Estimation of left ventricular operating stiffness from Doppler early filling deceleration time in humans

MARIO J. GARCIA,1 MICHAEL S. FIRSTENBERG,1 NEIL L. GREENBERG,1 NICHOLAS SMEDIRA,2 LEONARDO RODRIGUEZ,1 DAVID PRIOR,1 AND JAMES D. THOMAS1

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Garcia, Mario J., Michael S. Firstenberg, Neil L. Greenberg, Nicholas Smedira, Leonardo Rodriguez, David Prior, and James D. Thomas. Estimation of left ventricular operating stiffness from Doppler early filling deceleration time in humans. Am J Physiol Heart Circ Physiol 280: H554–H561, 2001.—Shortened early transmitial deceleration times (EVT) have been qualitatively associated with increased filling pressure and reduced survival in patients with cardiac disease and increased left ventricular operating stiffness (KLV). An equation relating KLV quantitatively to EVT has previously been described in a canine model but not in humans. During several varying hemodynamic conditions, we studied 18 patients undergoing open-heart surgery. Transesophageal echocardiographic two-dimensional volumes and Doppler flows were combined with high-fidelity left atrial (LA) and left ventricular (LV) pressures to determine KLV. From digitized Doppler recordings, EVT was measured and compared against changes in LV and LA diastolic volumes and pressures. EVT (180 ± 39 ms) was inversely associated with LV end-diastolic pressures (r = −0.56, P = 0.004) and net atrioventricular stiffness (r = −0.55, P = 0.006) but had its strongest association with KLV (r = −0.81, P < 0.001). KLV was predicted assuming a nonrestrictive orifice (Knonrest) from EVT as Knonrest = (0.07/EVT)2 with KLV = 1.01 Knonrest − 0.02; r = 0.86, P < 0.001, ΔK(Knonrest − KLV) = 0.02 ± 0.06 mmHg/ml. In adults with cardiac disease, EVT provides an accurate estimate of LV operating stiffness and supports its application as a practical noninvasive index in the evaluation of diastolic function.

METHODS

Patient population. We studied 18 patients (age 62 ± 11 yr, 13 male) undergoing elective open-heart surgery. Eleven patients had coronary artery bypass surgery (CABG) only, two had mitral valve repair only, two had aortic valve replacement only, one had combined CABG and mitral valve repair, one had combined CABG and mitral valve replacement, and one had CABG and aneurysmectomy. Baseline clinical characteristics are shown in Table 1. An institutional review committee approved the study, and all patients pro-

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vided informed consent. All patients were hemodynamically stable and in regular sinus rhythm at the time of the study.

Intraoperative studies. All patients underwent a complete transesophageal echocardiographic (TEE) study using a Hewlett-Packard Sonos 1500 or 2500 (Andover, MA), equipped with a multiplane transesophageal probe. These echocardiographs were chosen in part because they lacked any significant intrinsic temporal delay in the audio Doppler signal output that would effect comparison with the hemodynamic data. After the pericardium was opened and major cardiac vessels were cannulated, a calibrated dual-sensor, high-fidelity pressure transducer catheter (model SPC-751, Millar) was introduced through the right upper pulmonary vein and advanced under TEE guidance until the distal transducer was in the LV cavity and the proximal in the left atrium (LA). Two-dimensional images of the LA and LV were acquired and stored in 0.5 in. videotape and digital media. Pulsed Doppler velocities were obtained sequentially at the levels of the left upper pulmonary vein (PV), mitral annulus, and mitral leaflet tips. These were recorded at a speed of 100 mm/s on 0.5 in. super VHS videotape. A timing signal marker was coupled to the echocardiographic system and to the data acquisition board to match pressure and Doppler signals for each corresponding heartbeat (Fig. 1). LA and LV pressures, electrocardiograms, and timing marker signals were digitally acquired with 1-ms resolution using a multifunction I/O board (AT-MIO-16, National Instruments, Austin, TX) interfaced with a computer workstation (Pentium 200 MHz PC) using customized software developed using LabVIEW v.5.0 (National Instruments, Austin, TX). In addition, the audio Doppler signals (forward and reverse flow) were directly acquired at 20 kHz using a second multifunction I/O board (National Instruments). These were processed using a short-time Fourier transform to reconstruct spectral Doppler images with <5-ms resolution (Fig. 2). Extracted Doppler velocity profiles were resampled to allow precise temporal alignment with LV and LA pressure data. Color Doppler assessment of mitral regurgitant (MR) volume using the proximal isovelocity surface area method (PISA) was performed when MR was present (22).

