Validation of a novel noninvasive cardiac index of left ventricular contractility in patients

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Zhong L, Tan R-S, Ghista DN, Ng EY, Chua I-P, Kassab GS. Validation of a novel noninvasive cardiac index of left ventricular contractility in patients. Am J Physiol Heart Circ Physiol 292: H2764–H2772, 2007. First published January 19, 2007; doi:10.1152/ajpheart.00540.2006.—Although there are several excellent indexes of myocardial contractility, they require accurate measurement of pressure via left ventricular (LV) catheterization. Here we validate a novel noninvasive contractility index that is independent only on lumen and wall volume of the LV chamber in patients with normal and compromised LV ejection fraction (LVEF). By analysis of the myocardial chamber as a thick-walled sphere, LV contractility index can be expressed as maximum rate of change of pressure-normalized stress (dP/dt)max. To validate this parameter, dP/dtmax was determined from contrast cine-ventriculography-assessed LV cavity and myocardial volumes and compared with LVF, dP/dtmax, maximum active elastance (Ea,max), and singlebeat end-systolic elastance [Ees(SB)] in 30 patients undergoing clinically indicated LV catheterization. Patients with different tertiles of LVF exhibit statistically significant differences in dP/dtmax. There was a significant correlation between dP/dtmax and dP/dtmax (dP/dtmax = 0.0075dP/dtmax − 4.70, r = 0.88, P < 0.01), Ea,max (dP/dtmax = 1.20Ea,max + 1.40, r = 0.89, P < 0.01), and Ees(SB) (dP/dtmax = 1.60Ees(SB) + 1.20, r = 0.88, P < 0.01). In 30 additional individuals, we determined sensitivity of the parameter to changes in preload (intravenous saline infusion, n = 10 subjects), afterload (sublingual glyceryl trinitrate, n = 10 subjects), and increased contractility (intravenous dobutamine, n = 10 patients). We confirmed that the index is not dependent on load but is sensitive to changes in contractility. In conclusion, dP/dtmax is equivalent to dp/dmax, Ea,max, and Ees(SB) as an index of myocardial contractility and appears to be load independent. In contrast to other measures of contractility, dP/dtmax can be assessed with noninvasive cardiac imaging and, thereby, should have more routine clinical applicability.

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ing $E_{\text{es}}$ without loading interventions (37, 38, 44). Senzaki et al. (37) described a method for estimating $E_{\text{es(SB)}}$ that is based on normalized time-varying elastance curves. In subsequent studies, this method was improved by adjustment of the normalized elastance curve to compensate for load dependencies and contractility (38).

Zhong et al. (46) introduced the formulation of an active LV elastance term, $E_{a,max}$, derived from LV pressure-volume data. $E_a$ represents LV myocardial sarcomere activation; hence, the peak $E_a$ ($E_{a,max}$) is hypothesized to represent LV contractile function. Nevertheless, the use of $E_{a,max}$ as an intrinsic LV contractility index is tempered by the need for invasive LV pressure measurement and complex and time-consuming computations (see APPENDIX A).

The $dP/dt_{max}$ is based on LV intracavity pressure, which is generated by an active myocardial stress. Hence, it is more appropriate to formulate an LV contractility index on the basis of LV wall stress (5, 9, 24). Numerous methods have been devised to measure LV wall stress (13) or to approximate it by use of geometric models (8, 19, 36). Measurement of transmural wall stress (with implantable strain gauges) is hampered, however, by the degree of coupling between the transducer and the ventricular wall (5).

We previously hypothesized that LV contractility is the capacity of the LV to develop intramyocardial stress to eject blood volume as rapidly as possible (45). On the basis of this concept, we developed an LV contractility index based on wall stress in a spherical LV model. The LV contractility index is formulated as follows: $d(t^*/P)/dt_{max}$ or $d\sigma^*/dt_{max}$, where $\sigma^* = \sigma/P$. In contrast to $dP/dt_{max}$, $E_{a,max}$, and $E_{\text{es(SB)}}$, this novel index is derived solely from LV intracavity and myocardial wall volume data, which can be determined noninvasively. Since this approach obviates the need for invasive pressure measurement, it has the potential to become a clinical routine with noninvasive imaging of ventricular volume and myocardial mass.

In the present study, we describe a proof of concept for this novel stress-based LV contractility index by validating it against $dP/dt_{max}$, $E_{a,max}$, and $E_{\text{es(SB)}}$ in 30 individuals with disparate ventricular function. Furthermore, we verified the load independence of the index under different preload and afterload conditions.

**METHODS**

**Experiment I: comparison of $d\sigma^*/dt_{max}$ with $dP/dt_{max}$, $E_{a,max}$, and $E_{\text{es(SB)}}$ determined from invasive cardiac catheterization.** Thirty patients with diverse cardiac conditions undergoing clinically indicated invasive cardiac catheterization were enrolled in the study, which was approved by the Local Research Ethics Committee. Informed consent was obtained from each patient.

