Left Ventricular Filling Pressure Assessment Using Left Atrial Transit Time by Cardiac Magnetic Resonance Imaging

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Background—Left atrial (LA) size and function reflect left ventricular (LV) hemodynamics. In the present study, we developed a novel method to determine LA circulation transit time (LATT) by MRI and demonstrated its close association with LV filling pressure.

Methods and Results—All subjects were prospectively recruited and underwent contrast-enhanced MR dynamic imaging. Mean LATT was determined as the time for contrast to transit through the LA during the first pass. In an invasive study group undergoing clinically indicated cardiac catheterization (n=25), LATT normalized by R-R interval (nLATT) was closely associated with LV early diastolic pressure (r=0.850, P=0.001), LV end-diastolic pressure (r=0.910, P<0.001), and mean diastolic pressure (r=0.912, P<0.001). In a larger noninvasive group (n=56), nLATT was prolonged in patients with LV systolic dysfunction (n=47) (10.1±3.0 versus 6.6±0.7 cardiac cycles in normal control subjects, n=9; P<0.001). Using a linear regression equation derived from the invasive group, noninvasive subjects were divided into 3 subgroups by estimated LV end-diastolic pressure: ≤10 mm Hg, 11 to 14 mm Hg, and ≥15 mm Hg. There were graded increases from low to high LV end-diastolic pressure subgroups in echocardiographic mitral medial E/e’ ratio: 9±5, 11±4, and 13±3 (P=0.023); in B-type natriuretic peptide (interquartile range): 44 (60) pg/mL, 87 (359) pg/mL, and 371 (926) pg/mL (P=0.002); and in N-terminal pro–B-type natriuretic peptide: 57 (163) pg/mL, 208 (990) pg/mL, and 931 (1726) pg/mL (P=0.002), demonstrating the ability of nLATT to assess hemodynamic status.

Conclusions—nLATT by cardiac MR is a promising new parameter of LV filling pressure that may provide graded noninvasive hemodynamic assessment. (Circ Cardiovasc Imaging, 2011;4:130-138.)

Key Words: MRI ■ left atrium ■ circulation transit time ■ hemodynamics ■ natriuretic peptides

The major cause of congestive heart failure is an interrelated set of hemodynamic derangements including elevated left ventricular (LV) filling pressure. Although invasive hemodynamics remain the gold standard for assessment of hemodynamic and circulatory function in patients with heart failure, a variety of noninvasive techniques, including Doppler echocardiography1–3 and biomarkers,4–6 have proven helpful. However, none offers a graded direct assessment of hemodynamic or circulatory impairment.

Clinical Perspective on p 138

Circulatory transit time measures the time taken for blood to flow between or within circulatory structures. It was recognized more than half a century ago, using invasive methods, that global circulation time, from systemic vein to systemic artery, is prolonged in patients with heart failure.7–9 More recent studies have confirmed earlier observations using modern technologies such as nuclear scintigraphy,10,11 computed tomography,12 and magnetic resonance (MR) angiography.13 To date, studies of segmental circulation time have been limited to measurements of transit time between pulmonary artery and left atrium (LA),8 pulmonary artery and ascending aorta,13,14 or to femoral artery,15 or antecubital vein and peripheral tissues.16–18 In contrast, the clinical correlates of LA mean transit time have not been explored.

The timing and extent of LA emptying are closely related to LV diastolic filling pressure. In the presence of increased LV filling pressure, the deceleration time of early diastolic transmural inflow is decreased as is the inflow during atrial contraction.19–21 Hence, we hypothesized that prolongation of LA circulation transit time (LATT) was a marker of increased LV filling pressure. We have developed a novel method for determination of LATT using dynamic cardiac MRI and examined its relationship to LV filling pressure in a group of patients

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undergoing invasive heart catheterization. This relationship was then used to characterize the association of established noninvasive markers of hemodynamics with LATT in a larger noninvasive cohort with LV systolic dysfunction (LVSD).

