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ORIGINAL RESEARCH

Reliability of effective arterial elastance using peripheral arterial pressure as surrogate for left ventricular end-systolic pressure

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Abstract
To compare the effective arterial elastance (Ea) obtained from the arterial pressure with Ea calculated from left-ventricular (LV) pressure–volume analysis. Experimental study. LV pressure–volume data was obtained with a conductance catheter and arterial pressures were measured via a fluid-filled catheter placed in the proximal aorta, femoral and radial arteries. Ea was calculated as LV end-systolic pressure (ESP)/stroke volume (SV). Experimental protocol consisted sequentially changing afterload (phenylephrine/nitroprusside), preload (bleeding/fluid), and contractility (esmolol/dobutamine). 90% of systolic pressure (Ea_{ao}_SYS, Ea_{fem}_SYS, Ea_{rad}_SYS), mean arterial pressure (Ea_{ao}_MAP, Ea_{fem}_MAP, Ea_{rad}_MAP), and dicrotic notch pressure (Ea_{ao}_DIC, Ea_{fem}_DIC, Ea_{rad}_DIC) were used as surrogates for LV ESP. SV was calculated from the LV pressure–volume data. When Ea was compared with estimations based on 90% SAP, the relationship was $r^2 = 0.95$, 0.94 and 0.92; and the bias and limits of agreement (LOA): -0.01 ± 0.12, -0.09 ± 0.12, -0.05 ± 0.15 mmHg ml^{-1}, for Ea_{ao}_SYS, Ea_{fem}_SYS and Ea_{rad}_SYS, respectively. For estimates using dicrotic notch, the relationship was $r^2 = 0.94$, 0.95 and 0.94 for Ea_{ao}_DIC, Ea_{fem}_DIC and Ea_{rad}_DIC, respectively; with a bias and LOA: 0.05 ± 0.11, 0.06 ± 0.12, 0.10 ± 0.12 mmHg ml^{-1}, respectively. When Ea was compared with estimates using MAP, the relationship was $r^2 = 0.95$, 0.96 and 0.95 for Ea_{ao}_MAP, Ea_{fem}_MAP and Ea_{rad}_MAP, respectively; with a bias and LOA: 0.05 ± 0.11, 0.06 ± 0.11, 0.06 ± 0.11 mmHg ml^{-1}, respectively. LV ESP can be estimated from the arterial pressure. Provided that the SV measurement is reliable, the ratio MAP/SV provides a robust Ea surrogate over a wide range of hemodynamic conditions and is interchangeably in any peripheral artery, so it should be recommended as an arterial estimate of Ea in further research.

Keywords Effective arterial elastance · Afterload · Arterial pressure · Arterial load

1 Background

Effective arterial elastance (Ea) is increasingly being used in critical care medicine research as a simple estimate of total arterial load [1–8]. In the original conception, Sunagawa et al. proposed that, similar to the left ventricular characterization of a time-varying elastance [9], the arterial load could be also characterized by a time-varying elastance in the LV pressure-volume domain [10]. The ratio of the end-systolic values of both elastances was proposed as a measure of ventriculo-arterial coupling.

The arterial load to the left ventricle, or aortic input impedance, consists of the well-known Windkessel combination of arterial compliance and total peripheral resistance [11], characteristic impedance [12], total arterial inertance [13] and arterial wave reflections [14]. However, aortic impedance can only be measured from arterial pressure and flow as complex harmonics in the frequency domain [14]. Sunagawa et al. suggested that Ea as a single parameter that incorporates the main components of the arterial load [10], and therefore can be used to characterize the afterload in

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terms compatible with the matching between left ventricle and its afterload [10].

Ea was originally defined as the ratio of left ventricular (LV) end-systolic pressure (ESP) and stroke volume (SV), both obtained from the LV pressure–volume analysis [10]. Estimation of SV is now easily available at the bedside using standard hemodynamic monitors. However, the calculation of Ea from arterial data still requires a surrogate for LV ESP, for which have been proposed 90% of the systolic pressure (SAP) [1, 2, 7, 8], mean arterial pressure (MAP) [6, 10], and dicrotic notch pressure [15, 16]. Kelly et al. [17] and Chemla et al. [18] have shown that 90% of SAP could be used as a reasonable estimate of LV ESP when measured at the central aortic level. Sunagawa et al. using the aortic MAP for estimating LV ESP, proposed that Ea could be approximated by the ratio of R_T/T (a simplification of MAP/SV), with R_T being the total resistance and T the cardiac cycle length [10]. However, all these estimates rely on the measurement of central aortic pressure, which is not commonly used in clinical practice. Since radial and femoral arterial catheterization is part of the usual care in critically-ill patients with hemodynamic instability, Ea estimation has been mainly based on radial or femoral pressures [1, 5, 6, 8]. However, the assumption that all these peripheral estimates are comparable, regardless of where they are measured, ignores the differences in the arterial pressure shape from central aorta to the peripheral arteries, because of the structure of the arterial system and the arterial wave reflection phenomenon [19]. For that reason, some concerns have been raised about the use of these peripheral pressure surrogates for estimating Ea in clinical practice [20, 21].

We therefore aimed to compare the different Ea estimations using arterial pressure data measured at the aortic, femoral and radial sites, with Ea obtained from the LV ESP and LV SV derived from the LV conductance catheter as a reference, under different experimental hemodynamic conditions.

2 Methods

2.1 Animals

The study protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at the Edwards Research Center and performed in accordance with the USDA Animal Welfare Act regulations (AWArs), and the Guide for the Care and Use of Laboratory Animals (ILAR, NAP, Washington, DC, 2010, 8th edition).

Twelve anaesthetized and mechanically ventilated adult Yorkshire pigs (75–100) kg were studied. Animals were premedicated with intramuscular telazol (4.4 mg kg^{-1}), ketamine (2.2 mg kg^{-1}) and xylazine (1.1 mg kg^{-1}). They were intubated and mechanically ventilated in a volume-controlled mode (FIO_2 of 60–80%, tidal volume of 10 ml kg^{-1} at respiratory rate 13–15 cycles min^{-1}). Following endotracheal intubation, general anesthesia was maintained with isoflurane 1.5–2.5% and a mixture of oxygen, air and/or nitrous oxide. Fluid maintenance was provided intravenously by a continuous infusion of Ringer's lactate solution at 2–4 ml kg^{-1} h^{-1}. Rectal temperature was monitored and kept between 36 and 37 °C using a heating pad.

