Pressure-volume-based single-beat estimations cannot predict left ventricular contractility in vivo

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Kjørstad, Knut E., Christian Korvald, and Truls Myrmel. Pressure-volume-based single-beat estimations cannot predict left ventricular contractility in vivo. Am J Physiol Heart Circ Physiol 282: H1739–H1750, 2002. First published January 3, 2002; 10.1152/ajpheart.00638.2001.—The end-systolic pressure-volume relationship is regarded as a useful index for assessing the contractile state of the heart. However, the need for preload alterations has been a serious limitation to its clinical applications, and there have been numerous attempts to develop a method for calculating contractility based on one single pressure-volume loop. We have evaluated four of these methods. Pressure-volume data were obtained by combined pressure and conductance catheters in 37 pigs. All four methods were applied to 88 steady-state pressure-volume files, including eight files sampled during dopamine infusions. Estimates of single-beat contractility (elastance) were compared with preload-varied multiple-beat elastances, but when reevaluated by other groups, they have failed to be reproducible (14, 16).

In single-beat calculations, the slope of the linear end-systolic elastance curve is determined by two points: ESPVR and a point that has to be calculated using additional information from the PV loop. The latter is either the volume-axis intercept of the elastance curve (i.e., maximal first derivative of pressure (dP/dt max), time to dP/dt max, ratio between preejection period (PEP) and ejection time (ET), end-systolic volume, or stroke volume (SV)). Most of the methods described earlier have shown very good correlation and agreement between single-beat and multiple-beat-derived elastances, but when reevaluated by other groups, they have failed to be reproducible (14, 16).

The aim of this study was therefore to evaluate the usefulness of single-beat estimations of contractility. We applied four different methods (14–16, 21) on our extensive database of PV measurements in pigs based on data from intraventricular combined pressure and conductance catheters. We compared elastance values derived from conventional multiple-beat recordings during preload alterations with calculated single-beat elastance values from experiments using inotropic, metabolic, and ischemic interventions. Because the most important application of any such index is the ability to detect altered contractility, we tested whether the four different methods could detect inotropic changes during dopamine infusions. From these comparisons, we conclude that all the evaluated methods of single-beat estimations of contractility fail to comply with reasonable accuracy demands.

METHODS
PV data from 37 pigs obtained by combined pressure and conductance catheters (Millar Instruments or Cardiodynam...
ics were taken from our database of cardiac function analyses. The data came from three previous protocols conducted in our laboratory (7–9). The weight of the pigs ranged from 23 to 38 kg. We analyzed 88 separate, 8-s-long, averaged steady-state PV-loop sequences with a sampling frequency of 200 or 250 Hz, and divided them into four subgroups. Group I consisted of 42 baseline or control loops from two previous studies: 21 loops were sampled from 7 control pigs at 3 successive time points (7), and 21 loops were baseline recordings from 21 pigs before intervention (ischemia and inotropic stimulation) (7, 9). Data were collected before any pharmacological or other interventions. In group 2, eight files sampled during dopamine infusions were used. Dopamine was given as 5–10 μg·kg⁻¹·min⁻¹, adjusted to give an increased mean arterial pressure of at least 20 mmHg (9). Group 3 consisted of 18 files from a study using metabolic intervention (9 pigs) where one-half of the pigs received initial glucose-insulin-potassium (GIK) infusions, followed by Intralipid (Pharmacia), and the other half received Intralipid before GIK (8). Group 4 was a postischemic study, including 10 pigs subjected to repetitive occlusions of the left coronary main stem (2 × 1 min + 9 × 2 min, 1-min perfusion between occlusions). The left coronary artery perfused 81.5% of the volume (2), and those after which dP/dt had reached 300 mmHg/s were sampled 30 and 90 min after ischemia (7).

The reference multiple-beat ESPVRs were derived from conventional multiple PV loops sampled immediately after the steady-state loop recording during preload alterations. A 7-Fr balloon catheter (Sorin Biomedical) in the lower caval vein was used to alter preload. In most cases, two runs were performed and a mean value was used. The slope of the regression line or the multiple-beat elastance was denoted E_{\text{MB}}\text{SB}. The x-axis intercept of the regression line through the points of maximal PV relation was V_0\text{MB}.

