Validation of Noninvasive Indices of Global Systolic Function in Patients With Normal and Abnormal Loading Conditions
A Simultaneous Echocardiography Pressure–Volume Catheterization Study

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Background—Noninvasive indices based on Doppler echocardiography are increasingly used in clinical cardiovascular research to evaluate left ventricular global systolic chamber function. Our objectives were to clinically validate ultrasound-based methods of global systolic chamber function to account for differences between patients in conditions of abnormal load, and to assess their sensitivity to load confounders.

Methods and Results—Twenty-seven patients (8 dilated cardiomyopathy, 10 normal ejection fraction, and 9 end-stage liver disease) underwent simultaneous echocardiography and left heart catheterization with pressure-conductance instrumentation. The reference index, maximal elastance ($E_{\text{max}}$), was calculated from pressure–volume loop data obtained during acute inferior vena cava occlusion. A wide range of values were observed for left ventricular systolic chamber function ($E_{\text{max}}$, 2.8±1.0 mm Hg/mL) preload, and afterload. Among the noninvasive indices tested, the peak ejection intraventricular pressure difference showed the best correlation with $E_{\text{max}}$ ($R=0.75$). A significant but weaker correlation with $E_{\text{max}}$ was observed for ejection fraction ($R=0.41$), midwall fractional shortening ($R=0.51$), global circumferential strain ($R=-0.53$), and strain rate ($R=-0.46$). Longitudinal strain and strain rate failed to correlate with $E_{\text{max}}$ as did noninvasive single-beat estimations of this index. Principal component and multiple regression analyses demonstrated that peak ejection intraventricular pressure difference was less sensitive to load, whereas ejection fraction and longitudinal strain and strain rate were heavily influenced by afterload.

Conclusions—Current ultrasound methods have limited accuracy to characterize global left ventricular systolic chamber function in a given patient. The Doppler-derived peak ejection intraventricular pressure difference should be preferred for this purpose because it best correlates with the reference index and is more robust in conditions of abnormal load. (Circ Cardiovasc Imaging. 2014;7:164-172.)

Key Words: cardiac catheterization ■ echocardiography ■ hemodynamics ■ systole

In clinical practice, global left ventricular (LV) systolic function is typically assessed by means of LV volumes and ejection fraction (EF), most frequently measured using echocardiography. However, in metabolic diseases, known or suspected cardiomyopathies, or cardiotoxicity, the evaluation of global systolic chamber function sometimes entails more sensitive and robust indices than EF. In epidemiological research, alternative noninvasive methods derived from Doppler echocardiography have also proved to be more sensitive than EF to detect subtle abnormalities of systolic function. Consequently, several indices have been implemented based on the analysis of myocardial deformation (eg, global systolic myocardial strain or strain rate [SR]), of chamber fluid dynamics (eg, intraventricular pressure gradients), and on single-beat approximations to the end-systolic pressure–volume relationship (ESPVR). Importantly, however, whether these methods account for true global chamber systolic function in the clinical setting has not been established clearly. Also, their performance in disease conditions associated with an abnormal systolic load has not been studied specifically.

Clinical Perspective on p 172

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Invasive indices based on the pressure–volume relationship are the most reliable reference standards to evaluate global LV systolic chamber function in the intact heart. Therefore, the pressure–volume loop method has been used to validate most Doppler echocardiographic indices of systolic function in animal experiments. However, most of these validation studies have relied on repeated measures experiments in a small number of animals, focusing on acute load and inotropic interventions, frequently in normal ventricles. Extrapolating the results of these studies to compare differences in baseline systolic chamber function among patients may be misleading, particularly in the presence of abnormal load confounders.

The objectives of the present study were twofold: (1) to validate Doppler echocardiographic indices of systolic chamber function against LV maximal elastance \( (E_{\text{max}}) \) obtained from the ESPVR, and (2) to assess the influence of baseline preload and afterload confounders on noninvasive indices.

## Methods

### Patients

The study protocol was approved by the local institutional review board, and all subjects provided written informed consent. Twenty-seven patients in sinus rhythm undergoing left heart catheterization were included. Indications for the catheterization procedure were ruling out coronary artery disease in: (1) patients with chest pain of unknown cause with normal EF (n=10); (2) patients with dilated cardiomyopathy (n=8); and (3) patients with cirrhosis candidates for liver transplantation with >2 cardiovascular risk factors (n=9). Patients with cirrhosis were specifically selected because of their characteristically abnormal preload and afterload. Clinical and demographic data of patients are shown in Table 1. No patient underwent coronary revascularization in the same procedure.

