Left Atrial Remodeling and Function in Advanced Heart Failure With
Preserved or Reduced Ejection Fraction

Melenovsky et al: LA Dysfunction in HF

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circulation and disease, Heart failure:[11] Other heart failure
Abstract

**Background**—Left atrial (LA) structure and function are altered in most heart failure (HF) patients, but there may be fundamental differences in LA properties between HF with preserved (HFpEF) and reduced ejection fraction (HFrEF).

**Methods and Results**—198 HF patients (51% HFpEF, NYHA 3.1±0.7) and 40 HF-free controls underwent catheterization, echocardiography and follow-up. Compared to controls, HF patients had larger and more dysfunctional left atria. At identical mean LA pressure (20 vs 20 mmHg, p=0.9), HFrEF patients had larger LA volumes (LAVI 50 vs 41 ml.m⁻² p<0.001), while HFpEF patients had higher LA peak pressures, lower LA minimal pressures, higher LA stiffness (0.79 vs 0.48 mmHg.ml⁻¹, p<0.001), greater LA pulsatility (19 vs 13 mmHg, p<0.001) and higher wall stress variations. Despite smaller LA volumes, better function and less mitral regurgitation, HFpEF patients had more atrial fibrillation (AF: 42 vs 26%, p=0.02). LA dysfunction was associated with increased pulmonary vascular resistance and right ventricular dysfunction in both HF phenotypes. After a median follow-up of 350 days, 31 HFpEF and 28 HFrEF patients died. LA function (total LA EF) was associated with lower mortality in HFpEF (HR 0.43, 95% CI 0.2-0.9, p<0.05), but not in HFrEF.

**Conclusions**—HFrEF is characterized by greater eccentric LA remodeling, while HFpEF by increased LA stiffness, which might contribute to greater AF burden. LA function is associated with pulmonary vascular disease and right heart failure in both HF phenotypes, but is associated with outcome more closely in HFpEF, supporting efforts to improve LA function in this cohort.

**Key Words:** heart failure; heart failure with preserved EF; left atrial function; atrial fibrillation; pulmonary hypertension; right ventricle
The left atrium modulates left ventricular (LV) filling by acting as an elastic reservoir, passive conduit and active booster.\textsuperscript{1} Left atrial (LA) dysfunction and remodeling are commonly observed in patients with heart failure (HF). Growing evidence suggests that LA dysfunction is an active contributor to symptoms\textsuperscript{2-5} and to disease progression.\textsuperscript{3, 6, 7} HF-related LA remodeling is poorly understood and it is not known if there are fundamental differences between HF patients with preserved (HFpEF) or reduced LV ejection fraction (HFrEF), though prior studies suggest greater adverse effects from loss of LA function in HFpEF compared to HFrEF.\textsuperscript{8}

The LA also serves as a watershed between the LV and the pulmonary circulation, buffering pressure and flow oscillations due to the cyclic nature of cardiac work. Impaired LA function can thus impose greater hemodynamic stress on the pulmonary vasculature, promoting remodeling and worsening pulmonary hypertension (PH), as observed in patients with mitral stenosis.\textsuperscript{9,10} Increased pulmonary vascular resistance and stiffness may elevate right ventricular (RV) afterload,\textsuperscript{11} driving further the progression to RV failure.\textsuperscript{12-15}

We hypothesized that LA function is abnormal in patients with HF, that LA remodeling differs between patients with HFrEF and similarly advanced HFpEF and that LA dysfunction is associated with abnormal pulmonary vascular properties and RV dysfunction. To test this hypothesis, we examined HFrEF and HFpEF patients undergoing invasive and noninvasive hemodynamic assessment and compared them to HF-free controls to address the differences in LA structure, function and to assess the impact of LA dysfunction on pulmonary vasculature, right heart and clinical outcomes.
Methods

Study subjects

Consecutive patients referred to Mayo Clinic (Rochester, MN) undergoing right heart catheterization and echocardiography within a 48-hour window with sufficient raw data available for detailed assessment (pressure waveforms and echocardiographic images) were identified. HF was defined by cardiologist-adjudicated HF diagnosis (Framingham criteria) of >6 month duration and elevated pulmonary artery wedge pressure (PAWP $\geq$ 15 mmHg at rest or $\geq$ 25 mmHg at exercise). HFP EF and HFR EF were defined by LV EF $\geq$ 50% and <50%, respectively. Patients with congenital heart disease, endocarditis, carcinoid, amyloid, constrictive, restrictive or hypertrophic cardiomyopathy, intracardiac shunt (other than patent foramen ovale), high output HF, non-Group II PH, mitral valve replacement, organic valvular disease, acute coronary syndrome or hemodynamic instability were excluded.