Methods

Participant Recruitment

The study protocol was approved by the St Francis Hospital Institutional Review Board, and written informed consent was obtained from all participants. Participants were recruited prospectively and divided into invasive and noninvasive groups. Whereas all subjects underwent cardiac MR (CMR) and blood testing for biomarkers, those in the noninvasive arm also had an echocardiogram. The detailed recruitment scheme is illustrated in Figure 1. The invasive group consisted of patients who were undergoing clinically indicated left and right heart catheterization and consented to a research CMR study on the same day. Subjects with severe mitral regurgitation were excluded. In the noninvasive group, normal control subjects were recruited if they were free of hypertension, diabetes mellitus, and cardiovascular disease, whereas patients with LVSD were recruited from those referred for clinical CMR for evaluation of cardiomyopathy. Additional subjects with LVSD were recruited from the cardiac catheterization laboratory. Consistent with the invasive group, subjects with severe mitral regurgitation were excluded. The inclusion criteria for LVSD subjects were LV ejection fraction <50% with New York Heart Association functional class I to III with or without clinical history of decompensated heart failure. Exclusions were the same for all participants, including impaired renal function with glomerular filtration rate <45 ml/min/1.73 m²; claustraphobia; pacemaker/defibrillator implantation; or other metallic hazards. All participants completed a questionnaire for demographic information and medical history. Clinical charts were reviewed to confirm the cardiovascular history in all subjects.

Cardiac MRI

All participants underwent CMR in a 1.5-T Avanto scanner (Siemens, Malvern, PA) with an 8-element phased array surface coil. Cardiac volumes and systolic function were assessed using balanced steady-state free-precession (SSFP) cine imaging with retrospective ECG gating. Images were acquired during breath-hold at inspiration in a stack of short-axis planes (8-mm thickness with 2-mm gap) and 3 long-axis planes (2-, 3-, and 4-chamber views) with the following parameters: echo time, 1.3 ms; repetition time, 3.1 ms; flip angle, 70°; and average in-plane resolution of 1.3×1.3 mm². To determine LATT, dynamic images were acquired every cardiac cycle over at least 50 and up to 100 cardiac cycles in a sagittal plane, where the main pulmonary artery and LA were well defined (Figure 2) during the infusion of gadopentetate dimeglumine (Magnevist, Schering AG, Berlin, Germany) (0.01 mmol/kg) at 6 ml/s followed with a 15-ml saline flush. An ECG-gated saturation recovery SSFP sequence was used with an inversion time of 90 ms; field of view, 500 mm; echo time, 0.92 ms; imaging acquisition window, 160 ms per slice; slice thickness, 15 mm; and flip angle, 50°. Parallel imaging was applied with an acceleration factor of 2.

Echocardiography

A transthoracic color Doppler echocardiogram with tissue Doppler imaging was obtained by experienced research technologists in 9 normal control subjects and 38 patients with LVSD in the noninvasive group within 2 hours of cardiac MRI using Philips IE33 echocardiographs (Andover, MA). Six patients declined echocardiographic examination. Echocardiograms were not obtained in the invasive cohort. Mitral inflow velocities of the peak E and A waves were measured using pulsed Doppler. Tissue Doppler imaging was acquired from the medial and lateral mitral annulus and E/e' ratios calculated using the mitral inflow E and the peak velocity of the tissue e' wave of the medial and lateral mitral annulus. E/e' ratios were not available in 2 individuals in whom Doppler acquisitions were incomplete. The peak pulmonary artery systolic pressure was estimated using the peak velocity of the tricuspid regurgitant jet and right atrial pressure estimates based on phasic respiratory changes in the inferior vena cava.

There were 5 cases in which tricuspid regurgitation was not present and pulmonary artery systolic pressure could not be estimated.

BNP Assays

A blood sample was collected for B-type natriuretic peptide (BNP) or N-terminal proBNP (NT proBNP) before cardiac MRI for all study subjects (n=81). BNP was measured using a chemiluminescent microparticle immunoassay in EDTA plasma (ARCHITECT BNP assay by Abbott Laboratory, Abbott Park, IL). NT proBNP was measured using an electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IL).

Invasive Hemodynamic Testing by Right and Left Heart Catheterization

The right and left heart catheterization were performed under fluoroscopic guidance via a femoral vein and artery, respectively, following standard clinical protocols. Hemodynamic measurements included pressure recordings in the right atrium, main pulmonary artery, LV, and pulmonary capillary wedge (PCWP) positions. In addition, blood oxygen saturation in the pulmonary artery and aorta were measured, and oxygen content was estimated so that cardiac output and cardiac index by the assumed Fick method could be calculated and pulmonary vascular resistance determined. Hemodynamic tracings were recorded and stored electronically. Two experienced cardiologists reviewed tracings and the values of each hemodynamic measurement were determined by consensus. Three variables were derived from LV filling pressure tracings: early LV diastolic pressure (LVDP), LV end-diastolic pressure (LVEDP), and mean LV filling pressure, taken as the average of early and end LV filling pressure. Inspiratory hemodynamic values were used because MR dynamic imaging was acquired during an inspiratory breath-hold. The average time between invasive catheterization and CMR...
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was 5 hours and 28 minutes. There was no hemodynamic instability between studies among the participants.

