Left Atrial Function in Diastolic Heart Failure

Mustafa Kurt, MD; Jianwen Wang, PhD, MD; Guillermo Torre-Amione, PhD, MD; Sherif F. Nagueh, MD

Background—Abnormalities in left ventricular (LV) structure and function occur in patients with diastolic heart failure (DHF). The reasons for the transition from asymptomatic dysfunction to heart failure need better definition, including noninvasive measurements that can detect the transition.

Methods and Results—In 64 patients undergoing right heart catheterization, simultaneous echocardiographic imaging was performed. As a control group, 27 healthy subjects were included. There were 25 with ejection factor (EF) <50%, 20 in DHF, and 19 with normal EF and LV hypertrophy but not in heart failure (diastolic dysfunction). LV volumes, mass, left atrial (LA) volumes and EF, annular atrial velocity (a’), and LA strain during systole (LA_s) and atrial contraction (LA_A) were measured. The ratio of wedge pressure to LA_s strain was used as an index of LA stiffness, as was the ratio of E/e’ to LA_A strain. All 3 patient groups had increased LA volumes and depressed LA EF, a’, and LA_A strain, with no significant difference between patients with DHF and diastolic dysfunction in LA systolic function indices, LV mass, LA volumes, LV, and arterial elastance. LA_A strain was lower in patients with DHF, and LA stiffness (invasive and noninvasive) was higher (both P<0.01), related well to pulmonary artery systolic pressure (r=0.79, P<0.001), and was most accurate in identifying DHF patients from those with diastolic dysfunction (invasive area under the curve: 0.93, noninvasive: 0.85).

Conclusions—Patients with DHF have increased LV mass and LA volume in comparison with normal controls, but not versus patients with LV hypertrophy who are not in heart failure. On the other hand, LA_A strain is significantly reduced and LA stiffness is the most accurate index in identifying patients with DHF. (Circ Cardiovasc Imaging. 2009;2:10-15.)

Key Words: diastole  ■  echocardiography  ■  heart failure

P

atients with diastolic heart failure (DHF) suffer from a rising morbidity and mortality.1,2 Although older age, hypertension, diabetes, coronary artery disease, and female gender identify patients at higher risk for DHF, the underlying pathophysiological mechanisms for the transition from an asymptomatic state to one of heart failure are poorly defined. Recent studies have drawn attention to the presence of a higher left ventricular (LV) mass3 and left atrial (LA) volume4,6 as well as a lower LA contractile reserve in DHF patients. However, LA diastolic function was not assessed in these studies, and only clinical criteria were used to identify patients with DHF. It is now possible to examine LA function with reasonable accuracy using strain Doppler echocardiography.5–11 With this technique, LA systolic and diastolic function can be assessed in a comprehensive manner. We undertook this study primarily to determine the contribution of LA systolic and diastolic function to DHF by comparing patients with DHF and those with pathological LV hypertrophy who were not in heart failure.

Methods

The study protocol was approved by the institutional review board, and patients provided a written informed consent. Sixty-four consecutive patients were enrolled. All were in sinus rhythm and had simultaneous right heart catheterization and transthoracic echocardiographic imaging. There were 20 patients with DHF and 25 patients with systolic heart failure (SHF). DHF was diagnosed according to recent guidelines using clinical criteria for heart failure and the invasive measurement of wedge pressure.12 In addition, we enrolled 19 patients with LV hypertrophy (attributable to hypertension) and normal ejection factor (EF), who were not with heart failure for studying LA contribution to the development of DHF. The latter group was labeled as diastolic dysfunction (DD) to distinguish them from patients with DHF. Cardiac catheterization was performed in the DD group for evaluation of cardiac function because of dyspnea in the presence of comorbid conditions, namely diabetes mellitus, chronic kidney disease, and obesity. None of the patients (SHF, DHF, and DD) exhibited more than mild mitral regurgitation.

Twenty-seven normal healthy subjects with normal echocardiographic findings were included as a control group. The control group had no history of cardiovascular disease and was referred to the echocardiography laboratory for evaluation of cardiac function because of a cardiac murmur. Some of these patients were included in previous studies from our laboratory.

