Estimation of preload recruitable stroke work relationship by a single-beat technique in humans

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Methods

Study population. Forty-five adults referred for diagnostic catheterization (36 men and 9 women) participated in this study. All patients provided informed consent, and the Institutional Review Board of Taipei Veteran General Hospital approved the study protocol. Patients with aortic stenosis or LV outflow obstruction were excluded. Primary indications for cardiac catheterization were chest pain or heart failure. Clinical diagnoses included normal coronary artery anatomy and LV ejection fraction (n = 15), hypertensive cardiovascular disease (n = 10), coronary artery disease (n = 16), hyper-
trophic cardiomyopathy \((n = 3)\), and constrictive pericarditis \((n = 1)\). A summary of the patient characteristics is provided in Table 1. Among these, eight patients with coronary artery disease had obvious regional wall motion abnormalities of the LV defined by both transthoracic echocardiography and left ventriculography. Their clinical characteristics are summarized by both transthoracic echocardiography and Table 1. Among these, eight patients with coronary artery disease had obvious regional wall motion abnormalities of the LV defined by both transthoracic echocardiography and left ventriculography. A 6-Fr multielectrode conductance-micromameter catheter (SSD-767 and SSD-768, Millar) was then placed into the LV, with the pigtail tip advanced to the ventricular apex. Acute preloading reduction was produced in all subjects by temporarily impeding inferior vena cava inflow with a large occlusion balloon catheter (17-205, Boston Scientific) (7). In addition to rest data, intravenous dobutamine (5 and 10 \(\mu\)g·kg\(^{-1}\)·min\(^{-1}\), respectively) was administered to induce changes of contractility. Dobutamine infusion was withheld in patients with intolerable discomfort, systolic blood pressure (BP) >180 mmHg, or procedure time >1 h at the end of the rest study. In total, 12 dobutamine studies were collected from 8 patients (4 patients had regional wall motion abnormalities). All pressure and volume signals were digitized at 500 Hz using custom data-acquisition display software and analyzed off-line. Details of the invasive pressure-volume analysis have been previously reported (4, 20).

Digitized hemodynamic data were analyzed off-line with custom software (MATLAB for Windows, version 4.2b). The volume signals were calibrated using Fick principle-derived stroke volumes (SV) and contrast ventriculogram-derived ejection fractions (3). Pressure-volume relations were derived from a set of cardiac cycles at various preload volumes, starting with the beat just before the onset of LV systolic pressure decline and ending at the nadir of preload reduction or with a reflex rise in heart rate. SW was calculated as the integral of LV pressure with respect to chamber volume.

Echocardiographic examination was performed using a wide-band frequency-fusion phase-array transducer (Sonos-5500, Agilent) 1 h before the cardiac catheterization. Brachial systolic and diastolic BPs were obtained from a noninvasive oscillometric BP monitor. Two-dimensional guided M-mode echocardiograms were obtained for measurements including the interventricular septum thickness, posterior wall thickness, LV internal dimensions in diastole and systole (29), and LV mass (6). LV out-flow tract diameter (LVOT) was measured at the base of aortic leaflets from the parasternal long-axis view. Cross-sectional area (CSA) was calculated as \((\text{LVOT/2})^2 \times 3.14\). The pulsed-wave Doppler aortic flow spectrum was obtained by inching the sample volume toward the aortic valve in the apical five-chamber view. From this velocity spectrum, the time-velocity integral (TVI) was measured. SV was calculated as \(SV = \text{CSA} \times \text{TVI}\). The ejection fraction of the LV was calculated from \(M\)-mode measurements according to Teichholz’s formula (34). EDV was calculated as SV divided by ejection fraction.

