Minimally invasive intraoperative estimation of left-ventricular end-systolic elastance with phenylephrine as loading intervention†

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Editor’s key points

- Simple, non-invasive assessment of changes in cardiac contractility during and after surgery could help guide therapies to optimize tissue oxygen delivery.
- Unlike most measures of cardiac contractility, end-systolic elastance is largely independent of preload and afterload.
- Left-ventricular (LV) end-systolic elastance is calculated from a series of LV pressure–volume loops derived from measures of aortic pressure and LV volumes.
- This study found that it is feasible to estimate LV end-systolic elastance using a non-invasive continuous arterial pressure monitoring device along with LV volumes using echocardiography.

Background. Left-ventricular end-systolic elastance (Ees) is an index of cardiac contractility, but the invasive nature of its assessment has limited perioperative application. We explored the feasibility of a minimally invasive method of Ees estimation for perioperative assessment of cardiac function and evaluated the suitability of phenylephrine as a loading intervention.

Methods. In 17 surgical patients, Ees was determined as the slope of the end-systolic pressure–volume relation, which was obtained from non-invasive or invasive continuous arterial pressure measurements and left-ventricular volume determinations using transoesophageal echocardiography (TOE). Ees was determined using as loading interventions preload reduction by inferior vena cava compression (IVCC) and afterload increase by phenylephrine administration.

Results. Median invasive Ees determined with phenylephrine estimated 1.05 (0.59–1.21) mm Hg ml⁻¹ and with IVCC 0.58 (0.31–1.13) mm Hg ml⁻¹. Bland–Altman analysis to evaluate the level of agreement between minimally invasive and invasive Ees estimation revealed a bias of −0.03 (0.12) mm Hg ml⁻¹ with limits of agreement from −0.27 to 0.21 mm Hg ml⁻¹ and the percentage error was 33%. Agreement between Ees obtained with phenylephrine and IVCC revealed a bias of 0.15 (0.69) mm Hg ml⁻¹ with limits of agreement from −1.21 to 1.51 mm Hg ml⁻¹ and a percentage error of 149%.

Conclusions. It is feasible to determine Ees combining continuous non-invasive arterial pressure measurements and left-ventricular volume determinations using echocardiography. However, administration of phenylephrine cannot substitute IVCC as a loading intervention, indicating that estimation of Ees in the intraoperative setting remains a challenge.

Keywords: echocardiography, transoesophageal; monitoring, intraoperative; myocardial contraction; phenylephrine

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Perioperative haemodynamic monitoring is aimed towards maintaining adequate tissue perfusion. The latter is the result of the functional interaction between the heart (contractility), the vascular system (afterload) and filling state (preload). In the perioperative period, decision-making is routinely based on measurements of heart rate, arterial
pressure, central venous pressure, and sometimes cardiac output. Although very suitable to judge changes in global perfusion, vascular load and filling state, these parameters are not adequate for assessing cardiac contractility per se, because they reflect loading conditions or are sensitive to them.

Left-ventricular (LV) end-systolic elastance (Ees) allows load-independent characterization of cardiac contractility. A detailed background on Ees is provided in the Supplementary Appendix. Briefly, Ees is the linearly approximated slope of the end-systolic pressure–volume relation, which can be obtained from a series of LV pressure–volume loops obtained under different loading conditions, like IVCC, while maintaining a constant inotropic state (Fig. 1a and b). As demonstrated in Figure 1c, positive (+) or negative (−) inotropic interventions, as may be present in the perioperative period, induce a proportional change in Ees.

Perioperative changes in Ees can be measured using transoesophageal echocardiography (TOE) and invasive arterial pressure measurements. In this study, we aim to further enhance the practicability of this method, by investigating whether non-invasive arterial pressure measurements may replace the invasive arterial pressure measurement during Ees assessment. As invasive IVCC is not always applicable during surgery we further investigated whether a phenylephrine-induced augmentation in afterload provides a valid alternative as loading condition. We hypothesized that minimally invasive Ees estimations with non-invasive arterial pressure measurements show a high level of agreement with the more invasive approach, and that phenylephrine-based Ees estimates agree with those based on IVCC.