The catheterization laboratory employs a Philips Integris Allura 9 with the Dynamic Flat Detector (Philips Medical Systems, Best, The Netherlands) X-ray imaging system. Standard techniques used to advance catheters in retrograde fashion across the aortic valve allowed continuous measurement of LV chamber pressure. The LV pressure was then differentiated with respect to time for determination of maximal rate of increase during systole (LV $dP/dt_{max}$). The peak ECG R wave was used as an end-diastolic timing marker. Straight or angled six-side-hole pigtail catheters (5-F or 6-F) were used at the discretion of the operator. Each patient underwent rapid bolus infusion of 30–36 ml of nonionic radiopaque contrast into the LV through the pigtail catheter at 10–12 ml/s.

Ventriculograms were obtained in the standard 30° right anterior oblique projection with a 9-in. image intensifier at a speed of 50 frames per second. Ventriculography and hemodynamic data analyses were performed offline. Planimetry of single-plane LV endocardial and epicardial areas (aided by automated border detection) and LV long-axis length determination allowed calculation of frame-to-frame variation in LV intracavity volumes as well as LV myocardial volumes using the corresponding Viewstation (Philips Medical Systems; Fig. 1) (3, 30, 34). ECGs were recorded continuously with the ventriculograms. The images chosen for planimetry were from the first sinus beat with adequate opacification. LV ejection fraction (LVEF) was easily calculated from LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) as follows: LVEF = (LVEDV − LVESV)/LVEDV.

The $dP/dt_{max}$ was calculated, using Matlab software, as the maximum first time derivative of the LV pressure-time plot (Fig. 2). The formulation for calculation of active elastance is described in APPENDIX A, and that of the proposed wall stress-based LV contractility index is briefly described below and in more detail in APPENDIX B.

**Experiment II: load independence of echocardiographically derived $d\sigma^*/dt_{max}$.** An additional 30 volunteers were subsequently recruited for studies in which echocardiographic examinations were performed, and $d\sigma^*/dt_{max}$ was derived from noninvasively determined LV cavity and myocardial volumes at baseline and after physiological manipulations of preload, afterload, or myocardial contractility. The study was approved by the Local Research Ethics Committee, and informed consent was obtained from each individual.

There were three groups of volunteers: 10 healthy subjects were given sublingual glyceryl trinitrate (500–1,000 μg) to decrease afterload, with a target decrease in systolic blood pressure of ≥10% (group A), 10 healthy subjects received intravenous normal saline solution (500 ml) over 20–30 min to increase preload (group B), and 10 consecutive patients were scheduled to undergo clinically indicated dobutamine stress echocardiography (group C). In all subjects, echocardiography was performed at baseline, as well as after alterations of afterload, preload, and myocardial contractility. In group C, echocardiographic measurements were made during intravenous dobutamine infusion at 5.0 μg·kg⁻¹·min⁻¹, a dose that increases myocardial contractility but does not have significant cardiac chronotropic or volume effects.

![Fig. 1. ECG-triggered contrast cine left ventriculography at the right anterior oblique projection depicting opacified left ventricular (LV) cavity at the end-diastolic phase of the cardiac cycle. End-diastolic and end-systolic endocardial contours are outlined. An ~4-cm segment of LV free wall epicardium at the junction of the apical and middle thirds is also depicted. Average LV wall thickness is obtained from the quotient of this segmental area and segmental length. From this, myocardial wall volume can be estimated (30, 34).](image-url)
The algorithm is based on the elastance curve derived from the tance. It is primarily focused on the shape of the
pressure-volume loop (38). It is primarily focused on the shape of the
(AVA

velocity sampled at the LVOT and AVA is the aortic valve area
from beginning of isovolumic contraction (frame 1).

in 1 representative subject (subject x). Measurements have been corrected for geometric distortion from the respective recording systems. Bottom: pressure-volume relation in subject x. Ascending numbers indicate frame number (each frame lasts 20 ms) from beginning of isovolumic contraction (frame 1). Frames 1–5, isovolumic contraction; frames 5–17, ejection; frames 17–21, isovolumic relaxation; frames 21–36, ventricular filling.

All echocardiograms were acquired using Vivid 7 (General Electric). M-mode measurements of the LV were obtained, and LV mass was calculated using standardized methodology (6, 18). Myocardial volume was calculated by dividing LV mass by myocardial density (assumed to be 1.05 g/ml). Furthermore, two-dimensional apical four- and two-chamber views of the LV were acquired, and end-diastolic and end-systolic endocardial contours were manually outlined. The corresponding LVEDV and LVESV were then automatically determined using Simpson’s biplane method. Pulse-wave echocardiographic Doppler interrogation of the LV outflow tract (LVOT) allowed, in the absence of significant mitral regurgitation or aortic valve dysfunction, calculation of the maximal LV volume rate (dV/dt max) during ejection: 

\[ \frac{dV}{dt_{\text{max}}} = \frac{V_{\text{peak}}}{\text{AVA}} \]

where \( V_{\text{peak}} \) is the peak velocity sampled at the LVOT and AVA is the aortic valve area (AVA = \( \pi D^2/4 \), where \( D \) is the LVOT diameter measured in the 2-dimensional parasternal long-axis image of the heart). Substitution of values of myocardial volume and dV/dt max into Eq. 7 (see below) yields d\( \sigma \)/dt max.