Hemodynamic conditions. Three complete sets of data including LA and LV pressures, echocardiographic chamber volumes, and pulsed Doppler velocities at the pulmonary vein, mitral annulus, and leaflet tips were acquired during suspended ventilation before cardiopulmonary bypass, during partial (1.5–2 l/min) cardiopulmonary bypass, and after surgery. Ventilation was suspended for at most 20–30 s at a time during which time data collection was performed. All patients had continuous routine oxygen saturation monitoring, and at no time did the value decrease below 95%. The use of intravenous inotropes and vasoactive drugs was maintained steady throughout each phase of data collection. Intravenous neosynephrine was administered at the discretion of the anesthesiologist to increase mean blood pressure by 15% in the postpump study compared with the prepump study if the patient was clinically stable.

Data measurements and analysis. From each data set, LA and LV end-diastolic (EDV) and end-systolic volumes (ESV), and ejection fraction were measured using Simpson's biplane disk method, and LV systolic pressure was determined. Consistent with clinical practice, $t$, time constant of isovolumic LV relaxation; $K_{LV}$, LV operating stiffness; $K_{LA}$, left atrial (LA) operating stiffness.

### Table 1. Clinical and hemodynamic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>62 ± 11</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>13/5</td>
</tr>
<tr>
<td>LV end-diastolic volume, ml</td>
<td>92 ± 36</td>
</tr>
<tr>
<td>LV end-systolic volume, ml</td>
<td>45 ± 25</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>54 ± 13</td>
</tr>
<tr>
<td>LV systolic pressure, mmHg</td>
<td>107 ± 29</td>
</tr>
<tr>
<td>LV end-diastolic pressure, mmHg</td>
<td>16 ± 9</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>79 ± 18</td>
</tr>
<tr>
<td>$t$, ms</td>
<td>58 ± 16</td>
</tr>
<tr>
<td>$K_{LV}$, mmHg/ml</td>
<td>0.16 ± 0.11</td>
</tr>
<tr>
<td>$K_{LA}$, mmHg/ml</td>
<td>0.47 ± 0.52</td>
</tr>
</tbody>
</table>

All data are means ± SD. LV, left ventricle; $t$, time constant of isovolumic LV relaxation; $K_{LV}$, LV operating stiffness; $K_{LA}$, left atrial (LA) operating stiffness.

![Fig. 1. Example of simultaneously acquired left ventricular (LV) and left atrial (LA) pressures, Doppler audio signals, and electrocardiogram (ECG).](image-url)
From the LV pressure waveform, the time constant of isovolumic relaxation ($\tau$) was determined using Weiss' monoeponential equation (28), after curve fitting by use of the Levenberg-Marquardt nonlinear least-squares parameter estimation technique (21). To be consistent with previous work by Yellin et al. (30), a zero asymptote ($b = 0$) was used.