Subjects with no cardiovascular disease other than Stage 1 arterial hypertension were identified from patients undergoing preoperative evaluation, percutaneous closure of patent foramen ovale, or evaluation for dyspnea with no identifiable cardiovascular cause. Past medical history, medication use and contemporaneous laboratory data ($\pm$ 1 week) were abstracted from the medical records. Significant CAD was defined as one or more $\geq$ 70% epicardial artery stenosis or previous revascularization (angiography available in 28% controls, 82% of HFP EF and 100% of HFR EF). For time-to-event analysis, patient vital status was determined using outpatient records and the Social Security Death Index. Patients who underwent heart transplantation or ventricular assist device insertion were censored as alive at the day of surgery. The study was approved by Mayo Clinic institutional review board.
Assessment of Hemodynamics and Cardiac function

Right heart catheterization was performed in the supine position via the jugular or femoral vein using a balloon-tipped catheter as previously described. Right atrial (RA), RV, pulmonary artery (PA) pressures and PA wedge pressure (PAWP) were determined at end-expiration. All atrial waveforms were visually inspected by an experienced cardiologist blinded to clinical data and group allocation to determine minimal, maximal, v wave and a wave pressures within one cardiac cycle (Figure 1). Transpulmonary gradient (TPG) was calculated as PA mean-PAWP pressure, pulmonary vascular resistance (PVR) was calculated as TPG/cardiac output and PA compliance was calculated as stroke volume/PA pulse pressure.

Two-dimensional and Doppler echocardiography was performed according to ASE guidelines by experienced sonographers and cardiologists. Cardiac output was derived from heart rate, LV outflow tract diameter and pulsed Doppler time-velocity integral. LV mass was calculated using the Devereux formula. Diastolic function was assessed by measurements of transmitral flow velocities (E and A), E-wave deceleration, mitral annulus tissue velocities in early and late diastole (E’ and A’, average of septal and lateral) using pulsed Doppler echocardiography. Diastolic dysfunction was graded as described previously. Valve regurgitations were quantified according established guidelines. LV EF was determined by the modified Quinones formula that corrects for endocardial echo dropouts and image foreshortening.

Apical 4-chamber views were reviewed off-line to measure maximal LA volume (frame prior to mitral valve opening), diastasis LA volume (frame prior to LA contraction) and minimal LA volume using area-length method. Global and reservoir LA function was characterized by total LA EF, LA conduit function was characterized by passive LA EF and contractile function.
was characterized by active LA EF (Figure 1). Atrial function was also assessed by LA function index (LAFI), which normalizes function to stroke volume and is rhythm-independent. Operant LA diastolic stiffness was approximated as the slope of linear regression of minimal and maximal LA pressure-volume coordinates (Figure 1). Meridional LA wall stress was calculated from maximal to minimal LA volume and pressure using established formulas, assuming atrial wall thickness of 0.2 cm. RV function was assessed as previously by tracing the RV endocardium in the apical 4-chamber view in systole and diastole to obtain fractional area change (RV FAC %). The right atrial endocardium was tracked in the frame prior to tricuspid valve opening in order to obtain maximal RA volume using the area-length method.

Statistical Methods
Data were analyzed using JMP10 (SAS Institute Inc., Cary, NC). Distributions of continuous variables were visually assessed for normality and summary data in the tables are reported as mean (standard deviation) or median (25th-75th interquartile range). Between-group differences were compared by ANOVA with Tukey post-hoc test, 2x2 ANOVA or $\chi^2$ tests as appropriate. Univariate and multivariate Cox proportional hazard model were used to examine the impact of LA function on outcome. To allow comparisons, parameters describing LA function were z-standardized in individual subgroups. Graphs represent mean±SE.

Results
Clinical characteristics of controls (n=40) and both HF groups (HFpEF: n=101, HFrEF: n=97) are summarized in Table 1. Both HF groups were highly symptomatic (74% NYHA III-IV) with ≥80% of chronic diuretic use. Similar to prior studies, HFpEF patients were slightly older,
more likely to be women, more obese and more often in atrial fibrillation (AF). Prevalence of CAD, diabetes and renal dysfunction was similar. HfP EF patients had higher systemic blood pressure, cardiac output, LV EF and transmitral flow velocities, but smaller LV size, LV mass and mitral regurgitation grade compared to HFrEF (Table 2).

**LA structure and function in HfP EF vs HFrEF**

Compared to controls, patients with HFrEF and HfP EF displayed LA dilatation, coupled with reduced LA active contractile, reservoir and conduit functions (Table 2 and Figure 2). Patients with HfP EF displayed greater LA stiffness while HFrEF patients displayed more eccentric LA remodeling (Figure 2). At similar mean LA pressure (Table 2), patients with HFrEF had larger LA volumes and more depressed LA systolic function than HfP EF. In contrast, patients with HfP EF were characterized by higher maximal LA pressure (v-wave), lower minimal LA pressures and increased LA stiffness (Table 2), with a steeper, leftward-shifted LA diastolic pressure-volume relationship (Figure 2). Differences in LA volume and stiffness between HfP EF and HFrEF persisted after adjustments to gender, age, body size and mass, AF or mitral regurgitation grade (adjusted p-values <0.02).

