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

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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 (HFrEF) and reduced ejection fraction (HFrEF).

Methods and Results—One hundred ninety-eight HF patients (51% HFrEF, New York Heart Association 3.1±0.7) and 40 HFrEF controls underwent catheterization, echocardiography, and follow-up. Compared with controls, HF patients had larger and more dysfunctional left atria. At identical mean LA pressure (20 versus 20 mm Hg; P=0.9), HFrEF patients had larger LA volumes (LA volume index 50 versus 41 mL/m²; P<0.001), whereas HFrEF patients had higher LA peak pressures, lower LA minimal pressures, higher LA stiffness (0.79 versus 0.48 mm Hg/mL; P<0.001), greater LA pulsatility (19 versus 13 mm Hg; P<0.001), and higher wall stress variations. Despite smaller LA volumes, better function, and less mitral regurgitation, HFrEF patients had more atrial fibrillation (42 versus 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 HFrEF and 28 HFrEF patients died. LA function (total LA EF) was associated with lower mortality in HFrEF (hazard ratio 0.43; 95% confidence interval, 0.2–0.9; P<0.05), but not in HFrEF.

Conclusions—HFrEF is characterized by greater eccentric LA remodeling, whereas HFrEF by increased LA stiffness, which might contribute to greater atrial fibrillation burden. LA function is associated with pulmonary vascular disease and right HF in both HF phenotypes, but is associated with outcome more closely in HFrEF, supporting efforts to improve LA function in this cohort. (Circ Heart Fail. 2015;8:295-303. DOI: 10.1161/CIRCHEARTFAILURE.114.001667.)

Key Words: atrial fibrillation ■ heart failure ■ left atrial function ■ pulmonary hypertension ■ right ventricle

The left atrium modulates left ventricular (LV) filling by acting as an elastic reservoir, passive conduit, and active booster.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 symptoms2–5 and to disease progression.3,6,7 HF-related LA remodeling is poorly understood, and it is not known whether there are fundamental differences between HF patients with preserved (HFrEF) or reduced LV ejection fraction (HFrEF), though prior studies suggest greater adverse effects from loss of LA function in HFrEF compared with HFrEF.8

Clinical Perspective on p 303

The LA also serves as a watershed between the LV and the pulmonary circulation, buffering pressure and flow oscillations because of 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.9,10 Increased pulmonary vascular resistance and stiffness may elevate right ventricular (RV) afterload,11 driving further the progression to RV failure.12–15 We hypothesized that LA function is abnormal in patients with HF, that LA remodeling differs between patients with HFrEF and similarly advanced HFrEF, and that LA dysfunction is associated with abnormal pulmonary vascular properties and RV dysfunction. To test this hypothesis, we examined HFrEF and HFrEF patients undergoing invasive and noninvasive hemodynamic assessment and compared them with HF-free controls to address the differences in LA structure, function, and to assess the effect of LA dysfunction on the 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 (PA) wedge pressure (PAWP ≥ 15 mm Hg at rest or ≥ 25 mm Hg at exercise). HFpEF and HFrEF were defined by LV EF ≥ 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 (±1 week) were abstracted from the medical records. Significant coronary artery disease was defined as one or more ≥70% epicardial artery stenosis or previous revascularization (angiography available in 28% controls, 82% of HFpEF, and 100% of HFrEF). 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

Table 1. Clinical and Laboratory Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Controls, n=40</th>
<th>HFpEF, n=101</th>
<th>HFrEF, n=97</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63±7</td>
<td>71±10*</td>
<td>61±13†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex</td>
<td>53%</td>
<td>58%</td>
<td>20%*†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</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, y</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>
</tr>
<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<em>82‡38</em>†</td>
<td>all &lt;0.0001</td>
</tr>
<tr>
<td>NT-pro-BNP, pg/mL</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 m²</td>
<td>71±32</td>
<td>47±21*</td>
<td>46±21*</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Values are means±SD or medians (IQR). Analysis of variance and Tukey post hoc test or chi-square test. ACEi indicates angiotensin-converting enzyme inhibitors; AldoRA, aldosterone receptor antagonists; ARB, angiotensin receptor blockers; Bβ, β-blockers; BMI, body mass index; BSA, body surface area; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; and NYHA, New York Heart Association.