Single-beat estimation based on simulated isovolumic pressure curves. In 1991, Takeuchi et al. (21) described a method based on a previous work by Sunagawa et al. (20), and evaluated the method in 16 patients. A theoretical peak isovolumic pressure [P_{\text{max}}\text{E}]] was determined (Fig. 1A), and single-beat elastance [E_{\text{E}}\text{pmax(E)}] was given by the slope of the line through the point of maximum ESPVR, and the point defined by the coordinates P_{\text{max}}\text{E} and end-diastolic volume (EDV) (Fig. 1B). The pressure curve [P(t)] used to determine P_{\text{max}}\text{E} is a simulated isovolumic contraction at EDV, which is based on one ejection contraction and a nonlinear least-squares approximation technique (20, 21)

\[ P(t) = \frac{1}{2} P_{\text{max}}\text{E}[1 - \cos(\omega t + C)] + \text{EDP} \]  

where \( \frac{1}{2} P_{\text{max}}\text{E} \) is the amplitude, \( \omega \) is the angular frequency, \( C \) is the phase shift angle of the sinusoidal curve, and EDP is the LV end-diastolic pressure, which in this context is the distance from the lowest point of the curve to the x-axis. The theoretical peak isovolumic pressure (source pressure) is then given by

\[ P_{\text{max}}\text{E} = P_{\text{max}}\text{E} + \text{EDP} \]  

To get a better fit when the contraction and relaxation waveforms are very different [difference in numerical value of dP/dt_{\text{max}} and minimal first derivative of pressure (dP/dt_{\text{min}})], we made a modified isovolumic pressure approximation using a fifth-order polynomial function. The fifth-order function was derived from repeated curve approximations to assess a best fit.

The approximated isovolumic pressure curves were based on measurements from the first point after dP/dt had reached 100 mmHg/s to dP/dt_{\text{max}}, and from dP/dt_{\text{min}} to the last point before dP/dt exceeded −100 mmHg/s (called cutoff 100). To evaluate the impact of different cutoff points, we repeated the curve-fitting procedure, excluding the pressure points before dP/dt had reached 300 mmHg/s, and those after which dP/dt ≫ −300 mmHg/s (cutoff 300).

Modified isovolumic approach. A modification of this method was published by Shih et al. (15) as a computer algorithm intended for automated single-beat calculations. This method was evaluated in 16 patients after cardiopulmonary bypass. Pressure points within ±20% of either inflection point (dP/dt_{\text{max}} and dP/dt_{\text{min}}) in the upstroke and downstroke intervals were selected for linear fitting (Fig. 1C). The points around the left inflection point were fitted to a line via linear regression analysis. The same was done for the right inflection point, and the intersection point of the two lines was defined as the unadjusted pressure. The validity of the method then relies on the assumption that the unadjusted pressure, together with the pressure at the left and right inflection points, can be fitted to a sine curve with peak amplitude equals peak isovolumic pressure equals adjusted pressure (P_{\text{adj}})

\[ P_{\text{adj}} = 2 \times (P_{\text{unadj}} - \Delta) + \Delta \]  

where P_{\text{unadj}} is unadjusted pressure and Δ is left inflection pressure + right inflection pressure. Single-beat elastance [E_{\text{E}}\text{p(Padj)}] was then given by the line through the point of ESPVR, and the point defined by the coordinates P_{\text{adj}} and EDV (Fig. 1B).

Single-beat estimation based on normalized, averaged elastance curves. Senzaki et al. (14) described a method for estimating LV contractility based on normalized time-varying elastance curves [E_{\text{E}}\text{p(t)}]. In this method, the volume axis intercept of the elastance curve (V_{0}) is calculated from a single PV loop. The contractility is then given by the curve through V_{0} and the point of maximal ESPVR. E_{\text{E}}\text{p(t)} curves for all PV loops were calculated defining time-varying elastance [E_{\text{t}}] as the instantaneous ratio of P(t)/V(t) − V_{MB}. The normalized value of E_{\text{t}} [termed E_{\text{E}}\text{pmax(t)}] and the time from the R wave of the electrocardiogram to achieve E_{\text{E}}\text{pmax(t)} (termed t_{\text{max}}), were both determined. The normalized E_{\text{t}} function was then defined as

\[ E_{\text{E}}\text{pmax(t)} = E_{\text{t}}(t)/E_{\text{E}}\text{pmax(t)} \]  

where t_{\text{max}} = t_{\text{max}}/t_{\text{max}} (Fig. 1D). The individual E_{\text{E}}\text{pmax(t)} curves were then resampled and averaged to yield E_{\text{E}}\text{pmax(t)} curves for each subgroup and for all 88 PV loops (Fig. 2).