Image Analysis

Left and right ventricular end-diastolic volume (EDV), end-systolic volume (ESV), ejection fraction (EF), and myocardial mass were assessed from cine CMR images using MASS software (Medis, Leiden, The Netherlands). LA volume was assessed using the biplane area-length method as 0.85 × A1 × A2/L, where A1 and A2 were the areas by planimetry in the 4- and 2-chamber views and L was the left atrial length perpendicular to the mitral annular plane in the 4-chamber view. All measurements were normalized to body surface area. The CMR contrast-enhanced dynamic image series were analyzed to evaluate LATT using MASS software. Small circular regions of interest approximately 5 mm in diameter were placed at the center of the LA at a phase in which the anatomic structure was best defined by the contrast enhancement, then propagated through the image series to assess serial contrast signal intensity and a graph of signal intensity over time constructed. LATT was measured only during the first pass (Figure 3). The calculation of LATT was based on indicator dilution theory using the following equation:

\[ LATT = \frac{\int S(t)dt}{\int S(t)dt} \]

where \( S(t) \) is the signal from the time-intensity curve and \( t \) is the time at which contrast signal is measured passing through the LA. A derivative between 2 adjacent data points on the time-intensity curve was calculated to determine the starting and ending points of the contrast signal curve during first pass. All data points before the starting point were averaged to obtain a baseline signal, which was subtracted from the signal at each point on the time intensity curve. The signals beyond the ending point were attributed to recirculation and discarded from analysis. All data points were then fitted to the equation to calculate LATT using a custom Matlab (MathWorks Inc, Natick, MA) program. A normalized LATT (nLATT) was calculated as the measured LATT divided by the R-R interval in seconds.

Statistical Analysis

Statistical analyses were performed using SPSS 11.0 for Windows (SPSS Inc, Chicago, IL). The Student t test and \( \chi^2 \) test were used to compare the continuous and categorical variables, respectively, between normal control subjects and patients with LVSD. Probability values of \( t \) tests were determined assuming equal variances if the Levene test for equality of variance was not statistically significant \((P>0.05)\). Otherwise, probability values were determined without assuming equal variances. Continuous variables with nonnormal distributions were compared as medians using the Mann-Whitney
Pearson correlations were performed to assess the associations of hemodynamic indices and LATT. Probability values were further adjusted by Bonferroni correction for multiple testing in Pearson correlations. Using the linear regression equation relating nLATT to LV filling pressure in the invasive group, LVEDP was estimated in the noninvasive group. Predicted LVEDP was then divided into 3 subgroups with LVEDP <10 mm Hg, 11 to 14 mm Hg, and ≥15 mm Hg.

Cardiac structure and function and echocardiographic indices were compared across the subgroups to test for trends by comparing means using polynomial linear comparisons in ANOVA. Biomarker levels, which did not have a normal distribution, were compared using the Kruskal-Wallis test. Probability values <0.05 were considered statistically significant for all analyses. The limits of agreement between estimated LV filling pressure from nLATT, measured LV filling pressure, and estimated PCWP from E/e’ were calculated in pairwise Bland-Altman analyses. To determine interobserver and intraobserver variability, nLATT was analyzed in 9 randomly selected cases by 2 experienced analysts blinded to subjects’ clinical status. Intraclass correlation coefficients and paired t tests revealed strong agreement between readers (intraclass correlation 0.97, P=0.455 for paired t test) and within readers (intraclass correlation 0.99, P=0.362 for paired t test). The average difference was 0.11 seconds (1.4%) between readers and 0.08 seconds (1.1%) within readers.

