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ORIGINAL ARTICLE

Assessment of single beat end-systolic elastance methods for quantifying ventricular contractility

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Abstract

Multi-beat end-systolic elastance (E_{MB}) is considered a gold-standard index of ventricular contractility. However, it is difficult to measure clinically due to the need for transient manipulation of ventricular preload or afterload. We compared the performance of 5 'single-beat' methods that do not require loading interventions, for estimating the equivalent of E_{MB}. In 7 sheep instrumented with a micromanometer/conductance catheter, single-beat methods were compared with E_{MB}, obtained after transiently decreasing preload or increasing afterload under a broad range of heart rates and inotropic conditions. The single-beat elastance (E_{SB}) method described by Shishido et al. (Circulation 102(16):1983–1989, 2000) had the highest correlation ($R=0.69$, $y=0.52x+0.43$) with E_{MB}, although the absolute accuracy was poor. Interestingly, for all methods tested, a higher correlation was observed when E_{MB} was obtained with an afterload increase ($R=0.47-0.78$) rather than a preload reduction ($R=0.07$–0.57). Within-animal regression coefficients were higher than those obtained from pooled data, with excellent within-animal correlation observed for Shishido et al. method ($0.73 \leq R \leq 0.96$) when using afterload increase as the loading intervention. We conclude that (1) current methods perform better when using an afterload increase to obtain reference E_{MB}, (2) intra-individual E_{SB} comparisons may be more reliable than inter-individual comparisons and (3) Shishido et al.'s method demonstrated the strongest correlation with E_{MB}. Current E_{SB} methods have limited and variable accuracy, but may hold promise for tracking relative changes in ventricular contractility in individuals.

Keywords Heart function · Cardiac · Contractility · End-systolic pressure–volume relationship

Introduction

The slope of the end-systolic pressure–volume relationship (ESPVR), or end-systolic elastance (E_{es}), is considered a gold-standard measure of ventricular contractility [1]. However, the need to measure pressure–volume (PV) data during transient changes in loading conditions to obtain E_{es} from multiple beats (here called E_{MB}) limits its clinical application. To circumvent this issue, several single beat elastance (E_{SB}) methods have been proposed, where E_{SB} is an estimate of E_{es} obtained from a single heart beat and without a loading intervention [1–5]. Although the original papers describing these methods reported relatively good agreement between single-beat and multi-beat methods (Pearsons R ranging from 0.79 to 0.93), few independent confirmatory studies are available. Kjorstad et al. [1] found relatively poor accuracy and sensitivity when E_{MB} was obtained via preload reduction. However, the extent to which loading intervention type (e.g. preload reduction vs afterload increase) affects the relationship between E_{MB} and E_{SB} is unknown. It is also unclear whether E_{SB} methods may allow reliable tracking of contractility changes in individuals, even if absolute accuracy is poor and varies between individuals.

The aim of this study was to compare five currently available single-beat end-systolic elastance estimation methods [1–5] using high fidelity data obtained from sheep under a wide range of heart rates, contractile states and blood pressures, with E_{MB} reference values assessed via both preload

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reduction and afterload increase. We also investigated the ability of single-beat methods to track within-individual changes in contractility.

Methods

The protocol was approved by the Animal Ethics Committee of the Murdoch Childrens Research Institute, and conformed to the guidelines of the National Health and Medical Research Council of Australia.

Acute surgical preparation

Seven castrated male sheep (40.5 ± 6.8 kg, mean ± SD) were anaesthetized with an intramuscular injection of xylazine (0.05 mg/kg) and ketamine (5 mg/kg) followed by isoflurane (3–4%) in O_2 delivered by mask. After intubation of the trachea, anaesthesia was maintained with a mixture of 1–3% isoflurane and nitrous oxide (10–20%) in oxygen-enriched air delivered via a volume-controlled ventilator (900C Servo, Siemens-Elema; Solna, Sweden), supplemented by an intravenous infusion of ketamine (3–4 mg/kg/h) and midazolam (0.01–0.02 mg/kg/h) administrated through a 7-Fr triple lumen catheter inserted into the left external jugular vein. The left common carotid artery was cannulated for blood pressure monitoring and arterial sampling for blood gas analysis, with ventilation adjusted to maintain arterial O_2 tension at 100–120 mmHg and CO_2 tension at 35–40 mmHg.

After a thoracotomy in the third intercostal space, the second–fourth ribs were removed to increase exposure of the heart and great vessels. Fluid-filled catheters were inserted into the left atrium via the appendage and into the proximal portion of the aortic arch to measure blood pressures via an external transducer (Transpac, ICU Medical). Pacing wires were sutured to the left atrial appendage and the epicardium of the left ventricular (LV) anterior wall. A transit-time flow probe (20 mm A-series, Transonic Systems Inc; Ithaca, NY) was placed around the ascending aorta to measure LV output. The left carotid artery cannula was replaced with an 8-Fr vascular sheath, and a combined conductance micromanometer catheter with pig-tail (Millar Instruments; Houston, TX) was then passed into the LV under echocardiographic guidance for pressure–volume loop analysis. Finally, polyvinyl snares were placed around the inferior vena cava (IVC) and the distal descending thoracic aorta, for later manipulation of preload and afterload, respectively.