Echocardiographic Studies

All patients were imaged in a supine position using a GE Vivid 7 ultrasound system. Two-dimensional grayscale images were acquired in the standard parasternal and apical (apical 4, apical 2, and apical long) views, and 3 cardiac cycles were recorded. In the apical 4-chamber view, mitral inflow was recorded as previously de-
of 3 cardiac cycles with <10% variation). Arterial and LV systolic\textsuperscript{17} elastance were calculated.

### LA Stiffness Estimation

The ratio of invasively measured PCWP to LA systolic strain was used to estimate LA stiffness.\textsuperscript{18} The average of LA systolic strain from the 4 LA walls was used for this calculation. The $E/e'$ ratio (average $e'$) was also used in conjunction with $LAV$ strain to derive a noninvasive dimensionless parameter, because the ultimate clinical application is one where all data are obtained noninvasively.

### Statistical Analyses

Continuous data are presented as mean±SD, and dichotomous data in number and percentage. Comparisons were performed with 1-way ANOVA as the data were normally distributed per Kolmogorov-Smirnov test. Pairwise multiple comparison procedures were performed using the Holm-Sidak method. The relationship between continuous variables was analyzed using regression analysis. Receiver operating characteristic analysis was used to distinguish patients with DHF from those with DD, but not with heart failure. The study had a power of 80% to detect a 20% difference between patients with DHF and those with DD with a SD of 20%, at an $\alpha$ level of 0.05. A probability value $P<0.05$ was used to define a significant result. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

### Results

Patients with heart failure (SHF and DHF) had increased PA and mean PCWP pressure as expected, with patients with DHF having normal LV volumes and EF ($P<0.01$ vs SHF). LV stroke volume and cardiac output in patients with DHF were similar to the normal group (Table 1). Patients with DD had normal mean PCWP and did not show significant differences in LV volumes, mass, and cardiac index in comparison with patients with DHF. LV systolic function (EF and elastance) was similar in patients with DHF and DD. Arterial elastance was higher in all patients’ groups versus controls ($P<0.05$), but without a significant difference between DHF and DD patients.

The use of \textbeta-blockers, calcium channel blockers, and angiotensin converting enzyme inhibitors/angiotensin receptor blockers was not different between DHF and DD groups. However, the use of diuretics was significantly higher in patients with DHF ($P<0.05$).

### LA Volumes

LA maximum, minimum, and pre-A volumes were larger in patients than in normal controls (Table 2), but there were no significant differences between SHF, DHF, and DD groups. Both LA emptying and EFs were higher in normal controls versus the 3 patient groups ($P<0.05$). Both fractions were lowest in patients with SHF ($P<0.05$ vs DHF and DD), but without a significant difference between patients with DHF and DD ($P=0.2$).

### Mitral Annulus Late Diastolic Velocity (a’)

Lateral a’ was slightly higher than septal a’ in all 4 groups. Patients with SHF had the lowest velocities (Table 2, $P<0.05$), whereas no significant difference was noted between patients with DHF and those with DD ($P=0.3$).
LA Strain
It was feasible to measure LA deformation in the anterior wall in 76% of patients, the inferior wall in 79% of patients, whereas adequate septal measurements were obtained in 100%, and lateral measurements in 98%. Control subjects had significantly higher systolic and late diastolic SR signals than patients with SHF, DHF, and DD (P<0.01). Likewise, LA\textsubscript{S} and LAA strain were significantly higher in control subjects (P<0.01). Among the 3 patients’ groups, patients with SHF showed the lowest atrial deformation indices (P<0.05 vs patients with DHF and DD).

In patients with DHF, LA systolic SR and strain (LA\textsubscript{S}) were significantly lower than those in patients with DD. However, late diastolic SR and strain (LAA\textsubscript{S}) were similar in patients with DHF and DD.