Derivation of a novel wall stress-dependent LV contractility index.

For simplicity, we approximate the LV as a thick-walled spherical shell consisting of incompressible, homogeneous, isotropic, elastic material. The inner and outer radii of the shell are denoted \( r_i \) and \( r_e \) respectively. The epicardial (outer) surface is considered load free, whereas the endocardial surface is subjected to LV intracavity pressure P(t), where \( t \) is time. The circumferential wall stress (\( \sigma_e \)) can be expressed at any transmural radial position in the wall (r) as

\[
\sigma_e(r) = \frac{P \left( \frac{r_i^3}{r_e^3} \left( 1 + \frac{r_e^3}{2r_i^3} \right) \right)}{\left( 1 - \frac{r_i^3}{r_e^3} \right)}
\]

(see appendix B for derivation). In this model, the maximum wall stress occurs at the endocardium, \( r = r_i \), and is given by

\[
\frac{\sigma_e(r_i)}{P} = \frac{\frac{r_i^6}{r_e^6} + 1/2}{1 - \frac{r_i^3}{r_e^3}}
\]

(3)

The geometric relation between wall volume (\( V_w \)), LV cavity volume (V), \( r_i \), and \( r_e \) can be expressed as

\[
V_w = 4\pi(r_e^3 - r_i^3)/3 \quad \text{and} \quad V = 4\pi r_i^3/3
\]

(4)

If we combine Eqs. 3 and 4, we obtain the desired result

\[
\frac{\sigma_e(r_i)}{P} = \frac{\left( V/(V+w) + 1/2 \right)}{1 - V/(V+w)} = \frac{3V + V_w}{2V_w}
\]

(5)

By normalizing wall stress to LV intracavity pressure (P), an index of LV contractile function may result as

\[
\frac{\sigma_e/P}{V_w} = \frac{3V + V_w}{2V_w}
\]

(6)

This notion is based on the premise that LV wall stress (due to LV myocardial sarcomere contraction) is responsible for the development of LV pressure. Hence, it is more rational to base LV contractility index on LV wall stress per pressure, rather than on stress or pressure alone.

Analogous to dP/dt max, we propose an LV contractility index as the maximal rate of change of pressure-normalized wall stress

\[
\frac{d\sigma_e/P}{dt_{\text{max}}} = \frac{d(V/w)}{dt_{\text{max}}} = \frac{3}{2V_w} \left( \frac{dV}{dt} \right)_{\text{max}}
\]

(7)

Obviously, this index is independent of pressure by definition.

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ANOVA revealed significant intergroup differences. Linear regression analysis was employed to quantify the correlation between $d\sigma%/dt_{\text{max}}$ and other indexes of LV contractility [$dP/dt_{\text{max}}, E_{\text{a,max}},$ and $E_{\text{est(SB)}}$]. In experiment II, paired Student’s $t$-test was used to compare parameters measured at baseline and after physiological manipulation.

### RESULTS

**Correlation of $d\sigma%/dt_{\text{max}}$ with $dP/dt_{\text{max}}, E_{\text{a,max}}$, and $E_{\text{est(SB)}}$.** Thirty volunteers [mean 58.1 (range 48–77) yr of age, 13:2 male-to-female ratio] with diverse cardiac conditions were recruited for experiment I. Sample LV pressure-volume data from one patient are shown in Fig. 2. LVEF and $dP/dt_{\text{max}}$ were computed directly from these traces. $E_a$ at various times was also computed from the pressure-volume loops (Table 1), as described in APPENDIX A. $E_{\text{a,max}}$ was extrapolated from the peak of the $E_a$-time curve (Fig. 3). $E_{\text{est(SB)}}$ was also computed from the pressure-volume loop using Eq. 1.

Ages, heart rates, ejection fractions, and derived LV contractility parameters of the patients are shown in Table 2. The patients were divided into three groups on the basis of tertiles of LVEF, with 10 individuals in each group. Intergroup comparisons show significant differences ($P < 0.05$) between the mean values of $dP/dt_{\text{max}}, E_{\text{a,max}}, E_{\text{est(SB)}}$, and $d\sigma%/dt_{\text{max}}$ in those in the highest tertile compared with those in lowest and middle tertiles.