Left atrial pulsatility (LA max-min pressure) and wall stress variation was higher in HfP EF compared to HFrEF (Table 2). LA function curves (preload-stroke volume plots) were shallower in both HfP EF and HFrEF compared to controls, indicating LA contractile dysfunction regardless of LA geometry (Figure 3). LA functional index (LAFI) and A’ mitral annular velocities were also more reduced in HFrEF than in HfP EF or controls (Table 2).

The presence of AF was associated with more severe LA dilatation, lower total LA EF and higher LA stiffness, particularly in HfP EF group (Supplemental Figure). Both atrial rhythm...
and HF phenotype impacted LA structure and function as shown by factorial analysis. LA volume and stiffness increased, while total LA EF decreased with worsening NYHA class (Figure 4). Mitral regurgitation had greater effects in HFpEF than HFrEF, with higher peak LA pressure (LA v-wave) and greater LA wall stress variation with increasing mitral regurgitation in HFpEF compared to HFrEF (Figure 3).

The Left Atrium and Pulmonary Artery-Right Heart Function

Pulmonary hypertension was common in HF patients (82% HFpEF, 79% HFrEF), due to combination of elevated PAWP and increased transpulmonary gradient (Table 3). Mean PA pressure, transpulmonary gradient, pulmonary vascular resistance (PVR) and pulmonary arterial compliance (PAC) were similarly increased in both HF groups (Table 3), while PA pulse pressure was higher in HFpEF. Global left atrial function (total LA EF) correlated inversely with PVR and positively with PAC in both HF groups, but not in controls, and the slope the relationship was similar between HFpEF and HFrEF (Figure 5). Similarly, LA stiffness correlated with PAC in HFpEF and HFrEF (r=-0.35 and r=-0.41, both p<0.001), but only weakly with PVR in HFpEF (r=0.23, p=0.03) and was unrelated to PVR in HFrEF (r=0.12, p=0.3). LA volume was unrelated to PVR or PAC in both HF phenotypes.

Both HFpEF and HFrEF patients displayed RV dilation, but RV systolic function was somewhat lower in HFrEF. Global LA function (total LA EF) positively correlated with RV function in HFpEF and HFrEF with similar slope (Figure 5).
Impact of LA dysfunction on prognosis

Over a median follow-up duration of 350 days (IQR: 82-870) there were 59 deaths (HFpEF=28, HFrEF=31). Outcome was ascertained in 100% of HF subjects. In univariate Cox analysis, reduced global and active LA function (total LA EF and active LA EF), increased LA volume and AF were all associated with an increased risk of death in HFpEF, but not in HFrEF (Figure 6). In multivariate Cox model that included age and gender, known predictors of mortality in HFpEF\textsuperscript{29}, either total LA EF or active LA EF remained a significant predictor of death in HFpEF (p=0.03 and p=0.05), while LAVI was no longer predictive (p=0.16). NT-pro-BNP levels were not predictive of mortality in either HF group.

Discussion

This study examined LA structure and function in HF by combining invasive pressure and noninvasive volume data while contrasting LA parameters in the two HF phenotypes. Compared to controls, both HF types displayed abnormal LA size and function. The HFrEF group was characterized by greater eccentric LA remodeling, while the HFpEF group was characterized by increased LA stiffening and greater LA pressure pulsatility, indicating that higher wall stress variations may contribute to greater burden of AF observed in HFpEF. In both groups, LA function was associated with pulmonary vascular disease and right heart failure. While global LA function was less impaired in HFpEF than HFrEF, LA dysfunction was more strongly associated with mortality in this cohort, suggesting greater vulnerability to loss of LA function in HFpEF. These data highlight the importance of atrial dysfunction in HF and suggest that strategies to optimize LA function and/or to prevent its deterioration may mitigate progression of
pulmonary vascular and right heart dysfunction while improving outcomes in HF patients and particularly in HFrEF.

Two overarching mechanisms are thought to drive the development of atrial dysfunction in HF - chronic changes in loading (increased atrial preload and afterload) and the loss of normal atrial electrical activity.\textsuperscript{10, 34} Experimental and limited human studies\textsuperscript{22, 35} have illustrated that with increased preload, LA contractility initially rises\textsuperscript{22, 35, 36} but later declines, coinciding with adverse changes in remodeling, apoptosis, myosin isoform expression, collagen matrix turnover and reduced intrinsic contractility.\textsuperscript{36-38} As shown in the current data at the macro level, this
translates to an increase in atrial wall stiffness reflected by the steeper and upward-shifted pressure-volume relationship, predominantly in HFP EF and by a shift to the larger LA volumes, predominantly in HFrEF. Despite the difference in LA volumes, we noted that LA function curves (preload-stroke volume relations) were similarly flattened in HFrEF and HFP EF, indicating presence of intrinsic LA dysfunction. In HFP EF, the increase of LA stroke volume by preload recruitment (Frank-Starling mechanism) can be blunted by increased LA stiffness, as recently suggested.39