LA Stiffness Index
In the normal control group, there was no significant correlation between the stiffness index and age (P=0.13). The LA stiffness index was highest in patients with SHF, whereas patients with DD had a more compliant LA, when compared with patients with SHF and DD. Notwithstanding, LA stiffness was still significantly increased in patients with DD versus normal controls (P<0.05). When the 3 groups (SHF, DHF, DD) were combined, a significant inverse correlation was observed between PA systolic pressure and each of LA\textsubscript{S} strain (r=-0.56, P<0.05) and LA stiffness index (r=0.85, P<0.001, Figure 2) using invasively measured PCWP. PA systolic pressure related well to the noninvasive estimate of LA stiffness (r=0.8, P<0.001, Figure 3). LV stroke volume was significantly related to LA\textsubscript{S} strain, such that patients with higher LA\textsubscript{S} strain exhibited higher stroke volumes (r=0.35, P=0.04).

Identification of DHF Patients From DD Patients
LA\textsubscript{S} strain was not significantly different between the 2 groups, and the area under the curve (AUC) was only 0.59. LA\textsubscript{S} strain had a larger AUC (0.79), whereas LA stiffness index using invasively measured PCWP had the best performance with an AUC of 0.93 (Figure 4). An LA stiffness index >1.1 mm Hg had a sensitivity of 84%, and a specificity of 100% in distinguishing patients with DHF from those with DD.

Using E/e’ ratio in lieu of PCWP was also accurate in identifying DHF patients with an AUC of 0.85 (95% confidence interval: 0.72 to 0.98), and an index >0.99 had a sensitivity of 85%, and a specificity of 78% in distinguishing patients with DHF from those with DD (Figure 5).

Discussion
This study shows that patients with DHF have a significantly reduced LA\textsubscript{S} strain, increased LA stiffness, and reduced LA\textsubscript{S} strain. Increased LA stiffness as assessed invasively and noninvasively readily identified patients with DHF from those with DD. On the other hand, LV mass, volumes, and systolic function, arterial elastance as well as LA volumes
Table 2. Left Atrial Volumes and Function

<table>
<thead>
<tr>
<th></th>
<th>Control (n=27)</th>
<th>SHF (n=25)</th>
<th>DHF (n=20)</th>
<th>DD (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum volume index, mL/m²</td>
<td>20.6±6.4*</td>
<td>38±7.6</td>
<td>36±9</td>
<td>35±8</td>
</tr>
<tr>
<td>Minimum volume index, mL/m²</td>
<td>8±3.3†</td>
<td>23±10</td>
<td>20±8</td>
<td>20±9</td>
</tr>
<tr>
<td>Pre-A volume, mL/m²</td>
<td>11.7±4.4*</td>
<td>25±10.3</td>
<td>26±8.5</td>
<td>25±9.3</td>
</tr>
<tr>
<td>LA emptying fraction, %</td>
<td>63±7°</td>
<td>38±14†</td>
<td>44±10</td>
<td>44±9</td>
</tr>
<tr>
<td>LA ejection fraction, %</td>
<td>43±11*</td>
<td>13±9†</td>
<td>24±12</td>
<td>20±13</td>
</tr>
<tr>
<td>Septal a', cm/s</td>
<td>7.2±2.3*</td>
<td>4±2†</td>
<td>5.9±2.6</td>
<td>5.3±2.7</td>
</tr>
<tr>
<td>Lateral a', cm/s</td>
<td>7.5±2.8*</td>
<td>4.3±2.5†</td>
<td>6.3±2.7</td>
<td>6.1±2.8</td>
</tr>
<tr>
<td>LAA strain rate, s⁻¹</td>
<td>3.5±0.4*</td>
<td>1.2±0.3†</td>
<td>1.8±0.4‡</td>
<td>2.8±0.6</td>
</tr>
<tr>
<td>LAA strain, %</td>
<td>-2.8±0.5*</td>
<td>-1.8±0.5†</td>
<td>-2.4±0.5</td>
<td>-2.3±0.5</td>
</tr>
<tr>
<td>LAA strain rate, s⁻¹</td>
<td>44±9*</td>
<td>15±4‡</td>
<td>18±4‡</td>
<td>36±4</td>
</tr>
<tr>
<td>LAA strain, %</td>
<td>11±3.4*</td>
<td>6.4±3‡</td>
<td>8.5±3</td>
<td>8.3±3</td>
</tr>
<tr>
<td>LA stiffness index, mm Hg</td>
<td>0.3±0.1*</td>
<td>2.7±1.7†</td>
<td>1.6±0.7‡</td>
<td>0.6±0.3</td>
</tr>
<tr>
<td>E/e' ratio/LA strain</td>
<td>0.21±0.1*</td>
<td>2.4±1.2‡</td>
<td>1.8±0.7‡</td>
<td>0.9±0.3</td>
</tr>
</tbody>
</table>