There is agreement in regard to the proposed index $d\sigma%/dt_{\text{max}}$ with $dP/dt_{\text{max}}, E_{\text{a,max}},$ and $E_{\text{est(SB)}}$ across the three tertiles of ascending LVEF values, with statistically significant differences in LV contractility indexes among the three groups. The average values of $dP/dt_{\text{max}}, E_{\text{a,max}}, E_{\text{est(SB)}}$, and $d\sigma%/dt_{\text{max}}$ for the highest tertile were $1,360 \pm 97$ mmHg/s, $3.61 \pm 0.62$ mmHg/ml, $2.81 \pm 0.51$ mmHg/ml, and $5.64 \pm 1.13$ s$^{-1}$, respectively. Values of $dP/dt_{\text{max}}, E_{\text{est(SB)}}$, and $d\sigma%/dt_{\text{max}}$ were statistically significantly lower in patients in the lowest and middle tertiles than those in the highest tertile.

Figure 4 summarizes the correlation between $d\sigma%/dt_{\text{max}}, dP/dt_{\text{max}},$ and $E_{\text{a,max}}$ as well as $E_{\text{est(SB)}}$. Linear regression analysis revealed good correlation between $d\sigma%/dt_{\text{max}}$ and $dP/dt_{\text{max}}, E_{\text{a,max}}$, and $E_{\text{est(SB)}}$, with significant correlation coefficients of $-0.9$ in each case: $d\sigma%/dt_{\text{max}} = 0.0075 dP/dt_{\text{max}} - 4.70 \ (r = 0.88, P < 0.01)$, $d\sigma%/dt_{\text{max}} = 1.20 E_{\text{a,max}} + 1.40 (r = 0.89, P < 0.01)$, and $d\sigma%/dt_{\text{max}} = 1.60 E_{\text{est(SB)}} + 1.20 (r = 0.88, P < 0.01)$. In contrast, the correlation between $d\sigma%/dt_{\text{max}}$ and LVEF is less strong ($r = 0.71$), as is the correlation between $E_{\text{est(SB)}}$ and LVEF ($r = 0.78$), underscoring the lack of specificity of LVEF as an index of myocardial contractility.

**Load independence of $d\sigma%/dt_{\text{max}}$.** In experiment II, we studied alterations in $d\sigma%/dt_{\text{max}}$ under various loading conditions. We induced a significant decrease in blood pressure and increase in LVEDV in groups $A$ and $B$, respectively (Table 3). There was no significant change in $d\sigma%/dt_{\text{max}}$ in response to

### Table 1. $E_a$ at discrete time points during isovolumic contraction and relaxation in subject

<table>
<thead>
<tr>
<th>Frame No. ($i$)</th>
<th>$i$, s</th>
<th>$P$, mmHg</th>
<th>$V$, ml</th>
<th>$E_a$, mmHg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isonovolumic contraction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>18</td>
<td>136.7</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.02</td>
<td>22</td>
<td>135.7</td>
<td>0.0295</td>
</tr>
<tr>
<td>3</td>
<td>0.04</td>
<td>32</td>
<td>134.6</td>
<td>0.1038</td>
</tr>
<tr>
<td>4</td>
<td>0.06</td>
<td>52</td>
<td>133.5</td>
<td>0.2536</td>
</tr>
<tr>
<td>5</td>
<td>0.08</td>
<td>80</td>
<td>132.5</td>
<td>0.4636</td>
</tr>
<tr>
<td><strong>Isovolumic relaxation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>0.34</td>
<td>74</td>
<td>85.0</td>
<td>0.0590</td>
</tr>
<tr>
<td>19</td>
<td>0.36</td>
<td>50</td>
<td>85.5</td>
<td>0.1778</td>
</tr>
<tr>
<td>20</td>
<td>0.38</td>
<td>30</td>
<td>86.4</td>
<td>0.3127</td>
</tr>
<tr>
<td>21</td>
<td>0.40</td>
<td>17</td>
<td>90.6</td>
<td>0.4636</td>
</tr>
</tbody>
</table>

$I$. Time-in cardiac cycle (frame no. from end diastole); $i$, time from start of isovolumic contraction; $P$, measured left ventricular (LV) intracavity pressure; $V$, measured LV intracavity volume. For isovolumic contraction, active elastance ($E_a$) at time $i$ is calculated; for isovolumic relaxation, $E_{a,17}$ will be determined from curve fit of Fig. 2.