**Table 2. Correlation of LA Transit Times With Invasive Hemodynamic Measurements**

<table>
<thead>
<tr>
<th>Hemodynamic Variables</th>
<th>LATT (n=25)</th>
<th>P Value*</th>
<th>nLATT</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean right atrial pressure</td>
<td>0.624</td>
<td>0.01</td>
<td>0.359</td>
<td>0.93</td>
</tr>
<tr>
<td>PA systolic pressure</td>
<td>0.588</td>
<td>0.02</td>
<td>0.512</td>
<td>0.09</td>
</tr>
<tr>
<td>Mean PA pressure</td>
<td>0.620</td>
<td>0.01</td>
<td>0.528</td>
<td>0.07</td>
</tr>
<tr>
<td>PA oxygen saturation</td>
<td>−0.647</td>
<td>0.01</td>
<td>−0.605</td>
<td>0.01</td>
</tr>
<tr>
<td>Arterial oxygen saturation</td>
<td>−0.594</td>
<td>0.02</td>
<td>−0.463</td>
<td>0.23</td>
</tr>
<tr>
<td>Mean PCWP</td>
<td>0.613</td>
<td>0.01</td>
<td>0.783</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVDP</td>
<td>0.607</td>
<td>0.01</td>
<td>0.850</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>LVEDP</td>
<td>0.764</td>
<td>&lt;0.01</td>
<td>0.910</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean LV diastolic pressure</td>
<td>0.718</td>
<td>&lt;0.01</td>
<td>0.912</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiac index</td>
<td>−0.775</td>
<td>&lt;0.01</td>
<td>−0.717</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pulmonary vascular resistance</td>
<td>0.576</td>
<td>0.03</td>
<td>0.394</td>
<td>0.560</td>
</tr>
</tbody>
</table>

PA indicates pulmonary artery.

*P values shown are adjusted for multiple testing by Bonferroni correction.

Results

**Relationship of LA Circulation Transit Time and Invasive Hemodynamic Measurements**

In the invasive group, there were 25 patients undergoing clinically indicated invasive hemodynamic measurements. The average age was 58±16 years, and 13 were female. All had clinically suspected congestive heart failure. Eight had at least moderate valvular dysfunction including 3 with moderate mitral regurgitation, 2 with moderate tricuspid regurgitation, and 3 with moderate to severe aortic stenosis. The average hemodynamic indices, ventricular volumes, and systolic function and biomarker levels are shown in Table 1. There were 8 patients with LVEF below 50%. The Pearson correlation demonstrated closer association of LV filling pressure with nLATT than with LATT (Table 2), despite lack of a significant correlation between LATT and heart rate (P=0.214). There were strong correlations between nLATT and LV early diastolic pressure (r=0.850, P=0.001), LVEDP (r=0.910, P<0.001), mean LV diastolic pressure (r=0.912, P<0.001), and mean PCWP (r=0.783, P<0.001). Probability values remained consistently ≤0.01 or lower for nLATT correlations, with all LV diastolic pressure indices and mean PCWP after Bonferroni correction for multiple testing was performed. There were also strong associations between nLATT, cardiac index, and pulmonary artery oxygen saturation in Bonferroni-corrected comparisons. The correlations between nLATT and LV early, end, and mean filling pressures respectively are shown in scatterplots (Figure 4).

LV filling pressure was estimated noninvasively using the following regression equations derived from the invasive data:

```plaintext
A  
\[ y = 1.27x - 5.05 \]  
\[ r = 0.850, P=0.001 \]

B  
\[ y = 0.910, P>0.001 \]

C  
\[ y = 1.52x - 4.42 \]  
\[ r = 0.912, P>0.001 \]
```

![Figure 4](http://circimaging.ahajournals.org/Downloaded_from)
and mean LVDP of 1.52 ± 0.44 mm Hg. Invasively measured and estimated LV filling pressures from nLATT were then compared in Bland-Altman plots (Figure 5), demonstrating a mean difference of 0 mm Hg for all 3 filling pressure indices. Overall, estimated and measured mean LV filling pressure had the best agreement with the limits of agreement ±4.6 mm Hg, followed by ±5.4 mm Hg for early LVDP and ±5.6 mm Hg for LVEDP.

Comparison Between Patients With LV Dysfunction and Normal Control Subjects

The noninvasive group included 56 individuals, 47 with LVSD of various etiologies. The demographics of the LVSD cohort are shown in Table 3. Compared with the normal control subjects, patients with LVSD were older (57 ± 14 versus 48 ± 19 years, P < 0.001). Most were stable outpatients, but 2 were inpatients hospitalized for heart failure. The prevalence of New York Heart Association functional classification I through III was 46%, 23%, and 23%, respectively. There were no class IV patients. A history of coronary disease (myocardial infarction or coronary revascularization) was present in 26 (56%) patients. LV volume and mass were higher and LVEF and stroke volume lower in patients with LVSD (Table 4). Significant valvular disease (>2) among patients with LVSD included moderate mitral regurgitation in 4 (7%) subjects, moderate tricuspid regurgitation in 2 (4%), and moderate aortic regurgitation in 3 (5%).