Methods

Subjects

The Institutional Review Board of the VU University Medical Center approved this study, and written informed consent was obtained from all subjects (NTR 2941). Twenty-one patients (18–75 yr) undergoing elective open abdominal, cardiac, or vascular surgery were included. Exclusion criteria included contraindications for radial arterial catheterization, phenylephrine administration and TOE, such as all forms of oesophageal or gastric pathology, and all conditions increasing the risk of TOE-related complications. In patients undergoing abdominal surgery, additional exclusion criteria included known heart

Fig 1 Pressure–volume loops and left-ventricular Ees. The left upper corners of a series of pressure–volume loops are used to construct the end-systolic pressure–volume relation (ESPVR) with its slope Ees. The series of loops can be obtained by performing a loading intervention, such as a decrease in preload (a) or increase in afterload (a). The slope of the ESPVR, Ees, directly responds to positive (+) or negative (−) inotropic influences (c). Figure reproduced with permission from Burkhoff and colleagues.
disease and ECG, or echocardiography abnormalities. Perioperative haemodynamic instability such as hypotension, cardiac arrhythmias, or both were absolute contraindications for initiation or continuation of Ees measurements.

**Anaesthesia**

Patients received 20 mg oxazepam (EuroCept, Ankeveen, the Netherlands) before arrival at the operating theatre. In patients undergoing cardiac or vascular surgery, anaesthesia was induced with sufentanil (1 μg kg⁻¹; Janssen-Cilag, Tilburg, the Netherlands), diazepam (0.1–0.2 mg⁻¹; Centrafarm, Etten-Leur, the Netherlands), and pancuronium bromide (0.1 mg kg⁻¹; Organon, Oss, the Netherlands). In patients undergoing abdominal surgery, anaesthesia was induced with sufentanil (0.3 μg kg⁻¹), propofol (1–2 mg kg⁻¹), and rocuronium (0.5 mg kg⁻¹; Organon, Oss, the Netherlands). Anaesthesia was maintained with sufentanil, propofol (4–6 mg kg⁻¹ h⁻¹; Fresenius Kabi, Zeist, the Netherlands), isoflurane, or all.

**Study protocol**

The study protocol is shown in Figure 2. All measurements were performed solely when patients maintained a stable arterial pressure and were in sinus rhythm. Non-invasive and invasive arterial pressure measurements and left-ventricular volume determinations with TOE were performed simultaneously over eight consecutive heartbeats per preload/afterload modality. The study protocol included measurements during baseline, after IVCC or clamping and after a bolus of phenylephrine. In order to investigate an intrinsic effect of phenylephrine on Ees, 11 patients underwent IVCC during phenylephrine stimulation during a fourth measurement that was added to the protocol (Fig. 2; T=4).

The inferior vena cava was either clamped (cardiac and vascular surgery) or manually compressed (abdominal surgery) to reduce preload until the mean arterial pressure (MAP) decreased at least 10% with a maximum of 25%. A bolus of 100 μg phenylephrine (1 ml i.v.) was administered to induce a MAP increase of 10–25%, which was considered as a sufficient change in afterload. After stabilization of the phenylephrine response, the inferior vena cava was again clamped or compressed to induce a sufficient decrease in MAP of 10%.

When the described interventions failed to induce the required haemodynamic changes, the particular intervention was excluded from further analysis.

During loading interventions, haemodynamic parameters were monitored comprehensively and any form of haemodynamic instability, such as a change in arterial pressure >25%, the occurrence of arrhythmias, or both were criteria for discontinuation of the study protocol. To avoid such a decrease in arterial pressure during IVCC, a decrease of 20% was an indication for early release of the clamp or compression on the inferior vena cava.