### Signal Acquisition Protocol and Pressure–Volume Data Analysis

All catheterization procedures were performed by the femoral approach. A high-fidelity pressure-conductance 7F pig-tail catheter (CD-Leycom, The Netherlands) was placed inside the LV, connected to a dual-field conductance processor (CD-Leycom CFL-512), and calibrated using the hypertonic saline method. An occlusion balloon (PTS404, NuMED Canada, Inc) was placed at the junction of the inferior vena cava and the right atrium. A Swan–Ganz catheter was used to measure pulmonary pressures, thermodilution cardiac output, and stroke volume. Systemic vascular resistance was calculated from invasive recordings of systemic blood pressure. All signals were digitized at 250 Hz. Pressure and volume signals were acquired at end-expiratory apnea during transient caval occlusion. To minimize reflex activation, we obtain pressure–volume loops only during the first 5 to 6 seconds after balloon occlusion. This acquisition process was repeated 3× to 5× in each patient, waiting for stabilization periods of 5 minutes. \( E_{\text{max}} \) defined as the slope of the ESPVR, was calculated using the iterative regression method (Figure 1A).

Effective arterial elastance \( (E_a) \) was measured from the pressure-volume loops as the ratio of end-systolic pressure \( (P_{\text{es}}) \) to stroke volume. End-systolic wall stress \( (\sigma) \) was calculated from the pressure–volume measurements under the assumption of a thick-walled sphere using the following formula:

\[
\sigma = P_{\text{es}} \cdot \frac{1 + 3 \frac{ESV}{V_e}}{V_e}
\]

The volume of the LV wall \( (V_e) \) was obtained as the LV mass divided by myocardial density. In turn, LV mass was measured from 3-dimensional (3D) echocardiographic sequences and calibrated (Data Supplement).

From the intraventricular high-fidelity pressure signals, we extracted the peak LV pressure, end-diastolic LV pressure, and the maximum of the first time derivative of LV pressure \( (dP/dt_{\text{max}}) \).

### Echocardiographic Image Acquisition and Analysis

To avoid biological variability, all signals and images for measuring invasive and noninvasive indices of global systolic function were obtained simultaneously during the catheterization procedure. Broadband 2.0 to 4.0 MHz transducers were used either on a Vivid-7 or on a Vivid-9 (General Electric Healthcare) system. Echocardiographic acquisitions were performed 5 minutes after completing the set of caval occlusions to define the ESPVR. Invasive tracings and images were synchronized by cross correlation of a signal connected to the ultrasound scanner and the hemodynamic signal acquisition system. LV volumes and EF were calculated using biplane Simpson method. Midwall fractional shortening was calculated based on 2D measurements. Global longitudinal and circumferential strain and SR were measured using commercial speckle-tracking software (EchoPac v.110.1.2; General Electric) from the 4-chamber view and short-chamber views, respectively (Figure 1B).

Color Doppler M-mode images were obtained and processed from the 5-chamber view and obtained to process noninvasive indices derived from the intraventricular pressure difference waveform (Data Supplement). Using custom software, Doppler velocities are first decoded from the raw velocity coded data stored in the DICOM (Digital Imaging and Communications in Medicine) images via conversion to hierarchical data format. Raw, velocities are dealiased, filtered, and differentiates using smoothing splines. The 1D Euler momentum equation is solved to obtain the M-mode distributions of the intraventricular pressure gradients along a center ejection flow streamline (Figure 1C). Finally, the pressure gradient distributions are integrated to obtain the pressure difference waveform between the LV apex and the outflow tract (Figure 1C). Ejection intraventricular pressure difference (EIVPD) measurements have been validated previously in vivo and clinical reproducibility in our laboratory has been reported.