Instantaneous LV pressure–volume (PV) measurements were obtained from a dual-field conductance catheter and a high-fidelity pressure sensor (CA71083PL, CD Leycom, Zoetermeer, the Netherlands) connected to a PV signal processor (Inca®, CD Leycom, Zoetermeer, the Netherlands). The catheter tip was positioned in the LV apex and the correct placement confirmed by fluoroscopy and the examination of the segmental LV PV loops.

2.2 Data collection and analysis

Volume signal calibration consisted in the determination of cardiac output (CO) by the standard thermodilution method and correction for parallel conductance by the hypertonic saline method, as described elsewhere [22, 23]. Volume calibration was performed before starting the experimental protocol and repeated after the fluid bolus stage. LV pressure–volume signals were recorded at 250 Hz sampling rate and filtered using a 25 Hz low-pass filter and analyzed in a dedicated software (Conduct NT, version 3.18.1, CD Leycom, Zoetermeer, the Netherlands). LV ESP, SV, CO, end-diastolic and end-systolic volumes (EDV and ESV, respectively), end-diastolic pressure, and Ea were calculated from 5 to 7 beats during an end-expiratory pause. End-systole was defined as the maximal LV pressure–volume ratio during each cardiac cycle [24]. An example of analysis of PV loops analysis is shown in Fig. 1. The radial, femoral and proximal aortic pressure were continuously recorded with a fluid-filled pressure transducer (FloTracIQ sensor, Edwards Lifesciences, Irvine, CA, USA) using the EV1000 monitor (Edwards Lifesciences). Dicrotic notch pressure was beat-to-beat detected using a method based on the detection of the local maxima of the second derivative of arterial pressure [25].

2.3 Arterial estimations of effective arterial elastance

Three different approaches for estimating LV ESP were used: 90% of SAP, MAP and dicrotic notch pressure. All methods were applied in the aortic, femoral and radial pressure waveform for calculating Ea: Ea_{rad}_SAP = 0.9 × radial SAP/SV, Ea_{fem}_SAP = 0.9 × femoral SAP/SV, and Ea_{ao}_SAP = 0.9 × aortic SAP/SV, for the first approach; Ea_{rad}_MAP = radial MAP/SV, Ea_{fem}_MAP = femoral MAP/SV and

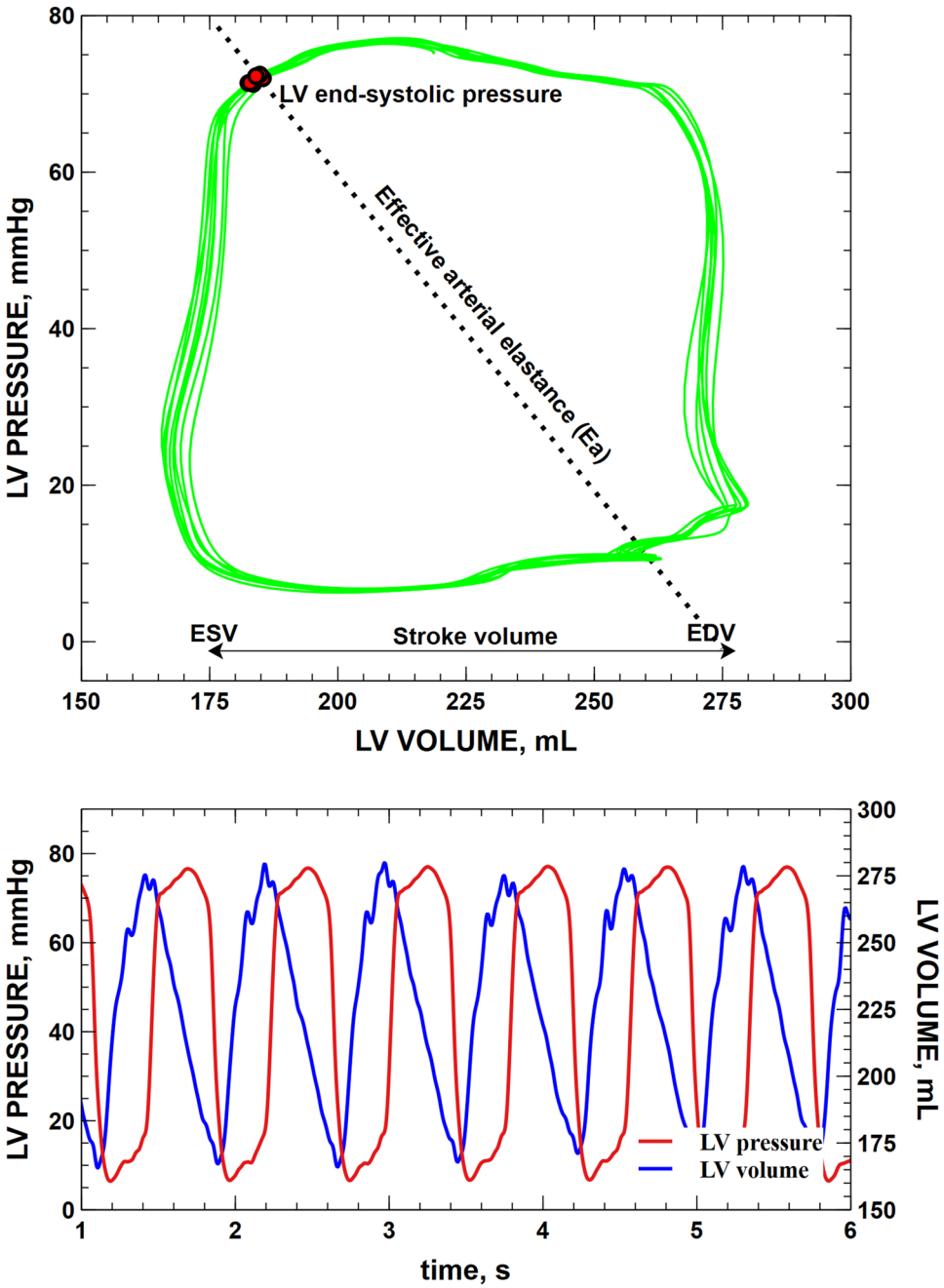

Fig. 1 Left ventricular pressure–volume analysis. Representative example of a left ventricular (LV) pressure–volume (PV) analysis obtained during an expiratory pause. The red dots are the LV end-systolic pressure (ESP) values, determined as the pressure at the time where LV elastance was maximal. Ea is represented as the line connecting the LV ESP/end-systolic volume (ESV) point to the point at 0, end-diastolic volume (EDV). The slope of this line equals to LV ESP/SV ratio, or effective arterial elastance (Ea)

EA_{ao}_MAP = aortic MAP/SV, for the MAP-based approach; and Ea_{rad}_DIC, Ea_{fem}_DIC and Ea_{ao}_DIC for the dicrotic pressure method. In all cases, SV was obtained from the PV loop analysis. An example of the evolution of the three methods for estimating LV ESP is shown in Fig. 2. An example of the morphological changes in the aortic, femoral and radial arterial pressure waveforms after each experimental intervention is shown in Fig. 3.

