Defining end-systolic pressure for single-beat estimation of right ventricle–pulmonary artery coupling: simple… but not really

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To the Editor:

Functional adaptation of the right ventricle (RV) to its afterload plays an important prognostic role in pulmonary hypertension (PH) [1]. The preferred "multibeat" (MB) method for assessing RV–pulmonary vascular interaction involves the measurement of end-systolic elastance (E_{es}), the slope of the end-systolic pressure (ESP) to end-systolic volume over sequential heart beats with varying preload. The E_{es} value is then matched to simultaneous pulmonary arterial (PA) elastance at end systole (E_a), calculated as ESP pressure divided by stroke volume (SV). The ratio of E_{es} to E_a (E_{es}/E_a) is termed RV–PA coupling, preservation of which indicates maintenance RV functioning in the face of increasing afterload [1]. However, while the MB method is generally regarded as the reference standard, it requires continuous, accurate measurement of RV volume and is therefore not readily applicable in most clinical settings.

An alternative approach to determining E_{es}/E_a is the "single beat" (SB) method that incorporates a prediction of P_{max} (the theoretical pressure generated by the RV during an isovolumic beat), an estimate of ESP, and a measurement of SV [2]. A common assumption of the SB method has been that mean PA pressure (mPAP) [3–6] or peak RV systolic pressure (RVSP) [7] represent adequate surrogates for ESP. However, in a hypertensive RV, the mPAP frequently underestimates the ESP [8]; while in a normotensive RV, the peak RVSP tends to overestimate ESP. To overcome these limitations, Tello *et al*. [8] developed a correction equation (ESP=1.65×mPAP−7.79) that demonstrates a strong correlation with measured ESP from the MB method. Following this, Richter *et al*. [9] demonstrated a significant correlation between the SB and MB methods. However, in this study, the ESP for SB estimation of E_{es} and E_a was derived from a presumably linear end-systolic pressure volume relationship (ESPVR), not as a specifically defined point in the cardiac cycle. More recently, Heerdt *et al*. [10] described a method to define the point of maximal time-varying elastance for individual beats based upon the second derivative of the right ventricular pressure (RVP) waveform, and used this point to determine ESP for SB estimation of RV ejection fraction.

Using an experimental dataset, the current study estimated RV ESP using the different methods described in published reports for SB calculation of E_{es}/E_a and determined the accuracy and precision of each relative to ESP directly measured from the ESPVR. In addition, the correlation between E_{es}/E_a calculated using each estimate of ESP and that defined by MB analysis was determined.

Archived measurements of mPAP, RVP and RV volume recorded from 13 anesthetised swine (50–55 kg) under protocols approved by the institutional animal care and use committee, and in accordance with the NIH Guide for the Care and Use of Laboratory Animals were used for the study. All pressure data had been acquired by micromanometry and volume by calibrated conductance catheter before and during interventions to alter RV afterload alone or in combination with inotropic manipulation. Under each condition, data were recorded at steady-state and during transient occlusion of the inferior vena cava to reduce preload. From steady-state recordings of RVP and volume, P_{max} was predicted as previously described [10], SV derived, and SB measures of E_{es} and E_a calculated using ESP defined by four different methods: 1) RV pressure at the point of estimated maximal time varying elastance (ESPtve) [10]; 2) mPAP [3]; 3) adjusted mPAP [8]; and 4) peak RVSP [7]. From MB caval occlusion data, E_{es} was determined as the slope of the ESPVR and E_a was calculated as ESP/SV with end-systole defined as the point of

Shareable abstract (@ERSpublications)
Surrogates of right ventricle (RV) end-systolic pressure (ESP) used to determine RV–pulmonary artery coupling vary across studies. ESP using point of maximal time varying elastance provides most accurate estimate of actual ESP. https://bit.ly/3xuqX3B