Noninvasive estimations of maximal elastance were obtained using 2 previously reported single-beat methods that do not require preload manipulation. Method 1 \( (E_{\text{max}}^{(1)}) \) requires an empirical estimation of normalized population-averaged elastance at the onset of ejection \( (E_{\text{max},\text{on}}) \). This normalized value is fitted by a 7-degree polynomial to the ratio of the pre-ejection to the total systolic ejection periods.
Figure 1. Examples of invasive and echocardiographic indices of left ventricular systolic function in representative patients with chest pain and normal ejection fraction (left), dilated cardiomyopathy (center), and liver cirrhosis (right). A. Pressure–volume loops obtained during inferior vena cava occlusion. Maximal elastance ($E_{\text{max}}$) is obtained as the slope of the end-systolic pressure–volume relationship. B. Circumferential (blue) and longitudinal (red) global strain and strain rate tracings obtained from 2-dimensional echocardiographic images using speckle-tracking software; the peak global strain and strain rate are depicted (*). C. Intraventricular pressure gradient maps obtained by postprocessing color Doppler M-mode images (top row) and pressure difference waveforms between the apex and the outflow tract (bottom row). The peak ejection intraventricular pressure difference is depicted in each curve (●).
measured from Doppler spectrograms. From this averaged value, normalized elastance at ejection onset (E_{max,sb}) is then calculated from diastolic and end-systolic pressures (P_d and P_es, respectively) as follows:

\[ E_{max,sb} = 0.0275 - 0.165 \cdot EF + 0.3656 \left( \frac{P_d}{P_s} \right) + 0.515 \cdot E_{Nd,avg} \]

and E_{max-sb} is obtained from systolic blood pressure P_s as follows:

\[ E_{max-sb} = \frac{P_s - (E_{Nd,avg} \cdot P_s \cdot 0.9)}{SV \cdot E_{Nd,avg}} \]

For method 2, single-beat elastance is measured assuming a volume intercept of 0 mmHg as follows:

\[ E_{max-sb} = \frac{P_s}{ESV} = \frac{P_s \cdot 0.9}{ESV} \]

To separate the error related to the inaccuracy of the noninvasive measurements from the error of the single-beat methods themselves, E_{max-sb1} and E_{max-sb2} were also calculated using conductance-derived volumes and invasive measurements of P_s and P_d.

To measure LV mass from LV real-time full-volume 3D acquisitions, a second echocardiographic examination was performed in the echocardiography laboratory in the same day of the invasive procedure. All ultrasound measurements other than LV mass were obtained in the catheterization laboratory.

### Statistical Analysis

Differences between hemodynamic data between patient groups (chest pain, dilated cardiomyopathy, and patients with cirrhosis) were assessed by ANOVA followed by Dunnet contrasts against the chest pain group. The correlation between noninvasive indices of systolic function and E_{max} was analyzed using the Pearson correlation coefficient (R) and corrected to avoid overfitting by bootstrap validation of 1000 repetitions (R_{boot}). Different regression slopes between E_{max} and noninvasive indices of systolic function were assessed by ANCOVA analysis.

Because neither preload nor afterload can be unequivocally characterized by a single hemodynamic measurement,27 we integrated physiologically related variables into unique synthetic surrogates of load using data reduction strategies.28 This approach of variable clustering simplifies regression modeling because it avoids trying to separate the effects of factors that are measuring the same phenomenon.28 Thus, we calculated a synthetic index of preload as the first principal component of the principal component analysis (R software, version 3.0.1) based on the correlation matrix of LV end-diastolic pressure and LV end-diastolic volume. The correlation of the synthetic index with these 2 raw variables was R=0.82 for both. We obtained the synthetic index of afterload integrating o, E_t, and systemic vascular resistance using the same method. Correlation of these raw variables with the integrated afterload synthetic index was R=0.90, 0.97, and 0.95, respectively. The effects of load confounders were analyzed using multiple linear regression models in which the noninvasive index was entered as the dependent variable, E_{max} as the independent variable, and LV mass, preload, and afterload as covariates. Standardized β-coefficients were used to compare the effects of individual predictors. Regression diagnostics (outlier exclusion, normality of residuals with constant variance, and lack of significant interactions and nonlinearities) were performed for all these regression models. We used principal component analysis with illustrative variables to visualize the autocorrelation among noninvasive indices and their relationship with E_{max}, LV mass, and load. Values of P<0.05 were considered significant.

### Results

#### Load and Hemodynamic Data

Patients with cirrhosis typically showed low afterload, with low values of systemic vascular resistance, E_t, and σ (Table 2). Patients with dilated cardiomyopathy showed higher E_t and σ, and a trend toward higher systemic vascular resistance. There was no significant difference among groups in LV end-diastolic pressure. E_{max} was reduced in patients with dilated cardiomyopathy but not in patients with cirrhosis. All noninvasive indices except E_{max-sb} demonstrated impaired systolic chamber function in patients with dilated cardiomyopathy (Table 2). Mean differences of most indices were not significantly different between the liver cirrhosis and the chest pain groups.