As shown in the current study, loss of normal atrial electrical activity in HF patients with AF is associated with more pronounced LA dilatation, systolic dysfunction and passive stiffening (Supplemental Figure). However, HF patients in sinus rhythm also demonstrated LA systolic impairment (active LA EF reduced by 37% in HFP EF and 54% in HFrEF), confirming that atrial mechanical dysfunction in HF is not restricted to patients with AF.30-32 At similar mean LA pressures, HFP EF patients demonstrated larger LA pressure pulsatility43 and greater LA wall stress variation. We speculate that this may contribute to the higher prevalence of AF noted in HFP EF compared to HFrEF, despite smaller LA volumes, similar LA pressures, and similar HF severity and mortality risk.44

The differences in LA structure-function also appear to influence how the LA copes with mitral regurgitation. With increasing regurgitation, LA pressure and wall stress increases much more steeply in HFP EF than in HFrEF, which may promote stretch-mediated atrial ectopy that plays a role in initiation of AF.34 While LA function was less impaired in HFP EF than HFrEF, its association with outcome was more pronounced, congruent with previous reports regarding the differential impact of AF on outcomes in HFP EF or HFrEF.8 The current data provide insight into the mechanisms by which this HF phenotype-specific difference may originate.
Previous studies have suggested a potential association between atrial dysfunction and pulmonary hemodynamics, but these non-invasive studies were not able to discriminate between the impact of intrinsic LA properties from passive LA pressure elevation due to volume overload.\textsuperscript{9, 30, 45} We observed that impaired LA global systolic function (quantified by total LA EF)\textsuperscript{7} correlated with increased PVR and reduced PAC measured directly by cardiac catheterization. Impaired diastolic LA function (LA stiffness) was associated with reduced PAC, a measure of oscillatory PA load. The relations between LA functional properties and pulmonary vasculature were similar between HFpEF and HFrEF. The current data strongly implicate that LA dysfunction belongs among the mediators of pulmonary vascular disease in HF.\textsuperscript{11} By having impact in PA hemodynamics, LA dysfunction can also indirectly influence RV function and contribute to progression towards biventricular failure with poor prognosis.\textsuperscript{26, 46}

These data suggest that maintenance or restoration of normal LA function may help to “protect” the pulmonary vasculature, and in doing so, to prevent deterioration of the right heart. Further studies are required to assess whether this approach is beneficial. Conversely, these data also indicate that LA interventions that might increase stiffness or impair systolic function might have unintended adverse consequences on the pulmonary vasculature. Left atrial wall scarring and volume reductions after repeated radiofrequency AF ablations have recently been associated with development of pulmonary hypertension,\textsuperscript{47} and removal of LA appendage, the most contractile and compliant part of the left atrium, increases atrial stiffness and reduces atrial performance.\textsuperscript{37} As LA interventions such as device closure and ablation become more widely utilized in HF patients, the potential for deleterious effects on pulmonary vascular-right heart function should be considered and evaluated in future trials.
Limitations

This study is retrospective, observational and is influenced by referral bias. All subjects underwent cardiac catheterization, so this sample is generally limited to patients with more advanced HF and may not be applicable to the entire HF population. The use of PAWP for inclusion into HF group assured that the patients studied truly had HF, but because patients with less advanced HF may have normal PAWP at rest, these results may not apply to HF patients with earlier stage disease. The primary cause of ventricular dysfunction in HF patients could not be assessed in this retrospective study. The control group was drawn from consecutive patients referred for invasive assessment, so by virtue of being referred for cardiac catheterization, this is not representative of completely healthy comparator group. However, this invasive study would not be feasible in healthy volunteers. Hemodynamic and echocardiographic data were not acquired simultaneously, but both occurred within a 48 hour time frame. The relations between HF phenotype and atrial characteristics were studied cross-sectionally so all inferences about causality are hypothesis-generating. Despite age-adjusted comparisons, differences in age between groups may confound the conclusions. Data on quality of life were not systematically recorded and all measures were performed at rest and in the supine position, so we were unable to address the relation of our findings to exertional symptoms or quality of life.

LA pressures were not measured directly, but assessed by PAWP, which is dampened compared to directly measures LA pressures, leading to systematic underestimation of diastolic LA stiffness and pulsatility, though this underestimation was uniform between HF groups and controls. The number of enrolled subjects and deaths was moderate, which both prevented multivariable analysis. Thus, further work is needed to confirm the univariate relationships we observed between LA size / function and outcomes, which could be potentially cofounded by
other intermediary factors. However, follow-up was complete in 100% of patients, enhancing confidence in our results.

In conclusion, the current data provide insight into pathophysiology of LA dysfunction and pulmonary hypertension in HF. The LA remodeling in HFpEF and HFrEF differs, with more dilation and systolic dysfunction in HFrEF and with increased stiffness, pulsatility and predilection for AF in HFpEF. Restoration of LA mechanical function may have favorable effects on pulmonary vasculature and right heart, while processes and interventions that reduce atrial contractility or adversely affect LA compliance may promote and exacerbate pulmonary hypertension, leading to right heart dysfunction and increased risk of adverse outcomes, especially in patients with HFpEF.