Experimental protocol

After completion of surgery, hemodynamics were allowed to stabilize over a period of ~ 15 min. While hemodynamics were recorded in the baseline state, the IVC snare was tightened over ~ 10 s in all animals to produce a transient preload reduction for later LV pressure–volume loop analysis (Fig. 1, left). The snare was released and hemodynamics allowed to return to baseline levels. Subsequently, hemodynamics were recorded whilst the snare around the descending thoracic aorta was tightened over ~ 10 s in all animals to produce a transient afterload increase for later LV pressure–volume loop analysis (Fig. 1, right). For each of the transient loading alterations, hemodynamic data were recorded during end-expiratory apnea with a positive airway pressure of 5 cmH_2O.

Hemodynamics were then recorded in all animals during the following sequential interventions: (1) left atrial pacing,

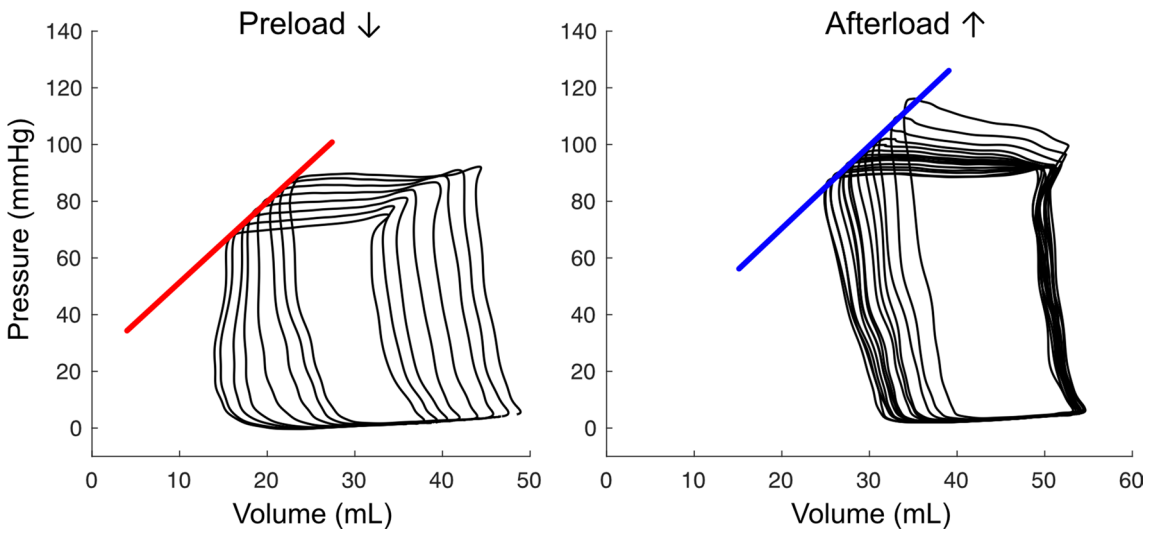

Fig. 1 Example of the end-systolic pressure–volume relationship (ESPVR, red and blue lines) derived from a preload reduction (inferior vena cava occlusion) and afterload increase (descending thoracic aorta constriction). Multi-beat E_{es} (i.e. E_{MB}) is equal to the slope of the ESPVR

(2) LV pacing, (3) steady-state increases in mean aortic blood pressure, and (4) infusion of incremental doses of the β-adrenergic agonist dobutamine to progressively increase cardiac contractility.

With left atrial and LV pacing (Grass SD9 stimulator, Grass Instruments Co., Quincy, MA), heart rate was increased at steady-state increments of 20 beats/min above the baseline rate (~ 80 beats/min), to a maximum of 160 beats/min. At each level of heart rate, data were recorded during a transient preload reduction and then a transient afterload increase, as described above.

After hemodynamics had returned to baseline levels following cessation of cardiac pacing, mean aortic blood pressure was increased in three steps of 5, 10 and 15–20 mmHg by tightening of the snare around the descending thoracic aorta. After hemodynamics had stabilized at each level of blood pressure for 2 min, data were recorded during a transient preload reduction, as described above.

After release of the snare around the descending thoracic aorta and return of hemodynamics to baseline levels, progressive steady-state rises in cardiac contractility were produced by an incremental intravenous infusion of dobutamine at doses of 0.5, 1, 1.5, 2, 2.5, 5 and 10 μg/kg/min. After hemodynamics had stabilized for 5 min at each dose, data were recorded during a transient preload reduction and then a transient afterload increase, as described above.