#### Correlation Between Noninvasive Indices and E_{max}

Peak EIVPD showed the closest correlation with E_{max} (Table 3; Figure 2). EF, midwall fractional shortening, and circumferential strain and SR showed a significant but weaker correlation with E_{max}, whereas E_{max-sb} failed to correlate with E_{max}. Even using volumes derived from the conductance catheter and invasive pressures in the single-beat formula, E_{max-sb} did not correlate with E_{max} (R=0.04). Slopes of the EIVPD–E_{max} relationship were not different among patient groups (P=0.37).

#### Effect of Load and Mass on Indices of Systolic Function

The multiple regression analysis of the hemodynamic determinants of the noninvasive indices is shown in Table 4. Peak EIVPD and global circumferential strain and SR were associated with systolic function (E_{max}) and were not significantly associated with LV mass, preload, or afterload. The magnitude of the association with E_{max} was highest for peak EIVPD. Other indices, such as EF and midwall fractional shortening, were significantly associated with E_{max} but also with load variables. E_{max-sb2} was only associated with LV mass, and E_{max-sb} and global longitudinal strain and SR were influenced mostly by afterload (Table 4). Principal component analysis demonstrated that peak EIVPD was the variable most closely associated with E_{max}, and that EF, longitudinal strain, SR, and E_{max-sb} were associated with afterload (Figure 3).

### Discussion

This is the first clinical study to investigate the accuracy of ultrasound indices of systolic global chamber function by direct comparison with the invasive gold standard method derived from the pressure–volume relationship. Using a between-subjects design in a group of patients with heterogeneous isotropic states and loading conditions, Doppler-derived peak EIVPD showed the closest relationship with E_{max}. Other noninvasive indices, such as EF, midwall fractional shortening, and circumferential strain and SR, showed a significant but weaker correlation with the reference method. Longitudinal strain and SR were closer to afterload than to systolic function in this population.
Effects of Load and Systolic Function on Strain and Strain Rate

The load dependence of strain and SR has been demonstrated in animal models, but the inotropic sensitivity and relative effect of load on circumferential versus longitudinal strain are not well known in humans, and contradictory data have been published. A study in patients with normal or mildly impaired EF undergoing cardiac catheterization and acute loading interventions suggested that longitudinal strain is less sensitive to afterload than circumferential strain. However, other studies indirectly suggest that circumferential strain may be more stable in patients with chronic abnormal afterload and secondary LV hypertrophy. In patients with aortic stenosis and hypertension, circumferential strain is preserved or even increased, whereas longitudinal and radial strains are decreased. Moreover, in patients with aortic stenosis, the afterload relief caused by aortic valve replacement results in an acute increase of longitudinal strain. The absence of changes in circumferential strain compared with longitudinal strain measurements has been interpreted frequently as a lower inotropic sensitivity of circumferential function. The results of our study suggest that this may be more likely related to a lower load dependency. Importantly, our study does not