### Table 2. LV contractility indexes classified into tertiles of LVEF

<table>
<thead>
<tr>
<th></th>
<th>Lowest</th>
<th>Middle</th>
<th>Highest</th>
</tr>
</thead>
<tbody>
<tr>
<td>EF</td>
<td>0.32 $\pm$ 0.07*</td>
<td>0.50 $\pm$ 0.06*</td>
<td>0.63 $\pm$ 0.05</td>
</tr>
<tr>
<td>Age, yr</td>
<td>58.30 $\pm$ 8.86</td>
<td>56.10 $\pm$ 6.15</td>
<td>59.90 $\pm$ 6.17</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>71.18 $\pm$ 10.72</td>
<td>71.77 $\pm$ 10.68</td>
<td>71.46 $\pm$ 9.09</td>
</tr>
<tr>
<td>$dP/dt_{\text{max}}, \text{mmHg/s}$</td>
<td>960 $\pm$ 115*</td>
<td>1,121 $\pm$ 113*</td>
<td>1,360 $\pm$ 97</td>
</tr>
<tr>
<td>$E_{\text{a,max}}, \text{mmHg/ml}$</td>
<td>0.95 $\pm$ 0.32*</td>
<td>1.85 $\pm$ 0.50*</td>
<td>3.61 $\pm$ 0.62</td>
</tr>
<tr>
<td>$E_{\text{est(SB)}}, \text{mmHg/ml}$</td>
<td>0.72 $\pm$ 0.26*</td>
<td>1.51 $\pm$ 0.20*</td>
<td>2.81 $\pm$ 0.51</td>
</tr>
<tr>
<td>$d\sigma%/dt_{\text{max}}, \text{s}^{-1}$</td>
<td>2.30 $\pm$ 0.58*</td>
<td>3.60 $\pm$ 1.06*</td>
<td>5.64 $\pm$ 1.13</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SD. EF, ejection fraction; $dP/dt_{\text{max}},$ peak first time derivative of ventricular pressure; $d\sigma%/dt_{\text{max}},$ LV contractility index; $E_{\text{a,max}},$ maximum LV elastance; $E_{\text{est(SB)}},$ single-beat LV end-systolic elastance. *Significantly different from highest tertile ($P < 0.05$).
afterload reduction or preload increase. In contrast, there was a significant increase in \( \frac{d\sigma}{dt_{\text{max}}} \) during dobutamine infusion (5 \( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \)) compared with baseline \( \frac{d\sigma}{dt_{\text{max}}} \) (4.1 ± 0.7 vs. 3.4 ± 0.6 s\(^{-1} \), \( P < 0.03 \)) in group C.

**DISCUSSION**

Any index of contractility in the intact heart may be criticized as somewhat arbitrary because of lack of an ideal descriptor of the intrinsic LV contractile state. Despite its established acceptability, LV \( \frac{dP}{dt_{\text{max}}} \) is an extrinsic measure of LV contractility that has been shown to be load dependent (23). It is therefore important to represent LV contractility by means of an intrinsic property of the LV that is independent of the preload and afterload. In this regard, \( E_{es} \) and \( E_{a,\text{max}} \) are effective contractility indexes (32, 33, 46). Similar to \( \frac{dP}{dt_{\text{max}}} \), however, their determination requires invasive catheterization for measurement of LV pressure.

During LV systole, LV wall stress is generated intrinsically by sarcomere contraction and results in the development of extrinsic LV pressure. LV wall stress is dependent on wall thickness, LV geometry, and chamber pressure and sarcomere contraction. Hence, it is rational to quantify the LV wall stress as an intrinsic measure of myocardial contractility. For example, Hood et al. (12) evaluated stress as an “index of the ’appropriateness’ of the anatomic and functional response to any given pressure or volume load,” but they were unable to provide a formulation for the normalized LV stress. A similar notion has been suggested by several investigators (5, 12, 24). Here, we present the first validated formulation of a stress-dependent contractility index \( \frac{d\sigma}{dt_{\text{max}}} \).

The LV wall stress also has a bearing on the myocardial oxygen supply-and-demand, which potentially influences contractile function. As wall stress increases, strain energy and myocardial oxygen demand increase in tandem (41). Increased wall stress can also reduce myocardial oxygen supply by compression of intramural arterial blood flow, which augments flow resistance (11). Hence, LV wall stress is only one determinant of LV myocardial perfusion. Other factors include pressure in the coronary vessels and coronary vasculature and LV myocardial porosity. The latter is in part influenced by LV wall stress.

We have validated a new LV contractility index, \( \frac{d\sigma}{dt_{\text{max}}} \), based on the maximum rate of development of LV wall stress with respect to LV pressure. From the right-hand side of Eq. 7, this index is also seen to represent the maximal flow rate from the ventricle (cardiac output) normalized to myocardial volume (or mass). The cardiac output has been used as a measure of myocardial contractility in rats, provided that the influences of afterload are taken into account (7). Furthermore, normalization of ventricular measurements to the myocardial volume or mass has been used to standardize pressure-volume relations (2, 10). The present model formalizes these features analytically.

The peak rates of myocardial stress (\( \frac{d\sigma}{dt} \) and LV pressure (\( \frac{dP}{dt} \)) development typically occur during the isovolumic contraction phase (Fig. 5, B and D, respectively). The rate of development of pressure-normalized wall stress (\( \sigma^* = \sigma/P \)) during isovolumic contraction, however, is nearly zero because of the small changes of LV geometry during isovolumic contraction (Fig. 5F). In Eq. 7, the peak rate of normalized wall stress.