**Arterial pressure measurement**

Before anaesthesia, a 20-gauge cannula was inserted into a radial artery for continuous invasive measurement of arterial pressure. On the ipsilateral middle finger, an appropriate size finger cuff of the non-invasive continuous arterial pressure monitoring device (ccNexfin, Edwards Lifesciences BMEYE, Amsterdam, the Netherlands) was applied to the midphalanx according to the manufacturer’s instructions. In order to co-register both arterial pressure measurements, invasive radial artery pressure recordings were used as input to the Nexfin using its in/output module. Systolic, diastolic arterial pressure, and MAP, heart rate, stroke volume, cardiac output, and systemic vascular resistance were continuously measured by the Nexfin device. Aortic pressure has been shown to be an accurate substitute for LV pressure in determining left-ventricular pressure–volume relations. Pressure data from non-invasive arterial and intra-arterial pressure measurements were translated offline to aortic pressure using custom software provided by BMEYE. The end-systolic pressure was defined as the dicrotic notch pressure obtained from the pressure waveforms.

**Transoesophageal echocardiography**

The TOE transducer (Omniplan III, Philips, Andover, MA, USA) of the TOE device (Envisor HD, Philips, Andover, MA, USA) was orally inserted into the oesophagus and advanced into the stomach. The left ventricle was seen in short-axis mid-papillary view by two-dimensional echocardiography and subsequently in M-mode for beat-to-beat recordings of changes in volume.
Intraoperative assessment of end-systolic elastance

Assessment of LV Ees

LV Ees was assessed from end-systolic pressure–volume relations derived from the respective combinations of non-invasive and invasive continuous arterial pressure recordings and concurrent left-ventricular volume estimations by TOE. Linear end-systolic pressure–volume relations were constructed by plotting volume against end-systolic pressure during baseline and subsequent IVCC or phenylephrine exposure (Fig. 2). The intrinsic effect of phenylephrine on Ees was determined from linear end-systolic pressure–volume relations during a steady-state phenylephrine-induced increase in arterial pressure from pressure–volume recordings without and after IVCC. LV Ees was defined as the slope of the end-systolic pressure–volume relation as determined by linear regression analysis.

Data analysis

Data analysis was performed using GraphPad Prism version 5.01 (GraphPad software, Inc., La Jolla, CA, USA) and SPSS statistical software version 17.0 (SPSS, Inc., Chicago, IL, USA).

Haemodynamic data are presented as mean (SD) or median with inter-quartile range. Differences in haemodynamic parameters between measuring points, groups, or both were calculated with (paired) t-tests and Mann–Whitney or Wilcoxon matched pairs test if non-parametric. P-values < 0.05 were considered statistically significant.

The level of agreement and bias between methods of Ees estimation was determined by Bland–Altman analysis. Bias was defined as the mean difference between Ees as determined by each method. In addition, percentage error was calculated as 2 × SD/mean, where SD is the standard deviation of the bias and the mean refers to the mean of Ees values. Limits of agreement were calculated as bias (1.96 × SD) and define the range in which 95% of the differences between methods is expected to lie. The results of the Bland–Altman analyses were interpreted considering the average values of Ees in anaesthetized adults, and the expected extent of changes in Ees during positive or negative inotropic stimulation.

Results

Data inclusion and exclusion

The data inclusion flow chart is depicted in Figure 2. Twenty-one patients underwent the study protocol; four were excluded because of insufficient quality of TOE recordings. Therefore, data on 17 patients were analysed. Data of four patients were not considered for loading interventions comparisons because phenylephrine did not induce the minimally required increase of 10% in MAP. In 11 of the included patients, the T=4 measurement was obtained.

Patient characteristics

Fourteen male and three female subjects, aged 59 (10) yr, undergoing elective liver resection (six patients), off-pump coronary artery bypass graft surgery (seven patients), aortic valve replacement (two patients), Bentall procedure (one patient), or a combination of coronary bypass and aortic valve replacement (one patient) were included for the study. The average height and weight was 178 (7) cm and 81 (17) kg. Eleven patients were classified as ASA class III and six as class II.