All Doppler measurements were performed from the spectra derived from the digitally stored audio signal. From the PV flow, systolic ($S$), diastolic ($D$), and atrial reversal ($AR$) velocities were obtained, as well as their respective time velocity integrals ($S_{TVI}$, $D_{TVI}$, $AR_{TVI}$). From the LV filling velocities recorded at the tips, peak early ($E$) and atrial contraction ($A$) velocities ($E_{VTI}$, $A_{VTI}$) and $E_{VTI}$ were also automatically determined using customized software. Because the LV stroke volume is equal to the mitral annular area multiplied by its Doppler velocity time integral and no significant area change is assumed, the pulsed Doppler velocity then provides instantaneous flow rate. Therefore, we estimated mitral flow rate as stroke volume divided by the velocity time integral where stroke volume is obtained from the two-dimensional measurements (EDV-ESV). Similarly, instantaneous flow rates across the pulmonary veins were determined from the sum of PV orifice areas and multiplied by their Doppler velocity time integral and no significant area change is assumed, the pulsed Doppler velocity then provides instantaneous flow rate. Therefore, we estimated mitral flow rate as stroke volume divided by the velocity time integral where stroke volume is obtained from the two-dimensional measurements (EDV-ESV). Similarly, instantaneous flow rates across the pulmonary veins were determined from the sum of PV orifice areas and multiplied by the PV $S$ wave velocity integral. The transmitral flow rate was combined with the simultaneous change in LV pressure to derive the LV operating stiffness ($K_{LV}$, $dP_{LV}/dV_{LV}$) during early filling ($K_{LV,E}$), atrial systole ($K_{LV,A}$), and during the total filling period ($K_{LV}$, Fig. 3, A and B). Using a similar method, LA stiffness ($K_{LA}$) during ventricular systole was determined by using LA volume measured after atrial contraction and at end-ventricular systole and by using the PV $S$ velocity tracing to determine the instantaneous flow rate combined with the high-fidelity LA pressure tracings. MR volume was added to the estimation of flow rate when MR was present. $K_{LA}$ during ventricular systole was then estimated as $K_{LA} = \frac{dP_{LA}}{dV_{LA}}$.

Statistical analysis was performed using commercially available software (Systat for Windows v. 7.0). Data are reported as means ± SD.

**Hypothesis testing.** To establish which physiological parameters influence $E_{DT}$, we compared $E_{DT}$ with LA and LV ESV and EDV, stroke volume, MR volume, LA and LV pressures, the LV pressure rise ($dP_{LV}$), and the LA pressure decay ($dP_{LA}$) during early filling, and LA and LV stiffness ($K_{LA}$, $K_{LV,E}$, $K_{LV,A}$, and $K_{LV}$) by using 1) Pearson's correlation with Bonferroni's adjustment for multiple comparisons and 2) single and multiple linear regression analysis.

To determine whether $E_{DT}$ and $K_{LV}$ respond in a similar manner to preload alterations, we compared $P_{LV-ED}$, $K_{LV}$, and $E_{DT}$ before and after preload reduction using paired Student's $t$-tests. We also tested whether the relationship between $K_{LV}$ and $E_{DT}$ was similar during low and normal preload by linear regression.

In an early attempt at predicting ventricular stiffness from transmitral flow, we showed that passive flow through a restrictive orifice between chambers of constant compliance should have a linear velocity decay ($-dV/dt = A_{o}K_{o}(p/5)$), where $A_{o}$ is orifice area, and $p$ is density. Because blood exiting the LA during early LV filling tends to be replaced by blood entering through the pulmonary veins, one can reasonably assume that $K_{LA}$ remains relatively constant and that $K_{o}$ directly reflects $K_{LV}$. Thus, according to this analytic expression, the deceleration rate of the early mitral filling wave ($E_{peak} = -dV/dt = E/E_{DT}$) is linearly related to $K_{LV}$. One limitation of this approach is that it neglects the effect of inertial forces, which significantly prolong flow across nonrestrictive orifices (6). Little et al. (16) more recently proposed a formula for nonrestrictive valves based on a simplified model of transmitral flow as a harmonic oscillator

$$K_{nonrest} = \frac{pL_{ma}}{A_{mv}} \left( \frac{\pi}{2E_{DT}} \right)^{2}$$

(1)