We also estimated Ea from arterial system properties using a 3-element Windkessel model: $Ea(Z) = R_T / \left[t_s + \tau \times \left(1 - e^{-t_d/\tau}\right)\right]$, where t_s and t_d are systolic and diastolic periods, respectively, R_T the total mean vascular resistance (aortic MAP/cardiac output), C the net arterial compliance (stroke volume/aortic pulse pressure), and τ the diastolic time constant ($\tau = R_T \times C$) [10, 17].

2.4 Experimental protocol

Before starting the protocol, animals received a fluid bolus (Voluven®, 130/0.4, Fresenius Kabi Deutschland GmbH, Bad Homburg, German) until no preload-dependency was observed. Then they were allowed to stabilize for at least

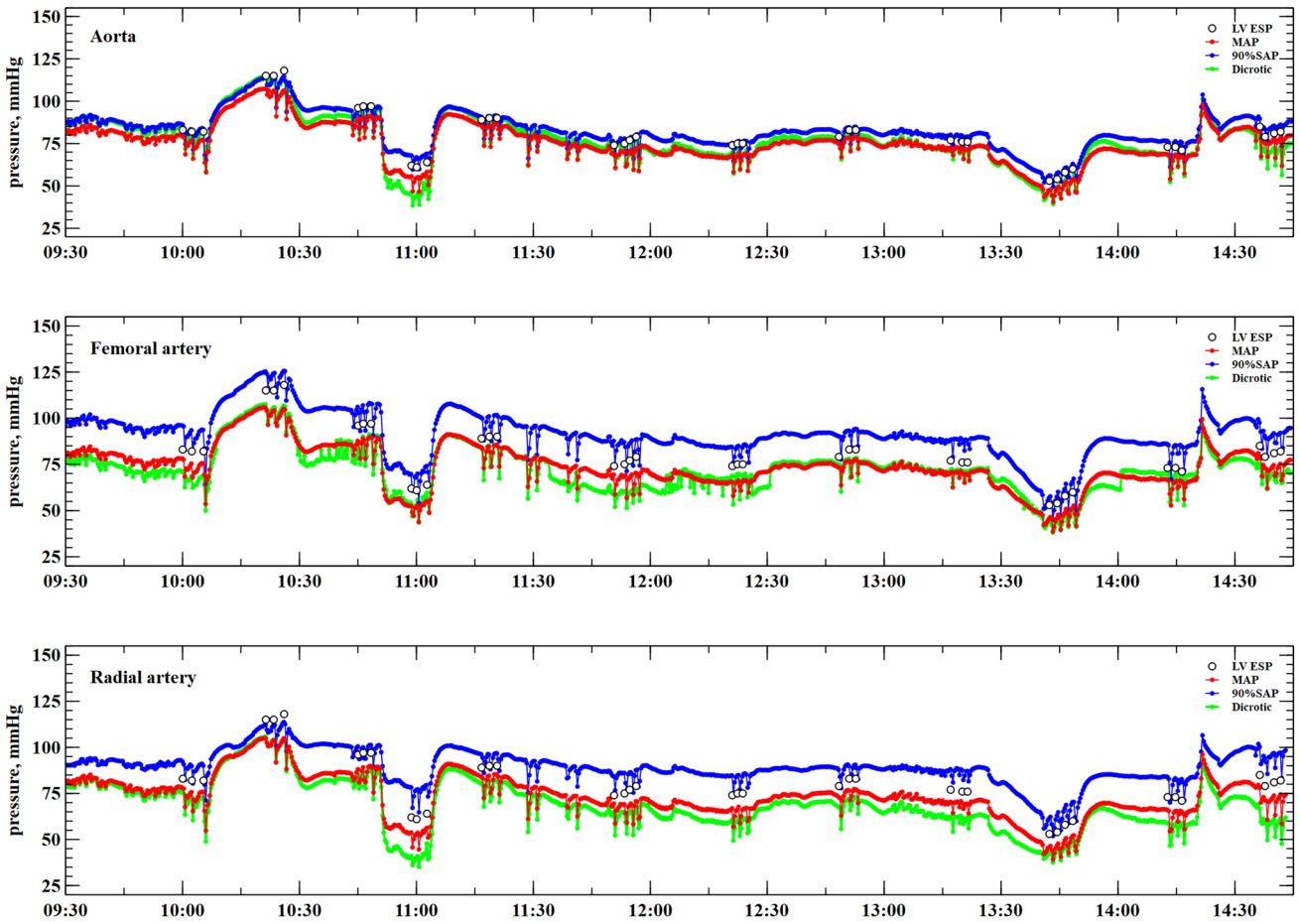

Fig. 2 Example of estimates of left ventricular end-systolic pressure. Evolution of the three estimates used as surrogates for left ventricular end-systolic pressure on aortic (above), femoral (middle) and radial (below) pressure waveforms: 90% of the systolic arterial pressure (90% SAP, blue line), mean arterial pressure (MAP, red line) and dicrotic notch pressure (Dicrotic, green line). Left ventricular end-systolic pressure (LV ESP) obtained from the conductance catheter is also shown (white closed circles). The observed sudden spike down in arterial pressure traces were produced by the inferior vena cava occlusion maneuvers for the left ventricular end-systolic elastance determination (pressure measurements were obtained just before each occlusion maneuver)

