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 elastance (Ees(MB)). All methods had a low average bias (−0.3 to 0.5 mmHg/ml) but limits of agreement (±2 SD) were unacceptably high (±2.6 to ±3.8 mmHg/ml). In the dopamine group, Ees(MB) showed an increase of 1.7 ± 0.8 mmHg/ml (mean ± SD) compared with baseline (P < 0.001). None of the single-beat methods predicted this increase in contractility. It is therefore doubtful whether any of the methods allow for single-beat assessment of contractility.

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 line (V₀) (14), or a point given by simulated end-systolic isovolumic pressure, and end-diastolic volume (15, 16, 21). The inherent problem in this approach is our limited knowledge of the heart as a mechanical pump in situ, which does not allow us to mathematically determine such a point accurately. Thus all single-beat indexes are therefore empirical approximations expressed as formulas reflecting one or more factors that are known to correlate with contractility [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-
H1740  
SINGLE-BEAT ESTIMATIONS OF CONTRACTILITY

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 interventions. In most cases, two runs were sampled 30 and 90 min after ischemia (7).

The approximated isovolumic pressure curves were based on measurements from the first point after dP/dt had reached 100 mmHg/s to dP/dt max, and from dP/dt 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 max and dP/dt 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 (Padj)

\[
P_{adj} = 2 \times \left( \frac{P_{unadj} - \Delta}{\pi} + \Delta \right)
\]

where \(P_{unadj}\) is unadjusted pressure and \(\Delta\) is left inflection pressure + right inflection pressure. Single-beat elastance \([Ees(P_{adj})]\) was then given by the line through the point of ESPVR, and the point defined by the coordinates \(P_{adj}\) 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 \([Ees(t)]\). 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. \(Ees(t)\) curves for all PV files were calculated defining time-varying elastance \([E(t)]\) as the instantaneous ratio of \(P(t)/[V(t) - V_{min}]\). The maximal value of \(E(t)\) \([termed E_{max(sb)}]\) and the time from the R wave of the electrocardiogram to achieve \(E_{max(sb)}\) \([termed t_{max}]\) were both determined. The normalized \(E(t)\) function was then defined as

\[
E_{2}(t_{S}) = E(t_{S})/E_{max(sb)}
\]

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

**Single-beat estimation of elastance was done by calculating \(V_{OS(I)}\) using the equation**

\[
V_{OS(I)} = \frac{[P_{N}(t_{S}) \times V(t_{max}) - V(t_{S}) \times E_{N}(t_{S})]}{[P_{N}(t_{S}) - \bar{V}(t_{S})]}
\]

The slope or elastance could then be calculated as

\[
E_{max(sb)} = \frac{P_{max}(t_{S}) [V(t_{max}) - V_{OS(I)}]}{[P_{N}(t_{S}) - \bar{V}(t_{S})]}
\]

The model assumes a constant \(V_{0}\) in a given cardiac cycle, linear elastance, and a species-specific \(E(t)\)/\(E_{max(sb)}\) relation, which means that for a given \(t_{S}\) there is a constant relation between the slopes of \(E(t_{S})\) and \(E_{max(sb)}\) 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 \(E_{2}(t_{S})\) curve comprising all 88 files (Fig. 2A). Equations 5 and 6 give \(V_{OS(I)}\) and \(E_{max(sb)}\) estimates at any time \(t_{S}\). However, \(V_{0}\) determined from Eq. 5 is unstable throughout most of the cardiac cycle (Fig. 3), as \(V_{OS(I)}\) is a hyperbolic function of \(E_{2}(t_{S})\) with a vertical asymptote at \(E_{2}(t_{S}) = \ldots\)

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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.’s (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

$$dV_0/dE_N(t_N) = \frac{-V(t_N)}{P_0(t_N) - E_N(t_N)} - \frac{P_{es}(t_N) \times V_{es} - V(t_N) \times E_N(t_N)}{(P_0(t_N) - E_N(t_N))^2}$$  \hspace{1cm} (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.
Fig. 3. Time-varying $V_{0SB}$ 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 [$V_{0MB}$]. Equation 5 is unstable throughout most of the cardiac cycle, and it is therefore necessary to determine $V_{0SB}$ at times where the error of the estimate is minimal.