At the end of the study, the dobutamine infusion was stopped and animals euthanized with intravenous sodium pentobarbitone (100 mg/kg).

Hemodynamic measurements and analysis

Aortic and left atrial fluid-filled catheters were connected to pressure transducers and referenced to the level of the mid thoracic vertebral spine. Ascending aortic flow was measured with a flowmeter (model T206, Transonic Systems Inc) and the LV micromanometer interfaced with transducer control units (TCB-600, Millar Instruments, Houston, TX).

Analogue signals were digitised at 1000 Hz (iNET-100B, GW Instruments, Somerville, MA) and recorded using programmable acquisition and analysis software (Spike2, Cambridge Electronic Design, Cambridge, UK). The LV micromanometer was calibrated against the left atrial fluid-filled catheter pressure at end-diastole for each condition in the protocol. LV conductance volumes and an ECG signal were obtained from the combined conductance micromanometer catheter interfaced with a signal processor (MPVS Ultra, Millar Instruments). Parallel conductance was calculated following injection of 2–4 ml of 10% saline into the left atrium, while the gain constant was calculated as the ratio of conductance to aortic flow probe-derived stroke volume [6].

Data analysis was performed in Spike2 (Cambridge Electronic Design, Cambridge, UK) and Matlab (R2016b, The MathWorks, Inc., Natick, MA, USA). A 48 Hz low pass filter was applied at the time of analysis to remove electrical interference from signals. After excluding files containing clear artefacts, a total of 234 data files were analysed. E_{MB} was calculated as the slope of the linear end-systolic pressure–volume relation (Fig. 1), which was obtained using the iterative method described by Baan and Van der Velde [7]. The end-systolic pressure–volume relationship was highly linear for both preload reduction and afterload increase, with an adjusted R^2 of 0.96 ± 0.05 for a linear fit and 0.97 ± 0.05 for a quadratic fit (fitting over 11 ± 5 points). E_{SB} from five estimation methods were calculated from an ensemble average of steady-state data immediately preceding the loading intervention used for the E_{MB} reference. The five estimation methods are briefly introduced below; for full descriptions, refer to the original publications [1–5].

Single beat elastance methods

Takeuchi et al.: P_{max} estimated with a sinusoid

Takeuchi et al. [5] described an approach whereby maximum isovolumic pressure, P_{max}, was estimated by fitting a sinusoidal wave (Eq. (1)) to isovolumic segments of the LV pressure waveform (Fig. 2). Pressure curve segments from end-diastolic pressure (EDP) to dP/dt_{max}, and from dP/dt_{min} to the same level as EDP, were used for the least squares fitting of the sinusoid. End-diastolic pressure was defined as the pressure at which dP/dt first exceeded 200 mmHg/s. The isovolumic pressure curve (P_{iso}) was estimated as

$$P_{iso}(t) = \frac{1}{2}P_{max}[1 - \cos(\omega t + C)] + EDP, \quad (1)$$

where ω is the angular frequency and C is a phase shift. A straight line was drawn from the upper left corner of the PV loop to the point (end-diastolic volume, P_{max}) and the slope of this line was taken as E_{SB}.

Kjorstad et al.: P_{max} estimated with a fifth order polynomial

A modification of [5] proposed by Kjorstad et al. [1] involved the use of a fifth order polynomial instead of a sinusoidal wave, which accounts for the fact that rate of pressure rise during isovolumic contraction may differ from the rate of pressure fall during isovolmic relaxation (Fig. 2). As in [1], we tested two threshold values of dP/dt for defining EDP, namely 100 and 300 mmHg/s. Derivation of P_{max} and calculation of E_{SB} otherwise followed that in [5]. While both thresholds were tested, results are only shown for 100 mmHg/s, since this yielded slightly better agreement with E_{MB}, as was also found in [1].