![Figure 4](https://example.com/figure4.png)

**Fig. 4.** Linear regression analysis demonstrates good correlation between \( \frac{d\sigma}{dt_{\text{max}}} \) and \( \frac{dP}{dt_{\text{max}}} \) (\( \frac{d\sigma}{dt_{\text{max}}} = 0.0075dP/dt_{\text{max}} - 4.70, r = 0.88; \) A), between \( \frac{d\sigma}{dt_{\text{max}}} \) and \( E_{a,\text{max}} \) (\( \frac{d\sigma}{dt_{\text{max}}} = 1.20E_{a,\text{max}} + 1.40, r = 0.89; \) B), and between \( \frac{d\sigma}{dt_{\text{max}}} \) and \( E_{es(SB)} \) (\( \frac{d\sigma}{dt_{\text{max}}} = 1.60E_{es(SB)} + 1.20, r = 0.88; \) C).
stress \(d\sigma/dt\) (left-hand side of Eq. 7) occurs during the ejection phase (Fig. 5F), consistent with the peak cardiac output during the ejection phase (right-hand side of Eq. 7). Hence, there is synchronization between the novel contractility index and the rate of ejection, as suggested by Eq. 7.

In the 30 patients studied in experiment I, \(d\sigma/dt\) correlated very well with the traditional and invasively determined \(dP/dt\) and \(E_a\), as well as with the computed end-systolic elastance \(E_{es(SB)}\) (Fig. 4). These data validate the proposed contractility index. Additionally, \(d\sigma/dt\) has the dual advantage of requiring relatively simple computations with no requirement for invasive LV pressure measurement. In Fig. 4, there exists a nonzero intercept for \(d\sigma/dt\), which implies a residual \(d\sigma/dt\), even in an LV with an impaired sarcomere and, hence, zero values of \(dP/dt\), \(E_a\), or \(E_{es(SB)}\).

In the 30 additional subjects/patients studied in experiment II, \(d\sigma/dt\) is insensitive to preload changes induced by intravenous saline infusion and afterload changes induced by glyceryl trinitrate but is sensitive to changes in contractility provoked by an infusion of dobutamine. The use of nitroglycerin to vary afterload results in a decline in preload (a decrease in EDV, albeit not statistically significant). In future studies, the afterload resistance or impedance must be measured to ensure the desired effect on afterload; i.e., the index needs to be further tested in the setting of acute changes in vascular impedance load.

### Table 3. Hemodynamic variables at baseline and after physiological manipulation with glyceryl trinitrate, saline, and dobutamine

<table>
<thead>
<tr>
<th>Variable</th>
<th>GTN Baseline</th>
<th>GTN After</th>
<th>Saline Baseline</th>
<th>Saline After</th>
<th>Dobutamine Baseline</th>
<th>Dobutamine After</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>96±12</td>
<td>84±12*</td>
<td>88±5</td>
<td>90±8</td>
<td>97±12</td>
<td>97±11</td>
</tr>
<tr>
<td>SV, ml</td>
<td>53±9</td>
<td>47±9</td>
<td>44±7</td>
<td>53±9*</td>
<td>47±14</td>
<td>44±14</td>
</tr>
<tr>
<td>LVEDV, ml</td>
<td>84±14</td>
<td>73±13</td>
<td>67±13</td>
<td>83±13*</td>
<td>80±19</td>
<td>76±16</td>
</tr>
<tr>
<td>(d\sigma/dt)</td>
<td>4.2±0.9</td>
<td>4.1±1</td>
<td>4.5±0.7</td>
<td>4.4±0.5</td>
<td>3.4±0.6</td>
<td>4.1±0.7*</td>
</tr>
</tbody>
</table>

Values are means ± SD. (n = 10). GTN, glyceryl trinitrate; LVEDV, left ventricular end-diastolic volume; MAP, mean arterial pressure; SV, stroke volume. *Significantly different from baseline (P < 0.05). Note significant decrease in MAP and LVEDV after glyceryl trinitrate administration and significant increase in LVEDV after saline infusion.

Fig. 5. Plot of wall stress (\(\sigma; A\)), rate of wall stress (\(d\sigma/dt; B\)), LV pressure (\(P; C\)), rate of LV pressure (\(dP/dt; D\)), pressure-normalized wall stress (\(\sigma^* = \sigma/P; E\)), and rate of \(\sigma^* (d\sigma/dt; F)\) vs. time. Data were obtained from 1 typical subject.
Traditional axisymmetric models of LV determine wall stress at the equator of a thick-walled sphere. For the formulation of the new index, the LV was modeled as a pressurized thick-walled sphere. Similar geometric assumptions had been made by investigators studying LV pressure-volume dynamics in small animal models (14, 26). This was done to reduce the mathematical complexity of calculation, which is especially pertinent in clinical cases. Regardless of the simplified LV spherical model, the present results indicate that dP/dmax can distinguish between impaired and normal LVEF and correlates well with dP/dmax, E\textsubscript{a,max}, and E\textsubscript{es} (SB). Future studies must consider more realistic geometries, such as an ellipsoid or patient-specific finite-element model of the heart. Those improvements in model must be weighed against the incurred computational cost.