**Sources of Funding**

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**Disclosures**

None.
References


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Table 1. Clinical and laboratory characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls n = 40</th>
<th>HFP EF n = 101</th>
<th>HFr EF n = 97</th>
<th>p</th>
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<tbody>
<tr>
<td>Age, years</td>
<td>63 ± 7</td>
<td>71 ± 10 *</td>
<td>61 ± 13 †</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Female gender</td>
<td>53 %</td>
<td>58%</td>
<td>20% * †</td>
<td>&lt; 0.0001</td>
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<tr>
<td>BMI, kg.m⁻²</td>
<td>29 ± 5.8</td>
<td>34 ± 8.6 *</td>
<td>31 ± 6.9 †</td>
<td>0.006</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>2.0 ± 0.3</td>
<td>2.0 ± 0.3</td>
<td>2.1 ± 0.3 *</td>
<td>0.02</td>
</tr>
<tr>
<td>NYHA grade</td>
<td>1.0 ± 0.2</td>
<td>3.0 ± 0.6 *</td>
<td>3.2 ± 0.7 * †</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HF hospitalization, ever</td>
<td>0</td>
<td>43 %</td>
<td>91 %</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HF diagnosis duration, years</td>
<td>0</td>
<td>1.0 (1.5–2.0)</td>
<td>3.0 (1.0–7.5)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0 %</td>
<td>44 % *</td>
<td>46 % * †</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>57 %</td>
<td>93 % *</td>
<td>56 % †</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pacemaker or ICD</td>
<td>0 %</td>
<td>12 % *</td>
<td>66 % * †</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>0 %</td>
<td>42 % *</td>
<td>26 % * †</td>
<td>&lt; 0.0001</td>
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<tr>
<td>Diabetes mellitus</td>
<td>0 %</td>
<td>47 % *</td>
<td>41 % *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diuretics</td>
<td>23 %</td>
<td>83 % *</td>
<td>87 % *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Loop diuretics daily dose, mg</td>
<td>0</td>
<td>45 ± 46 *</td>
<td>75 ± 97 * †</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>BB/ACEi or ARB / AldoRA, %</td>
<td>13 / 42 / 5</td>
<td>67* / 59 / 16</td>
<td>95* † / 82* † / 38* †</td>
<td>all &lt; 0.0001</td>
</tr>
<tr>
<td>NT-pro-BNP, pg.ml⁻¹</td>
<td>19 (14–65)</td>
<td>1142 (408–2914) *</td>
<td>2481 (1174–4757)* †</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>GFR, ml.min.1.73 m⁻²</td>
<td>71 ± 32</td>
<td>47 ± 21 *</td>
<td>46 ± 21 *</td>
<td>0.01</td>
</tr>
</tbody>
</table>
Values a means±SD or medians (IQR). ANOVA and Tukey post-hoc test or Chi-square test. * p<0.05 vs controls, † p<0.05 vs HFpEF. NTproBNP tested after log-transformation. § GFR: glomerular filtration rate, estimated with MDRD formula. BMI: body mass index, BSA: body surface area, BB: beta-blockers, ACEi: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, AldoRA: aldosterone receptor antagonists.
### Table 2. Left atrial and left ventricular function

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>HFpEF</th>
<th>HFrEF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 40</td>
<td>n = 101</td>
<td>n = 97</td>
<td></td>
</tr>
<tr>
<td><strong>Left atrial function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LA pressure mean, mmHg</td>
<td>8.1 ± 2.8</td>
<td>20 ± 6.1 *</td>
<td>20 ± 8.1 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>minimum, mmHg</td>
<td>5.5 ± 3.7</td>
<td>16 ± 6.1*</td>
<td>18 ± 7.3*†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>A§ and V wave, mmHg</td>
<td>12±4 / 12±5</td>
<td>23±8 * / 34±13 *</td>
<td>24±9 */ 30±12 *</td>
<td>&lt; 0.0001 / &lt; 0.0001</td>
</tr>
<tr>
<td>min-max difference, mmHg</td>
<td>7.9 ± 2.8</td>
<td>19 ± 10 *</td>
<td>13 ± 7.8 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LA volume max, ml</td>
<td>45 ± 12</td>
<td>85 ± 28 *</td>
<td>104 ± 38 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>pre-A§, ml</td>
<td>30 ± 10</td>
<td>35 ± 17*</td>
<td>47 ± 29 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>min, ml</td>
<td>16 ± 6.3</td>
<td>54 ±27 *</td>
<td>71 ± 35 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LA volume max/BSA, ml.m⁻²</td>
<td>23 ± 5</td>
<td>41 ± 12 *</td>
<td>30 ±17 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LA EF - total, %</td>
<td>65 ± 8.9</td>
<td>39 ± 17 *</td>
<td>35 ± 15 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>- active§, %</td>
<td>48 ± 11</td>
<td>30 ± 14 *</td>
<td>22 ± 13 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>- passive§, %</td>
<td>33 ± 11</td>
<td>26 ± 9.3*</td>
<td>21 ± 10 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LA stiffness, mmHg.ml⁻¹</td>
<td>0.30 ± 0.20</td>
<td>0.79 ± 0.75 *</td>
<td>0.48 ± 0.44 †</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LA function index (LAFI)</td>
<td>220 ± 118</td>
<td>60 ± 65 *</td>
<td>30 ± 37 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LA wall stress max, kdynes.cm⁻²</td>
<td>80 ± 31</td>
<td>294 ± 120 *</td>
<td>281 ± 123 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>min, kdynes.cm⁻²</td>
<td>38 ± 25</td>
<td>137 ± 59 *</td>
<td>167 ± 74 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>change, kdynes.cm⁻²</td>
<td>41 ± 18</td>
<td>158 ± 92 *</td>
<td>113 ± 74 *†</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>
**Left ventricular function**