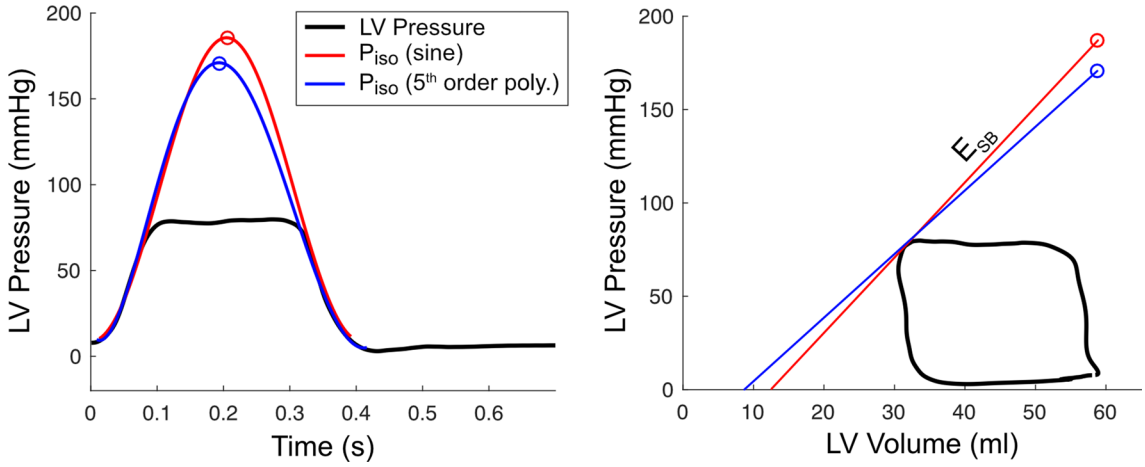

Fig. 2 (Left) Example of estimating isovolumic pressure (P_{iso}) and its maximum value (P_{max}, circles) by fitting a sinusoidal curve [5] or fifth-order polynomial [1] to the isovolumic parts of the measured left ventricular (LV) pressure waveform. (Right) Use of P_{max} to estimate the end-systolic pressure–volume relationship and its slope, E_{SB}, from a single pressure–volume loop

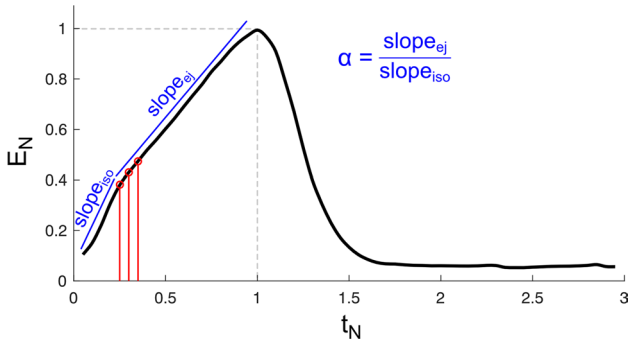

Fig. 3 Normalised elastance curve ($E_N(t_N)$) from Senzaki et al. [4]. Red lines indicate the normalised elastance values used to estimate E_{SB} via Senzaki et al.'s method [4]. The ratio of ejection phase elastance slope to isovolumic phase elastance slope is equal to α; in Shishido et al.'s method [2], α is estimated empirically from ejection fraction, pre-ejection period and ejection time

Senzaki et al.: normalized elastance curve

Time-varying elastance, $E(t)$, is defined as $P(t)/[V(t) - V_0]$, where V_0 is the volume intercept of the ESPVR. The maximum of this curve is E_{es}; however, the unknown V_0 must be calculated first. Elastance curves normalized by maximum elastance and time were shown to be similar for a wide range of physiological conditions [4]. A normalized, averaged elastance curve from 72 PV loops (54 patients) from [4] was used to estimate $V_{0(SB)}$ and then E_{SB} (Fig. 3). Normalized $E(t)$ was first defined as

$$E_N(t_N) = E(t_N)/E_{\max(SB)}, \tag{2}$$

where $t_N = t/t_{max}$ such that t_{max} is the time corresponding to $E_{max(SB)}$, the maximum elastance with $V_0 = 0$. For a chosen t_N, $V_{0(SB)}$ can be calculated using the following equation:

$$V_{0(SB)} = \frac{P_N(t_N)V(t_{\max}) - V(t_N)E_N(t_N)}{P_N(t_N) - E_N(t_N)}, \tag{3}$$

where normalized pressure (P_N) is defined in a similar way to elastance. End-systolic elastance is then estimated with

$$E_{SB} = P(t_{\max})/[V(t_{\max}) - V_{0(SB)}]. \tag{4}$$

As $V_{0(SB)}$ is a hyperbolic function of $E_N(t_N)$, it is unstable for most of the cardiac cycle. Senzaki et al. [4] used a method to minimize physiological and mathematical variances and found that t_N between 0.25 and 0.35 was optimal for stability. The same range was used for this study, with the final E_{SB} estimate being the average of the three estimates obtained with t_N of 0.25, 0.30 and 0.35 (Fig. 3, red lines).

Shishido et al.: Normalised elastance curve with bilinear approximation

Shishido et al. [2] found that, in contrast to [4], the normalized elastance curve varied under different inotropic and loading conditions. Therefore, they proposed a method that depends on a bilinear approximation of the rising phase of the $E(t)$ curve. The ratio of the slope of the ejection phase to the slope of the isovolumic contraction phase, α (see Fig. 3), was estimated empirically by quantifying the relationship between α and ejection fraction (EF), pre-ejection period (PEP) and ejection time (ET) under changed contractility and loading conditions.