Table 2. Hemodynamic and Echocardiographic Data

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Chest Pain</th>
<th>Dilated cardiomyopathy</th>
<th>Liver Cirrhosis</th>
<th>ANOVA P Value</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>27</td>
<td>10</td>
<td>8</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>72±14</td>
<td>70±10</td>
<td>83±17</td>
<td>66±12</td>
<td></td>
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<tr>
<td>Catheterization data</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>98±19</td>
<td>102±11</td>
<td>110±20</td>
<td>82±13</td>
<td>0.001</td>
</tr>
<tr>
<td>dP/dt max, mm Hg s⁻¹</td>
<td>123±327</td>
<td>1529±242</td>
<td>957±231*</td>
<td>1216±212*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac index, L/min per m²</td>
<td>6.9±2.4</td>
<td>6.2±1.5</td>
<td>5.5±1.5</td>
<td>8.9±2.7*</td>
<td>0.003</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>4.0±1.2</td>
<td>3.9±0.8</td>
<td>3.2±0.8</td>
<td>4.8±1.4</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean pulmonary pressure, mm Hg</td>
<td>10±4</td>
<td>8±4</td>
<td>8±5</td>
<td>12±2*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure, mm Hg</td>
<td>24±6</td>
<td>23±5</td>
<td>27±9</td>
<td>21±6</td>
<td>0.5</td>
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<tr>
<td>Pulmonary vascular resistance, dyn·cm⁻¹ s⁻¹</td>
<td>15±5</td>
<td>13±3</td>
<td>17±6</td>
<td>16±5</td>
<td>0.4</td>
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<tr>
<td>Systolic chamber function</td>
<td></td>
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<td></td>
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<tr>
<td>E max, mm Hg/mL</td>
<td>2.8±1.0</td>
<td>3.1±0.8</td>
<td>2.1±0.7*</td>
<td>3.2±1.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Preload</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-diastolic LV volume, mL</td>
<td>114±46</td>
<td>88±24</td>
<td>162±49*</td>
<td>102±34</td>
<td>0.003</td>
</tr>
<tr>
<td>End-diastolic LV pressure, mm Hg</td>
<td>20±7</td>
<td>18±4</td>
<td>21±10</td>
<td>20±7</td>
<td>0.9</td>
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<tr>
<td>Preload index</td>
<td>0.0±1.2</td>
<td>−0.6±0.6</td>
<td>0.9±1.4*</td>
<td>−1.3±1.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Afterload</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-systolic wall stress, mm Hg</td>
<td>348±117</td>
<td>347±76</td>
<td>454±120*</td>
<td>257±68*</td>
<td>&lt;0.001</td>
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<tr>
<td>Effective arterial elastance, mm Hg/mL</td>
<td>1.5±0.7</td>
<td>1.6±0.3</td>
<td>2.2±0.7*</td>
<td>0.9±0.3*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systemic vascular resistance, dyn·cm⁻¹ s⁻¹</td>
<td>119±589</td>
<td>130±400</td>
<td>1624±659</td>
<td>683±273*</td>
<td>0.001</td>
</tr>
<tr>
<td>Afterload index</td>
<td>0.0±1.7</td>
<td>0.2±0.9</td>
<td>1.5±1.7*</td>
<td>−1.5±0.7*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chamber remodeling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-systolic volume, mL</td>
<td>51±38</td>
<td>28±13</td>
<td>99±37*</td>
<td>35±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV mass, g</td>
<td>140±52</td>
<td>109±17</td>
<td>184±74*</td>
<td>134±21</td>
<td>0.005</td>
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<tr>
<td>Noninvasive systolic chamber function</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ejection fraction, %</td>
<td>54±20</td>
<td>65±7</td>
<td>26±9*</td>
<td>65±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Midwall fractional shortening, %</td>
<td>13±6</td>
<td>15±3</td>
<td>6±1*</td>
<td>16±6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global circumferential strain, %</td>
<td>−14±7</td>
<td>−19±4</td>
<td>−6±2*</td>
<td>−18±2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global circumferential strain rate, s⁻¹</td>
<td>−0.8±0.3</td>
<td>−1.0±0.3</td>
<td>−0.4±0.1*</td>
<td>−1.0±0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global longitudinal strain, %</td>
<td>−16±7</td>
<td>−19±4</td>
<td>−8±2*</td>
<td>−22±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Global longitudinal strain rate, s⁻¹</td>
<td>−0.8±0.4</td>
<td>−0.9±0.2</td>
<td>−0.4±0.1*</td>
<td>−1.1±0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peak EIVPD, mm Hg</td>
<td>3.4±1.7</td>
<td>4.0±2.0</td>
<td>2.1±0.6*</td>
<td>4.0±1.5</td>
<td>0.02</td>
</tr>
<tr>
<td>E max-sb1, mm Hg/mL</td>
<td>1.6±0.7</td>
<td>1.7±0.5</td>
<td>2.0±0.6</td>
<td>1.0±0.4</td>
<td>0.02</td>
</tr>
<tr>
<td>E max-sb2, mm Hg/mL</td>
<td>3.6±1.9</td>
<td>5.3±1.4</td>
<td>1.6±0.6*</td>
<td>3.5±1.3*</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values show mean±SD. dP/dt indicates derivative of LV pressure with respect to time; E max, maximal elastance; E max-sb1, single-beat E max estimated by method 1; E max-sb2, single-beat E max estimated by method 2; LV, left ventricular; and peak EIVPD, peak ejection intraventricular pressure difference between the apex and the outflow tract.