There were significant prolongations in LATT and nLATT (P < 0.001 for both) in patients with LVSD when compared with normal control subjects. Using the linear regression equation described above, LVEDP was estimated for the participants in the noninvasive group. Predicted LVEDPs in the normal control subjects were all below 10 mm Hg, with a mean value of 8.6 ± 1.2 mm Hg. Comparing the predicted LVEDP subgroups from low to high (>10 mm Hg, 11 to 14 mm Hg, and ≥15 mm Hg), there were graded decreases in LV and RV systolic function and stroke volume and graded increases in mitral annular E/e’ ratio and BNP level (Table 5), demonstrating the ability of nLATT to assess hemodynamic status. The significant associations of nLATT and mitral E/e’ ratio were also demonstrated by the Pearson correlation, comparing them as continuous variables with r = 0.590 (P < 0.001) for mitral lateral E/e’ (Figure 6A) and r = 0.495 (P < 0.001) for mitral medial E/e’.

Table 3. Demographics of Patients With LVSD (n = 47) in the Noninvasive Cohort

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean ± SD or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57 ± 14</td>
</tr>
<tr>
<td>Male, %</td>
<td>31 (66)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>28.5 ± 5.5</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>1.96 ± 0.23</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>64 ± 12</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>128 ± 22</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>72 ± 12</td>
</tr>
<tr>
<td>Medical history, %</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (57)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (23)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>28 (62)</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>25 (57)</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>17 (36)</td>
</tr>
<tr>
<td>History of coronary revasculariza-</td>
<td>15 (32)</td>
</tr>
<tr>
<td>tion</td>
<td></td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>21 (47)</td>
</tr>
</tbody>
</table>

Figure 5. Bland-Altman plots comparing measured early LVDP with estimated early LVDP from the nLATT (A), LVEDP with estimated LVEDP from nLATT (B), and mean LVDP with mean LVDP estimated from nLATT (C). Corresponding linear regression lines and equation are shown.

early LVDP = 1.27nLATT – 5.05; LVEDP = 1.78nLATT – 3.78, and mean LVDP = 1.52nLATT – 4.40. Invasively measured and estimated LV filling pressures from nLATT were then compared in Bland-Altman plots (Figure 5), demonstrating a mean difference of 0 mm Hg for all 3 filling pressure indices. Overall, estimated and measured mean LV filling pressure had the best agreement with the limits of agreement ±4.6 mm Hg, followed by ±5.4 mm Hg for early LVDP and ±5.6 mm Hg for LVEDP.
MRI variables
difference of 0.7 mm Hg and limits of agreement predicted LVEDP from nLATT, which showed a mean theory.\textsuperscript{26,27} The relationship of prolonged LATT to increased volume to flow, based on the principles of indicator dilution measurement of LATT by CMR is derived from the ratio of hemodynamic significance of LA circulation transit time. To our knowledge, this is the first study to explore the derangement among those with LVSD.
demonstrated a relationship between prolongation of various
differentiated between patients with and without hemodynamic
drivation and diastolic filling durations give rise to variable
diastolic filling, it is physiologically plausible to find the mean rather than early or end-diastolic LV filling pressure that can best be predicted using integrated LA measures such as nLATT, although early, end, and mean LV filling pressures are closely interrelated.

Table 4. Comparison of Cardiac MRI, Echocardiographic, and Biomarker Characteristics Between Normal Subjects and Patients With LVSD in the Noninvasive Cohort