According to [2], EF and PEP/(PEP + ET) were both well correlated with α. With these results, two regression models to estimate α were investigated: a univariate model based on ejection fraction alone ($\alpha = 0.022 + 1.171\text{EF}$) and a trivariate model based on EF and PEP/(PEP + ET) as follows:

$$\alpha = -0.210 + 1.348\text{EF} + 0.682\frac{\text{PEP}}{\text{PEP} + \text{ET}}. \tag{5}$$

Note that we only present results calculated via Eq. (5) due to its slightly better performance than the univariate model. Once α was known, E_{SB} was calculated with Eq. (6) using pressures at end-isovolumic contraction (P_{ad}), end-diastole (P_{ed}) and end-systole (P_{es}),

$$E_{SB} = \frac{1}{SV}\left[P_{ad} + \alpha\left(\frac{P_{ad} - P_{ed}}{PEP}\right)ET - P_{es}\right]. \quad (6)$$

For a full derivation of the above equation, see [2]. End-diastole was defined as the point at which LV dP/dt reached 30% of dP/dt_{max}, the end of isovolumic contraction was defined as the time at which the rapid rise in LV began to slow (via visual inspection), and end-systole was defined as the time at which LV dP/dt fell to 20% of dP/dt_{min}.

Chen et al.: Normalized elastance curve with adjustment

A non-invasive modification of [4] using brachial pressure and pulse-wave Doppler flow to approximate aortic pressure and ventricular volume was described by Chen et al. [3]. The ratio of elastance at mid-isovolumic contraction to elastance at end-systole was found to be conserved and this was used to derive $V_{0(SB)}$ and E_{SB} using a t_N during isovolumic contraction, denoted t_d. Due to the variation of normalized elastance around this point (E_{Nd}), a regression model was used to find an estimate (E^*_{Nd}) which could correct for such variation. The resulting regression model Eq. (7) was dependent on EF, the ratio of arterial pressure at diastole to systole and the value of the group averaged elastance curve from [4] represented by a seven-term polynomial (last term of Eq. (7)). t_{Nd} was defined as the ratio of PEP to total systolic period while coefficients a_i are (0.35695, −7.2266, 74.249, −307.39, 684.54, −856.92, 571.95, −159.1) for $i = 0$ to 7.

$$E^*_{Nd} = 0.0275 - 0.165EF + 0.3656\frac{P_d}{P_s} + 0.515\sum_{i=0}^{7} a_i\left(t_{Nd}\right)^i, \quad (7)$$

where P_s and P_d are the arterial systolic and diastolic pressures, respectively. E^*_{Nd} could then be used to find E_{SB} via

$$E_{SB} = \left(P_d - E^*_{Nd}P_s\right)/\left(SV \times E^*_{Nd}\right). \quad (8)$$

For our assessment of this method, aortic pressure and ventricular volume were available and used directly; hence, Eq. (8) has been modified from the original publication to replace approximated with measured aortic pressure.

Statistical analysis

Data were analysed using regression analysis after logarithmic transformation due to a large range and non-normal distribution of values. Separate analyses were performed on the entire data set, by loading intervention and by individual animals. Strength of correlation is expressed via Pearson's correlation coefficient (R) and departure from the line of unity is indicated by regression coefficients, where $y = ax + b$. When analysing individual data, individual regression lines were calculated, along with an average regression line obtained by averaging the coefficients. Bland–Altman analysis was not performed since the strength of correlation is arguably more clinically relevant than absolute agreement.

Results

Scatter plots of E_{SB} vs E_{MB} are shown in Fig. 4 for all data points, with data points associated with preload reduction for E_{MB} in red and afterload increase in blue. Values of E_{MB} ranged from 1.33 to 71.7 mmHg/mL. All single beat methods tended to overestimate low values of E_{MB} and underestimate high values of E_{MB}, resulting in slopes < 1 (0.14 to 0.52, Table 1). There was also substantial scatter, with R values between 0.30 and 0.69. Shishido et al.'s method yielded the strongest correlation ($R = 0.69$, $y = 0.52x + 0.43$), with data points closer to the line of unity but still with substantial scatter.