*P<0.05: Dunnet comparison against the group of patients with chest pain and normal EF.
question the independent prognostic value of global longitudinal strain recently demonstrated in several conditions. As occurs with EF, the ability of longitudinal strain measurements to predict outcomes may be related to their capacity to amalgamate several variables related to integral pump performance.

### EIVPD as an Index of Systolic Chamber Function

The inotropic sensitivity of the peak EIVPD is based on established fluid dynamic principles and has been empirically confirmed in animals as well as in patients undergoing pharmacological interventions. The potential use of Doppler-derived EIVPD as an index of LV systolic chamber function was first demonstrated in an animal experimental study that showed a close correlation with reference indices based on the pressure–volume relationship. The present study confirms that peak EIVPD closely correlates with $E_{\text{max}}$ in patients and supports its value as an index of LV systolic chamber function in the clinical setting. The relative load independence of peak EIVPD was also previously suggested by animal experimental data and is confirmed in the present clinical study. EIVPD reaches its peak early during ejection, and this fact can probably explain the lower afterload dependence of this index in comparison with other ejection phase indices. We think that the closest relationship with $E_{\text{max}}$ and its relative load stability renders peak EIVPD as one of the most robust and sensitive indices of LV systolic function available using echocardiography.

### Noninvasive Single-Beat Surrogates of Maximal Elastance

Combining LV volumes derived from echocardiography with peripheral arterial pressure has been proposed by several

### Table 3. Correlations Between Noninvasive Indices of LV Systolic Chamber Function and $E_{\text{max}}$

<table>
<thead>
<tr>
<th></th>
<th>$R_{\text{boot}}$</th>
<th>$R_{\text{boot}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction</td>
<td>0.41*</td>
<td>0.30</td>
</tr>
<tr>
<td>Midwall fractional shortening</td>
<td>0.51*</td>
<td>0.40</td>
</tr>
<tr>
<td>Peak EIVPD</td>
<td>0.75*</td>
<td>0.69</td>
</tr>
<tr>
<td>Global circumferential strain</td>
<td>−0.53*</td>
<td>−0.45</td>
</tr>
<tr>
<td>Global circumferential strain rate</td>
<td>−0.46*</td>
<td>−0.34</td>
</tr>
<tr>
<td>Global longitudinal strain</td>
<td>−0.35</td>
<td>−0.16</td>
</tr>
<tr>
<td>Global longitudinal strain rate</td>
<td>−0.37</td>
<td>−0.17</td>
</tr>
<tr>
<td>$E_{\text{max-sb1}}$</td>
<td>−0.05</td>
<td>0.30</td>
</tr>
<tr>
<td>$E_{\text{max-sb2}}$</td>
<td>0.38*</td>
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</tbody>
</table>

$E_{\text{max}}$ indicates ejection intraventricular pressure difference; $E_{\text{max-sb1}}$, single-beat $E_{\text{max}}$ estimated by method 1; $E_{\text{max-sb2}}$, single-beat $E_{\text{max}}$ estimated by method 2; LV, left ventricular; $R$, Pearson correlation coefficient; and $R_{\text{boot}}$, Bootstrap validation after 1000 repetitions.

*P<0.05.
investigators as a surrogate method to noninvasively approximate the ESPVR.\textsuperscript{10,35} Our study demonstrates that these methods have important limitations related not only to the accuracy of the pressure and volume estimation but also to the single-beat approach. The simplest method based on the ratio of end-systolic pressure and end-systolic volume ($E_{\text{max-sb}}$) was more closely related to $E_{\text{max}}$ than the more complex method based on the estimation of the $E_{\text{Nd}}$ ($E_{\text{max-sb}}$). This result confirms that the estimation of $E_{\text{Nd}}$ is the main source of inaccuracy in single-beat calculations as previously demonstrated in experimental studies.\textsuperscript{36} Some authors have assumed that $E_{\text{Nd}}$ is a constant value in humans in the presence or absence of cardiac disease.\textsuperscript{35} However, in ischemic cardiomyopathy, it has been demonstrated that $E_{\text{Nd}}$ differs quantitatively from normal hearts in all phases of the heart cycle.\textsuperscript{35} In addition, for noninvasive application, $E_{\text{Nd}}$ is estimated using a regression model derived from a small group of patients and based on noninvasive measurements of EF and arterial load.\textsuperscript{10} Our results suggest that application of this regression model to heterogeneous groups of patients can be misleading.