<table>
<thead>
<tr>
<th>MRI variables</th>
<th>Normal Control Subjects (n = 9)</th>
<th>Systolic Dysfunction (n = 47)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDV, mL/m²</td>
<td>88±22</td>
<td>104±27</td>
<td>0.092</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>55±5</td>
<td>39±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RV mass, g/m²</td>
<td>57±6</td>
<td>65±18</td>
<td>0.159</td>
</tr>
<tr>
<td>RV stroke volume</td>
<td>84±22</td>
<td>73±20</td>
<td>0.095</td>
</tr>
<tr>
<td>RV mass, g/m²</td>
<td>42±20</td>
<td>52±4</td>
<td>0.747</td>
</tr>
<tr>
<td>LA volume, mL/m²</td>
<td>6.8±1.4</td>
<td>9.0±2.4</td>
<td>0.002</td>
</tr>
<tr>
<td>LATT, seconds</td>
<td>6.6±0.7</td>
<td>9.5±2.6</td>
<td>0.002</td>
</tr>
<tr>
<td>nLATT, cardiac cycles</td>
<td>6.6±0.7</td>
<td>9.5±2.6</td>
<td></td>
</tr>
<tr>
<td>Pulmonary systolic pressure, mm Hg</td>
<td>25±4</td>
<td>28±8</td>
<td>0.110</td>
</tr>
<tr>
<td>Mitral lateral E/e\textsuperscript{'} ratio</td>
<td>5.0±1.8</td>
<td>8.3±2.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Mitral medial E/e\textsuperscript{'} ratio</td>
<td>7.3±2.3</td>
<td>11.5±4.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP, pg/mL (interquartile range)</td>
<td>26 (24)</td>
<td>86 (134)</td>
<td>0.009*</td>
</tr>
<tr>
<td>NT-proBNP, pg/mL (interquartile range)</td>
<td>29 (44)</td>
<td>200 (702)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

RV indicates right ventricle.
*BNP and NT-proBNP were not normally distributed variables and are shown as medians (interquartile range) and analyzed using the Mann-Whitney test for nonparametric comparison.

constructed comparing predicted PCWP, based on the mitral lateral E/e\textsuperscript{'} ratio using a published regression equation\textsuperscript{22} and predicted LVEDP from nLATT, which showed a mean difference of 0.7 mm Hg and limits of agreement ±8.5 mm Hg (Figure 6B).

Discussion
In this prospective study, we developed and applied a novel strategy for estimation of LV filling pressure using nLATT by contrast-enhanced dynamic CMR imaging. The nLATT not only predicted normal LV filling pressures in control subjects but also differentiated between patients with and without hemodynamic derangement among those with LVSD.

Early observations as well as more recent studies have demonstrated a relationship between prolongation of various indices of circulation time and LV enlargement, LV dysfunction, reduced cardiac output, and congestive heart failure.\textsuperscript{7–17} To our knowledge, this is the first study to explore the hemodynamic significance of LA circulation transit time. The measurement of LATT by CMR is derived from the ratio of volume to flow, based on the principles of indicator dilution theory.\textsuperscript{26,27} The relationship of prolonged LATT to increased LV filling pressure that we demonstrated is consistent with a large body of echocardiographic literature characterizing the intricate interplay between reduced mitral inflow velocity and increased LV filling pressure.\textsuperscript{28} Comparison of estimated PCWP from E/e\textsuperscript{'} using a published regression equation to LV filling pressure estimates from nLATT demonstrated a small mean difference (0.7 mm Hg), further supporting the feasibility of assessing LV filling pressure by nLATT. A potential advantage of MR dynamic imaging over Doppler echocardiography is the ability of MR to assess blood flow kinetics within the LA through the entire first pass, providing a more stable and comprehensive evaluation of LV filling and circulatory function than assessment of the filling period in a single heart beat by Doppler.

LA enlargement is a powerful marker for prediction of cardiovascular events in population-based studies.\textsuperscript{29–32} However, it lacks specific value in guiding diagnosis and therapy in individual patients. In our LVSD cohort, there was only a trend suggesting an association of larger LA volume with hemodynamic derangement. In contrast, nLATT directly assesses hemodynamic status, which has major significance for patient evaluation and treatment. Although nLATT correlated well with all 3 LV filling pressure variables measured, it appeared to best estimate the mean filling pressure as shown in Bland-Altman analysis. This finding is in agreement with observations made in the catheterization laboratory when LA pressure and LVEDP were measured simultaneously.\textsuperscript{33} Because the effect of LV filling pressure on LA contrast kinetics is expected to span the entire period of diastolic filling, it is physiologically plausible to find the mean rather than early or end-diastolic LV filling pressure that can best be predicted using integrated LA measures such as nLATT, although early, end, and mean LV filling pressures are closely interrelated.