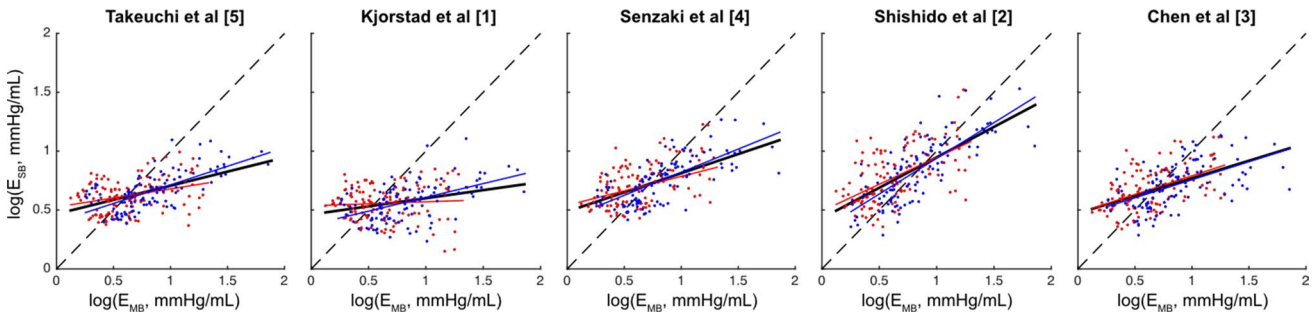

Fig. 4 Scatter plots of single beat elastance (E_{SB}) vs multi-beat elastance (E_{MB}) for the five single beat estimation methods using pooled data from $n = 7$ sheep, where E_{MB} was obtained via preload reduction (red dots) or afterload increase (blue dots). Regression lines are shown for the entire data set (black lines) and for preload reduction (red lines) and afterload increase (blue lines). Dashed lines indicate the line of unity. See Table 1 for regression statistics

Compared with preload reduction, substantially stronger correlations were obtained when afterload increase was used to calculate E_{MB}, with R being 0.29 higher and slopes closer to unity (0.13 higher) on average across the various E_{SB} methods (Table 1), with the exception of Chen et al. method where little difference was observed between loading interventions. Shishido et al.'s method [2] produced the strongest correlation for both loading interventions.

Figure 5 shows individual regression lines in grey and average regression lines in red. Stronger correlations were found within individuals compared with pooled data (Fig. 6). Of the total 35 regressions (5 methods for each of the 7 sheep), 27 (77%) were highly significant ($P<0.001$), while four regressions (including two with negative slopes seen with Kjorstad et al. method) were non-significant. Average strength of correlation was higher with afterload increase (average $R=0.62$ to 0.87 across methods) compared with preload reduction ($R=0.38$ to 0.74). For individual regressions, Shishido et al.'s method vs E_{MB} via afterload increase demonstrated the strongest correlation (average $R=0.87$, range $0.73-0.96$; average regression equation, $y=0.67x+0.28$). Scatterplots of individual and pooled data for Shishido et al.'s method are shown in Fig. 7, separated by loading condition. Correlation coefficients based on preload

Table 1 Linear regression statistics for E_{SB} vs. E_{MB}

	All			Preload reduction			Afterload increase		
	R	*A*	*B*	*R*	*A*	*B*	*R*	*A*	*B*
Takeuchi et al. [5]	0.53	0.24	0.47	0.32	0.15	0.53	0.68	0.32	0.4
Kjorstad et al. [1]	0.3	0.14	0.46	0.07*	0.03*	0.54*	0.50	0.23	0.37
Senzaki et al. [4]	0.51	0.33	0.49	0.31	0.25	0.54	0.71	0.39	0.43
Shishido et al. [2]	0.69	0.52	0.43	0.57	0.45	0.49	0.78	0.61	0.33
Chen et al. [3]	0.54	0.3	0.47	0.53	0.32	0.47	0.56	0.31	0.45

$P<0.001$ for all regressions except that indicated with *

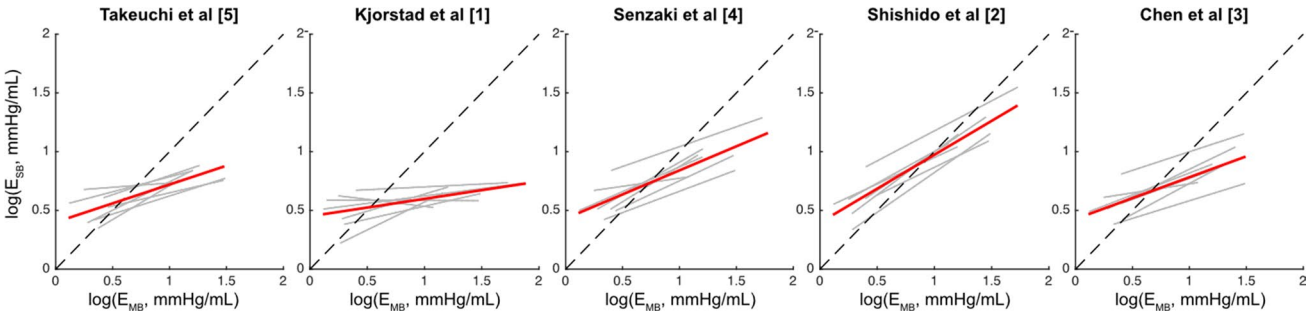

Fig. 5 Individual regression lines (grey lines) relating multi-beat elastance (E_{MB}) and single beat elastance (E_{SB}) for the five single beat estimation methods, along with the average regression line (red lines) obtained by averaging regression coefficients from individuals. Dashed line indicates the line of unity