where $A_{mv}$ is mitral valve area and $L_{ma}$ is the effective mitral acceleration length (critical for estimating the inertial component of transmitral flow). Previous in vitro work (4) has shown that $L_{ma}$ is approximately given by $3D + L_{mll}$, where $D$ is effective mitral annular diameter ($4A_{mv}/\pi^{1/2}$) and $L_{mll}$ is mitral leaflet length. Applying typical values of $A_{mv}$ (4 cm$^{2}$) and $L_{ma}$ (3 cm) yields $L_{ma} \approx 9.8$ cm. Substituting this back into Eq. 1 and converting from centimeter-gram-second units to conventional ones (1 mmHg $= 1.333$ dyn/cm$^{2}$) yields $K_{nonrest} = (0.07E_{DT})^{2}$. This equation was used to generate $K_{nonrest}$ for all hemodynamic data sets in all patients, which were then compared with measured $K_{LV}$ by linear regression and analysis of agreement.
To determine whether the relationship between \(E_{DT}\) and \(K_{LV}\) is better supported by physical principles of flow across a restrictive \((K_{rest})\) versus nonrestrictive \((K_{nonrest})\) mitral orifices, we compared the differences between measured and predicted \(K_{LV}\) by both methods using paired Student’s \(t\)-tests. The mean difference \((D_{K})\) between the predicted and the actual LV stiffness was determined as: \(D_{K_{rest}} = K_{rest} - K_{LV}\) and \(D_{K_{nonrest}} = K_{nonrest} - K_{LV}\).

**RESULTS**

Hemodynamic measurements were obtained in 18 patients. In each patient, recording of measurements from three different conditions were attempted. Fifteen patients had all three measurements recorded. One patient undergoing mitral valve replacement had two data sets recorded but did not have invasive data following valve replacement. One patient only had two conditions collected because of hemodynamic instability and, in one patient, two data sets were rejected because of technical problems during acquisition. Overall, 50 of the 52 available data sets were analyzed. No complications related to the experimental protocol occurred.

Two-dimensional and Doppler echocardiographic variables and hemodynamic characteristic for the group are shown in Table 1. LV EDV ranged from 31 to 158 ml (92 ± 36 ml), ejection fraction from 0.20 to 0.74 (0.54 ± 0.13), \(P_{LV-ED}\) from 6 to 40 mmHg (16 ± 9 mmHg), and \(K_{LV}\) from 0.02 to 0.51 mmHg/ml (0.16 ± 0.11 mmHg/ml), indicating significant heterogeneity in the study group.

The correlation between \(E_{DT}\) and hemodynamic parameters is shown in Table 2. By univariate analysis, a shorter \(E_{DT}\) (180 ± 39 ms) was associated with higher LV \(P_{LV-ED}\) \((r = -0.56, P < 0.005)\), higher LV \(dP_{LV}\) \((r = -0.67, P < 0.001)\), higher LV \(K_{LV-A}\) \((r = -0.73, P < 0.001)\), and higher LV operating stiffness during the total filling period \((K_{LV}, r = -0.81, P < 0.001)\). In addition, higher \(P_{LA-Y}\) \((r = -0.49, P = 0.04)\) was also associated with a shorter \(E_{DT}\). There was an inverse relationship between the \(E_{DT}\) and MR volume as determined by PISA \((r = -0.49, P = 0.05)\). The magnitude of \(dP_{E\_LA}\) during early LV filling was significant \((12 ± 10 mmHg)\) and also correlated significantly with \(E_{DT}\) \((r = -0.54, P = 0.008)\). This LA pressure drop was significantly higher than the LV pressure rise during early filling \((LV_{dPE} = 1.3 ± 1.6 mmHg, P < 0.001)\). Neither \(LV_{dPE}\) nor \(K_{LV-E}\) had a significant association with \(E_{DT}\). Figure 3A illustrates an example of the simultaneous pulsed Doppler, LV and LA pressure, and pressure-volume curve (Fig. 3B). As demonstrated...
between observed (K).