Angiocardiography is frequently used for determination of heart dimensions in humans. Numerous studies have shown that, when used properly, such measurements are reliable and reasonably accurate (3, 20, 34, 35). There is no doubt that MR Angiocardiography is frequently used for determination of LV pressure and volume data during isovolumic relaxation. The governing differential equation relating LV intracavity pressure (P) and volume (V) is given by Zhong et al. (46)

\[ dP = M(dV) + d(EV) = M(dV) + VdE + EdV \quad (A1) \]

where \( M \) is the inertia term and \( E \) is the sum of LV passive and active elastance (\( E_p \) and \( E_a \)). \( E_a \) governs the pressure response to volume change and can be expressed as a monoeponential function, and \( E_p \) characterizes intrinsic LV stiffness attributable to activation of the myocardial sarcomere during active contraction and relaxation. The relaxation can also be deemed to be an active process requiring active decoupling of Ca\textsuperscript{2+} from myocardial contractile proteins.

An \( E_a \) term was previously formulated as (46)

\[ E_a = E_{a,0} \left[ 1 - e^{-\left(\frac{1}{\tau_c}\right)^2} \right] \left[ 1 - e^{-\left(\frac{v}{\tau_e}\right)^2} \right] \quad (A2) \]

where \( t \) represents time from the start of isovolumic contraction, \( E_{a,0} \) is the \( E_a \) coefficient, \( \tau_c \) is the time coefficient of the rate of elastance rise during LV contraction, \( \tau_e \) is the time coefficient of the rate of elastance fall during LV relaxation, and \( d \) is a time constant. The exponents \( Z_c \) and \( Z_R \) were introduced to smooth out the \( E_a \) curve during isovolumic contraction and relaxation. It was proposed that \( E_{a,max} \) may be adopted as an intrinsic measure of LV contractility. The parameter \( d \) is a time constant during the ejection phase; the term \( u(t - d) \) is the unit step function: \( u(t - d) = 0 \) for \( t < d \). During isovolumic contraction, when \( u(t - d) = 0 \), Eq. A2 reduces to

\[ E_a = E_{a,0} \left[ 1 - e^{-\left(\frac{v}{\tau_e}\right)^2} \right] \quad (A3) \]

During isovolumic contraction and isovolumic relaxation, LV volume and \( E_a \) are constant. With \( dV = 0 \) and \( du = 0 \), Eq. A1 becomes VdE = dP, which can be discretized for any time \( i \) during the isovolumic contraction as

\[ V_i(E_i - E_{i-1}) = V_i[(E_{ai} + E_{pi}) - (E_{ai-1} + E_{pi-1})] = V_i(E_{ai} + E_{pi,es} - E_{ai-1} - E_{pi,es}) = dP_i \quad (A4) \]

and, for time \( i \) during the isovolumic relaxation, as

\[ V_i(E_{ai} + E_{pi} - E_{ai-1} - E_{pi-1}) = V_i(E_{ai} + E_{pi,es} - E_{ai-1} - E_{pi,es}) = dP_i \quad (A5) \]

where \( V_i \) and \( P_i \) are LV volume and pressure measured at time \( i \), \( E_{pi,es} \) is passive elastance at end diastole, and \( E_{pi,es} \) is passive elastance at end systole.

Applying Eqs. A4 and A5 to study measured LV pressure and volume data allows calculation of \( E_a \) during isovolumic contraction and relaxation for various patients (Table 1). In each patient, \( E_{a,0}, Z_c, \) and \( Z_R \) in Eq. A3 can be determined from a curve fit of LV pressure and volume data during isovolumic contraction. Substituting the values of these parameters into the more general \( E_a \) of Eq. A2, the remaining parameters \( d, Z_c, \) and \( Z_R \) can be determined similarly to fit LV pressure and volume data during isovolumic relaxation. The resultant smooth curve fit function of Eq. A2 represents \( E_a \) at all times and enables determination of \( E_{a,max} \) (Fig. 2).

**APPENDIX B**

Analysis of wall stress in a thick-walled spherical LV model based on the theory of elasticity (39). The LV was modeled as a pressurized thick-walled spherical shell. If \( u_r \) represents the radial displacement of a spherical surface element in the LV wall at radius \( r \), then, at the outer surface of radius \( r + \Delta r \), the corresponding radial displacement can be expressed as \( u_r + \Delta u_r \text{d}r \). Strain in the radial direction (\( \epsilon_r \)) is then given by

\[ \epsilon_r = \frac{u_r + \Delta u_r}{\text{d}r} - u_r = \frac{\Delta u_r}{\text{d}r} \quad (B1) \]

Spherical symmetry implies that strains in the orthogonal circumferential axes (\( \epsilon_\theta \) and \( \epsilon_\phi \)) are identical. Therefore, strain in the circumferential direction (\( \epsilon_\theta \)) is

\[ \epsilon_\theta = \frac{2\pi(r - u_r) - 2\pi \frac{u_r}{r}}{2\pi r} = \frac{u_r}{r} \quad (B2) \]