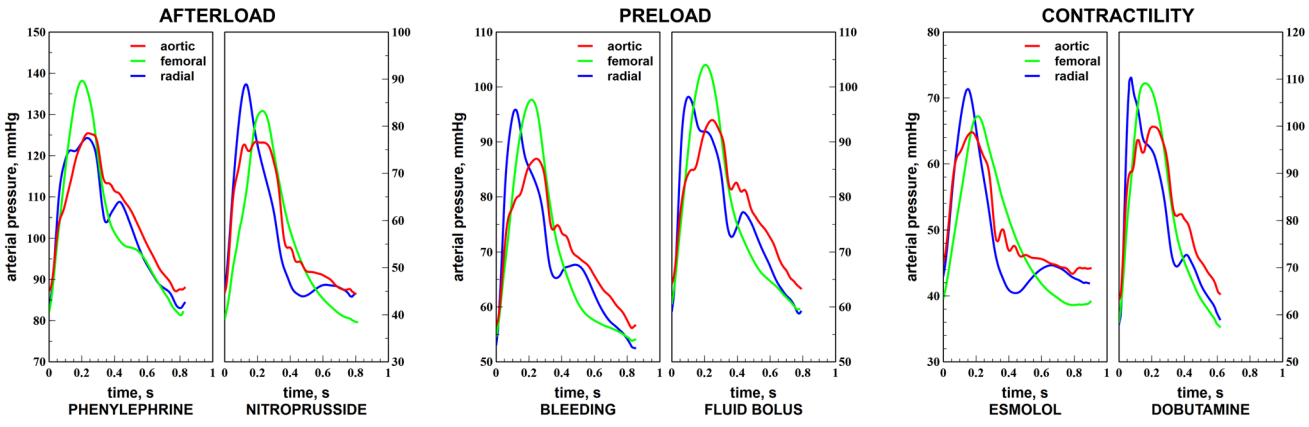

Fig. 3 Differences in the shape of the aortic, femoral and radial arterial pressure waveforms during different experimental stages. An illustrative example obtained from one animal showing the impact on the morphological characteristics of the aortic, femoral and radial arterial pressure waveforms after each experimental intervention. Peripheral arterial waveforms were obtained using the ensemble average pressure waveforms during the apnea period just before the inferior vena cava occlusion, and foot-to-foot aligned to provide a representative waveform for each experimental intervention

10 min (heart rate and MAP variation < 5%). The study protocol consisted of three consecutive stages with up and down interventions each: changes in afterload (phenylephrine and nitroprusside), preload (bleeding and fluid bolus), and contractility (esmolol and dobutamine). The experiment started with the afterload interventions: the pigs were treated with sodium nitroprusside (100–200 mg kg^{-1} min^{-1}) to decrease MAP to 40% from baseline, followed by recovery to baseline status. Then they were treated with a phenylephrine infusion (30–120 mg kg^{-1} min^{-1}) to increase MAP by 40% mmHg from baseline and were allowed to recover. Subsequently, for preload interventions, the animals were submitted to a stepwise bleeding of 12 ml kg^{-1} (50 ml min^{-1}) and the blood stored into a heparinized sterie bag. Then the blood was reinfused at 50 ml min^{-1} and a fluid bolus of 10 ml kg^{-1} of colloid in 5 min was infused. After the fluid administration, the contractility interventions followed: an esmolol infusion was introduced at 50 µg kg^{-1} min^{-1} and increased until decreasing LV dP/dt_{max} by 50% from its previous value (maximal dose: 200 µg kg^{-1} min^{-1}). Then the esmolol infusion was stopped and, after a period of recovery, the animals were treated with dobutamine (5 µg kg^{-1} min^{-1}) to increase LV dP/dt_{max} by 50%. LV PV loops and arterial pressure waveforms were obtained during baselines and after each intervention stage.

2.5 Statistical analysis

Data are expressed as the mean ± SD, unless otherwise stated. The normality of data was checked by the Shapiro–Wilk test. Comparison between Ea derived from the LV pressure–volume analysis and Ea_{ao}, Ea_{fem} and Ea_{rad} were performed using a linear regression. Bland–Altman analysis was used to assess the agreement between Ea and peripheral estimates of Ea. Bias was defined as the mean difference between Ea and Ea surrogates. Limits of agreement (LOA) were calculated as mean bias ± 1.96 SD. We also performed a linear mixed-effects analysis for determining the contribution of SV and LV ESP to Ea variations. Models were constructed using individual animals as subjects for random factors, and sequential experimental stages as repeated measurements. A heterogeneous first-order autoregressive covariance structure was selected based on the corrected Akaike's Information Criteria. A P value < 0.05 was considered statistically significant. All statistical analyses were two-tailed and performed using MedCalc Statistical Software version 18.5 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016).

3 Results

The evolution of the main LV hemodynamic variables obtained from the conductance catheter during different experimental stages is presented in Tables 1, 2 and 3. Data from aortic pressure was lost in one animal due to technical reasons. As expected, changes in afterload by phenylephrine increased Ea by 65 ± 28% and decreased by 40 ± 11% with nitroprusside. Bleeding significantly reduced Ea by 17 ± 11%, whereas fluid administration and contractility changes did not induce any substantial changes in Ea. The contribution of LV ESP and SV to Ea variations throughout the study was shown in Table 4. If holding SV constant, an increase of 1 mmHg of LV ESP will increase Ea by 0.009 mmHg/ml, while, keeping constant LV ESP, an increase of 1 ml of SV will decrease Ea by 0.006 mmHg/ml.

The relationship between Ea and estimates using 90% of SAP was excellent ($r^2 = 0.95$, bias and LOA: 0.01 ± 0.12 mmHg ml^{-1} for aortic pressure; $r^2 = 0.94$, bias and LOA: − 0.09 ± 0.12 mmHg ml^{-1} for femoral pressure; $r^2 = 0.92$, bias and LOA: − 0.05 ± 0.15 mmHg ml^{-1} for radial pressure, respectively). The 90% of SAP consistently overestimated LV ESP, although these differences depended on the arterial pressure measurement site (mean bias and LOA: 1.3 ± 11.7 mmHg for the aortic level; 9.6 ± 12.2 mmHg for the femoral artery; and 5.9 ± 14.7 mmHg for the radial artery). Moreover, the coefficient of determination between Ea and the arterial surrogates was lower and the LOA wider as the LV ESP estimation by SAP was made further away from the heart (Figs. 4, 5).