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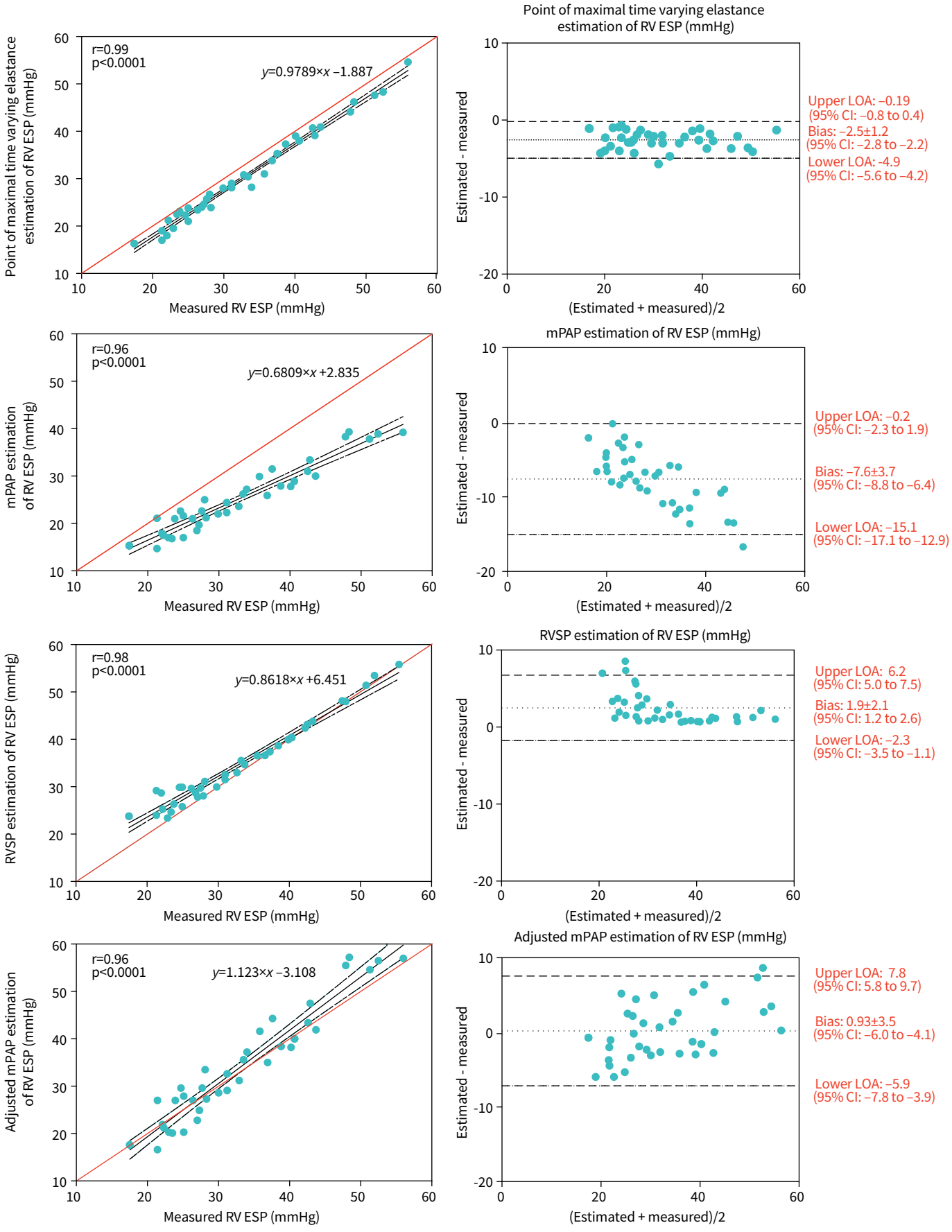
Point of maximal time varying elastance estimation of RV ESP (mmHg)
r=0.99
p<0.0001
y=0.9789×x –1.887
Measured RV ESP (mmHg)
Point of maximal time varying elastance estimation of RV ESP (mmHg)
Estimated - measured
(Estimated + measured)/2
Upper LOA: –0.19
(95% CI: –0.8 to 0.4)
Bias: –2.5±1.2
(95% CI: –2.8 to –2.2)
Lower LOA: -4.9
(95% CI: –5.6 to –4.2)
mPAP estimation of RV ESP (mmHg)
r=0.96
p<0.0001
y=0.6809×x +2.835
Measured RV ESP (mmHg)
mPAP estimation of RV ESP (mmHg)
Estimated - measured
(Estimated + measured)/2
Upper LOA: –0.2
(95% CI: –2.3 to 1.9)
Bias: –7.6±3.7
(95% CI: –8.8 to –6.4)
Lower LOA: –15.1
(95% CI: –17.1 to –12.9)
RVSP estimation of RV ESP (mmHg)
r=0.98
p<0.0001
y=0.8618×x +6.451
Measured RV ESP (mmHg)
RVSP estimation of RV ESP (mmHg)
Estimated - measured
(Estimated + measured)/2
Upper LOA: 6.2
(95% CI: 5.0 to 7.5)
Bias: 1.9±2.1
(95% CI: 1.2 to 2.6)
Lower LOA: –2.3
(95% CI: –3.5 to –1.1)
Adjusted mPAP estimation of RV ESP (mmHg)
r=0.96
p<0.0001
y=1.123×x –3.108
Measured RV ESP (mmHg)
Adjusted mPAP estimation of RV ESP (mmHg)
Estimated - measured
(Estimated + measured)/2
Upper LOA: 7.8
(95% CI: 5.8 to 9.7)
Bias: 0.93±3.5
(95% CI: –6.0 to –4.1)
Lower LOA: –5.9
(95% CI: –7.8 to –3.9)