Strains along the three orthogonal axes are

\[ \epsilon_r = \frac{\Delta u_r}{\text{d}r}, \quad \epsilon_\theta = \frac{u_r}{r} \quad \text{and} \quad \epsilon_\phi = \frac{u_r}{r} \quad (B3) \]

Similarly, \( \sigma_\theta = \sigma_\phi \). For equilibrium in the radial direction, we have

\[ -\sigma_r(2\pi r)(2\pi r) + (\sigma_r + \Delta \sigma_r)(r + \Delta r)2\pi(r + \Delta r)20 \]

\[ -2 \left( r + \frac{\Delta r}{2} \right) 20\Delta \sigma_r \sin \theta - 2 \left( r + \frac{\Delta r}{2} \right) 20\Delta \sigma_r \sin \theta = 0 \quad (B4) \]

Since \( \sigma_\theta = \sigma_\phi, \text{d}r = (\sigma_r/\sigma_\theta)\Delta r, \) and Eq. B4 reduces to

\[ \Delta \sigma_r = \sigma_r \left( \frac{\Delta r}{2r} \right)^2 \quad (B5) \]
On the basis of Hooke’s law, we can express the constitutive equation as
\[ \sigma_r = \frac{1}{E} \left[ \sigma_\sigma - \nu (\sigma_\sigma + \sigma_\theta) \right] = \frac{\partial u_r}{\partial r} \quad \text{or} \quad \frac{d\sigma_r}{dr} = \frac{1}{E} \left[ (1 - \nu) \sigma_\theta - \nu \sigma_\sigma \right] \] (B6)
where \( E \) is the elastic modulus and \( \nu \) is the Poisson’s ratio. Similarly, from Eq. B2
\[ \sigma_\theta = \frac{1}{E} \left[ \sigma_\sigma - \nu (\sigma_\theta + \sigma_r) \right] = \frac{u_\theta}{r} \quad \text{or} \quad \frac{d\sigma_\theta}{dr} = \frac{1}{E} \left[ (1 - \nu) \sigma_r - \nu \sigma_\sigma \right] \] (B7)

Differentiating Eq. B7 with respect to \( r \), we obtain
\[ \frac{d\sigma_r}{dr} = \frac{1}{E} \left[ (1 - \nu) \frac{\partial (\sigma_\theta)}{\partial r} - \nu \frac{\partial (\sigma_r)}{\partial r} \right] \] (B8)

Equations B6 and B8 can be combined as
\[ (1 - \nu) \frac{d^2\sigma_r}{dr^2} - \frac{\sigma_\theta}{r} - \sigma_\sigma + \frac{\nu}{r} \frac{d\sigma_\sigma}{dr} = 0 \] (B9)

If we combine \( \sigma_\theta \) (Eq. A5) into Eq. A9, we obtain
\[ 1 - \nu \frac{d^2\sigma_r}{dr^2} \quad 2 \quad \frac{d\sigma_\beta}{dr} \quad \frac{\sigma_\sigma}{r} \quad \sigma_\sigma + \frac{\nu}{r} \frac{d\sigma_\sigma}{dr} = 0 \] (B10)

If we substitute \( r^2 \sigma_r = \gamma \), Eq. B10 becomes
\[ \frac{1}{2} \left( 1 - \nu \right) \frac{d^2 \gamma}{dr^2} - \frac{\gamma}{r^2} + \frac{\nu}{r^2} \frac{d\gamma}{dr} = 0 \] (B11)

This yields a homogeneous linear equation with the solution
\[ y = Ar^2 + B \quad \frac{\sigma_\sigma}{r} = \frac{\gamma}{r} = A + \frac{B}{r} \] (B12)
where \( A \) and \( B \) are constants. From Eqs. B5 and B12, we find
\[ \sigma_\theta = A - \frac{B}{2r^3} \] (B13)

For a thick-walled spherical shell subjected to internal pressure (\( P_i \)) and zero external pressure, the boundary conditions are \( \sigma_r = -P_i \) when \( r = r_i \) and \( \sigma_\sigma = 0 \) when \( r = r_o \). From Eq. B12, we obtain
\[ A + \frac{B}{r_i} = -P_i \quad \text{and} \quad A + \frac{B}{r_o} = 0 \] (B14)

Hence, we can determine the constants of integration as
\[ A = \frac{r_i^2 P_i}{r_o^3 - r_i^3} \quad \text{and} \quad B = \frac{r_o^2 r_i P_i}{r_o^3 - r_i^3} \] (B15)

From Eqs. B12–B14, expressions for radial and circumferential stresses are
\[ \sigma_r = P \frac{r_i^3}{r_o^3 - r_i^3} \left( 1 - \frac{r_i^3}{r} \right) \] (B16)
\[ \sigma_\theta = \sigma_\sigma = P \frac{r_i^3}{r_o^3 - r_i^3} \left( 1 + \frac{r_i^3}{2r_o^2} \right) \] (B17)

The present formulation will focus on the circumferential stress, which is significantly larger in magnitude than and opposite in sign (tensile) from the radial (compressive) stress.
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