| Table 1 | Haemodynamic parameters during four consecutive pressure–volume determinations: baseline (T=1), after IVCC (T=2), after phenylephrine administration (T=3), and after IVCC during phenylephrine stimulation (T=4). Data present mean (SD) or median with inter-quartile range. ESV, end-systolic volume; ESP, end-systolic pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; HR, heart rate; SV, stroke volume; CO, cardiac output; SVR, systemic vascular resistance. *Indicate a significant (P<0.05) deviation from baseline parameters. Significantly differ from the previous measurement |
|---|---|---|---|---|
| T=1 (n=17) | T=2 (n=17) | T=3 (n=13) | T=4 (n=11) |
| E SV (ml) | 58 (27–82) | 40 (18–60)* | 58 (41–90)* | 47 (34–95)* |
| ESP (mm Hg) | 77 (10) | 61 (14)* | 89 (14)* | 70 (19)* |
| SAP (mm Hg) | 88 (12) | 69 (17)* | 104 (16)* | 79 (24)* |
| DAP (mm Hg) | 61 (9) | 52 (10)* | 70 (12)* | 57 (10)* |
| MAP (mm Hg) | 71 (10) | 58 (12)* | 83 (14)* | 64 (16)* |
| HR (beats min⁻¹) | 74 (15) | 75 (13) | 73 (14) | 77 (17) |
| SV (ml) | 59 (13) | 42 (12)* | 59 (11)* | 41 (12)* |
| CO (litre min⁻¹) | 4.4 (1.1) | 3.0 (0.8)* | 4.3 (1.1)* | 3.1 (0.8)* |
| SVR | 1.1 (0.3) | 1.3 (0.5)* | 1.3 (0.5)* | 1.4 (0.6)* |
Haemodynamic effects of loading interventions

The haemodynamic parameters at the four consecutive timepoints are given in Table 1. No arrhythmias occurred during loading interventions, and a 25% arterial pressure decrease was prevented in three patients by shortening of the vena cava clamping or occlusion duration. Preload reduction by IVCC ($T=2$) resulted in clear decreases in end-systolic pressure and volume with respect to baseline ($T=1$). Arterial and hence end-systolic arterial pressure increased significantly after administration of phenylephrine ($T=3$), but end-systolic volume did not change with respect to baseline ($T=1$). Heart rate did not change with any loading intervention. Systemic vascular resistance was increased with respect to baseline with all interventions.

Level of agreement between minimally invasive and invasive estimation of Ees

Median minimally invasive and invasive Ees were estimated as 0.59 (0.39–0.94) and 0.58 (0.31–1.13) mm Hg ml$^{-1}$, respectively ($n=17$). An example of a minimally invasive and invasive reconstruction of the end-systolic pressure–volume relation and Ees estimation is shown in Figure 3A. Minimally invasive and invasive Ees were not different (Fig. 3A). Bland–Altman analysis of minimally invasive and invasive Ees estimation revealed a bias of $-0.03 \pm 0.12$ mm Hg ml$^{-1}$ with limits of agreement from $-0.27$ to 0.21 mm Hg ml$^{-1}$ and a percentage error of 33% (Fig. 3C).

Phenylephrine vs IVCC as a loading intervention

Median invasive Ees determined from the combination of baseline and phenylephrine end-systolic pressure–volume points was estimated as 1.05 (0.59–1.21) mm Hg ml$^{-1}$, and for baseline and vena cava compression as 0.58 (0.31–1.13) mm Hg ml$^{-1}$. A typical example of linear end-systolic pressure–volume relation construction and Ees estimation from baseline and phenylephrine administration vs baseline and IVCC pressure–volume points is shown in Figure 4A. The median Ees values obtained with phenylephrine or IVCC did not significantly differ (Fig. 4B). Bland–Altman analysis for both loading interventions revealed a bias of $-0.15 \pm 0.69$ mm Hg ml$^{-1}$ with limits of agreement from $-1.21$ to 1.51 mm Hg ml$^{-1}$ and a percentage error of 149% (Fig. 4C).
Effect of phenylephrine on Ees

To investigate the intrinsic effect of phenylephrine, the Ees was determined from baseline and inferior vena cava pressure–volume points in the absence or presence of phenylephrine (Fig. 5). There was no statistically significant difference in the median Ees before phenylephrine stimulation [0.58 (0.31–1.13) mm Hg ml\(^{-1}\)] and during phenylephrine stimulation [0.81 (0.51–1.04) mm Hg ml\(^{-1}\)].