Single-beat estimation of elastance was done by calculating V_{\text{E(SB)}} using the equation

\[ V_{\text{E(SB)}} = \frac{[P_{\text{E}}(t) - V(t)] - V(t) \times E_{\text{E}}\text{pmax(t)}]}{[P_{\text{E}}(t) - E_{\text{E}}\text{pmax(t)}]} \]  

The slope or elastance could then be calculated as

\[ E_{\text{E}}\text{pmax(SB)} = \frac{P_{\text{E}}(t) - V(t) \times E_{\text{E}}\text{pmax(t)}}{V(t)} \]  

The model assumes a constant V_{0} in a given cardiac cycle, linear elastance, and a species-specific E_{\text{E}}\text{pmax(t)}/E_{\text{E}}\text{pmax(t)} relation, which means that for a given t_{\text{E}} there is a constant relation between the slopes of E_{\text{E}}\text{pmax(t)} and E_{\text{E}}\text{pmax(t)} for individuals within the same species, independent of parameters as heart rate, preload, afterload, and contractility.

This single-beat method was tested using the averaged E_{\text{E}}\text{pmax(t)} curve comprising all 88 files (Fig. 2A). Equations 5 and 6 give V_{\text{E(SB)}} and E_{\text{E}}\text{pmax(SB)} estimates at any time t_{\text{E}}. However, V_{0} determined from Eq. 5 is unstable throughout most of the cardiac cycle (Fig. 3), as V_{\text{E(SB)}} is a hyperbolic function of E_{\text{E}}\text{pmax(t)} with a vertical asymptote at E_{\text{E}}\text{pmax(t)} =
Furthermore, during the ejection phase, the function is increasingly affected by the normalization. It is therefore crucial to choose a value for $E_N(t_N)$ that most likely will give a reliable estimate of $V_0$. This $E_N(t_N)$ value must be sought in a time frame where the effects of measurement errors are lowest. Senzaki et al. (14) provided a set of analyses to evaluate the effect of physiological and mathematical variability on the $V_0$ estimate, and we applied this test battery on our data. The physiological variance is shown in Fig. 4A. The standard deviation (SD) is here plotted against normalized time, reflecting the instantaneous variance $|dE_N(t_N)|$ as a function of $t_N$. This plot also reveals the quite substantial variation between our subgroups with respect to SD. The last, steep part of the curve is increasingly unreliable because of the normalization effect, which implies that $E_N(t_N) = 1$ with a variance of 0 at $t_N = 1$, by definition.

According to the authors

$$
\frac{d V_0}{d E_N(t_N)} = \frac{-V(t_N)}{[P_{\text{adj}}(t_N) - E_N(t_N)]}
- \frac{P_{\text{max}}(t_N) \times V_{\text{es}} - V(t_N) \times E_N(t_N)}{[P_{\text{max}}(t_N) - E_N(t_N)]^2}
$$

(7)
where $dE_N(t_N)$ is the standard deviation of $E_N(t_N)$, expresses the time-varying mathematical-based sensitivity of the $V_0$ estimate as a function of $E_N(t_N)$. Figure 4B shows the curve with the use of the mathematically corrected version of this equation as a function of $t_N$ (see APPENDIX), and we found the sensitivity to be least when $t_N = 0.47$. Multiplying the curve, including all groups in Fig. 4A with the curve shown in Fig. 4B, yields a plot of $dV_0$ as a function of $t_N$ (Fig. 4C), reflecting the variance of a $V_0$ estimate at a given $t_N$ (see APPENDIX). Figure 4D shows the time derivative of normalized elastance.
[dE_N(t_N)/dt_N] as a function of normalized time. By choosing E_N(t_N) at times where the E_N(t_N) curve itself shows minimal instantaneous changes, the reliability of the V_0 estimate is optimized. After an initial peak, the curve reaches a plateau from t_N = 0.4 – 0.5. Consequently, our estimates of V_0(SB) and E_max(SB) were defined as the average of results using t_N = 0.40, 0.45, and 0.50.