Little’s equation for nonrestrictive orifices to the 50

which could be attributed to significant unaccounted

6 to 196

the early transmitral filling deceleration time

Table 2. Univariate and multivariate determinants of
the early transmitral filling deceleration time

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>P (Univariate)</th>
<th>P (Multivariate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV end-diastolic volume</td>
<td>0.007</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>LV end-systolic volume</td>
<td>-0.23</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.48</td>
<td>0.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LV end-systolic pressure</td>
<td>-0.24</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>LV end-diastolic pressure</td>
<td>-0.56</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.19</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>( \tau )</td>
<td>-0.15</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mitral regurgitant volume</td>
<td>-0.49</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>( P_{LA-Y} )</td>
<td>-0.49</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>( dP_{LA} )</td>
<td>-0.54</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>( K_{LA} )</td>
<td>-0.44</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>( dP_{LV} )</td>
<td>-0.11</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>( K_{LV-E} )</td>
<td>0.04</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>( K_{LV-A} )</td>
<td>-0.73</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>( K_{5} )</td>
<td>-0.55</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>( K_{15} )</td>
<td>-0.61</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\( P_{LA-Y} \), peak LA pressure during LV systole (v wave); \( dP_{LA} \), LA pressure decay during early LV filling; \( K_{LA} \), LA operating stiffness; \( K_{LV-E} \), LV pressure rise during early filling; \( dP_{LV} \), LV diastolic pressure rise; \( K_{LV-A} \), LV operating stiffness during early filling; \( K_{5} \), LV operating stiffness during atrial systole; \( K_{15} \), LV diastolic operating stiffness. \( r \), correlation coefficient; NS, not significant.

in this case, LV filling starts before the nadir of LV pressure, and LV pressure crossover occurs before a significant LV pressure rise, indicating a negative value for LV operating stiffness during early filling, a phenomenon that could be explained by the effect of active relaxation (12).

By multiple linear regression, both LV ejection fraction and deceleration time were independent determinants of \( K_{LV} \), with no additional significant independent contribution from any other physiological variable.

Effect of preload reduction in \( E_{DT} \) and \( K_{LV} \). LV EDV decreased from 102 \( \pm \) 36 ml before cardiopulmonary bypass to 87 \( \pm \) 38 ml during partial cardiopulmonary bypass (\( P = 0.009 \)). As expected, \( K_{LV} \) decreased during preload reduction from 0.20 \( \pm \) 0.12 mmHg/ml at \( P_{LV-ED} = 19 \pm 10 \) mmHg to \( K_{LV} = 0.11 \pm 0.07 \) mmHg/ml at \( P_{LV-ED} = 14 \pm 7 \) mmHg, \( P = 0.0008 \), Fig. 4A. In a similar manner, \( E_{DT} \) increased from 166 \( \pm \) 37 to 196 \( \pm \) 35 ms, \( P = 0.0006 \) (Fig. 4B). The relationship between observed (\( K_{LV} \)) and predicted stiffness assuming nonrestrictive orifice (\( K_{nonrest} \)) was similar during normal (\( r = 0.83, K_{LV} = 1.06K_{nonrest} - 0.01 \) mmHg/ml, \( P < 0.01 \)) and low preload (\( r = 0.91, K_{LV} = 0.87K_{nonrest} - 0.01 \) mmHg/ml, \( P < 0.001 \), Fig. 5). There was no significant change in LV relaxation (\( \tau = 57 \pm 15 \) ms before vs. \( 53 \pm 10 \) ms during partial bypass, \( P = 0.22 \)).