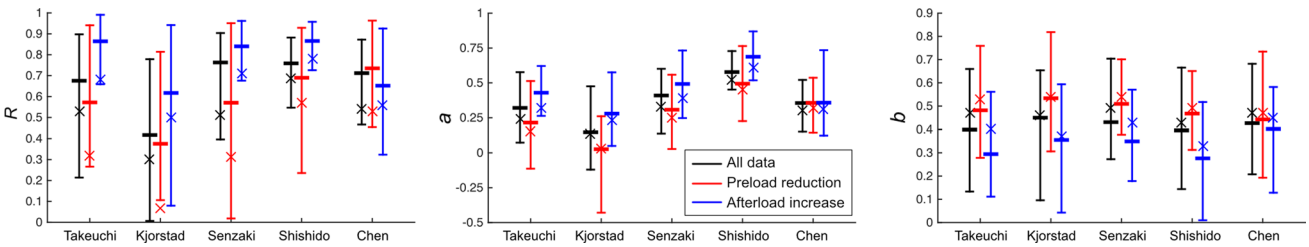

Fig. 6 Correlation coefficient (R) and regression coefficients (a and b) for the linear regressions on individual data (see Fig. 5), shown for all data for the respective animal (black lines) and with E_{MB} derived from preload reduction (red lines) or afterload increase only (blue lines). Vertical bars span the entire range of values encountered; thick horizontal bars indicate the average regression, while the crosses indicate values from the single regression performed on pooled data. Twelve (34%) individual regressions were non-significant for preload reduction, but only one regression was non-significant for afterload increase. Note that these statistics relate to regressions of log-transformed data

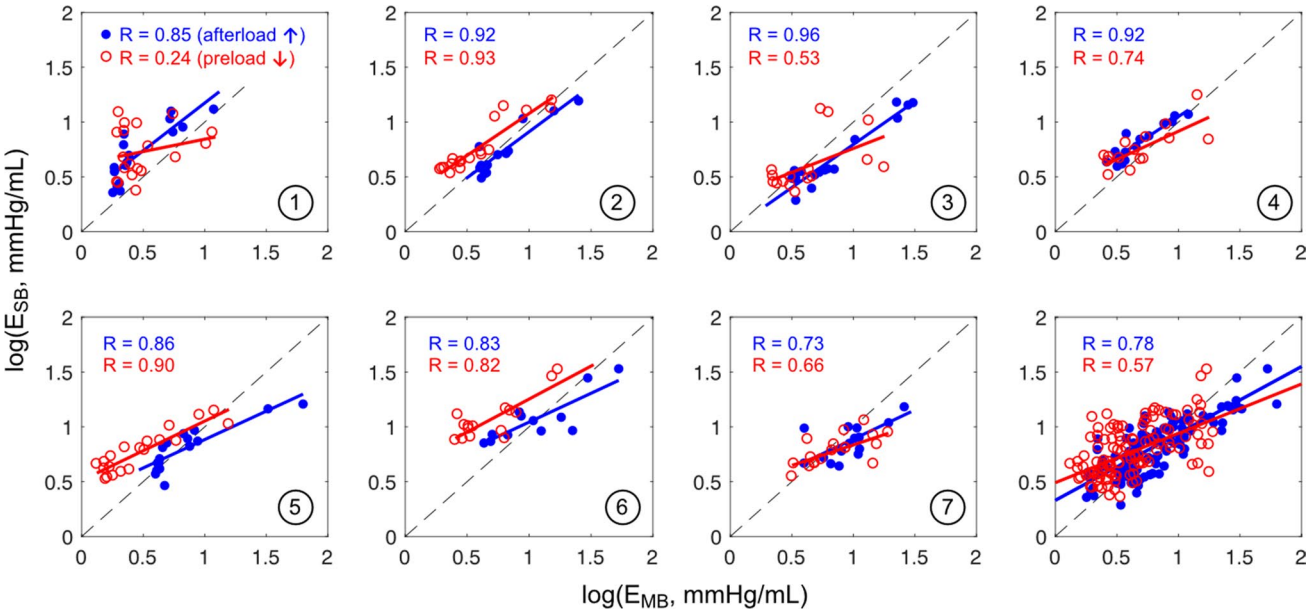

Fig. 7 Scatter plots of E_{SB} vs. E_{MB} for the single beat elastance method described by Shishido et al. [2], showing data points and regression lines for individual animals (1–7) and when data from all animals are pooled (lower right panel). Data are separated into points for which E_{MB} was calculated via afterload increase (blue closed circles) and preload decrease (red open circles)

reduction were comparable to those based on afterload in four animals (2, 5, 6, 7), but were substantially lower in three animals (1, 3, 4).