Single-beat estimation using bilinearly approximated time-varying elastance. This method was described by Shishido et al. (16). It is based on the elastance curve derived from the PV loop, but is primarily focused on the shape of the curve, assuming that the curve is dependent on contractility and loading conditions. Single-beat contractility is then given by the equation

\[ E_{es(SB)} = \frac{P_{ed} - P_{es}}{P_{es}} \times ET \times \alpha - P_{es}/SV \] (8)

where P_{ed} is the pressure at the end of isovolumic contraction (the moment when the steep rise of the aortic pressure wave begins), P_{es} is end-systolic pressure defined as the pressure when LV dP/dt decreases to 20% of dP/dt_{min} (Fig. 1E), PEP is the time from end diastole to end of isovolumic contraction, ET is the time from end of isovolumic contraction to end systole, and \alpha is the ratio of the slope in the ejection phase to that in the isovolumic phase (Fig. 1F).

Fig. 3. Time-varying V_0(SB) calculated from Eq. 5 with the use of a representative PV loop, and the corresponding volume axis intercept of the elastance curve at multiple beats [V_0(MB)]. Equation 5 is unstable throughout most of the cardiac cycle, and it is therefore necessary to determine V_0(SB) at times where the error of the estimate is minimal.

Fig. 4. Analysis of physiological and mathematical stability of the V_0 estimation, according to Senzaki et al. A: standard deviation (SD) for the pooled E_N(t_N) curve (Fig. 2A) and for each of the four subgroups (Fig. 2, B–E) as a function of t_N, giving a measure of dE_N(t_N). B: dV_0/dE_N(t_N) plotted against t_N (Eq. 12) reflecting the time-varying sensitivity of V_0 to changes in the pooled E_N(t_N) curve (Fig. 2A). dV_0/dE_N(t_N) were calculated for all 88 files at t_N intervals of 1:200, and the curve represents the mean values. C: Total curve in A multiplied with the curve in B gives a plot of dV_0 as a function of t_N. The curve stabilizes on a minimal variance at a t_N of 0.40. D: plot of the derivative of the pooled and grouped normalized elastance curves (Fig. 2, A–E) against t_N. The curves show that the most linear part of the E_N(t_N) curve is bounded by 0.40 \leq t_N \leq 0.50. For clarity, only selected points are shown in A and D.
We also calculated the estimated effective arterial elastance (Ea) as Pmax/SV, and effective ejection fraction (EF) as SV/(Ved - V0) where Ved is end-diastolic volume.

**Computer calculations.** The least-square approximations to the sine curve were done in Matlab (MathWorks) and initial values set for our calculations were 170 mmHg/ml for Pmax(e), 2πT/ω for ω, where T is the duration of the approximated isovolumic pressure curve, 0 rad for C, and 8 mmHg for EDP. The maximal number of iterations was set to 30,000, which was sufficient for complete convergence in all cases. The Ees(tN) curves were resampled by linear interpolation with spacing tN = 0.005 by a customized algorithm written in Visual Basic for Applications (Microsoft). All other calculations were done with the use of Excel software (Microsoft), using macros as needed.

**Comparisons of multiple-beat and single-beat ESPVR estimations.** Ees(Pmax), Ees(Padj), Ees(max(SB)), and Ees(es(SB)) for all 88 steady-state files were compared with Ees(es(MB)) by applying analysis of agreement (1). To determine whether the single-beat methods detected acute changes in contractility, ΔEes(Pmax), ΔEes(Padj), ΔEes(max(SB)), and ΔEes(es(SB)) were compared with ΔEes(es(MB)) in the eight animals in group 2 receiving continuous dopamine infusions (9). Changes in contractility were assessed using a paired t-test.

**RESULTS**

Single-beat estimations of contractility (elastance) were compared with the corresponding multiple-beat values by application of an analysis of agreement (1). These results are outlined in Table 1 and Fig. 5. All of the single-beat methods showed the same characteristics in their ability to predict elastance in terms of bias and limits of agreement (LOA). The bias was quite low for all methods, except for Ees(Pmax) using Pmax(e) based on cutoff 300. The variability (expressed as 2SD or LOA) was high for all methods. The precision of the estimates, in terms of LOA, was better in the baseline/control group than in the total material, whereas bias was slightly lower in the total material than in the baseline/control group for all methods but one.