$[dE_N(t_N)/dt_N]$ 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 $V_{0SB}$ 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

$$E_{es(SB)}/H_1 = \text{Pad}/H_1 \times \text{Ped}/PEP/ET/HT_2/HT_3/HT_9$$

where $\text{Pad}$ is the pressure at the end of isovolumic contraction (the moment when the steep rise of the aortic pressure wave begins), $\text{Ped}$ is end-diastolic pressure defined as the pressure when $LV dP/dt$ exceeds 30% of $dP/dt_{max}$, $\text{Pes}$ is end-systolic pressure defined as the pressure when $dP/dt$ 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. 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 ($E_a$) as $P_{max}/SV$, and effective ejection fraction (EF$_e$) as $SV/(V_{end} - V_0)$ where $V_{end}$ 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 $P_{max}$, $2\pi T$ for $\alpha$, 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 $E_N(t_N)$ curves were resampled by linear interpolation with spacing $t_N = 0.005$ by a customised 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. $E_{est}(P_{max})$, $E_{est}(P_{adj})$, $E_{max(SB)}$, and $E_{est(SB)}$ for all 88 steady-state files were compared with $E_{est(MB)}$ by applying analysis of agreement (1), and the same comparisons were done between $V_{end}^{SB}$ (Eq. 5) and $V_{end}^{MB}$. To determine whether the single-beat methods detected acute changes in contractility, $\Delta E_{est}(P_{max})$, $\Delta E_{est}(P_{adj})$, $\Delta E_{max(SB)}$, and $\Delta E_{est(SB)}$ were compared with $\Delta E_{est(MB)}$ 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 $E_{est}(P_{max})$ using $P_{max}(e)$ based on cutoff 300. The variability (expressed as 2SD or LOA), on the other hand, 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 $E_N(t_N)$ 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 $V_{end}^{SB}$ (Eq. 5) and $V_{end}^{MB}$ 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 $\alpha$ is supposed to operate as a correction factor for differences in loading conditions (Fig. 1P). Shishido et al. (16) found $\alpha$ to correlate well to other load-dependent parameters. We found weak but significant correlations between $\alpha$ and the parameters EF and $E_a$, but $\alpha$ did not correlate to neither $E_{est(MB)}$ nor EF$_e$ (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 $dP/dt_{max}$ increased from 1,366 mmHg/s at baseline to 2,470 mmHg/s during dopamine infusions [AdP/d$dt_{max} = 1.104 \pm 397$ mmHg/s (means ± SD), $P < 0.001$, $V_{end}^{MB}$ 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 $E_{est(MB)}$ 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 $P_{max(e)}$ estimate, showed negative $\Delta E_{est}$. All of the other single-beat methods showed increased elastance, but this was statistically significant in only one method (our modified $E_{est}(P_{max})$, where $P_{max(e)}$ 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 $E_{est(MB)}$. 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

$$\frac{[E_{est(MB)\text{High}} - E_{est(MB)\text{Low}}] \times 100}{(E_{est(MB)\text{High}} + E_{est(MB)\text{Low}})/2} = (9)$$

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

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>Bias ±2SD</th>
<th>LOA ±2SD</th>
<th>Baseline/Control Group, mmHg/ml</th>
<th>Bias ±2SD</th>
<th>LOA ±2SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{est}(P_{max})$ (see Ref. 21)</td>
<td></td>
<td>0.7</td>
<td>3.6</td>
<td>−2.8 and 4.3</td>
<td>1.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Sine curve, cutoff 100</td>
<td></td>
<td>1.4</td>
<td>4.0</td>
<td>−2.6 and 5.5</td>
<td>1.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Polynomial function, cutoff 100</td>
<td></td>
<td>0.5</td>
<td>3.8</td>
<td>−3.3 and 4.3</td>
<td>0.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Polynomial function, cutoff 300</td>
<td></td>
<td>1.1</td>
<td>3.9</td>
<td>−2.9 and 5.0</td>
<td>1.3</td>
<td>3.0</td>
</tr>
<tr>
<td>$E_{est}(P_{adj})$ (see Ref. 15)</td>
<td></td>
<td>0.0</td>
<td>3.3</td>
<td>−3.3 and 3.3</td>
<td>−0.8</td>
<td>2.5</td>
</tr>
<tr>
<td>$E_{max(SB)}$ (see Ref. 14)</td>
<td></td>
<td>−0.3</td>
<td>2.6</td>
<td>−2.9 and 2.3</td>
<td>−0.1</td>
<td>1.5</td>
</tr>
<tr>
<td>$E_{est(SB)}$ (see Ref. 16)</td>
<td></td>
<td>−0.3</td>
<td>2.9</td>
<td>−3.2 and 2.6</td>
<td>0.4</td>
<td>2.1</td>
</tr>
</tbody>
</table>

Values are means ± SD. LOA, limits of agreement; SD, standard deviation. $E_{est}(P_{max})$ 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.

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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.

Fig. 5. Scatterplots of analysis of agreement between single-beat and multiple-beat estimates. A: our modified version of the isovolumic pressure method (21) where $P_{max}(E)$ is calculated using a fifth-order polynomial function with cutoff 100 (see text). B: modified isovolumic approach (15). C: comparing $V_0_{SB}$ based on Eq. 5 (Senzaki et al.), and $V_0_{MB}$. D: agreement between multiple beat estimates and single beat estimates of elastance using Senzaki et al.’s method based on normalized elastance curves. E: comparison of elastance determined by the bilinear approximation method (16), and MB elastance.
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 ± 2.2 (mean ± 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, \( \Delta E_{\text{es}}(\text{Pmax}) \) 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 ± 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 \( E_N(t_N) \) 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...