Ea estimates based on the dicrotic notch pressure offered a good performance, with a relationship with Ea of $r^2 = 0.94$ for aortic pressure (with no significant intercept), and $r^2 = 0.95$ and 0.94 for femoral and radial

Table 1 Hemodynamic variables during afterload changes

	Phenylephrine		Sodium nitroprusside	
	Before	After	Before	After
CO (L min^{-1})	7.92 ± 1.34	7.08 ± 0.94†	8.57 ± 2.12	9.53 ± 2.26*
SV (ml)	106 ± 10	94 ± 12†	101 ± 11	117 ± 14‡
HR (beats min^{-1})	75 ± 10	75 ± 9	85 ± 21	82 ± 22
EDV (ml)	218 ± 51	212 ± 47	200 ± 46	200 ± 50
ESV (ml)	112 ± 45	118 ± 44	99 ± 42	82 ± 45‡
LV EDP (mmHg)	12 ± 4	18 ± 4‡	10 ± 6	5 ± 4‡
LV ESP (mmHg)	84 ± 10	122 ± 14‡	87 ± 15	58 ± 7‡
Ea (mmHg ml^{-1})	0.69 ± 0.12	1.13 ± 0.21‡	0.77 ± 0.15	0.46 ± 0.09‡

Data are presented as mean ± SD

LV left ventricle, *CO* cardiac output, *SV* stroke volume, *HR* heart rate, *EDV* left ventricular end-diastolic volume, *ESV* left ventricular end-systolic volume, *LV EDP* left ventricular end-diastolic pressure, *LV ESP* left ventricular end-systolic pressure, *Ea* effective arterial elastance

*P < 0.05, †P ≤ 0.001, ‡P ≤ 0.0001 versus before stage

Table 2 Hemodynamic variables during preload changes

	Bleeding		Fluid bolus	
	Before	After	Before	After
CO (L min^{-1})	8.70 ± 3.16	8.31 ± 2.23	8.06 ± 1.59	9.56 ± 2.43*
SV (ml)	109 ± 18	109 ± 16	107 ± 15	119 ± 20*
HR (beats min^{-1})	78 ± 16	76 ± 15	76 ± 13	80 ± 11*
EDV (ml)	239 ± 67	215 ± 68†	212 ± 53	263 ± 44‡
ESV (ml)	129 ± 56	106 ± 57‡	105 ± 49	144 ± 43‡
LV EDP (mmHg)	12 ± 3	4 ± 4‡	6 ± 4	15 ± 4‡
LV ESP (mmHg)	84 ± 12	63 ± 8‡	72 ± 8	82 ± 9*
Ea (mmHg ml^{-1})	0.68 ± 0.16	0.55 ± 0.10†	0.63 ± 0.14	0.58 ± 0.14

Data are presented as mean ± SD

LV left ventricle, *CO* cardiac output, *SV* stroke volume, *HR* heart rate, *EDV* left ventricular end-diastolic volume, *ESV* left ventricular end-systolic volume, *LV EDP* left ventricular end-diastolic pressure, *LV ESP* left ventricular end-systolic pressure, *Ea* effective arterial elastance

*P < 0.05, †P ≤ 0.001, ‡P ≤ 0.0001 versus before stage

Table 3 Hemodynamic variables during contractility changes

	Esmolol		Dobutamine	
	Before	After	Before	After
CO (L min^{-1})	9.36 ± 2.11	5.64 ± 1.92‡	8.59 ± 2.27	11.73 ± 3.34‡
SV (ml)	119 ± 15	80 ± 20‡	111 ± 16	133 ± 23‡
HR (beats min^{-1})	78 ± 11	70 ± 9†	76 ± 13	87 ± 13‡
EDV (ml)	223 ± 56	215 ± 56	227 ± 50	220 ± 41
ESV (ml)	103 ± 49	135 ± 39†	115 ± 45	87 ± 34†
LV EDP (mmHg)	15 ± 4	12 ± 2*	14 ± 4	14 ± 6
LV ESP (mmHg)	76 ± 14	54 ± 9†	75 ± 12	87 ± 13‡
Ea (mmHg ml^{-1})	0.52 ± 0.14	0.54 ± 0.12	0.56 ± 0.13	0.56 ± 0.15

Data are presented as mean ± SD

LV left ventricle, *CO* cardiac output, *SV* stroke volume, *HR* heart rate, *EDV* left ventricular end-diastolic volume, *ESV* left ventricular end-systolic volume, *LV EDP* left ventricular end-diastolic pressure, *LV ESP* left ventricular end-systolic pressure, *Ea* effective arterial elastance

*P < 0.05, †P ≤ 0.001, ‡P ≤ 0.0001 versus before stage

arteries, respectively. The mean bias was 0.05 mmHg ml^{-1} (LOA ± 0.11 mmHg ml^{-1}) for the aortic level and 0.06 and 0.10 mmHg ml^{-1} for the femoral and radial arteries (LOA ± 0.12 mmHg ml^{-1}, respectively). The dicrotic notch pressure showed a progressive underestimation of LV ESP when measurements were performed away from the central aorta (bias ± LOA: − 4.8 ± 11.5, − 6.1 ± 11.9 and − 10.4 ± 12.4 mmHg ml^{-1} for aortic, femoral and radial sites, respectively).

Table 4 Estimated values of fixed effects on effective arterial elastance (Ea) according to a linear mixed-effects analysis

Fixed effects	Estimate	95% confidence interval	P value
LV ESP (mmHg)	0.0095	0.0092 to 0.0098	< 0.0001
SV (ml)	− 0.0061	− 0.0063 to − 0.0058	< 0.0001

LV ESP left ventricular end-systolic pressure, *SV* stroke volume

Estimate reflects the average change in effective arterial elastance (Ea) per unit increase of each fixed effect

When MAP was used as a surrogate for LV ESP, Ea_MAP systematically underestimated Ea, although this difference was small and constant across the arterial system (mean bias for Ea_MAP: range from 0.05 to 0.06 mmHg ml^{-1} and LOA ± 0.11 mmHg ml^{-1}) (Figs. 3, 4). This difference resulted from the discrepancy between MAP and ESP (mean bias and LOA: − 4.5 ± 10.9 for the aortic level; − 5.7 ± 11 mmHg for the femoral pressure; and − 5.8 ± 11.6 mmHg for the radial pressure).

The mean bias between radial and aortic MAP values, which defines the pressure gradient across the arterial system, was − 0.8 mmHg (LOA ± 4.2 mmHg). However, the differences for SAP between radial artery and the aorta were 5.32 mmHg (LOA ± 7.3 mmHg) and for diastolic pressure were − 1.2 mmHg (LOA ± 4.7 mmHg), which was consistent with the physiological pulse pressure amplification described from central aorta to the peripheral arterial system. The mean bias between radial and aortic dicrotic notch pressure was − 4.7 mmHg (LOA ± 9 mmHg), which describes the narrowing of the dicrotic notch pressure towards the peripheral arterial system.