Quantitative prediction of \( K_{LV} \) using \( E_{DT} \). Using the simplified equation for restrictive orifices, we found a modest correlation between observed and predicted (\( K_{rest} \)) stiffness (\( r = 0.71, P < 0.001 \), Fig. 6) but a significant underestimation \( [K_{LV} = 2.56 K_{rest} + 0.01 \) mmHg, \( \Delta K (K_{rest} - K_{LV}) = -0.10 \pm 0.09 \) mmHg/ml], which could be attributed to significant unaccounted effects of inertial forces. On the other hand, applying Little’s equation for nonrestrictive orifices to the 50

hemodynamic states yielded \( K_{nonrest} \) ranging from 0.07 to 0.52 mmHg/ml (0.18 \( \pm \) 0.10 mmHg/ml). There was a significantly closer agreement between \( K_{nonrest} \) and \( K_{LV} \): \( K_{LV} = 1.01K_{nonrest} - 0.02, r = 0.86, P < 0.001 \), \( \Delta K = 0.02 \pm 0.06 \) mmHg/ml (Fig. 7, A and B). These differences between observed and predicted LV stiffness using both methods [(\( K_{rest} - K_{LV} \)) vs. (\( K_{nonrest} - K_{LV} \))] were highly significant (\( P < 0.0001 \)).

Fig. 4. A: changes in LV end-diastolic pressure (\( P_{LV-ED} \)) and LV operating stiffness (\( K_{LV} \)) during preload reduction. B: changes in \( P_{LV-ED} \) and transmitral early filling deceleration time (\( E_{DT} \)) during preload reduction.

Fig. 5. Correlation between observed \( K_{LV} \) and predicted LV stiffness assuming nonrestrictive mitral valve orifice (\( K_{nonrest} \)) under normal and low preload conditions.
DISCUSSION

The results of the present study indicate that in adults with cardiac disease, early LV $E_{DT}$ provides a good estimate of $K_{LV}$ and thus may be used as a practical noninvasive clinical index in the evaluation of diastolic function. In addition, our findings suggest that changes in measurements of $E_{DT}$ in individual patients or study populations over time may be caused by changes in preload.

$K_{LV}$ is governed by a complex interplay of myocardial stiffness (largely related to the tissue collagen content) (10), ventricular geometry (hypertrophy) (9), and myocardial relaxation (26). In a “compliant” LV (low $K_{LV}$) increasing filling volumes result in proportionally smaller increments in end-diastolic pressure than in a “stiffer” ventricle. Increased stiffness may occur as a result of LV remodeling in hypertensive cardiac disease and infiltrative hypertrophic and dilated cardiomyopathies, part of the normal aging process, and is often responsible for reduced cardiac output during exercise. Unfortunately, $K_{LV}$ is difficult to measure in clinical practice even with invasive techniques, which require simultaneous high-fidelity pressure measurements and volume assessment with high temporal resolution. Several Doppler echocardiographic indexes of LV filling have been proposed as qualitative estimates of $K_{LV}$, including deceleration time of the early mitral filling wave ($E_{DT}$) (2, 24). Shortened deceleration times have been associated with reduced ventricular compliance in patients with restrictive cardiomyopathy (14) and poor survival in congestive heart failure (29). Whereas these observations have been of great value in identifying patients with reduced ventricular compliance, the lack of quantitative rigor in relating $E_{DT}$ to compliance has limited the utility of this index in serial follow-up of patients undergoing pharmacological therapy.

Prior in vitro work has suggested that the deceleration rate through a restrictive orifice is proportional to $K_{LV}$ (5). In this early attempt, we showed that passive flow through a restrictive orifice at constant stiffness should have a linear velocity decay ($-dV/dt = A_p K_{LV} / \rho$), with convincing in vitro proof (6), suggesting for the first time that $K_{LV}$ be measurable noninvasively. This observation neglects Newton’s second law, assuming that blood velocity across the mitral valve is given instantaneously by the simplified (noninertial) Bernoulli equation: $\Delta P = \frac{1}{2} \rho V^2$. Net stiffness is by definition $d\Delta P/dV$, where $dV$ reflects the movement of blood from the LA to the LV. By the derivative chain rule, because $\Delta P$ and $V$ are unique functions of time, $d\Delta P/dV$ can be written as $(d\Delta P/dt)/(dV/dt)$. From the Bernoulli equation, $d\Delta P/dt$ is $\rho(dV/dt)$, and $dV/dt$ is given from the mitral valve area ($A_{mv}$) and instantaneous velocity ($v$) as $-A_{mv} v$. Thus $K_{LV} = -\rho (dV/dt)/A_{mv}$.