Figure 2 shows Ees(tN) curves (means ± SD) for each subgroup and for all files. According to the original description (14), the curves should be congruent. However, there was considerable variation among the group-specific curves with respect to SD (Fig. 4A), and the angle between the two parts of the curve describing the isovolumic phase and the ejection phase. The average bias between V0(SB) (Eq. 5) and V0(MB) was 0.1 ml and LOA were −28.5 and 28.6 ml (Fig. 5C).

In the single-beat method based on bilinearly approximated time-varying elastance curves (16), the parameter α is supposed to operate as a correction factor for differences in loading conditions (Fig. 1F). Shishido et al. (16) found α to correlate well to other load-dependent parameters. We found weak but significant correlations between α and the parameters EF and Eo, but α did not correlate to neither Ees(es(MB)) nor EF, (Fig. 6).

**Ability of the single-beat estimates of contractility to detect inotropic changes.** Heart rate, cardiac output, and mean arterial pressure were slightly higher during dopamine infusions compared with baseline (see Table 1 in Ref. 9). Contractility assessed as dP/dt\text{max} increased from 1,366 mmHg/s at baseline to 2,470 mmHg/s during dopamine infusions [dP/dt\text{max} = 1,104 ± 397 mmHg/s (mean ± SD), P < 0.001]. V0(MB) increased from −12.4 ml at baseline to −1.4 ml during dopamine infusion (P = 0.02).

Table 2 and Fig. 7 show the changes in LV elastance induced by inotropic stimulation with dopamine. The mean ΔEes(es(MB)) was 1.7 ± 0.8 mmHg/ml (means ± SD, P < 0.001), and each of the eight pigs showed an increased elastance. The two variants of Takeuchi et al.’s (21) method, using the nonlinear least-squares approximation technique as basis for the Pmax(E) estimate, showed negative ΔEes(e). All of the other single-beat methods showed increased elastance, but this was statistically significant in only one method (our modified Ees(Pmax)), where Pmax(e) was calculated using a fifth-order polynomial function.

**Evaluation of the multiple-beat recordings.** Two consecutive multiple-beat measurements during preload reduction were done in 71 of the 88 recordings, and mean value was used as Ees(es(MB)). The discrepancy between the two measurements, which reflects the reproducibility of multiple-beat elastance, can be expressed in percent by a modified analysis of agreement

\[
\frac{[E_{es(MB)}\text{High} - E_{es(MB)}\text{Low}] \times 100}{(E_{es(MB)}\text{High} + E_{es(MB)}\text{Low})/2}
\]

The mean discrepancy was 5.9% for the baseline group (n = 35) and 7.9% for the intervention groups (n = 36).

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**Table 1. Analysis of agreement between single-beat and multiple-beat estimations of contractility**

<table>
<thead>
<tr>
<th>Single-Beat Method</th>
<th>All Groups, mmHg/ml</th>
<th>Baseline/Control Group, mmHg/ml</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Bias ±2SD</td>
<td>LOA</td>
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<tr>
<td>Ees(Pmax) (see Ref. 21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sine curve, cutoff 100</td>
<td>0.7 3.6</td>
<td>−2.8 4.3</td>
</tr>
<tr>
<td>Sine curve, cutoff 300</td>
<td>1.4 4.0</td>
<td>−2.6 5.5</td>
</tr>
<tr>
<td>Polynomial function, cutoff 100</td>
<td>0.5 3.8</td>
<td>−3.3 4.3</td>
</tr>
<tr>
<td>Polynomial function, cutoff 300</td>
<td>1.1 3.9</td>
<td>−2.9 5.0</td>
</tr>
<tr>
<td>Ees(Padj) (see Ref. 15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0 3.3</td>
<td>−3.3 3.3</td>
<td>−0.8 2.5</td>
</tr>
<tr>
<td>Ees(max(SB)) (see Ref. 14)</td>
<td>−0.3 2.6</td>
<td>−2.9 2.3</td>
</tr>
<tr>
<td>Ees(es(SB)) (see Ref. 16)</td>
<td>−0.3 2.9</td>
<td>−3.2 2.6</td>
</tr>
</tbody>
</table>

Values are means ± SD. LOA, limits of agreement; SD, standard deviation. Ees(Pmax) is calculated using both the original nonlinear least-square approximation technique (sine curve) and our modification of the method based on a fifth-order polynomial function. Cutoff 100 and 300, see METHODS.
The multiple-beat files showed a highly linear ESPVR with a median $r^2$ at 0.98, and a 95% confidence interval of 0.97–0.99 ($n = 159$).

