 2.0 <sup>†‡</sup>	<0.0001
HR, beats/min	117 ± 25*	101 ± 17 <sup>‡§</sup>	92 ± 15	94 ± 21	<0.0001
CO, l/min	10.3 ± 3.8*	9.2 ± 2.9*	7.7 ± 2.7	6.5 ± 2.4	<0.0001
CO/ Vo <sub>2</sub> , ml/ml	6.8 (5.0–7.9)*	5.9 (4.2–6.8)	4.7 (2.9–7.4)	4.4 (2.0–5.1) <sup>†‡</sup>	<0.0001
CO, % predicted	113 (83–131)*	99 (69–114)	79 (49–123)	73 (33–85) <sup>†‡</sup>	<0.0001
SV, ml	89 ± 32	91 ± 29	86 ± 33	71 ± 28 <sup>†‡</sup>	0.002
SVI, ml/m <sup>2</sup>	46 ± 14	45 ± 12	42 ± 13	36 ± 14 <sup>†‡</sup>	0.0002
CI, l/min <sup>*</sup> ·m <sup>2</sup>	5.4 ± 1.9*	4.6 ± 1.3*	3.8 ± 1.1	3.2 ± 1.1	<0.0001
Afterload					
PVR, dynes/cm <sup>-5</sup>	105 ± 74	134 ± 104	182 ± 119#*	232 ± 132#*	<0.0001

	Control Subjects (n = 146)	HFpEF <sub>no-AF</sub> (n = 181)	HFpEF <sub>parox-AF</sub> (n = 49)	HFpEF <sub>perm-AF</sub> (n = 48)	p Value
PAC, ml/mm Hg	3.6 ± 2.1 <sup>*</sup>	2.6 ± 1.2	2.2 ± 1.1	1.8 ± 0.8 <sup>†‡</sup>	<0.0001
PA Ea, mm Hg/ml	0.5 ± 0.2 <sup>*</sup>	0.8 ± 0.4 <sup>*</sup>	0.9 ± 0.4 <sup>‡//</sup>	1.1 ± 0.6 <sup>*</sup>	<0.0001

Values are mean ± SD or median (interquartile range). Correction for multiple hypothesis testing was not performed.

<sup>\*</sup> p < 0.05 vs. all by Tukey's test.

<sup>†</sup> p < 0.05 vs. sinus HFpEF by Tukey's test.

<sup>‡</sup> p < 0.05 vs. control subjects by Tukey's test.

<sup>§</sup> p < 0.05 vs. HFpEF<sub>parox-AF</sub> by Tukey's test.

<sup>//</sup> p < 0.05 vs. HFpEF<sub>perm-AF</sub> by Tukey's test.

AVo<sub>2</sub>diff = ●●●; other abbreviations as in Tables 1 and 3.

TABLE 5

## LA Structure and Function

	Control Subjects (n = 146)	HFpEF <sub>no-AF</sub> (n = 181)	HFpEF <sub>parox-AF</sub> (n = 49)	HFpEF <sub>perm-AF</sub> (n = 48)	p Value
LA reservoir function					
Volume/strain					
LA maximal volume, ml	44 ± 16*	52 ± 19*	71 ± 30*	97 ± 41*	<0.0001
LA minimum volume, ml	18 ± 9*	24 ± 15*	44 ± 24*	74 ± 33*	<0.0001
LA reservoir volume, ml	27 ± 9	28 ± 10	28 ± 15	23 ± 18	0.06
LA expansion index, %	163 (122–209)	147 (89–200) <sup>†‡</sup>	72 (39–104)*	34 (15–54)*	<0.0001
LA total EF, %	62 ± 11*	57 ± 15*	40 ± 16*	24 ± 14*	<0.0001
LA reservoir strain, %	40 ± 13*	35 ± 15*	23 ± 11*	12 ± 6*	<0.0001
Pressure, mm Hg					
LA x-y height rest	5 ± 3*	8 ± 6*	10 ± 7	13 ± 7 <sup>§  </sup>	<0.0001
LA x-y height exercise	9 ± 5*	19 ± 10 <sup>‡§</sup>	24 ± 12	22 ± 11	<0.0001
Pressure-volume relation					
LA volume compliance, ml/mm Hg	5.5 (3.9–9.5)*	4.3 (2.4–8.5)*	2.2 (1.4–4.2)	1.7 (0.9–3.5) <sup>§  </sup>	<0.0001
LA strain compliance, %/mm Hg	9.3 (5.7–13.7)*	5.7 (2.8–9.6)*	1.7 (1.1–4.0)*	1.2 (0.7–1.4)*	<0.0001
LA conduit function					
Volume/strain					
LA pre A volume, ml	30 ± 13*	37 ± 16*	56 ± 25*	–	<0.0001
LA passive volume, ml	14 ± 7	15 ± 8	16 ± 12	–	0.5
LA passive EF, %	33 ± 13	30 ± 14	22 ± 13*	–	<0.0001
LA conduit strain, %	22 ± 10*	19 ± 11	14 ± 6	–	<0.0001
Pressure, mm Hg					
LA v-y height rest	4 ± 3*	7 ± 7*	10 ± 7*	14 ± 8*	<0.0001
LA v-y height exercise	8 ± 5*	18 ± 10*	24 ± 12	23 ± 11 <sup>§  </sup>	<0.0001
LA booster function					
Volume/strain					
LA booster volume, ml	13 ± 6	14 ± 7	13 ± 10	–	0.5

	Control Subjects (n = 146)	HFpEF <sub>no-AF</sub> (n = 181)	HFpEF <sub>parox-AF</sub> (n = 49)	HFpEF <sub>perm-AF</sub> (n = 48)	p Value
LA active EF, %	42 ± 11	39 ± 14	25 ± 17 <sup>*</sup>	–	<0.0001
LA booster strain, %	17 ± 8	17 ± 9	10 ± 6 <sup>*</sup>	–	<0.0001
Pressure, mm Hg					
LA y-a height rest	3.2 ± 1.9	5.0 ± 2.6 <sup>§</sup>	4.3 ± 3.0 <sup>§</sup>	–	<0.0001
LA y-a height exercise	5.7 ± 3.8	7.6 ± 4.8 <sup>§</sup>	8.0 ± 6.6 <sup>§</sup>	–	0.0007

Values are mean ± SD or median (interquartile range). Correction for multiple hypothesis testing was not performed.

<sup>\*</sup> p < 0.05 vs. all by Tukey's test.

<sup>†</sup> p < 0.05 vs. HFpEF<sub>parox-AF</sub> by Tukey's test.

<sup>‡</sup> p < 0.05 vs. HFpEF<sub>perm-AF</sub> by Tukey's test.

<sup>§</sup> p < 0.05 vs. control subjects by Tukey's test.

// p < 0.05 vs. sinus HFpEF by Tukey's test.