**M\(_w\) estimation algorithm.** The PRSW relationship was determined by linear regression analysis of SW and EDV from multiple beats obtained during each vena caval occlusion, according to the equation

\[
\text{SW} = M_w \times (\text{EDV} - V_w) \tag{1}
\]

By rearranging Eq. 1, \(M_w\) is given by the equation

\[
M_w = \frac{\text{SW}}{(\text{EDV} - V_w)} \tag{2}
\]

Previous studies have demonstrated that \(V_w\) remains essentially constant within an individual, regardless of any short-term change of loading or inotropic conditions (8, 10, 17, 25). Therefore, it is apparent from Eq. 2 that \(M_w\) can be calculated from a baseline beat \((\text{SW}_B, \text{EDV}_B)\) once the value of \(V_w\) is known for the individual subject. Karunanithi et al. (16) assumed, on the basis of allometric principles (11, 22, 26, 32), that the ratio of the volume within the epicardial shell corresponding to \(V_w\) \((V_{w,\text{epi}})\) to the volume within the epicardial shell corresponding to \(EDV_B\) \((EDV_{B,\text{epi}})\) is relatively constant \((k)\). Therefore

\[
\frac{V_{w,\text{epi}}}{EDV_{B,\text{epi}}} = k \tag{3}
\]

Expressing this ratio in terms of chamber volume yields

\[
\frac{V_w + LV_{\text{wall}}}{EDV_B + LV_{\text{wall}}} = k \tag{4}
\]

where \(LV_{\text{wall}}\) is the wall volume. By rearranging Eq. 4

\[
V_w = k \times EDV_B + (k - 1) \times LV_{\text{wall}} \tag{5}
\]

Substituting for \(V_w\) in Eq. 2 yields the following equation for \(SBM_w\)

\[
SBM_w = \frac{\text{SW}_B}{[EDV_B - k \times EDV_B + (1 - k) \times LV_{\text{wall}}]} \tag{6}
\]

Because LV mass equals LV wall times 1.05 (specific gravity of the heart muscle) (21), the \(LV_{\text{wall}}\) was estimated from the echocardiography-derived LV mass. The empirical \(V_{w,\text{epi}}\)-to-\(EDV_{B,\text{epi}}\) ratio \(k\) for each individual was calculated from \(V_w,\) EDV\(_B\), and LV\(_{\text{wall}}\) accordingly. \(V_w\) was determined from multiple beats during preload reduction (10). To apply the single-beat technique noninvasively, SW was estimated as the product of Doppler-derived SV and the oscillometrically derived mean systemic BP (23).

**Statistical analysis.** All hemodynamic data are expressed as means ± SD. Linear regression was performed to examine the correlations between individually calculated \(k\) values from multiple-loop data and other variables, including age, height, body weight, systolic BP, ejection fraction, EDV, and LV mass. The agreement between \(M_w\) and \(SBM_w\) was examined using Bland-Altman analysis (1). Similar analyses were done in subgroups of large and small LV volume or large and small mass. The agreement of changes of \(SBM_w\) and \(M_w\) was expressed as means ± SD.
induced by intravenous dobutamine infusion was also examined with univariate linear regression. Statistical significance was reported at $P < 0.05$.

RESULTS

Characteristics of the ratio of the epicardial shell volumes. Similar to reported canine data, in which the average $k$ value was $0.72 \pm 0.01$ (16), the $k$ value calculated from individual patients varied in the range of $0.66$–$0.81$ with a mean of $0.72 \pm 0.04$. There was no significant correlation between the individual $k$ value and age (Fig. 1A), height, body weight, body mass index, steady-state systolic BP (Fig. 1B), EDV$_B$ (Fig. 1C), or ejection fraction. On the other hand, the individual $k$ value was significantly correlated with LV mass in the regression equation:

$$\text{Individual } k = 0.0004 \times \text{LV mass} + 0.6408 \ [r = 0.60, \text{SE of the estimate (SEE)} = 0.0316, \ P < 0.001; \text{Fig. 1D}].$$

The relationship between LV mass and the $k$ value was preserved in patients with regional wall motion abnormalities (Fig. 1D, open symbols). On the basis of the regression equation, LV mass was used to estimate individual $k$ values for calculating SBM$_w$.