The relationship between the Ea calculated from the steady-state ratio LV PES/SV and that derived from the arterial system parameters [Ea(Z)] was excellent (r^2 = 0.96), although Ea(Z) was higher than LV ESP/SV, with a mean bias of 0.23 ± 0.15 mmHg/ml (Fig. 6).

4 Discussion

Our results confirmed that, provided that the SV measurement is reliable, Ea obtained from the analysis of the LV pressure–volume analysis can be estimated from the peripheral arterial pressure. Although all arterial estimates of Ea analyzed offer good results, the Ea calculation based on MAP/SV provides a more consistent estimation of Ea across the arterial system with a minimal bias and narrow limits of agreement.

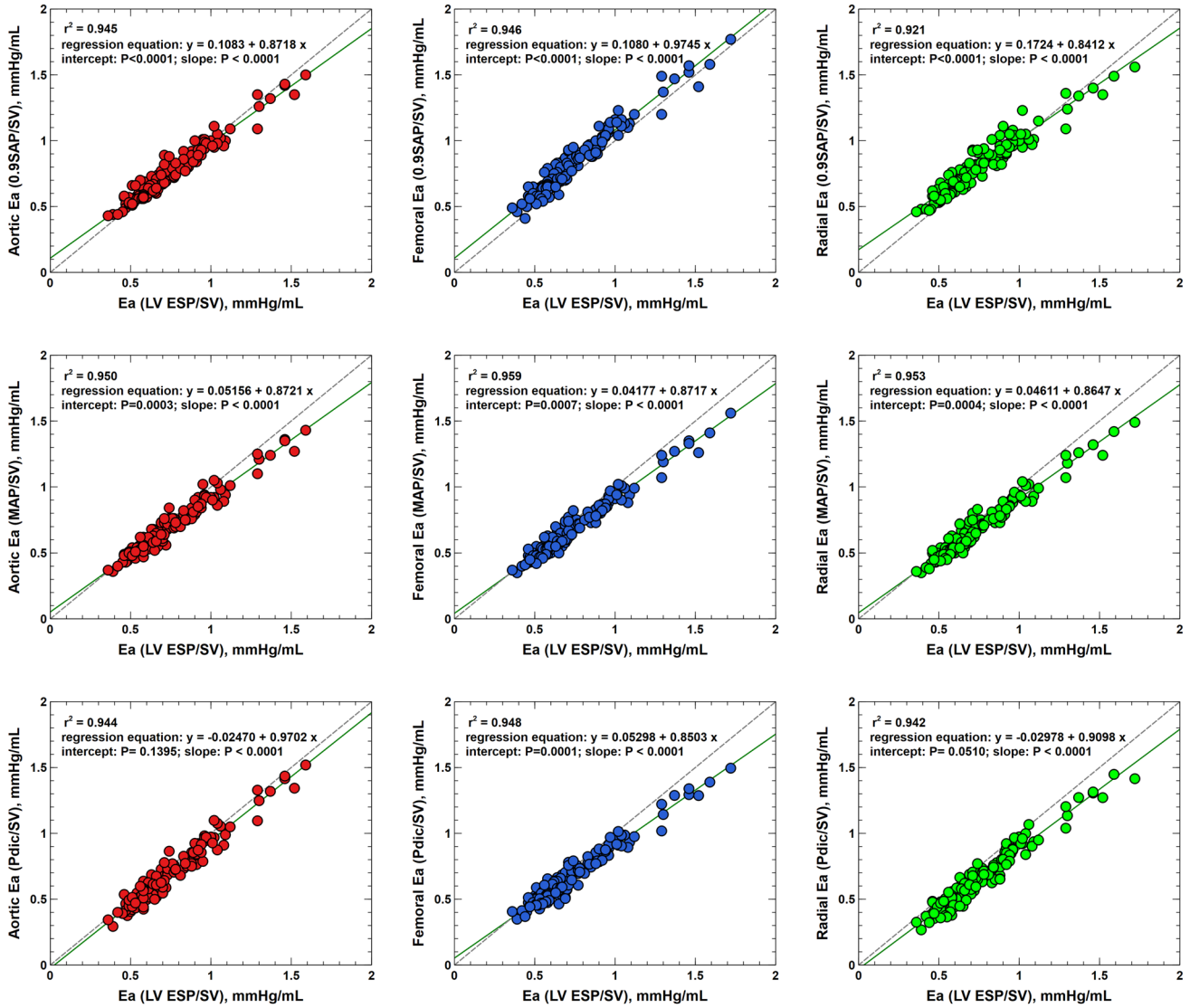

Fig. 4 Relationship between effective arterial elastance and aortic, femoral and radial estimates of Ea. Linear regression analysis between effective arterial elastance (Ea) estimated from the left ventricular (LV) pressure–volume data and aortic, femoral and radial estimates of Ea, using 90% of systolic arterial pressure (SAP), mean arterial pressure (MAP) and dicrotic notch pressure (Pdic). Stroke volume (SV) was obtained from the LV pressure–volume analysis. Dashed line represents the line of equality

The term arterial load describes all the extracardiac factors opposing LV ejection [3]. In absence of any valvular disease, arterial load is mainly represented by the physical arterial system properties and arterial wave reflections [3]. Although arterial load is commonly expressed as the relationship between mean pressure and flow, i.e., systemic vascular resistance, this description ignores the cyclic nature of the blood pressure and flow imposed by cardiac contractions. The most comprehensive and precise definition of the arterial load is provided by the aortic input impedance, which describes the relationship between pulsatile pressure and flow in the frequency domain, and has dimensions of amplitude and phase [19]. However, its complex nature and interpretation make aortic impedance unfeasible for daily clinical practice and usual hemodynamic monitoring.

Sunagawa et al. [10] was the first to propose that all the components of aortic impedance could be integrated under a single variable called effective arterial elastance or Ea. This Ea has unit of elastance but does not represent a true physical elastance or arterial stiffness, but rather an operative measure of the main features of the arterial system, such as resistance, compliance, characteristic impedance and systolic and diastolic time intervals [10]. This simplification, however, cannot replace arterial impedance: it lumps the steady and pulsatile components of arterial load into one parameter but does not inform about their relative contribution [18, 26].