This equation was implicitly validated in humans with mitral stenosis when we showed that the mitral pressure half-time was directly related to net atrioventricular compliance and the square root of the initial pressure gradient and inversely related to valve area (27). However, for patients with normal mitral valve area, inertia keeps blood moving forward, even after the atrioventricular gradient has fallen to zero, significantly prolonging deceleration time (relative to what would be expected without inertia) and thus underestimating true stiffness. Thus it is not surprising that applying this principle to the current data set yielded a predicted $K_{LV}$, based on assumption of a $K_{rest}$ of $0.06 \pm 0.03$ mmHg/ml, correlating with true $K_{LV}$ ($r = 0.71$), but with significant underestimation: $K_{LV} = 2.56 K_{rest} + 0.01$, $r = 0.71$, $P < 0.001$, $\Delta K = K_{rest} - K_{LV} = -0.10 \pm 0.09$ mmHg/ml.

To avoid this restrictive orifice requirement, Little’s group has modeled the atrium, ventricle, and valvular apparatus as a simple harmonic oscillator, a purely inertial system, with validation in a canine model (16, 19). With this inertial paradigm, they showed that $E_{DT}$
is inversely proportional to the square root of ventricular stiffness $K_{LV}$, or $E_{DT} \propto 1/\sqrt{K_{LV}}$. With the development of congestive heart failure over a 4-week period of rapid atrial pacing (with LV end-diastolic pressure rising from 9.8 to 34.3 mmHg), deceleration time fell from 88 to 51 ms with close correlation to $1/\sqrt{K_{LV}}$ ($r = 0.94$). Although encouraging, extrapolating their results to humans with various cardiac diseases needs to be done cautiously because the number of animals was small and constituted a homogeneous group, all with dilated cardiomyopathy. One of the assumptions that Little made is that the effect of LA stiffness is negligible, because during early LV filling the LA behaves mostly as a conduit, maintaining relatively constant volume and pressure as the volume of blood that moves to the LV is replaced by incoming flow from the pulmonary veins. Although our results indicate that this assumption may not be entirely correct in humans, where a significant LA pressure drop occurred during early LV filling, it is gratifying that direct application of Little’s formula to the current data suggests that $K_{LV}$ can indeed be predicted quantitatively from $E_{DT}$ in patients with cardiac disease.