**DISCUSSION**

We have evaluated four different methods using PV-based single-beat estimation of contractility, and demonstrated that all methods predict elastance with good accuracy. The accuracy reflects the systematic errors of a test, and can be corrected as needed. However, all methods had low and insufficient precision, an important parameter when evaluating any diagnostic test.

The precision reflects the random errors of the test, and is directly related to the predictive value of the test.

The other crucial requirement for a single-beat-based contractility index is the ability to detect acute changes in contractility induced by inotropic stimulation or pathological alteration (i.e., stunning). An index fulfilling these criteria would for instance open for a much higher reliability in the clinically important distinction between acute pump failure and suboptimal loading conditions. However, all evaluated indexes failed to comply with these requirements.
In a study by Regen et al. (11), cardioactive drugs did not affect the shape of the isovolumic pressure curve. We observed that during dopamine infusion, the pressure curve was considerably steeper during isovolumic contraction than during isovolumic relaxation compared with baseline. This implies that $P_{\text{max}}(e)$ (21) is shifted to the left (Fig. 1A). However, the rigid nature of the sine curve with respect to symmetry makes it incapable of reflecting this leftward shift, and we observed a minimum mean-square-error increase (total minimum square error divided by the number of points) in the curve fitting with a factor of 4.8 (mean $\pm$ SD) compared with baseline ($P = 0.002$). As a consequence, mean increase in $P_{\text{max}}(e)$ was only 14 mmHg, and combined with a decrease in end-systolic volume, $\Delta E_{\text{es}}(P_{\text{max}})$ turned out to be negative (Table 2). In contrast to the sine curve, a fifth-order polynomial function reflected this leftward shift of nadir and subsequently the increased source pressure. With the use of the fifth-order polynomial function with cutoff 100 and $-100$ mmHg/s to calculate $P_{\text{max}}(E)$, the method did detect increased inotropy as a response to continuous dopamine infusion (Table 2 and Fig. 7B). The increase was small, although statistically significant ($0.6 \pm 0.6$ mmHg/ml, $P = 0.03$). This observation points to the experience gained from developing single-beat methods; empirical adaptation to the methods will be precise but probably not reproducible. Shih et al.’s (15) computer algorithm also reflects this skewness of the pressure wave because the unadjusted pressure is equally affected by the contraction and relaxation waveforms. However, even with the use of this method, increased inotropy during dopamine infusion could not be observed.

A crucial assumption in Senzaki et al.’s (14) method, is that the average $E_{\text{n}}(t_{\text{N}})$ curve shows very little variation in the region used to estimate the single-beat elastance. The authors found this variation, expressed as SD, to be 0.05 in their optimal time frame. In our analysis, SD was 0.07. However, there were considerable differences between the subgroups. SD in the baseline or control group was 0.05, whereas in the dopamine group it was 0.09 (Fig. 4A). In Senzaki et al.’s (14) material, the curves for each patient group and/or test condition showed very little variability with respect to the shape of the curves. In our study, there was a considerable variability among the groups, especially with respect to the angle between the isovolumic phase and the ejection phase. The same observation

![Fig. 6. Relationship between α and $E_{\text{es}}(\text{MB})$ (A), arterial elastance ($E_a$) (B), ejection fraction (EF) (C), and effective EF ($E_{\text{f}}$) (D). The lines represent linear regression ($R$) and 95% confidence limits of mean. As shown, α was weakly correlated to $E_a$ and EF. NS, not significant.](image)