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

<table>
<thead>
<tr>
<th>Changes in Elastance, mmHg/ml</th>
<th>( \Delta E_{\text{es}}(\text{MB}) )</th>
<th>( \Delta E_{\text{es}}(\text{Pmax}) ) (see Ref. 21)</th>
<th>( \Delta E_{\text{es}}(\text{maxSB}) ) (see Ref. 16)</th>
<th>( \Delta E_{\text{es}}(\text{SB}) ) (see Ref. 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.7 ± 0.8</td>
<td>( -0.6 \pm 0.5 )</td>
<td>( 0.8 \pm 0.5 )</td>
<td>( 0.8 \pm 0.5 )</td>
</tr>
<tr>
<td></td>
<td>0.001</td>
<td>0.02</td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>( \Delta E_{\text{es}}(\text{Pmax}) )</td>
<td>(see Ref. 14)</td>
<td>( 0.6 \pm 0.6 )</td>
<td>( 0.8 \pm 1.1 )</td>
<td>( 0.3 \pm 0.5 )</td>
</tr>
<tr>
<td></td>
<td>0.03</td>
<td>0.05</td>
<td>0.08</td>
<td>0.1</td>
</tr>
<tr>
<td>( \Delta E_{\text{es}}(\text{maxSB}) )</td>
<td>(see Ref. 14)</td>
<td>( 0.8 \pm 0.9 )</td>
<td>( 0.8 \pm 0.9 )</td>
<td>( 0.8 \pm 0.9 )</td>
</tr>
<tr>
<td></td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Values are means ± SD. MB, multiple beats, \( E_{\text{es}}(\text{Pmax}) \) 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. \( P \), significance level using a paired t-test.

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

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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 $E_{\text{max}}(\text{SB})$ for all the 88 files applying the $E_N(t_N)$ values obtained from the baseline group. We also recalculated $E_{\text{max}}(\text{SB})$ 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 $0.25 \leq t_N \leq 0.30$ in their experiments.
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, Ees, and Ea. They found $\alpha$ to be tightly positively correlated to EF and EF. $\alpha$ also correlated positively with Ees and negatively with Ea. We found only weak correlations between $\alpha$ and two of the parameters (EF and Ea), and no correlation with EF and Ees(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 $E_{es,MB} = 3.4 \pm 1.1$ (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.
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 a single beat has its cost. All of the single-beat methods failed to detect increased contractility, whereas \( \frac{dP}{dt} \) and \( \frac{dV_0}{dt} \) contain elements that are highly load dependent, as a single beat has its cost. All of the single-beat methods therefore allow for renewed inclusion in loop assessments.

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 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

\[
\frac{dV_0}{dE_s(t_s)} = \frac{\frac{dP_s(t_s)}{dt} \times \frac{dE_s(t_s)}{dt}}{E_s(t_s) - E_s(t_s)} 
\]

\[
\text{d}V_0 / \text{d}E_s(t_s) = \frac{[P_s(t_s) - E_s(t_s)] \times [-V(t_s)] - (-1)}{[P_s(t_s) \times V_s - V(t_s) \times E_s(t_s)]} 
\]

\[
\text{d}V_0 / \text{d}E_s(t_s) = \frac{V(t_s)}{\frac{P_s(t_s) - E_s(t_s)}{V_s - V(t_s)}} 
\]

\[
\text{d}V_0 / \text{d}E_s(t_s) = \frac{P_s(t_s) - V(t_s)}{[P_s(t_s) - E_s(t_s)]^2} 
\]

Equation 11 can be simplified as

\[
\frac{dV_0}{dE_s(t_s)} = \frac{[P_s(t_s) \times E_s(t_s)] + [V(t_s) \times E_s(t_s)]}{[P_s(t_s) \times V_s] - V(t_s) \times E_s(t_s)} 
\]

\[
\text{d}V_0 / \text{d}E_s(t_s) = \frac{P_s(t_s) \times E_s(t_s) + V(t_s) \times E_s(t_s)}{[P_s(t_s) \times V_s] - V(t_s) \times E_s(t_s)} 
\]

\[
\text{d}V_0 / \text{d}E_s(t_s) = \frac{V(t_s)}{[P_s(t_s) - E_s(t_s)]^2} 
\]

It follows from the PV model, regardless of species and inotropic state, that end-systolic volume \( (V_s) \) is smaller than the volume at end systole for all values of \( t_s \) between 0 and 1. The numerator in Eq. 14 is therefore always negative in this time frame. Because \( P(t_s) \) and the denominator are always positive, \( dV_0 / dE_s(t_s) \) must be negative in the same time frame. However, the shape of the curve and its relation to the x-axis is unchanged, so the basis for the conclusion regarding window of measurements \( (0.40 \leq t_s \leq 0.50) \) remains unaltered.

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