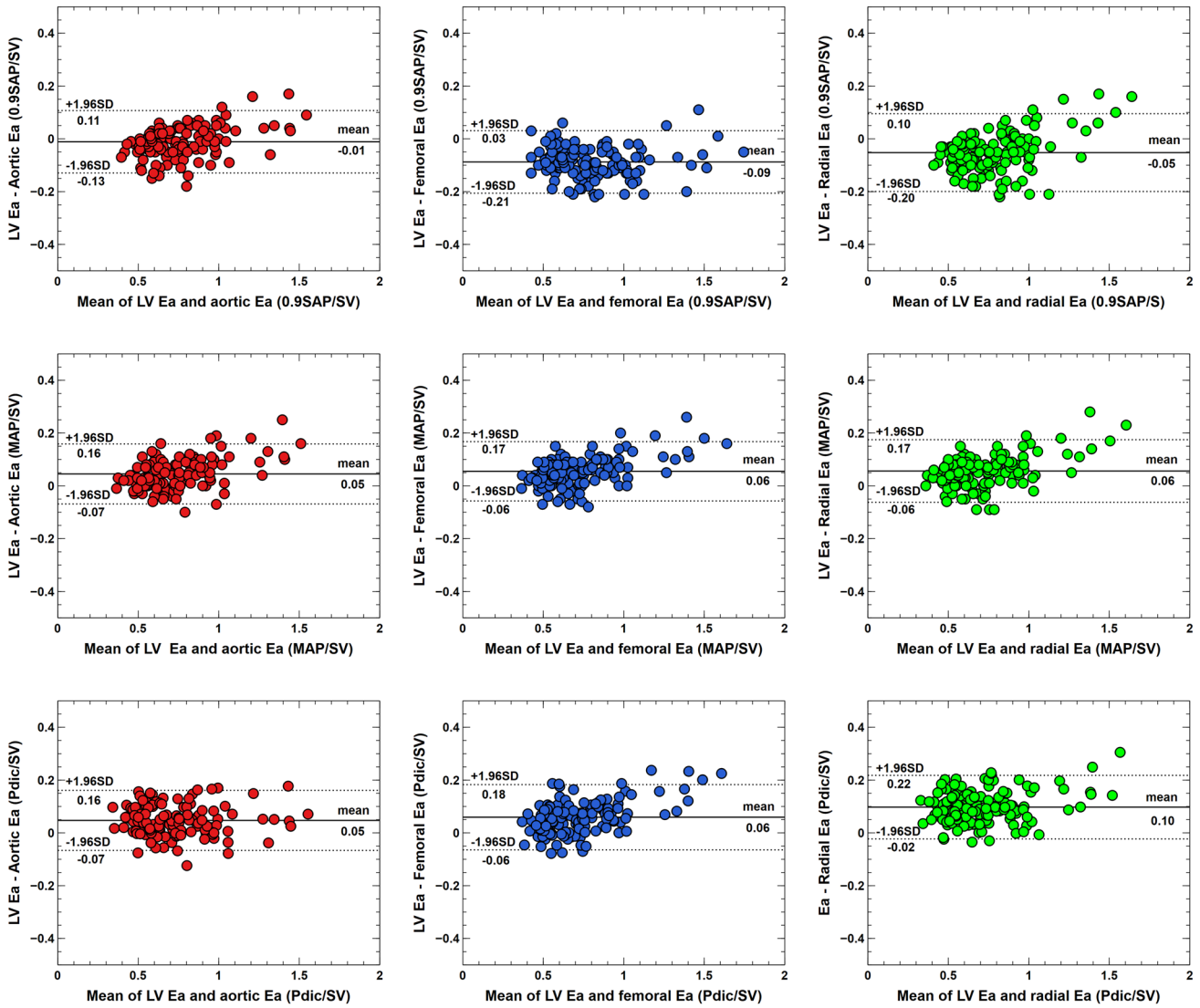

Fig. 5 Bland–Altmann analysis for effective arterial elastance (Ea) and aortic, femoral and radial estimates of Ea. Agreement between conductance-derived effective arterial elastance (Ea) and the arterial estimates using 90% of systolic arterial pressure (SAP), mean arterial pressure (MAP) and dicrotic notch pressure (Pic) in aortic, femoral and radial arteries. Solid lines represent bias (mean difference between Ea and arterial estimate measurements). Dotted lines are the upper and lower limit of agreement (1.96 SD)

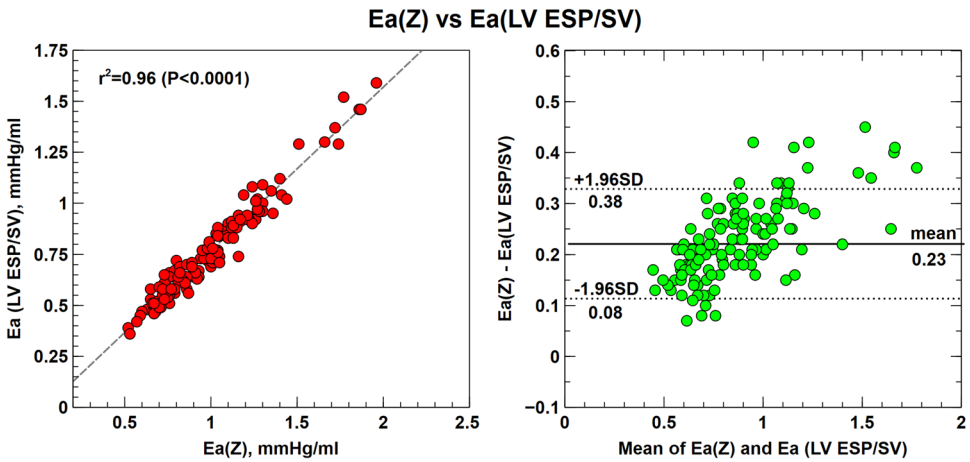

Fig. 6 Comparison of Ea (LV ESP/SV) and 3-element Windkessel model-derived Ea(Z). Linear regression analysis and Bland–Altman plot comparing both methods for estimating effective arterial elastance (Ea): steady-state ratio of left ventricular end-systolic pressure and stroke volume (LV ESP/SV), and Ea derived by the analysis of the arterial system properties [Ea(Z)]

Importantly, Ea can be estimated using the steady-state ratio of LV ESP/SV and be related with LV elastance to evaluate ventriculo-arterial coupling [10]. However, as Ea requires LV catheterization for measuring LV ESP, several attempts have been made to simplify the assessment of Ea using the arterial pressure, such as mean aortic pressure [10, 27], 90% of the aortic systolic pressure [17, 18, 28, 29] or the aortic dicrotic notch pressure [15, 16, 30]. Our study confirmed previous clinical observations about the accuracy of using 90% of aortic SAP for estimating LV ESP [17, 18]. However, our results also show that the radial estimate of LV ESP provides the lowest coefficient of determination and the widest LOA for estimating Ea. Therefore, Ea surrogates based on the SAP will probably require individualized approaches depending on the arterial measurement site, such as 90% for the aortic level, 80% for the femoral artery, and the 85% for the radial pressure the most appropriate correction factors based in our results. These individuations, however, only reflect the heterogeneous nature of the arterial system, with the presence of a progressive stiffness gradient from ascending aorta towards the peripheral arteries, and stress the importance of how arterial wave reflections may influence on peripheral measurements [19]. Moreover, the individuation may be different and could be particularly unpredictable in critically-ill patients and change under pathological conditions, such as septic shock [31, 32].