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>HFpEF</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, min⁻¹</td>
<td>68 ± 13</td>
<td>69 ± 13</td>
<td>72 ± 14</td>
<td>0.14</td>
</tr>
<tr>
<td>Cardiac index, l.min⁻¹.m⁻²</td>
<td>3.0 ± 0.5</td>
<td>3.0 ± 0.5</td>
<td>2.4 ± 0.6 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Systemic pressure mean, mmHg</td>
<td>123 ± 13</td>
<td>128 ± 19</td>
<td>107 ± 18 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>49 ± 13</td>
<td>60 ± 18 *</td>
<td>42 ± 13 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LV end-diastolic diameter, mm</td>
<td>48 ± 41</td>
<td>49 ± 5.8</td>
<td>67 ± 11 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>62 ± 4.3</td>
<td>62 ± 5.9</td>
<td>24 ± 9.7 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>LV mass index, g.m⁻²</td>
<td>85 ± 18</td>
<td>102 ± 31 *</td>
<td>149 ± 46 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mitral regurgitation grade, (0-3)</td>
<td>0.8 ± 0.8</td>
<td>1.8 ± 0.8 *</td>
<td>2.5 ± 0.9 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Transmitral E vel., cm.s⁻¹</td>
<td>68 ± 18</td>
<td>106 ± 31</td>
<td>89 ± 27 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>67 ± 21</td>
<td>74 ± 53</td>
<td>52 ± 27 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>E deceleration time, ms</td>
<td>210 ± 27</td>
<td>189 ± 54</td>
<td>155 ± 46 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Mitral annulus E⁺ vel., cm.s⁻¹</td>
<td>8.0 ± 1.2</td>
<td>7.7 ± 2.2</td>
<td>6.2 ± 2.1 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td>11 ± 2.3</td>
<td>8.5 ± 3.5</td>
<td>5.7 ± 2.9 *†</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Diastolic dysfunction grade, %</td>
<td>8/50/25/17/0</td>
<td>34/9/15/23/19</td>
<td>27/0/5/16/52</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Values a means±SD. ANOVA and Tukey post-hoc test or Chi-square test. * p<0.05 vs controls, † p<0.05 vs HFpEF. LA: left atrial, EF: ejection fraction, BSA: body surface area, LV: left ventricular, § parameters available only in HF patients with sinus rhythm (n=130).
Table 3. Right heart and pulmonary vascular function

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>HFpEF</th>
<th>HFrEF</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 40</td>
<td>n = 101</td>
<td>n = 97</td>
<td>ANOVA</td>
</tr>
<tr>
<td>RA mean pressure, mmHg</td>
<td>5.3 ± 3.0</td>
<td>13 ± 5.6 *</td>
<td>12 ± 6.6 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>PA pressure systolic, mmHg</td>
<td>28 ± 6.2</td>
<td>56 ± 19 *</td>
<td>51 ± 15 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>diastolic, mmHg</td>
<td>9.0 ± 3.8</td>
<td>21 ± 7.3 *</td>
<td>22 ± 8.1 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>mean, mmHg</td>
<td>17 ± 4.4</td>
<td>35 ± 11 *</td>
<td>35 ± 10 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>pulse, mmHg</td>
<td>19 ± 4.0</td>
<td>35 ± 14 *</td>
<td>28 ± 10 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Transpulmonary gradient, mmHg</td>
<td>8.7 ± 3.4</td>
<td>15 ± 8.0 *</td>
<td>14 ± 6.6 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pulm. arterial compliance (PAC), ml.mmHg⁻¹</td>
<td>4.5 ± 1.5</td>
<td>5.1 ± 1.4 *</td>
<td>5.0 ± 1.4 *</td>
<td>0.0004</td>
</tr>
<tr>
<td>Pulm. vascular resistance (PVR), w.u.</td>
<td>1.5 ± 0.6</td>
<td>2.6 ± 1.7 *</td>
<td>3.0 ± 1.7 *</td>
<td>0.005</td>
</tr>
<tr>
<td>RV end-diastolic area, cm²</td>
<td>15 ± 3.7</td>
<td>21 ± 6 *</td>
<td>22 ± 7 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>RV fractional area change (RV FAC) %</td>
<td>50 ± 7.3</td>
<td>40 ± 10 *</td>
<td>36 ± 13 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>RA max volume, ml</td>
<td>37 ± 12</td>
<td>72 ± 37 *</td>
<td>83 ± 44 *</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Tricuspid regurgitation grade, (0-3)</td>
<td>0.7 ± 0.8</td>
<td>2.2 ± 1.1 *</td>
<td>2.3 ± 1.0 *</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