Estimation of M$_w$ by SBM$_w$ in the steady state. On the basis of a constant $k$ of $0.7$ (16), SBM$_w$ predicted M$_w$ well ($M_w = 0.88 \times \text{SBM}_w + 24.15$, $r = 0.88$, $\text{SEE} = 16.94$, $P < 0.0001$; Fig. 2A), and Bland-Altman analysis demonstrated that all points of difference were within $2\text{SD}$ of the mean difference except for two outliers (Fig. 2C). The absolute differences for these two outliers were $53.4$ and $48.4$ erg·cm$^{-3}$·10$^3$, respectively. The first patient was a 61-yr-old female with hypertrophic cardiomyopathy and hypertension, whose LV mass was 283.0 g. The second patient was 65-yr-old male with hypertensive cardiovascular disease and concentric LV hypertrophy, whose LV mass was 284.1 g. When the $k$ value was estimated from the individual LV mass, the prediction improved slightly ($M_w = 0.89 \times \text{SBM}_w + 15.55$, $r = 0.93$, $\text{SEE} = 13.58$, $P < 0.0001$; Fig. 2B). Bland-Altman analysis revealed only

Table 2. Characteristics of study subjects with significant regional wall motion abnormalities

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Age, yr</th>
<th>LV mass, g</th>
<th>EDV, ml</th>
<th>EF, %</th>
<th>$M_w$, erg·cm$^{-3}$·10$^3$</th>
<th>Individual $k$</th>
<th>Abnormal Wall Motion Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>74</td>
<td>192.9</td>
<td>117.5</td>
<td>58.8</td>
<td>94.62</td>
<td>0.66</td>
<td>Mild hypokinesia over anterolateral wall</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>81</td>
<td>188.0</td>
<td>96.1</td>
<td>56.4</td>
<td>121.73</td>
<td>0.74</td>
<td>Akinesia over inferior wall</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>68</td>
<td>115.4</td>
<td>121.3</td>
<td>46.1</td>
<td>105.67</td>
<td>0.69</td>
<td>Akinesia over anteroseptal wall</td>
</tr>
<tr>
<td>4</td>
<td>Male</td>
<td>67</td>
<td>237.7</td>
<td>132.1</td>
<td>60.1</td>
<td>119.75</td>
<td>0.71</td>
<td>Akinesia over anteroseptal wall</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>65</td>
<td>203.0</td>
<td>81.6</td>
<td>73.6</td>
<td>97.99</td>
<td>0.70</td>
<td>Akinesia over inferolateral wall</td>
</tr>
<tr>
<td>6</td>
<td>Female</td>
<td>71</td>
<td>282.6</td>
<td>138.1</td>
<td>21.2</td>
<td>53.94</td>
<td>0.72</td>
<td>Akinesia over anteroseptal and inferior wall</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>75</td>
<td>243.7</td>
<td>121.6</td>
<td>60.8</td>
<td>161.42</td>
<td>0.76</td>
<td>Moderate hypokinesia over anteroseptal wall</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>70</td>
<td>365.0</td>
<td>214.9</td>
<td>40.3</td>
<td>107.35</td>
<td>0.80</td>
<td>Dyskinesia over apex</td>
</tr>
</tbody>
</table>

Fig. 1. Relations between individual ratios of epicardial shell volumes at zero stroke work (unstressed volume) and during steady state (stressed volume) ($k$ values) derived from multiple-beat pressure-volume data and age (A), systolic blood pressure (SBP; B), left ventricular (LV) end-diastolic volume (LVEDV; C), and LV mass (D) in patients with various heart diseases. •, Patients without regional wall motion abnormalities; ○, patients with significant regional wall motion abnormalities. SEE, SE of the estimate. Solid line, linear regression.
one outlier outside the 2SD boundary, who was a 68-yr-old female with hypertensive cardiovascular disease, Type 2 diabetes mellitus, and concentric LV hypertrophy (LV mass = 198.3 g; Fig. 2).

The median values for LV mass and EDV were 193.7 g and 95.7 ml, respectively. Except for the group with small LV mass, LV mass was significantly related to individual k values in each subgroup. Average individual k values and correlation coefficients between SBMw and Mw in each subgroup are provided in Table 3. In each of the four groups, the correlation between SBMw and Mw was reasonably good, whether SBMw was calculated from a constant k or an estimated k. It appeared that SBMw predicted best in patients with small LV mass.

**Responses of SBMw to intravenous dobutamine.** To further test the robustness of the single-beat technique, changes in SBMw induced by intravenous dobutamine infusion in 12 studies were compared with changes in Mw. Absolute changes in SBMw before and after dobutamine infusion correlated significantly with Mw using either a constant k (ΔMw = 0.57 × ΔSBMw + 24.53, r = 0.84, SEE = 13.76, P = 0.0007; Fig. 3A) or an estimated k (ΔMw = 0.55 × ΔSBMw + 21.65, r = 0.82, SEE = 14.47, P = 0.0011; Fig. 3B).