**Limitations**

The study was designed to comprehensively validate noninvasive methods against reference standards of global baseline systolic chamber function. Because of the relatively small patient group, validation results may deserve confirmation in a larger sample. We did not perform repeated measurements within subjects to avoid further complexity in the pressure–volume loop catheterization procedure. Although a repeated measures design would have been useful for clarifying load dependence, this design has been reported previously by our group in the animal setting.\textsuperscript{9} Our aim was to analyze the value of different noninvasive indices to account for LV systolic chamber function. The evaluation of myocardial contractility is a different issue that is, difficult to evaluate in vivo. It has been recognized that LV global systolic chamber function, and consequently $E_{\text{max}}$, depends on myocardial contractility, muscle mass, and geometry. Only when mass and geometry are fixed, a shift of the ESPVR can be interpreted as a change in myocardial contractility. However, when evaluating patients with differences in LV mass and shape, as occurs in clinical practice and in the present study, ESPVR reflects changes of chamber properties but not necessarily of myocardial properties. Some authors have suggested normalizing $E_{\text{max}}$ for muscle mass and geometry.\textsuperscript{38} However, important limitations have been recognized for $E_{\text{max}}$ normalization methods, particularly when relative wall thickness is abnormal.\textsuperscript{39} We
think the results of our multiple regression and principal component analyses, showing an irrelevant role of LV mass as a confounder, suggest that mass normalization would not have modified the major findings of our study.

The method to obtain EIVPD is based on offline processing of digital color M-mode Doppler images using a custom-build algorithm that currently is not commercially available. This could limit the clinical application of this tool. However, computational requirements are low, and it could be easily incorporated into the analysis software of future ultrasound scanners to be used at bedside. Currently, strain and SR measurements are used increasingly in clinical practice and also require offline processing.

All noninvasive indices tested in the present study were obtained using Doppler echocardiography. Other modalities such as MRI provide a more accurate estimation of LV volumes, and tagging methods may also provide myocardial strain and SR measurements. However, our specific load-sensitivity results suggest that limitations of indices of systolic chamber function are modality independent.

**Clinical Implications**

Relevant conclusions about the physiopathological mechanisms involved in heart failure have been supported by noninvasive single-beat estimators of pressure–volume indices. Noninvasive single-beat estimations of $E_{\text{max}}$ have been used in the general population to analyze the effect of aging and sex on LV performance and to compare patients with heart failure and normal EF with control subjects. The weak or absent between-subject correlation demonstrated in the present study makes a critical review of these previous studies necessary and encourages the implementation of new Doppler-derived methods in the design of future large-scale studies.

Although EF is currently the pivotal index of systolic function in the clinical setting, under extreme or changing loading conditions, its applicability is limited, and the use of novel noninvasive indices that correlate with $E_{\text{max}}$ could add valuable diagnostic information. Peak EIVPD arises as a reliable index of systolic function that provides additional information not captured by other noninvasive indices.

Examples of potentially relevant scenarios are situations of abnormal load, such as valve regurgitation, congenital heart disease, liver cirrhosis, systemic arteriovenous fistulae, or end-stage renal disease.

**Conclusions**

Noninvasive indices based on Doppler echocardiography have limited accuracy to characterize global LV systolic chamber function in the clinical setting. The Doppler-derived peak EIVPD best correlates with reference indices. This index should be preferred for assessing the state of global LV systolic chamber function, particularly in conditions associated with abnormal load.

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**Disclosures**

None.