Data presented as mean±SD. SHF indicates systolic heart failure; DHF, diastolic heart failure; DD, diastolic dysfunction; LV, left ventricular; LA, left atrial.

*P<0.05 vs SHF, DHF, and DD groups.
†P<0.05 vs DHF and DD groups.
‡P<0.05 vs DD group.

and atrial pump function, were not significantly different between the 2 groups.

LA Function in SHF

Patients with SHF usually have a dilated LA, which by itself predicts outcome irrespective of clinical data, LV EF, and exercise tolerance. In the current study, LA systolic function was depressed in patients with SHF. This conclusion is supported by the concordance in several measurements of LA booster pump function, namely: LA EF, mitral annulus a’ velocity, and LA strain and SR. It is likely that intrinsic problems with LA myocardial contractility play a role, in addition to increased LA afterload, because of the elevated LV diastolic pressures. Few studies have evaluated atrial function in this population using myocardial strain, and likewise showed abnormal LA systolic function, particularly in patients with idiopathic dilated cardiomyopathy.

Figure 2. Regression plot between PA systolic pressure as measured during right heart catheterization and LA stiffness index (mean wedge pressure measured invasively/LA strain). The best fit model was a quadratic function given by \( y = \alpha + ax + bx^2 \).

Figure 3. Regression plot between PA systolic pressure as measured during right heart catheterization and the noninvasive estimate of LA stiffness, namely: E/e’/LA strain. The best fit model was a quadratic function given by \( y = \alpha + ax + bx^2 \).

Figure 4. Receiver operating characteristic curve showing the accuracy of PCWP/LA strain in differentiating patients with DHF from those with diastolic dysfunction but not in heart failure. PCWP (wedge pressure) was measured invasively.

LV Systolic Function and Arterial Elastance in Patients With DD With and Without Heart Failure

There is an ongoing debate regarding LV systolic function in patients with DHF and DD, and the role of systolic dysfunc-
tion in the pathogenesis of DHF remains unclear. We did not observe a significant difference in EF and LV elastance between patients with DHF and DD, which is similar to previous studies. Likewise similar to a previous study, arterial elastance was not significantly different between these 2 groups, albeit significantly higher than normal controls. Therefore, one cannot attribute the development of DHF to either of these 2 parameters in our study sample.

LA Volumes and Systolic Function in DHF

Patients with LV DD have increased LA volumes that parallel the severity of DD, such that patients with restrictive LV filling have the largest atrial volumes. Previous studies have confirmed that LA dilatation is common in patients with heart failure, irrespective of LV EF. However, unlike a previous report, we did not notice a difference in LA volumes (maximum, minimum, and pre-A volume) between patients with DHF and those with DD but not in heart failure. Although small differences may exist between the 2 patient groups that we could not identify because of the sample size of our study, such differences are unlikely to have played a major role in the development of heart failure status in the current patient population.

It is well recognized that abnormalities in LA booster pump function occur in patients with restrictive LV filling. These have been attributed to LA myopathy, and increased LA afterload attributable to the elevated late diastolic LV pressures. Likewise, we observed abnormalities in several indices that measure LA ejection performance including LA EF, septal and lateral mitral annulus a’ velocities, and LA\textsubscript{s} strain and SR. However, although these were significantly lower than the control group, they were not significantly different, and could not separate patients with DHF from those with LV hypertrophy but not with heart failure. It is possible that we could have identified significant differences in LA contractile reserve had we used isometric hand grip, which is a limitation to this study.