*P<0.05 vs controls.
†P<0.05 vs HFpEF.
‡GFR, glomerular filtration rate, estimated with MDRD formula.
described. Right atrial (RA), RV, PA pressures, and 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 was calculated as PA mean–PAWP pressure, pulmonary vascular resistance (PVR) was calculated as transpulmonary gradient/cardiac output, and PA compliance was calculated as stroke volume/PA pulse pressure.

Two-dimensional and Doppler echocardiography was performed according to American Society of Echocardiography guidelines by

Table 2. Left Atrial and Left Ventricular Function

<table>
<thead>
<tr>
<th>Left atrial function</th>
<th>Controls, n=40</th>
<th>HFP EF, n=101</th>
<th>HFr EF, n=97</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LA pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, mm Hg</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, mm Hg</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, mm Hg</td>
<td>23±8*/34±13*</td>
<td>24±9*/30±12*</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Min–max difference, mm Hg</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</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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>55±17*</td>
<td>77±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/m²</td>
<td>23±5</td>
<td>41±12*</td>
<td>50±17†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LA EF</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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, mm Hg/mL</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</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max, kdynes/cm²</td>
<td>80±31</td>
<td>294±120*</td>
<td>281±123*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Min, kdynes/cm²</td>
<td>38±25</td>
<td>137±59*</td>
<td>167±74†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Change, kdynes/cm²</td>
<td>41±18</td>
<td>158±92*</td>
<td>113±74†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<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/m²</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</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, mm Hg</td>
<td>123±13</td>
<td>128±19</td>
<td>107±18†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulse, mm Hg</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/m²</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>Transmirtal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E vel., cm/s</td>
<td>68±18</td>
<td>106±31*</td>
<td>89±27†</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>A vel.,‡ cm/s</td>
<td>67±21</td>
<td>74±31</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 anulus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E' vel., cm/s</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>A' vel.,‡ cm/s</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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indeterminate/0/1/2/3</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 are means±SD. ANOVA and Tukey post hoc test or chi-square test. BSA indicates body surface area; EF, ejection fraction; HF, heart failure; HFP EF, heart failure with preserved ejection fraction; HFr EF, heart failure with reduced ejection fraction; LA, left atrial; and LV, left ventricular.

*P<0.05 vs controls.
†P<0.05 vs HFP EF.
‡Parameters available only in HF patients with sinus rhythm (n=130).
was assessed as previously 26 by tracing the RV endocardium in the right heart. The effect of mitral regurgitation grade on peak LA pressure (LA v-wave, V C) and min–max LA wall stress (W C) and LA conduit function was characterized by passive LA EF,7 LA conduit function was characterized by passive LA EF, and contractile function was characterized by active LA EF (Figure 1).21 Atrial function was also assessed by LA function index, which normalizes function to stroke volume and is rhythm-independent.7 Operant LA diastolic stiffness was approximated as the slope of linear regression of minimal and maximal LA pressure–volume coordinates (Figure 1).21,22 Meridional LA wall stress was calculated from maximal to minimal LA volume and pressure using established formulas,24 assuming atrial wall thickness of 0.2 cm.23 RV function was assessed as previously26 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 before tricuspid valve opening to obtain maximal RA volume using the area–length method.27

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, 2×2 ANOVA, or χ2 tests as appropriate. Univariate and multivariate Cox proportional hazard model were used to examine the effect 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 (HFrEF, n=101; HFpEF, n=97) are summarized in Table 1. Both HF groups were highly symptomatic (74% New York Heart Association [NYHA] III–IV) with ≥80% of chronic diuretic use. Similar to prior studies,23 HFpEF patients were slightly older, more likely to be women, more obese, and more often in atrial fibrillation (AF). Prevalence of coronary artery disease, diabetes mellitus, and renal dysfunction was similar. HFrEF patients had higher systemic blood pressure, cardiac output, LV EF, and transmitial flow velocities, but smaller LV size, LV mass, and mitral regurgitation grade compared with HFrEF (Table 2).

LA Structure and Function in HFpEF Versus HFrEF

Compared with controls, patients with HFrEF and HFpEF displayed LA dilatation, coupled with reduced LA active contractile, reservoir, and conduit functions (Table 2 and Figure 2). Patients with HFpEF displayed greater LA stiffness, whereas...
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 HFpEF. In contrast, patients with HFpEF 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 HFpEF and HFrEF persisted after adjustments to sex, 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 HFpEF compared with HFrEF (Table 2). LA function curves (preload-stroke volume plots) were shallower in both HFpEF and HFrEF compared with controls, indicating LA contractile dysfunction regardless of LA geometry (Figure 3). LA functional index and A′ mitral annular velocities were also more reduced in HFrEF than in HFpEF 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 HFpEF group (Figure in the Data Supplement). Both atrial rhythm and HF phenotype affected LA structure and function as shown by factorial analysis. LA volume and stiffness increased, whereas 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 with HFrEF (Figure 3).