Discussion

This study has used PV loops in sheep to compare five E_{SB} methods [1–5] to the reference E_{MB}. The relationship between E_{SB} and E_{MB} using pooled data was characterised by (1) relatively poor correlation for all methods ($0.3 \leq R < 0.7$) compared with the original studies describing the E_{SB} techniques ($R \geq 0.8$) and (2) relatively low sensitivity to changes in contractility ($a \leq 0.5$). Both of these findings are consistent with the prior study by Kjorstad et al. [1].

A key novel finding of this study was that the type of loading intervention used to calculate E_{MB} (preload reduction vs afterload increase) had a major effect on the strength of correlation between E_{SB} and E_{MB}, with R increasing by 0.29 on average across the five E_{SB} methods when using afterload increase only. Interestingly, the relatively strong correlations reported in the original papers describing E_{SB} methods used preload reduction, except for [5], which used afterload reduction and elevation via infusion of nitroglycerin and angiotensin II, respectively. While the reason for this disparity is not clear, species differences, age differences and the presence of cardiovascular disease in the human studies and the wide range of inotropic conditions tested in this study may play a role. Further studies are needed to elucidate the reasons why afterload increase resulted in better correlations than preload reduction.

Variation amongst individual sheep was also a key factor affecting the relationship between E_{SB} and E_{MB} (Fig. 6), given that within-animal correlations were consistently stronger than for pooled data. This may suggest that certain individual-specific variables may need to be accounted for in the E_{SB} calculation to improve inter-individual comparisons. Further work is needed to identify these variables and incorporate them into the E_{SB} calculation.

Of the five methods tested, the use of a fifth-order polynomial to estimate maximum isovolumic pressure performed the worst. This method was proposed by Kjorstad et al. [1] based on the observation that the non-symmetric polynomial curve achieved better fitting of the isovolumic pressure segments compared with the symmetric sinusoidal curve used by Takeuchi et al. [5]. We also found that the fitting was improved, however, this did not translate to better prediction of E_{MB}. Major drawbacks of these methods are the reliance on a mathematical extrapolation to P_{max} and the assumption that the ESPVR is linear over a large range of pressures.

Senzaki et al.'s method relies on a population-averaged normalised elastance curve, based on an observation that this curve was nearly constant across a wide variety of physiological conditions in humans [4]. However, others subsequently found significant variation in the normalised elastance curve with altered contractility and load [1, 2]. The correlation coefficient found in the present study for

Senzaki et al. method ($R = 0.51$) was almost identical to that reported by Shishido et al. [2] in dogs ($R = 0.49$). In our analysis, we used Senzaki et al.'s normalised elastance that was developed from human data. Although not presented, we also tested the use of a sheep-specific normalised elastance curve developed from the same experimental group from this study; this did not have a major impact on the results, increasing R from 0.51 to 0.59 for the pooled data analysis. Chen et al. [3] proposed a variation of the normalised elastance curve that is more amenable to non-invasive measurement, since it depends on end-diastolic and end-systolic LV volumes (obtainable by echocardiography or MRI) and systolic and diastolic arterial pressure (obtainable by standard blood pressure recording). Due to the use of ejection-phase variables, E^*_{Nd} was estimated empirically. A potential limitation of our implementation of this method is the use of the same empirical equation (Eq. (7)) as developed by Chen et al. [3] from human data.

The best performing E_{SB} method was that described by Shishido et al. [2], which is a modification of Senzaki et al.'s normalised elastance method [4] involving empirically accounting for variation in the relative slopes of the ejection and isovolumic contraction phases. This method was tested initially in dogs and a linear regression between E_{SB} and E_{MB} resulted in $R = 0.927$ and $y = 0.970x + 0.458$ [2]. Although this excellent correlation was not reproduced in our study when using pooled data, which resulted in $R = 0.69$ and $y = 0.52x + 0.43$ (Table 1, 'all'), strong correlations were obtained ($0.73 \leq R \leq 0.96$) when assessing within-individual changes and calculating E_{MB} via an afterload increase only (see Fig. 7). This correlation was also very good when compared to E_{MB} derived from preload reduction in 4/7 of the individual animals. Although these findings support those of Shishido et al. [2], they differ from those reported by Kjorstad et al. [1], who found a non-significant increase in this single beat estimate ($P = 0.1$) despite a significant increase in E_{MB} ($P < 0.001$). Possible explanations for this divergence include species differences (pigs vs dogs/sheep) or more likely the relatively small range of E_{MB} values in Kjorstad et al. study (2–6 mmHg/mL) compared with our study (most data between 1.5 and 30 mmHg/mL) and Shishido et al.'s study (7–22 mmHg/mL).

Conclusion

In our data acquired from sheep over a broad range of heart rates and inotropic states, absolute accuracy of the single-beat elastance estimation methods was poor. Although the correlation with E_{MB} was moderate at best when using pooled data, stronger correlations were observed within individuals and when afterload increase was used as the loading intervention. Shishido et al.'s method [2] demonstrated the best performance, with excellent within-animal correlation with E_{MB}.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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