Discussion

The present study investigated the clinical feasibility of minimally invasive assessment of Ees in the perioperative setting. It was feasible to determine the end-systolic pressure and volume during major surgery using the combination of continuous non-invasive arterial pressure measurements and left-ventricular volume determinations with TOE. There was a clinically acceptable level of agreement when this approach was compared with Ees estimations based on intra-arterial pressure measurements, as previous studies showed that our observed limits of agreement allow the detection of changes in contractility.\(^{13}\) Administration of phenylephrine however could not substitute IVCC as a loading intervention. Although our findings indicate that Ees estimates may be obtained by minimally invasive pressure–volume measurements, an alternative for the highly invasive IVCC or clamping manoeuvre is warranted to strengthen the minimally invasive approach.

Haemodynamic parameters such as arterial pressure and cardiac output are not necessarily representative of cardiac contractility, as they are highly influenced by vascular load and filling state of the circulation. The effects of preload, afterload and cardiac contractility on system haemodynamics are therefore difficult to distinguish, thereby hindering adequate decision-making in the perioperative period. A method to perceive changes in cardiac contractility would be a valuable addition to current haemodynamic monitoring.

The combination of peripheral arterial pressure measurements and TOE was applied based on previous studies, demonstrating that left-ventricular volume determinations with echocardiography combined with arterial tonometry\(^{14}\) or non-

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Fig 4. Phenylephrine vs IVCC for Ees estimation. (a) Example of end-systolic pressure–volume relation construction and Ees determination from baseline and phenylephrine pressure–volume points (line) and baseline and IVCC pressure–volume points (dotted line) with linear regression. (b) Mann–Whitney test showed no significant difference between phenylephrine- (blue box) and IVCC-obtained (green striped box) Ees values. (c) Bland–Altman analysis of agreement between phenylephrine vs IVCC as a loading intervention for Ees estimation. IVCC, inferior vena cava compression or clamping.
invasive\textsuperscript{15–19} and also invasive\textsuperscript{20} arterial pressure measurements enable reliable determination of Ees in the clinical and the intraoperative setting.\textsuperscript{562 1–23} In this study, we proposed a less invasive method for tracking end-systolic pressure and -volume for the estimation of Ees in a population where extensive monitoring by means of invasive continuous arterial pressure monitoring and TOE is already indicated.\textsuperscript{7} Moreover, the open surgical procedures included in this study allowed for physical access to the inferior vena cava, providing the opportunity of testing alternative methods against this experimental gold standard. To further enhance the practicability of intraoperative Ees measurements, we tested whether continuous non-invasive arterial pressure monitoring would provide an alternative when radial artery catheterization is contra-indicated, not possible or problematic.

Determination of Ees requires a construction of the end-systolic pressure–volume relation based on at least two different loading conditions. The loading intervention should induce isolated changes in preload (Fig. 1A) or afterload (Fig. 1B), and should not invoke autonomous compensation or changes in contractility.\textsuperscript{4} IVCC, evoking rapid changes in preload, is commonly used for this purpose and is considered the gold standard.\textsuperscript{3} However, given its invasive nature, the IVCC manoeuvre is not applicable in most procedures and patient populations. Therefore, we sought an alternative for this intervention in phenylephrine-induced changes in afterload.

Previous studies applied pharmacological changes in loading conditions, such as preload increase with nitroglycerine, afterload decrease with nitroprusside, or both.\textsuperscript{3} Alternatively, afterload has previously been augmented by administration of angiotensin\textsuperscript{24} and phenylephrine.\textsuperscript{20 25} Phenylephrine administration for arterial pressure support is part of daily practice in the intraoperative setting and its pharmacologic and physiologic actions are well characterized.\textsuperscript{26} The alpha-1 adrenergic agonist phenylephrine causes vasoconstriction and, thereby, an afterload-increase. In the present study, we found that Ees obtained with phenylephrine as a loading intervention significantly differs from Ees obtained with IVCC, as can be gleaned from the unacceptable levels of agreement shown by Bland–Altman analysis. To further substantiate this finding, we determined Ees using IVCC as a loading intervention, also during the phenylephrine stimulated state, aiming to determine whether Ees estimation itself is influenced by administration of phenylephrine. Analysis showed no significant difference between these values, despite a trend towards higher Ees values during phenylephrine stimulation as has also been shown by others.\textsuperscript{27} Possibly, the absence of this effect can be explained by the small amount of patients in our study, or by interference of anaesthesia with this effect. Nevertheless, the use of a phenylephrine challenge by itself does not produce Ees estimates that are interchangeable with those obtained with the gold standard vena cava compression. It has earlier been shown that phenylephrine-induced changes in afterload are influenced by the preload status.\textsuperscript{26 28} This indicates that the actions of phenylephrine exceed those of simply constricting the arterioles, and that preload variables, like the fluid-status of the patient, should be taken into account. This may provide an explanation for the different responses to phenylephrine in our study, as fluid status may vary substantially between patients, types of surgery, and at different time-points during the surgical procedure.