**Noninvasive SBMw estimation.** The calculation of SBMw requires the estimation or measurement of SWB, EDVB, and LVwall, and all can be derived noninvasively. According to our invasive data, SWB calculated directly from the pressure-volume loop was highly significantly correlated with the estimation from the product of mean aortic systolic BP and SV: SWB(loop area) = 1.0 × SWB(mean BP × SV) + 403 (SEE = 518, r = 0.98, P < 0.001). Therefore, noninvasive SWB was estimated from the product of mean brachial arterial pressure and echocardiographically derived SV (23). However, because the noninvasive examination was performed ~1 h before the cardiac catheterization, the correlations between the invasive and noninvasive measurements of the pressure, volume, and estimated SWB were

| Table 3. Observed k values and correlation coefficients in patients with different heart sizes |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                 | LV Mass          |                 | EDV             |                 |
|                 | <193.7 g         | ≥193.7 g        | <95.7 ml        | ≥95.7 ml        |
| n               | 22               | 23              | 22              | 23              |
| Individual k values | 0.71 ± 0.03    | 0.74 ± 0.04    | 0.73 ± 0.04    | 0.72 ± 0.04    |
| r Values of individual k vs. LV mass | 0.09           | 0.61*           | 0.58*           | 0.73*           |
| r Value of SBMw vs. Mw | k = 0.7         | 0.96*           | 0.87*           | 0.87*           |
|                 | Estimated k      | 0.95*           | 0.92*           | 0.89*           | 0.94*           |

Individual k values are means ± SD; n = no. of subjects. SBMw, single-beat Mw. *P < 0.01.
significant but less satisfactory: EDV\textsubscript{(invasive)} = 0.83 \times \text{EDV\textsubscript{(noninvasive)}} + 20.8 (SEE = 24.8, r = 0.64, P < 0.001); systolic BP\textsubscript{(invasive)} = 0.92 \times \text{systolic BP\textsubscript{(noninvasive)}} + 14.0 (SEE = 7.1, r = 0.94, P = 0.002); and SW\textsubscript{B(invasive)} = 0.76 \times \text{SW\textsubscript{B(noninvasive)}} + 2,131 (SEE = 1,983, r = 0.73, P < 0.001). Subsequently, noninvasively derived SBM\textsubscript{w} correlated significantly with invasively derived M\textsubscript{w} (M\textsubscript{w} = 0.63 \times \text{SBM\textsubscript{w}} + 53.68, r = 0.66, SEE = 27.21, P < 0.0001) using a constant $k$ (Fig. 4, A and C). With the use of an estimated $k$, the predicted power of noninvasively derived SBM\textsubscript{w} improved slightly (M\textsubscript{w} = 0.68 \times \text{SBM\textsubscript{w}} + 43.16, r = 0.71, SEE = 25.25, P < 0.0001; Fig. 4, B and D).

**DISCUSSION**

In this study, we demonstrated that it is feasible to use a single steady-state heart beat to estimate M\textsubscript{w} of the PRSW relationship in humans with various heart diseases, including patients with significantly remodeled hearts. In addition, we found that the $k$ value, the ratio of the epicardial shell volumes at zero SW (unstressed volume) and during steady state (stressed volume), varied significantly with the LV mass. Therefore, the single-beat technique can further be improved with the use of a $k$ value estimated from the LV mass instead of a constant of 0.7 (16). We also demonstrated
that the modified technique has the potential for noninvasive application in routine clinical practice.

The anatomic and physiological basis of the k value. The underlying rationale for the calculation of SBMw is the allometric hypothesis (16). According to this theory, within all species of animals the size of each organ bears a specific allometry exponent to body weight (11, 12, 32). On the basis of the allometry theory, the ratio of Vw,epi to EDVw,epi (unstressed volume to stressed volume) was assumed to be a constant k, and this assumption appeared to be valid in healthy canines (16). In the current study, we found that k values in patients with diseased or healthy hearts varied in a narrow range, whereas the mean k value (0.72) was essentially the same as that in healthy canines. Furthermore, the variation of k values could be predicted from the LV mass in the patients. The relationship between LV mass and k was preserved even in patients with significant LV remodeling, i.e., with dilated LV volume, LV hypertrophy, or regional wall motion abnormalities due to previous myocardial infarction.