**Table 2. Effect of inotropic stimulation on left ventricular elastance**

<table>
<thead>
<tr>
<th>Changes in Elastance, mmHg/ml</th>
<th>$P$</th>
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<tbody>
<tr>
<td>$\Delta E_{\text{es}}(\text{MB})$</td>
<td>$1.7 \pm 0.8$</td>
</tr>
<tr>
<td>$\Delta E_{\text{es}}(P_{\text{max}})$ (see Ref. 21)</td>
<td>$-0.6 \pm 0.5$</td>
</tr>
<tr>
<td>Sine curve, cutoff 100</td>
<td>$-0.5 \pm 0.9$</td>
</tr>
<tr>
<td>Sine curve, cutoff 300</td>
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<tr>
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<td>$0.8 \pm 0.9$</td>
</tr>
<tr>
<td>$\Delta E_{\text{es}}(P_{\text{adj}})$ (see Ref. 15)</td>
<td>$0.3 \pm 0.4$</td>
</tr>
<tr>
<td>$\Delta E_{\text{es}}(\text{SB})$ (see Ref. 14)</td>
<td>$0.8 \pm 1.1$</td>
</tr>
<tr>
<td>$\Delta E_{\text{es}}(\text{SB})$ (see Ref. 16)</td>
<td>$0.3 \pm 0.5$</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SD. MB, multiple beats, $E_{\text{es}}(P_{\text{max}})$ is calculated using both the original nonlinear least-square approximation technique (sine curve) and our modification of the method based on a fifth-order polynomial function. Cutoff 100 and 300, see METHODS. $P$, significance level using a paired t-test.
was made by Shishido et al. (16) when loading conditions and contractility was significantly changed. These authors subsequently incorporated this angle into their algorithm for single-beat estimation of contractility.

To quantify the influence of the variability of the 
\[ E_{N}(t_N) \]
curve on the accuracy and precision of the single beat elastance estimates, we recalculated \[ E_{\text{max}}(SB) \] for all the 88 files applying the \[ E_{N}(t_N) \] values obtained from the baseline group. We also recalculated \[ E_{\text{max}}(SB) \] applying subgroup-specific \[ E_{N}(t_N) \] values. In all subgroups, the accuracy improved when we used the subgroup-specific \[ E_{N}(t_N) \], but the precision of the estimates remained unchanged (Fig. 9). The explanation for this is that accuracy largely depends on the difference between the subgroup-specific \[ E_{N}(t_N) \] curve and the total \[ E_{N}(t_N) \] curve (i.e., the difference in shape of the curves), whereas the precision of the estimate is a function of the variance of \[ E_{N}(t_N) \] within each group in the optimal time frame.

To summarize, our group-specific \[ E_{N}(t_N) \] curves showed less congruence than those of Senzaki et al. (14). The \[ E_{N}(t_N) \] curve for our baseline or control group showed about the same variance as the \[ E_{N}(t_N) \] curve representing their total material, whereas the variance of \[ E_{N}(t_N) \] in our intervention groups were considerably larger. Consequently, the assumption that normalized elastance is constant among individuals of the same species, and independent of pharmacological interventions, was not confirmed in our material.

Because Eq. 5 is inherently unstable throughout most of the cycle (Fig. 3), the \( V_0 \) estimate has to be made in an optimal time frame of the normalized PV loop. We found this time frame to be \( 0.40 \leq t_N \leq 0.50 \). A possible explanation for the difference from \( 0.25 \leq t_N \leq 0.40 \)
In the bilinear approximated time-varying elastance model of Shishido et al. (16), $\alpha$ reflects the relation between the slopes of the elastance curve in the ejection phase and PEP. In this method, $\alpha$ is regarded as an important factor (Eq. 8) because it is sensitive to changes in contractility and loading conditions, and serves as a correction factor for the lack of congruence between individual elastance curves. These authors therefore examined the dependence of $\alpha$ on the parameters EF, EF\text{c}, E\text{es}, and $E_a$. They found $\alpha$ to be tightly positively correlated to EF\text{c} and EF. $\alpha$ also correlated positively with $E\text{es}$ and negatively with $E_a$. We found only weak correlations between $\alpha$ and two of the parameters (EF and $E_a$), and no correlation with EF\text{c} and $E\text{es(MB)}$ (Fig. 6). This is not surprising, because all of these parameters can influence $\alpha$, but to a variable extent in individual elastance curves. $\alpha$ is also influenced by other properties of the PV loop. Small artefacts in the PV loop, as for instance a blunted upper right corner, increases $\alpha$ considerably. Furthermore, $\alpha$ is influenced by afterload, and we observed that a significant pressure increase during ejection was associated with a high $\alpha$-value.

In this study, we have used hemodynamic data from pigs, which have lower contractility indexes than dogs and humans. ESPVR are low with $E\text{es,MB} = 3.4 \pm 1.1$ (means $\pm$ SD). It is possible that the agreement between multiple-beat and single-beat end-systolic elastance is better in species with higher elastance values. However, Shih et al. (15) reported a mean (single beat + multiple beat)/2 of 19.5 mmHg/ml, a bias of $-1.42$ and LOA of $-10.98$ and $8.15$ in their material of 16 patients, indicating that the lack of precision of the estimate is independent of the absolute slope of the elastance curve.