### Left Atrium and Pulmonary Artery-Right Heart Function

Pulmonary hypertension was common in HF patients (82% HFpEF, 79% HFrEF) because of combination of elevated PAWP and increased transpulmonary gradient (Table 3). Mean PA pressure, transpulmonary gradient, PVR, and pulmonary arterial compliance (PAC) were similarly increased by guest on January 27, 2018 http://circheartfailure.ahajournals.org/Downloaded from
in both HF groups (Table 3), whereas PA pulse pressure was higher in HFrEF. 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 HFrEF and HFrEF (Figure 5). Similarly, LA stiffness correlated with PAC in HFrEF and HFrEF ($r=-0.35$ and $r=-0.41$; both $P<0.001$), but only weakly with PVR in HFrEF ($r=0.23; P=0.03$) 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 HFrEF 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 HFrEF and HFrEF with similar slope (Figure 5).

**Effect of LA Dysfunction on Prognosis**

Over a median follow-up duration of 350 days (IQR, 82–870), there were 59 deaths (HFrEF=28 and 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 HFrEF, but not in HFrEF (Figure 6). In multivariate Cox model that included age and sex, known predictors of mortality in HFrEF, either total LA EF or active LA EF remained a significant predictor of death in HFrEF ($P=0.03$ and $P=0.05$), whereas 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, contrasting LA parameters in the 2 HF phenotypes. Compared with controls, both HF types displayed abnormal LA size and function. The HFrEF group was characterized by greater eccentric LA remodeling, whereas the HFrEF 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 HFrEF. In both groups, LA function was associated with pulmonary vascular disease and right HF. Although global LA function was less impaired in HFrEF than HFrEF, LA dysfunction was more strongly associated with mortality in this cohort, suggesting greater vulnerability to loss of LA function in HFrEF. These data highlight the importance of atrial dysfunction in HF and suggest that strategies to optimize LA function or to prevent its deterioration may mitigate progression of pulmonary vascular and right heart dysfunction to improve outcomes in HF patients and particularly in HFrEF.

Few studies have compared LA structure/function in HFrEF and HFrEF; and none have reported associations between LA function and outcome. In an echocardiographic study, Triposkiadis et al compared LA remodeling in HFrEF and HFrEF and found more eccentric LA remodeling in HFrEF group, similarly to the current data. In a smaller sample, Kurt et al reported that HFrEF patients had LA enlargement, reduced LA function, and increased LA stiffness compared with controls, but in contrast to the current study, LA stiffness was not as high in HFrEF as in HFrEF. However, the Kurt study measured only mean PAWP rather than peak and minimal LA pressures, and the authors estimated LA stiffness simply as the ratio of mean PAWP to LA systolic strain, in contrast to the more robust methods used in the current study incorporating maximal and minimal LA pressure–volume coordinates. The current observation of smaller and stiffer left atrium in HFrEF as compared with HFrEF is congruent with known structure–function differences noted at the left ventricular level, supporting the notions that HFrEF and HFrEF represent 2 distinct pathophysiological entities and that the systemic processes favoring stiffening in all cardiac...
chambers, such as microvascular inflammation or impaired nitric oxide availability, may contribute to the pathophysiology of HFPpEF.33

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 electric activity.19,34 Experimental and limited human studies22,23 have illustrated that with increased preload, LA contractility initially rises22,35,36 but later declines, coinciding with adverse changes in remodeling, apoptosis, myosin isoform expression, collagen matrix turnover, and reduced intrinsic contractility.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 HFPpEF, 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 HFPpEF, indicating presence of intrinsic LA dysfunction. In HFPpEF, 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 electric activity in HF patients with AF is associated with more pronounced LA dilatation, systolic dysfunction, and passive stiffening (Figure in the Data Supplement). However, HF patients in sinus rhythm also demonstrated LA systolic impairment (active LA EF reduced by 37% in HFPpEF and 54% in HFrEF), confirming that atrial mechanical dysfunction in HF is not restricted to patients with AF.30–42 At similar mean LA pressures, HFPpEF patients demonstrated larger LA pressure pulsatility41 and greater LA wall stress variation. We speculate that this may contribute to the higher prevalence of AF noted in HFPpEF compared with HFrEF, despite smaller LA volumes, similar LA pressures, and similar HF severity and mortality risk.44