FIGURE 1 Correlation between measured right ventricle end-systolic pressure (RV ESP) and estimated RV ESP using different single beat methods. Data presented as means and 95% confidence intervals of the linear regression functions. Red line denotes the line of identity (left-hand panels). Bland–Altman plot showing the mean difference between methods (bias) and 95% limits of agreement (LOA) and their respective confidence intervals between estimated and measured RV ESP (right-hand panels). mPAP: mean pulmonary arterial pressure; RVSP: right ventricle systolic pressure.

maximal pressure/volume ratio [11]. A dataset was constructed containing 39 simultaneous measures (three from each animal) of ESP defined by different methods, SB E_{es} and E_a calculated using the different measures of ESP, and MB E_{es} and E_a.

Comparison between measured RV ESP and that defined by different SB methods was performed using linear regression to define correlation, Bland–Altman plots to define accuracy and precision of estimated data, and four quadrant concordance plots with a 10% zone of exclusion to assess uniformity of directional change [12]. Measurements were considered potentially interchangeable when the average difference between them (bias) was <10% of the mean of measured ESP values, and the overall error calculated as: (bias standard deviation×1.96)/mean of all data compared was ⩽30%. These criteria are consistent with previously reported method comparison studies in swine involving haemodynamics [13]. Statistical analyses were performed using GraphPad Prism 9 (GraphPad Software, LLC, La Jolla, CA, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

There was strong correlation between measured ESP and all estimates (figure 1). Bland–Altman analysis indicated that the ESPtve demonstrated acceptable accuracy and precision with a bias of −2.5±1.2 mmHg (8% of the mean of measured ESP values) and an overall mean error of 8%. Adjusted mPAP provided an ESP estimate that was slightly more accurate (bias=0.9±3.5 mmHg, 3% of the measured ESP mean) but less precise (mean error=21%). In contrast, the poorest ESP estimate was mPAP which was neither accurate (bias=−7.6±3.8 mmHg, 21% of the measured ESP mean) or precise (mean error=26%). Concordance between measured ESP and the different estimates was 100% except for RVSP (92%, data not shown).

With pooled data, the only difference between MB and SB E_{es}/E_a occurred when mPAP was used as a surrogate for ESP (ANOVA on ranks with all comparisons to MB E_{es}/E_a, data not shown). However, for individual data points significant correlation with MB E_{es}/E_a was evident for only the ESPtve (r=0.5, p=0.0009) and adjusted mPAP (r=0.3, p=0.02) methods.

The present study demonstrates that among the different methods for estimating ESP, the approach based upon approximation of the point of maximal time varying elastance (ESPtve) provided greatest accuracy and precision while mPAP provided the worst. However, when adjusted using the equation reported by Tello *et al*. [8], mPAP did yield an estimate of ESP that was accurate and acceptably precise (figure 1). In contrast, although peak RVSP demonstrated strong linear correlation with measured ESP when RVP was high, the relationship overall appears nonlinear with RVSP overestimating the measured ESP when RVP was low (figure 1). Presumably, this reflects the fact that with a normotensive RV there is continued ejection well beyond the point of peak RVSP due to the high capacitance and low resistance pulmonary circulation [14], resulting in ESP being reached later in the cardiac cycle. Overall, the study results highlight previous reports [8] that although mPAP is correlated with RV ESP and has been frequently used as a surrogate [3–6], it progressively underestimates ESP as RVP rises (figure 1).

Across all methods, a significant relationship between both pooled and individual SB and MB E_{es}/E_a data was evident only for ESPtve and adjusted mPAP. This underscores the importance of considering how ESP was defined when interpreting absolute values for E_{es}/E_a reported in the literature.

Results from the current study need to be interpreted in the context of limitations. Data for analysis were compiled from 13 anesthetised, ventilated pigs with acute pulmonary vasoconstriction. Further work is required for clinical validation of the study results across different PH phenotypes. In addition, while the study results are broadly consistent with the concept that SB measures of E_{es}/E_a using ESPtve can effectively represent the MB reference standard, specific definition of the accuracy and precision of this representation is beyond the scope of the current investigation.

In summary, the current study demonstrates that estimation of ESP using an RVP-based approximation of the point of maximal time varying elastance can provide an accurate and precise value. This method eliminates the need for simultaneous measurement of mPAP when performing SB analysis of RV E_{es}/E_a.

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