On the contrary, when Ea was calculated using MAP as a surrogate for LV ESP, all estimators were interchangeable regardless of the artery used for measuring blood pressure. Although MAP underestimated LV ESP by 5–6 mmHg, this bias was constant from the aorta to the radial artery. Furthermore, the limits of agreement, a measure of dispersion between measurements, was also relatively narrow and stable from the central aorta to the peripheral arteries (11–12 mmHg). Therefore, considering the small bias and the relatively constant precision across the arterial system, Ea_MAP surrogates offer similar or even better efficiency for estimating Ea without applying any specific correction factor. These results confirmed the physiological constancy of MAP values across the arterial system, which supports the common recommendation about the use of MAP for monitoring organ perfusion and triggering therapeutic interventions [33], and also corroborated previous knowledge about the small MAP gradient from the aorta to the radial artery [28, 31].

The incisura in aortic pressure waveform usually marks the closure of the aortic valve and has been also used as a surrogate for LV ESP [15, 16, 30]. Our results confirm the good performance of the pressure at the aortic incisura for estimating LV ESP. However, we observed an increasing bias ranging from 0.05 to 0.10 mmHg ml^{-1} from the aortic to the radial level, because of a progressive underestimation of LV ESP by the dicrotic notch pressure towards the periphery. Since dicrotic notch pressure is influenced by changes in arterial wall properties and wave reflections [19, 34], dicrotic notch is usually smaller, occurs later, and has a smoother appearance in the peripheral arteries than at the aortic level [30, 35]. Therefore, considering the impact of arterial tone changes and the additional technical difficulties for a reliable continuous detection of the dicrotic notch [34, 36], we think that this approach does not offer advantage over MAP based estimation when using on peripheral arteries.

Our results, although apparently of a pure physiological significance, are of interest for the clinician. First, considering that arterial load can be precisely characterized by Ea and that common pathological conditions, such as heart failure or septic shock, are profoundly related to an impaired arterial load [5, 37], one can reliably estimate its effects at the bedside using Ea in a more comprehensive way than the gross calculation of arterial resistance. Moreover, when MAP was used as surrogate for LV ESP, Ea measurements did not depend on the arterial pressure site, but only on the reliability of the SV estimation. Second, from our results it becomes evident the heterogeneity of the arterial system and how arterial wave reflections could impact on peripheral pressure measurements: while MAP values are relatively constant across the arterial tree, systolic and pulse pressure could be significantly different depending on the artery studied.

Our study has some limitations that need to be addressed. First, we did not directly evaluate Ea using a 3-element Windkessel, as Sunagawa et al. and Kelly et al. did [10, 17]. Instead, we used the simplification proposed by these authors and many others [17, 18, 27], using the steady-state ratio of LV ESP and SV, which it has been consistently found to be equivalent to the complex Windkessel-derived calculation of Ea [18, 26, 38]. We have indeed confirmed that the relationship between that the ratio LV PES/SV and Ea(Z) was excellent, and the bias observed likely attributable to our estimation of the arterial system properties, which it was not obtained from the analysis of the aortic input impedance. Furthermore, as the ratio ESP/SV has been generally accepted and widely used for the estimation of Ea during the assessment of ventriculoarterial coupling, it has become a *de facto* standard in clinical research [4, 37]. Finally, we have used conductance-derived SV for calculating Ea in all studied surrogates instead of estimating SV from one the available cardiac output monitoring methods, such as arterial pulse pressure analysis or thermodilution. We intentionally decided not using any of these techniques to avoid limiting our results to any specific technique. Moreover, as our findings did not depend on SV measurements, they could be extrapolated to any monitoring device.

In conclusion, being Ea increasingly used for assessing arterial load in critical care research, our study demonstrates

that, provided that the SV measurement is reliable, all peripheral estimates of LV ESP provide a good surrogate for Ea. However, as peripheral arterial pressure sampling site is varied, MAP becomes a more generalizable estimate of LV ESP, because reflected waves disproportionately alter SAP than MAP and also affect to dicrotic notch pressure. Therefore, Ea estimate based on MAP/SV especially offers a robust surrogate over a wide range of hemodynamic conditions and interchangeably when measured in any arterial site, so it should be considered as a preferable estimate of Ea in further research.

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Author contributions Study conception: MIMG, MRP and MC. Study design: MIMG, ZJ, MRP. Performed experimental research: MIMG, ZJ, FH. Analyzed and interpreted the data: MIMG, ZJ, MRP, FH. Drafted the manuscript: MIMG, ZJ, JJS and FH. All authors reviewed it, contributed significantly to its critical review, and approved the final version of the manuscript. All authors ensure the accuracy or integrity of the results of this study and will be accountable for any question related with this work.

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Compliance with ethical standards

Conflict of interest MIMG is a consultant to Edwards Lifesciences and received honoraria and/or travel expenses from Deltex Medical. MRP is a consultant to Edwards LifeSciences, LiDCO Ltd., and Cheetah. MC has received honoraria and/or travel expenses from Edwards Lifesciences, LiDCO, Cheetah, Bmeye, Masimo and Deltex Medical. ZJ, JJS, and FH are Edwards Lifesciences employees.

Ethical approval The study was approved for the use of Yorkshire crossbred pigs by the Institutional Animal Care and Use Committee (IACUC) at the Edwards Research Center, and all experimentation was performed in accordance with the USDA Animal Welfare Act regulations (AWArs), and the Guide for the Care and Use of Laboratory Animals (ILAR, NAP, Washington, DC, 2010, 8th edition). The Test Facility is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALACi) and registered with the United States Department of Agriculture to conduct research with laboratory animals. The ARRIVE guidelines were used for the elaboration of this manuscript.

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