The differences in LA structure–function also seem to influence how the LA copes with mitral regurgitation. With increasing regurgitation, LA pressure and wall stress increases much more steeply in HFPpEF than in HFrEF, which may promote stretch-mediated atrial ectopy that plays a role in initiation of AF.44 Although LA function was less impaired in HFPpEF than in HFrEF, its association with outcome was more pronounced, congruent with previous reports regarding the differential effect of AF on outcomes in HFPpEF or HFrEF.4 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 noninvasive studies were not able to discriminate between the effect of intrinsic LA properties from passive LA pressure elevation because of volume overload.39,30,45 We observed that impaired LA global systolic function (quantified by total LA EF)3 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 HFPpEF and HFrEF. The current data strongly implicate that LA dysfunction belongs among the mediators of pulmonary vascular disease in HF.11 By having effect in PA hemodynamics, LA dysfunction can also indirectly influence RV function and contribute to progression toward biventricular failure with poor prognosis.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 PH,47 and removal of LA appendage, the most contractile and compliant part of the left atrium, increases atrial stiffness and reduces atrial performance.37 As LA interventions, such as device closure and ablation, become more widely used 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 with directly measured 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 PH 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, whereas processes and interventions that reduce atrial contractility or adversely affect LA compliance may promote and exacerbate PH, leading to right heart dysfunction and increased risk of adverse outcomes, especially in patients with HFrEF.

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Disclosures
None.

References


**CLINICAL PERSPECTIVE**

The left atrium plays an important role in the pathophysiology of heart failure, but it is unknown whether there are fundamental differences in atrial properties between the patients with preserved (HFpEF) or reduced (HFrEF) left ventricular ejection fraction. It is also unknown whether left atrial (LA) dysfunction might affect the pulmonary circulation or long-term survival. To address these questions, we examined atrial, ventricular, and pulmonary vascular function using echocardiography and invasive hemodynamic measurements in control subjects and in patients with both types of HF. We demonstrate that LA remodeling in HFpEF and HFrEF differs, with more dilation and systolic dysfunction in HFrEF and with increased stiffness, pulsatility, and predilection for atrial fibrillation in HFpEF. In both heart failure groups, LA dysfunction was associated with pulmonary vascular disease and right heart failure. Although global LA function was less impaired in HFpEF than HFrEF, LA dysfunction was more predictive of mortality in this cohort, suggesting greater vulnerability to loss of LA function in HFpEF. These data highlight the importance of atrial dysfunction in heart failure and suggest that strategies to optimize LA function or to prevent its deterioration may mitigate progression of pulmonary vascular and right heart dysfunction, while improving outcomes in heart failure patients and particularly in HFpEF.
Left Atrial Remodeling and Function in Advanced Heart Failure With Preserved or Reduced Ejection Fraction
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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.

**LAVI max**

HF type: $p < 0.001$
Rhythm: $p < 0.001$

**LA total EF**

HF type: $p < 0.001$
Rhythm: $p = 0.008$

**LA stiffness**

HF type: $p = 0.003$
Rhythm: $p = 0.06$
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 좌심방압 (20 vs. 20mmHg; P=0.9)은 차이가 없었으나, 구혈률저하 심부전군의 좌심방 크기가 더 증가되어 있었다(좌심방 용적자수 50 vs. 41mL/m²; P<0.001). 반면, 구혈률보존 심부전군은 좌심방의 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 많았다(42 vs. 26%; P=0.02). 양군 모두 좌심방의 기능부전은 폐혈관 저항의 증가 및 유심실기능 저하와 연관되어 있었다. 추적 관찰 기간(중앙값 350일) 중에 구혈률보존 심부전 환자 31명과 구혈률저하 심부전 환자 28명이 사망하였다. 좌심방기능(cast 좌심방 구혈률)은 구혈률보존 심부전에서 는 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 양근 모두에서 폐혈관저항 및 심부전과 관련되었으나, 구혈률보존 심부전이 보다 더 밀접하게 연관되어 있었으며, 이는 구혈률보존 심부전 환자들에서 좌심방기능의 호전시키기 위한 노력에 대한 의학적 근거가 될 것이다.