LA Diastolic Function in DHF

To our knowledge, this is the first study to examine the contribution of LA DD to the development of DHF. Abnormal LA\textsubscript{s} strain and SR were present in both DHF and DD groups, and LA systolic (systolic phase of the cardiac cycle) expansion was significantly less than that in patients with DD. In that regard, this parameter seems to be a more sensitive indicator of the change in reservoir function than LA emptying fraction.

Combining LA\textsubscript{s} strain with invasively measured, and noninvasively estimated mean PCWP, was accurate in identifying patients with DHF. Interestingly, LA stiffness in our study accounted well for the observed PA systolic pressure quite similar to the findings in patients with mitral stenosis where LA compliance related well to symptomatic status, PA pressures at rest and exercise, and subsequent need for percutaneous or surgical intervention. Furthermore, a recent report noted significant correlations between PA systolic pressure and mean PCWP.

Although LA structure was not examined in this investigation, a previous canine study in a model with LV DD has shown the association of increased LA stiffness with LA hypertrophy and upregulation of the $\beta$-myosin heavy chain isoform. One can speculate that patients with DHF likely have more profound changes in the extracellular matrix composition and the expression of cytoskeletal proteins and myofilaments in the LA, which remains to be proven.

Limitations

It would have been ideal to assess LA function using pressure-volume loops. However, a transeptal approach is needed for this purpose, which is not performed for routine clinical care. It was also difficult to subject these patients to the procedure for the sole purpose of this study. The need for invasive measurements of LV filling pressures led to a small sample size, but the study had adequate power to detect at least a 20% difference in the primary parameter of interest, LA\textsubscript{s} strain, between patients with DHF and those with DD. Nevertheless, the use of multiple comparisons among several patients’ groups is a limitation to this study.

The large AUC for the invasively estimated LA stiffness is expected given the fact that PCWP was invasively measured and is one of the parameters needed to identify patients with DHF from patients not in heart failure. Given the small sample size, additional studies are needed to examine the ability of LA stiffness, particularly using the noninvasive approach, to predict the transition to DHF in a larger population. LV and LA function were assessed only at rest and not exercise, and the assessment of LV and LA contractile reserve may have uncovered other important differences between the patients’ groups. The study did not investigate the molecular mechanisms that account for the changes in LA function, and additional research can shed light in that regard.

Disclosures

None.

References

The underlying pathophysiological mechanisms for the transition from an asymptomatic state of diastolic dysfunction to one of diastolic heart failure are poorly defined. A noninvasive index that can help identify patients with diastolic heart failure from nonfailing hypertensive left ventricular dysfunction is of clinical interest. This study compared several parameters of left atrial function after cessation of pacing in accompanying chronic rapid pacing-induced atrial failure.

Kurt et al. LA Function in DHF

15

Clinical Perspective

The underlying pathophysiological mechanisms for the transition from an asymptomatic state of diastolic dysfunction to one of diastolic heart failure are poorly defined. A noninvasive index that can help identify patients with diastolic heart failure from those with asymptomatic diastolic dysfunction is of clinical interest. This study compared several parameters of left atrial (LA) and left ventricular function and arterial elastance between patients with diastolic dysfunction and left atrial systolic and diastolic function after cessation of pacing in accompanying chronic rapid pacing-induced atrial failure.
Left Atrial Function in Diastolic Heart Failure
Mustafa Kurt, Jianwen Wang, Guillermo Torre-Amione and Sherif F. Nagueh

Circ Cardiovasc Imaging. 2009;2:10-15
doi: 10.1161/CIRCIMAGING.108.813071
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circimaging.ahajournals.org/content/2/1/10

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Imaging can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Imaging is online at:
http://circimaging.ahajournals.org//subscriptions/