Fig. 8. Bland-Altman plot showing the agreement between two consecutive multiple-beat elastance measurements during preload reduction. Top, baseline recordings. Bottom, results after intervention.

Fig. 9. Agreement between multiple-beat and single-beat elastance based on Senzaki et al.'s method showing the impact of diversity among group-specific $E_N(t_N)$ curves. ●, Mean bias; ○, mean $\pm$ 2SD. SB-MB = difference between single-beat- and multiple-beat-derived elastance. 1, Results when applying the total $E_N(t_N)$ curve (Fig. 2A); 2, results when applying the baseline/control $E_N(t_N)$ curve (Fig. 2B); 3, results when applying the subgroup-specific $E_N(t_N)$ curve (Fig. 2, C–E).
In our group of baseline/control loops, we have included 21 measurements from 7 pigs, i.e., 3 measurements from each animal (7). These were longitudinal time controls with repeated measurements. The use of repetitive measurements could potentially introduce a bias. However, a time span of 90 min will induce different physiological states in these pigs, and should therefore allow for renewed inclusion in loop assessments.

From load-dependent to load-independent indexes and back again. Since the introduction of elastance as a measurement of contractility, it is now generally agreed that this index is not completely frequency or load independent (5, 12, 17, 22), and that the relation has contractility-dependent curvilinearity (3, 17, 22). Despite this, it reflects the contractile state of the left ventricle rather well within a physiological range of heart rate and loading conditions, given constant \(V_0\) (5, 10, 17). During the past decade, there have been numerous attempts to make it clinically applicable by making invasive procedures obsolete, and the focus has been on predicting end-systolic elastance from one single cardiac cycle. However, the transition from measurements based on multiple beats during preload alteration to less invasive measurements based on one single beat has its cost. All of the single-beat methods contain elements that are highly load dependent, as \(dP/dV_{max}\) (15, 21), ET/PEP (14, 16), SV (14–16, 21), and EDV (21). Load dependency is thus reintroduced, and we are basically left with empirical indexes composed of different load-dependent measures combined with pressure and volume data at critical time points. It is therefore more meaningful to regard the single-beat indexes as load-dependent approximations of the load-independent elastance. These indexes would be clearly insufficient in predicting contractility in a large range of load and frequency situations. However, they are designed to work in a clinical setting within a physiological range of load, heart rate, and contractility, and the influence of these parameters would therefore not necessarily be of significant magnitude (3, 10). Despite this, they seem too susceptible to “noise” from varying frequency and loading conditions.

In conclusion, we found the present methods of single-beat estimation of contractility unable to predict elastance at a sufficient level of precision. Furthermore, all of the single-beat methods failed to detect increased contractility, whereas \(dP/dV_{max}\) did, suggesting that in vivo assessment of contractility still needs refinement.

APPENDIX

Application of Eq. 7 to our data revealed an inverse shape of the curve (Fig. 4B) compared with what Senzaki et al. (14) reported. To clarify this, we differentiated Eq. 5 with respect to \(E_{NS}(t_s)\), and found their expression for the derivative to be incorrect

\[
\frac{dV_o}{dE_{NS}(t_s)} = \frac{d}{dE_{NS}(t_s)} \times \frac{P_{NS}(t_s) \times V_o - V(t_s) \times E_{NS}(t_s)}{P_{NS}(t_s) - E_{NS}(t_s)}
\]

However, the incorrect differentiation procedure does not explain the inverted curve. With the use of the correct formula (Eq. 12), the curve is shifted slightly upward along the vertical axis, but it is still inverted and positioned below the \(x\)-axis. Could the inverted curve then be explained by differences in data?

Equation 11 can be simplified as

\[
\frac{dV_o}{dE_{NS}(t_s)} = \frac{P_{NS}(t_s) \times V_o - V(t_s) \times E_{NS}(t_s)}{P_{NS}(t_s) - E_{NS}(t_s)}
\]

Finally, changing the sign of the numerator from \(\) to \(+\) in the first term of Eq. 7 gives a curve similar to the one Senzaki et al. (14) presented, but doing so has no mathematical basis.

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