An absent effect on the autonomic nervous system is one of the most important requirements for a loading intervention to construct end-systolic pressure–volume relations and estimate Ees, as reflex sympathetic or parasympathetic innervation is likely to modulate heart rate and cardiac contractility. Because the haemodynamic effects of phenylephrine are relatively slow in onset, as opposed to the rapid decrease in preload provoked by IVCC, autonomous compensation could occur,

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig5.png}
\caption{The effect of phenylephrine on Ees in the total study population (a) and individual patients (a). Wilcoxon matched pairs test showed no significant influence of phenylephrine on Ees.}
\end{figure}
and influence Ees values. We however found no changes in heart rate after administration of phenylephrine, despite a significant increase in arterial pressure, concluding that autonomic compensation did not occur as a response to phenylephrine stimulation. On the other hand, while lowering cardiac preload, vena cava compression appeared to produce a concurrent increase in systemic vascular resistance, suggesting that this intervention may also elicit autonomic reflex responses in our patients.

A limitation of our study is the relatively small number of patients considered. Although we convincingly demonstrated good agreement between minimally invasive and invasive methods of Ees estimation with this sample size, the data on phenylephrine as a loading intervention appear to be inconclusive.

In the future, it would be worthwhile to test how Ees, as estimated with our method, would respond to, for example, dobutamine infusion. Finally, three-dimensional TOE instead of 2D would likely provide more accurate means to estimate LV volume, contributing to a more reliable estimation of Ees. The use of a more sensitive method for LV volume estimation would further allow to construct end-systolic pressure–volume relations using less dramatic loading interventions. For instance, the application of positive end-expiratory pressure in ventilated patients may induce subtle changes in loading conditions, which may be used to construct the end-systolic pressure–volume relation.

In conclusion, our findings indicate that in patients undergoing major surgery it is possible to minimally invasively assess the end-systolic pressure–volume relation to estimate Ees. Although this is a first step towards practically suitable and improved assessment of left-ventricular contractile function in the perioperative setting, the required loading intervention remains a challenge as phenylephrine-induced afterload increase appears not to be interchangeable with the preload lowering IVCC.

We conclude that perioperative estimation of Ees can be performed using minimally invasive pressure–volume measurements in those surgeries were the inferior vena cava is accessible for clamping, compression, or both, but that application of Ees in the general intraoperative setting remains a challenge.

Supplementary material
Supplementary material is available at British Journal of Anaesthesia online.

Authors’ contributions
C.A.B.: patient recruitment, data collection, data analysis, and writing of the manuscript. K.D.R.: study design, data analysis, and writing of the manuscript. M.P.T.: patient recruitment and data collection. E.K.J.: patient recruitment and data collection. B.E.W.: data analysis and writing of the manuscript. C.B.: study design, patient recruitment, data collection, and writing of the manuscript. R.A.B.: study design, patient recruitment, data collection, and writing of the manuscript.

Declaration of interest
B.E.W. works for Edwards Lifesciences BMEYE. Edwards Life-sciences BMEYE was not involved in any part of the study with regard to design, performing, data analysis, or writing the manuscript. B.E.W. performed offline transformation of the arterial pressure data into aortic pressures, but he was blinded to the data and not involved in the data analysis.

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