Values a means±SD. ANOVA and Tukey post-hoc test. * p<0.05 vs controls, † p<0.05 vs HFpEF. RA: right atrial, RV: right ventricular, w.u.: Wood’s units.
Figure Legends

**Figure 1. Characteristics of left atrial (LA) function.** A) Representative ECG, LA pressure and LA volume waveforms. B) Schematic example of LA pressure-volume loop with smaller a-loop and larger v-loop. LA stiffness is represented by slope of dashed line (α) that connects maximal and minimal pressure-volume points. C) Equations used for LA functional characterization.

**Figure 2. Left atrial (LA) remodeling and dysfunction in controls vs HFpEF and HFrEF.** A) increased maximal, diastasis and minimal LA volumes and B) reduced total, active and passive LA ejection fraction in patients with HFpEF and HFrEF compared to controls. C) Slope of P-V relationships in controls and in patients with HFpEF or HFrEF. *p<0.05 vs controls, #p<0.05 vs HFrEF. Thus, HFrEF patients display greater LA chamber dilation and lower contractility, while HFpEF patients display stiffer LA chambers.

**Figure 3. LA performance in HF and controls and the influence of mitral regurgitation on the left atrium.** A) Relations between LA volume prior the onset of LA contraction (LA pre-A volume) and LA active stroke volume in controls and HF patients with sinus rhythm (n=130). B) The impact of mitral regurgitation grade on peak LA pressure (LA v-wave, left) and min-max LA wall stress change (right) in controls, HFrEF and HFpEF. Lines represent results of linear regression with 95% confidence intervals and correlation coefficients. Thus, LA performance is reduced due to impairment of the Frank-Starling mechanism in both HF groups, while the presence of mitral regurgitation is associated with higher wall stress variations and greater v-wave height in HFpEF.
Figure 4. The impact of HF severity on the left atrium. The impact of HF severity (NYHA functional class) on LA characteristics assessed by ANOVA and Tukey post-hoc test, *p<0.05 vs controls, §p< 0.05 vs NYHA II, #p<0.05 vs NYHA III. LAVI max: body surface area-indexed maximal LA volume. Thus, LA dysfunction is related to HF severity.

Figure 5. The left atrium and pulmonary vascular properties/right heart function. A) Relation of global LA function (total LA EF, %) to pulmonary vascular resistance (PVR) and pulmonary artery compliance (PAC) and right ventricular systolic function (RV fractional area change, RV FAC %) in HFrEF (red), HFpEF (blue) controls (black). Lines represent results of linear regression with 95% confidence intervals, r: Pearson’s correlation coefficient. Thus, LA dysfunction is associated with greater pulmonary vascular disease and RV dysfunction in HF.

Figure 6. The impact of LA characteristics and atrial fibrillation on survival in HFpEF and HFrEF. Univariate Cox model was used to determine the hazard ratio for death associated with being in a group above median of a parameter (or yes/no for AF). Continuous parameters were z-standardized within HF subgroups.*p<0.05. Thus, LA dysfunction is associated with mortality in HFpEF but not HFrEF.
**Figure 1**

A. 
- ECG
- LA pressure
- a wave
- v wave
- LA volume
- $V_{\text{diastasis}}$
- $V_{\text{min}}$
- $V_{\text{max}}$

B. 
- LA pressure
- $P_{\text{max}}$
- $P_{\text{min}}$
- v loop
- a loop

C. 
- **Total LA EF** = \[
\frac{V_{\text{max}} - V_{\text{min}}}{V_{\text{max}}}
\]
- **Active LA EF** = \[
\frac{V_{\text{diastasis}} - V_{\text{min}}}{V_{\text{diastasis}}}
\]
- **Passive LA EF** = \[
\frac{V_{\text{max}} - V_{\text{diastasis}}}{V_{\text{max}}}
\]
- **LA stiffness** = $\alpha$
Figure 3

(A) LA performance

- Controls
  - $r = 0.8$
  - $p < 0.001$
- HFrEF
  - $r = 0.3$
  - $p = 0.02$
- HFrER
  - $r = 0.6$
  - $p = 0.5$

(B) LA pressure V-wave

- Controls
  - $r = 0.06$
  - $p = 0.7$
- HFrEF
  - $r = 0.3$
  - $p = 0.005$
- HFrER
  - $r = 0.3$
  - $p = 0.0007$

LA wall stress change in a cardiac cycle

- Controls
  - $r = 0.1$
  - $p = 0.3$
- HFrEF
  - $r = 0.3$
  - $p = 0.2$
Figure 4