Assessment of LV filling pressure can be challenging in patients with atrial fibrillation because variable systolic ejection and diastolic filling durations give rise to variable diastolic volume and pressure during invasive evaluation. Similar challenges exist in applying noninvasive parameters such as E/e\textsuperscript{'} which estimates LV filling pressure using single-beat evaluations. Our findings suggest that nLATT may have added advantages in patients with atrial fibrillation because LV filling pressure assessment is obtained through all cardiac cycles in the entire first pass, thereby providing an average value over time. In patients with atrial fibrillation, we did not observe any recognizable qualitative differences in the shape or duration of time-intensity curves when compared with those with normal sinus rhythm and similar filling pressure.

The development of fast single-beat MR imaging makes it possible to measure subintervals of the global circulation time with high spatial and temporal resolution. Most contemporary noninvasive strategies such as first-pass nuclear scintigraphy\textsuperscript{11} and MR angiography\textsuperscript{13,14} allow circulation time to be measured only between central veins and the aorta due to limited visualization of the cardiac chambers. This makes assessment of LATT difficult with those techniques. The use of a planar saturation recovery SSFP dynamic sequence in our study enabled us to obtain images with well-defined anatomy and to use minute amounts of gadolinium contrast to acquire dynamic
images adequate for transit time measurement. This technique, with a single acquisition, can be easily added to any research or clinical CMR protocol. In addition, the very small contrast doses required make repeated measurement of nLATT feasible both in a single study session and serially over time.

To date, invasive hemodynamic evaluation remains the gold standard for LV diastolic filling pressure assessment, but it is not without risk. Noninvasive strategies such as assessment of the relationship between transmitral inflow and mitral annular diastolic velocities by echocardiography have been used widely to assess LV filling pressure. However, a major limitation of E/e' ratio is its largely dichotomized assessment of LV filling pressure, which limits flexible clinical use. We found that graded increases in average E/e' correlated well with estimated LVEDP.
subgroups from low to high values. However, the linear correlation was only modest. This observation is consistent with published work comparing estimated LVEDP by E/e’ with invasively measured LVEDP.3 BNP and NT proBNP are used clinically for diagnosis and treatment of patients with heart failure but, in addition to heart failure, many other conditions may be associated with small increases in BNP level, making it nonspecific in the intermediate range.34 Therefore, there is a need to develop new noninvasive indices with high specificity in detecting hemodynamic derangement. Our observations provide very promising initial results for a new approach to noninvasive assessment of LV filling pressure.

We recognize the limitations of our study. The cohort size is small and does not include a large number of patients having heart failure with preserved EF, nor does it permit assessment of effects of age, sex, and ethnicity. Thus, larger studies of more diverse populations are needed to confirm and extend our findings. Our CMR dynamic imaging protocol was to acquire images over 50 cardiac cycles at the early phase of the study, but we soon recognized that longer acquisition spans up to 100 cardiac cycles were warranted in patients with severely elevated LVEDP. Future research should evaluate free-breathing acquisitions validated with invasive hemodynamics. Furthermore, LA pressure often exceeds LVEDP in the presence of severe mitral regurgitation, which probably alters blood transit through the LA and may lead to impaired assessment of LVEDP. Therefore, we excluded subjects with severe mitral regurgitation, which needs to be addressed in a cohort with large number of patients having this condition. Last, the current study is a cross-sectional evaluation. The serial use and prognostic significance of nLATT measurement are yet to be defined.

In conclusion, nLATT by CMR is a very promising new parameter of LV filling pressure that may provide graded noninvasive assessment of abnormalities of circulatory and hemodynamic function in patients with LVSD.

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Disclosures
None.

References
CLINICAL PERSPECTIVE

Assessment of left ventricular filling pressure is of clinical importance in guiding therapy and evaluating prognosis in patients with systolic dysfunction. In this prospective study, we developed and applied a novel strategy for estimation of left ventricular filling pressure using mean circulation transit time in the left atrium by contrast-enhanced dynamic MRI. The normalized left atrial transit time not only predicted normal left ventricular filling pressures in control subjects but also differentiated between patients with and without hemodynamic derangement among those with left ventricular systolic dysfunction. Cardiac MRI is increasingly used in diagnosis and follow-up of patients with systolic dysfunction of various etiologies. This simple technique of single imaging acquisition with minute amount of gadolinium contrast can be complementary to any clinical or research study for comprehensive evaluation of patients with systolic dysfunction.
Left Ventricular Filling Pressure Assessment Using Left Atrial Transit Time by Cardiac Magnetic Resonance Imaging
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