The relative consistency of k values across species and various diseased hearts in humans implies that k values reflect not only anatomic similarity (allometric hypothesis) but also physiological similarity for some fundamental processes of cardiac muscle contraction. We hypothesize that the ratio of the sarcomere length of the cardiac myocyte at zero SW (unstressed) to that at stressed conditions for canines or humans (15, 27, 28). Prior studies have revealed that at diastole, the cardiac sarcomere length was ~2.2 μm during maximally stressed conditions for canines or humans (15, 27, 28). At unstressed conditions, the sarcomere length may vary narrowly from ~1.85 to 2.0 μm (27, 30), probably due to the restriction from passive force and restoring force development by titin (14, 35). Therefore, it appears that the ratio of length of the normal functioning sarcomere at unstressed and stressed conditions is relatively constant, which might contribute to the preservation of k values even when hearts have been remodeled.

Impact of LV mass, EDV, and regional wall motion abnormality on the SBMw technique. Cardiomegaly and LV hypertrophy are consequences of progressive heart failure and LV remodeling. Regional wall motion abnormality is a frequent consequence of previous myocardial infarction. It might be anticipated that the allometric theory is not valid in patients with enlarged heart sizes. According to Eq. 4, it is expected that the k value would increase with an increase in LV mass if EDVw and Vw were held constant. Our data were consistent in that patients with larger LV mass or smaller EDV tended to have greater k values. However, because the variation of k values with LV mass or chamber size was small, the SBMw technique remained valid in patients with wide ranges of LV mass (92–365 g) or EDV (52–215 ml), using either a constant k or an estimated k value. In patients with regional wall motion abnormalities, k values were within the same range, and the relations with the LV mass were preserved (Fig. 1D, open symbols).

Noninvasive applications of the SBMw technique. The single-beat technique was the foundation for the potential wide application of PRSW in clinical practice. According to Eq. 6, the calculation of SBMw requires measurements of SWw, EDVw, and LV mass, all of which can be derived from noninvasive echocardiographic and brachial BP measuring. In the current study, noninvasively derived SBMw was significantly related to invasively derived SBMw, using either a constant k or an estimated k. The correlation coefficients were slightly lower than those from the invasive studies. This less satisfactory result was most likely due to the fact that the echocardiographic examination was performed 1 h earlier than the catheterization. It is reasonable to assume that the echocardiographic measurements and oscillometric brachial BPs obtained during the cardiac catheterization should yield better results. However, we were reluctant to do so because the lengthened catheterization time might risk the patients’ safety.

Other single-beat techniques for assessment of LV contractility. In addition to Mw, the slope (Ees) of the end-systolic pressure-volume relationship (ESPVR) is also recognized as a load-insensitive index of LV contractility. We (3) have developed and validated a novel single-beat technique to estimate Ees noninvasively. Because Mw and Ees describe LV performance in different perspectives, the availability of both techniques should provide a more comprehensive evaluation of LV performance. The PRSW relationship is highly linear and relative afterload independent (5, 10, 19, 24, 25); the ESPVR, however, is less linear than the PRSW relationship (2, 18). The range of change of the PRSW relationship is less than that of the ESPVR when the contractility changes (25). The PRSW relationship is not a pure systolic contractility index but rather integrates both systolic and diastolic properties (19, 25). Therefore, the PRSW relation can be considered as a measure of integrated pump function and the ESPVR as systolic function. Because of the different hemodynamic characteristics, it would be ideal to have both Mw and Ees to enhance clinical interpretation. Although the theories behind the single-beat technique for estimating Ees and Mw are quite different, both parameters can be obtained during the same echocardiographic examination, and this should facilitate the clinical application of both techniques.

In conclusion, Mw can be estimated from a steady-state beat without alteration of preload. This technique is not significantly affected by different LV size, LV mass, and the presence of regional wall motion abnormalities and has the potential for noninvasive applications.

REFERENCES


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