- **LAVI max**
  - ANOVA $p < 0.0001$
  - Controls, NYHA II, NYHA III, NYHA IV
  - Values for Controls, NYHA II, NYHA III, NYHA IV marked with asterisks

- **LA total EF**
  - ANOVA $p < 0.0001$
  - Controls, NYHA II, NYHA III, NYHA IV
  - Values for Controls, NYHA II, NYHA III, NYHA IV marked with asterisks

- **LA stiffness**
  - ANOVA $p=0.0002$
  - Controls, NYHA II, NYHA III, NYHA IV
  - Values for Controls, NYHA II, NYHA III, NYHA IV marked with asterisks
Figure 6

**Total mortality, hazard ratio**

- **AFib present**
  - HFrEF: *p < 0.05*
  - HFpEF:  

- **Higher LAVI max**
  - HFrEF:  
  - HFpEF: *p < 0.05*

- **Higher LA stiffness**
  - HFrEF:  
  - HFpEF: *p < 0.05*

- **Higher active LA EF**
  - HFrEF:  
  - HFpEF: *p < 0.05*

- **Higher total LA EF**
  - HFrEF:  
  - HFpEF: *p < 0.05*

**Total mortality, hazard ratio**

*yes/no or above/below z-standardized median, *p < 0.05*
Left Atrial Remodeling and Function in Advanced Heart Failure With Preserved or Reduced Ejection Fraction
Vojtech Melenovsky, Seok-Jae Hwang, Margaret M. Redfield, Rosita Zakeri, Grace Lin and Barry A. Borlaug

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Supplemental Material

Supplemental Figure. The impact of HF type or atrial rhythm (SR: sinus rhythm, AF: atrial fibrillation) on LA characteristics assessed by 2-way ANOVA in HF subjects. Thus, LA dysfunction is not simply ascribable to AF, but there is atrial dysfunction even in SR.
구혈률저하 심부전의 좌심방은 크기가 증가하고 기능이 저하되나, 구혈률보존 심부전에서는 좌심방 경직도가 증가하여 심방세동이 증가한다

최 진 오 교수 · 삼성서울병원 순환기내과

초록

배경
 대부분의 심부전 환자에서 좌심방의 구조와 기능은 변화한다. 구혈률보존 심부전(heart failure with preserved ejection fraction)과 구혈률저하 심부전(heart failure with reduced ejection fraction) 간에 좌심방의 변화 양상에는 근본적인 차이가 있을 수 있다.

방법 및 결과
 총 198명의 심부전 환자(구혈률보존 심부전 환자 51%, 뉴욕심장학회 기능 분류 3.1±0.7)와 40명의 심부전이 없는(heart failure-free) 대조군 환자에게 심도자 및 심초음파 검사를 시행하고, 그 경과를 추적하였다. 대조군에 비하여 심부전 환자들은 좌심방이 크고, 기능이 저하되어 있었다. 심부전 환자군 간의 비교를 보면, 평균 좌심방적이 (20 vs. 20mmHg; P=0.9)은 차이가 없었으나, 구혈률저하 심부전군의 좌심방은 크기가 더 증가되어 있었다(좌심방 용적수 50 vs. 41mL/m²; P<0.001). 반면, 구혈률보존 심부전군은 좌심방 최대 압력이 더 높고 최소 압력은 더 낮아, 더 높은 좌심방 경직도를 보였고(0.79 vs. 0.48mmHg/mL; P<0.001), 좌심방 박동성(19 vs. 13mmHg; P<0.001)과 벽장력의 변동성(wall stress variations)이 더 증가되어 있었다. 구혈률보존 심부전군은 좌심방 용적이 더 작고, 기능은 더 좋았으며, 승모판 역류도 덜 심하였지만, 심방세동은 더 많았다고(42 vs. 26%; P=0.02). 양 군 모두 좌심방의 기능부전은 폐혈관 저항의 증가 및 우심실기능 저하와 연관되어 있었다. 추적 관찰 기간(중앙값 350일) 중에 구혈률보존 심부전 환자 31명과 구혈률저하 심부전 환자 28명이 사망하였다. 좌심방기능(총 좌심방 구혈률)은 구혈률보존 심부전에서는 낮은 사망률과 연관되어 있었으나(HR 0.43; 95% CI, 0.2~0.9; P<0.05), 구혈률저하 심부전에서는 연관이 없었다.

결론
 구혈률저하 심부전에서의 좌심방 리모델링은 편심성 (eccentric) 확장이 주된 양상인 반면, 구혈률보존 심부전에서는 좌심방 경직도가 증가하는 것이 특징으로, 이는 심방세동의 발생에 영향을 줄 수 있다. 좌심방기능은 양 군 모두에서 폐혈관저항 및 우심부전과 관련되었으나, 구혈률보존 심부전이 보다 더 밀접하게 연관되어 있었으며, 이는 구혈률보존 심부전 환자들에서 좌심방기능을 호전시키기 위한 노력에 대한 의학적 근거가 될 것이다.