It should be recognized that the concept of LV “compliance” during early diastole is complicated because of the competing effects of ongoing ventricular relaxation and filling. The relatively low rise in LV pressure during early filling (which even falls early after mitral valve opening) can be explained by ongoing active LV relaxation reducing early LV operating stiffness, explaining the prolonged $E_{DT}$ in patients with delayed LV relaxation. In contrast, the presence of a rapid isovolumic descent toward the concave-downward portion of the LV pressure-volume curve at low ESV in vigorous ventricles with rapid active relaxation may explain the apparent paradox of the “pseudorestrictive filling pattern” seen in healthy children and athletes: below the equilibrium volume, the diastolic pressure-volume curve actually is stiffer than at the equilibrium volume, thus producing shorter deceleration times. For purposes of this study, we used a simple but clinically appealing definition of stiffness, the change in pressure during diastole divided by the change in volume, which showed the strongest (inverse) correlation with $E_{DT}$. Other authors have sought indexes of end-diastolic LV stiffness, because it best reflects the passive properties of the fully relaxed LV chamber. Rossvoll and Hatle (24) have shown that the duration of the pulmonary venous A wave was prolonged when LV end-diastolic pressure was elevated, whereas the transmitral A wave was shortened by the rapid rise in pressure in the ventricle. A pulmonary A wave longer in duration than the mitral A wave predicted patients with LV end-diastolic pressure $>15$ mmHg with a sensitivity of 85% and a specificity of 79%. Furthermore, the difference in flow duration was correlated with end-diastolic pressure ($r = 0.68$) and the rise in LV pressure with atrial contraction ($r = 0.70$). Appleton et al. (1) noted a similar value to the mitral and pulmonary venous A wave duration in estimating LV end-diastolic pressure, as well as the importance of LA size in identifying patients with diastolic dysfunction when the transmitral flow profile is equivocal (1). These observations, although clinically helpful, have been so far empirical and have certain limitations. The latter method requires the presence of regular sinus rhythm and stable heart rates because both mitral inflow and PV flow cannot be recorded simultaneously. Furthermore, the duration of the mitral A wave, but not the AR, may be shortened by the onset of ventricular systole, therefore changes in heart rate or P-R interval will alter their relationship. Pulmonary venous AR waves are often difficult to record by transthoracic Doppler. In addition, patients with restricted LV filling have small or absent atrial reversal waves possibly due to either atrial mechanical failure (20) or increased stiffness in the pulmonary venous vasculature.

Limitations. Our study was performed in the operating room on patients with an open chest and pericardium. The pericardial influence on diastolic filling has been investigated using animal models and in patients undergoing cardiac surgery (15). The end-diastolic pressure-volume relationship may be shifted downward slightly after pericardiectomy (3, 11). Whereas removing the pericardium alters the interventricular and the atrioventricular interdependence, these effects tend to be very small and should not alter significantly the overall relationship of intracardiac hemodynamic parameters.

The effects of positive pressure ventilation are to reverse the usual respirophasic changes in left- and right-sided flows, with right-sided flow decreasing rather than increasing with inspiration, partially blunted when the thorax is open. However, these effects were minimized by collecting the data during apnea at atmospheric pressure.

We have used TEE measurements of LV volumes and added mitral annular flow calculation of flow rates ($dV/dt$) to derive LV stiffness. Volume measurements derived by TEE may be less accurate than those provided by transthoracic or epicardial echo but are more practical for application in our experimental setting. In addition, there are inherent and often operator-dependent errors in measuring LV and LA volumes using the Simpson’s biplane disk method. To minimize these errors, all TEE studies were performed by a single physician with advanced training and expertise in echocardiography (M. J. Garcia). Particular attention was placed on careful manipulation of the TEE probe to minimize LV foreshortening. However, despite careful attention to technique and analysis methods, these inherent limitations in assessing volumes may, in part, account for the observed scattering of the data.

Measurements of $E_{DT}$ may be difficult to obtain in patients with tachycardia and shortened A-V intervals because of E and A fusion. Fortunately, in our study population, a clear separation between the E and A waves was observed in all patients under all conditions.

The association between $E_{DT}$ and $K_n$ and the importance of $K_{LA}$ may be underestimated due to greater inaccuracy of the method that we employed for LA.
volume calculations, because we used the ratios of systolic over total pulmonary venous flow derived from a single pulmonary vein sample and adjusted for mitral regurgitant volumes.

Although our study demonstrates a strong correlation between \( E_{VT} \) derived \( K_{piston} \) and \( K_{LV} \), there was significant scattering of the data. Therefore, this quantitative index may be most useful in interpreting changes that occur within an individual over time.

In conclusion, this study demonstrated that \( E_{VT} \), an easily obtained Doppler filling parameter, may not only provide qualitative and prognostic information in patients with diastolic dysfunction, but it can also provide a quantitative estimate of \( K_{LV} \). Because \( K_{LV} \) may vary with preload alterations, this index may also be utilized to evaluate the effect of therapeutic interventions in patients with congestive heart failure.

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