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**CLINICAL PERSPECTIVE**

An accurate and reliable assessment of left ventricular systolic function remains a clinical challenge. Because of the well-known limitations of ejection fraction, several alternative methods have been implemented based on myocardial deformation, intraventricular flow dynamics, and single-beat estimations of the end-systolic pressure–volume relationship. In research and clinical practice, these noninvasive methods are increasingly used to assess systolic function in several disease conditions. The purpose of our study was to validate these new methods against maximal elastance obtained from invasive pressure and volume recordings. Specifically, we selected a population with a wide range of loading conditions, including patients with chest pain and normal ejection fraction, dilated cardiomyopathy, and liver cirrhosis. Our results showed that the Doppler-derived peak ejection intraventricular pressure difference was the index that most closely correlated with the reference method. Longitudinal strain–based deformation indices and noninvasive surrogates of maximal elastance were heavily influenced by afterload. In this study, the peak ejection intraventricular pressure difference was the most reliable index to characterize global systolic chamber function in the individual patient. Our findings show that this index is a reliable surrogate of maximal elastance in the clinical setting and may be particularly useful to assess intrinsic left ventricular systolic function. Prospective clinical studies are justified to clarify the definite role of Doppler-derived ejection intraventricular pressure difference for guiding patient care in these scenarios.
Validation of Noninvasive Indices of Global Systolic Function in Patients With Normal and Abnormal Loading Conditions: A Simultaneous Echocardiography Pressure–Volume Catheterization Study

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SUPPLEMENTAL MATERIAL
CALIBRATION OF LV-MASS MEASUREMENTS

Left ventricular (LV) mass was measured with the twofold purpose of 1) computing LV wall volume to calculate end-systolic wall stress (see equation in the main article) and 2) entering LV mass as a covariate for the multivariate analysis of load confounders (Table 4) and as an illustrative variable in the principal components analysis (Figure 3). We measured LV mass using 3-dimensional echocardiography in a specific exam performed for this purpose in the 24 hours following the catheterization study, using either a Vivid 7 or a Vivid 9 system (GE Healthcare). Echo-Pac (General Electric) volumetric quantitation tools were used for processing. To ensure accuracy, were first calibrated 3D-echocardiographic measurements against magnetic-resonance sequences (1.5-T Philips Intera System, cine FISP sequences; measurements processed using QMASS software v. 7 by MEDIS).

Blindly using both techniques (< 24 hours apart), we studied a group of 20 patients with either normal hearts or nonischemic dilated cardiomyopathy (LV mass = 160 ± 55 g, range 104 to 345 g). We observed moderate correlation between modalities (R= 0.76) although there was a systematic overestimation of LV mass using echocardiography (up to 30%) that was responsible for limited agreement (intraclass correlation coefficient: 0.51). Therefore, the regression equation from this training population (MassMR = 0.68 · Mass3D-echo + 13 g) was obtained for calibration.

We tested the performance of the calibration equation in a separate group of 15 patients (LV mass = 132 ± 39 g, range 76 to 239 g). In this testing population, the agreement between values of LV mass obtained by calibrated 3D-echo and MR was now excellent: R= 0.89, intraclass correlation coefficient= 0.90 (95% CI 0.71 to 0.96), error: 1 +- 10%. Therefore, calibrated values of LV mass are used for the estimation of LV end-systolic stress as well as in Table 4 and Figure 3.

MEASUREMENT OF EJECTION INTRAVENTRICULAR PRESSURE DIFFERENCES

If the M-mode cursor closely approximates a flow streamline, the spatiotemporal velocity distribution of a discrete blood sample is provided by the value of its corresponding pixel color: v(s,t), where v represents velocity, s represents the linear dimension of the
streamline, and \( t \) is time. Thus, the color-Doppler M-mode recording provides the data necessary to solve Euler’s momentum equation:

\[
\frac{\partial p}{\partial s} = -\rho \left( \frac{\partial v}{\partial t} + v \frac{\partial v}{\partial s} \right)
\]

where \( P \) is pressure and \( \rho \) is blood density. The first and second terms on the right side of the equation account for inertial and convective acceleration, respectively. Once pressure gradient maps are obtained, total, inertial, and convective EIVPDs are calculated by spatial integration between the apex and the LVOT. Instead of a fixed distance between locations, these 2 positions are traced in each image based on the grayscale layer and the pressure-gradient overlay. Peak values of EIVPD curves were measured constrained to the ejection period.

Values of flow velocity were read directly from the raw velocity data stored digitally in the General Electric proprietary DICOM tags, via hierarchical data format conversion using Echo-Pac.\(^1\) Then velocities are semi-automatically de-aliased based on derivative thresholds. One degree of aliasing is used in image acquisition to increase dynamic range.\(^2\) Smoothing B-splines are used for data filtering and differentiation, and the smoothing parameter has been carefully validated against high-fidelity catheters to remove noise without truncating significant EIVPD waveform features.\(^3,4\) The accuracy of the method has been previously reported\(^4\) and described in detail elsewhere.\(^5\)


