Pulmonary blood volume measured by contrast enhanced ultrasound: a comparison with transpulmonary thermodilution

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Editor’s key points

- This study investigates the agreement between measuring intrathoracic blood volume (ITBV⁰𝐶) by Ultrasound contrast agent (UCA)-dilution using contrast enhanced ultrasound (CEUS) or transpulmonary thermodilution (TPTD) in vitro and in vivo.
- In vitro, ITBV⁰𝐶 showed an excellent agreement over the whole range of true volumes and flows.
- In patients, a good correlation was found between the ITBV⁰𝐶 and PBV by TPTD.
- A considerable bias was noted in the thermodilution derived volumes compared with literature.

Background. Blood volume quantification is essential for haemodynamic evaluation guiding fluid management in anaesthesia and intensive care practice. Ultrasound contrast agent (UCA)-dilution measured by contrast enhanced ultrasound (CEUS) can provide the UCA mean transit time (MTT) between the right and left heart, enabling the assessment of the intrathoracic blood volume (ITBV⁰𝐶). The purpose of the present study was to investigate the agreement between UCA-dilution using CEUS and transpulmonary thermodilution (TPTD) in vitro and in vivo.

Methods. In an in vitro setup, with variable flows and volumes, we injected a double indicator, ice-cold saline with SonoVue®, and performed volume measurements using transesophageal echo and thermodilution by PICCO®. In a pilot study, we assigned 17 patients undergoing elective cardiac surgery for pulmonary blood volume (PBV) measurement using TPTD by PICCO® and ITBV by UCA-dilation. Correlation coefficients and Bland-Altman analysis were performed for all volume measurements.

Results. In vitro, 73 experimental MTT’s were obtained using PICCO® and UCA-dilution. The volumes by PICCO® and UCA-dilution correlated with true volumes; rₛ=0.96 (95% CI, 0.93–0.97; P<0.0001) and rₛ=0.97 (95% CI, 0.95–0.98; P<0.0001), respectively. The bias of PBV by PICCO® and ITBV⁰𝐶 were −380 ml and −42 ml, respectively. In 16 patients, 86 measurements were performed. The correlation between PBV by PICCO® and ITBV⁰𝐶 was rₛ=0.69 (95% CI 0.55–0.79; P<0.0001). Bland-Altman analysis revealed a bias of −323 ml.

Conclusions. ITBV assessment with CEUS seems a promising technique for blood volume measurement, which is minimally-invasive and bedside applicable.

Clinical trial registration. ISRCTN90330260

Keywords: blood volume determination; contrast echocardiography; indicator dilution techniques; thermodilution

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Blood volume quantification is an essential part of haemodynamic evaluation to guide fluid management in anaesthesia and intensive care practice. While cardiac filling pressures, such as central venous pressure and pulmonary artery occlusion pressure, are frequently used to estimate preload, volumetric preload parameters obtained with transpulmonary thermodilution (TPTD) proved to be superior to this end.¹⁻³ With TPTD, arterial thermodilution curves are obtained after injection of a bolus of cold saline in a central vein, providing intrathoracic blood volume (ITBV) and global end-diastolic volume (GEDV).⁴ Both parameters significantly relate to changes in stroke volume and cardiac index in various clinical settings.¹⁻³⁻⁵⁻¹¹ However, TPTD requires insertion of catheters and installation of a device, which is time consuming and not always feasible during anaesthesia.

Recently, contrast-enhanced ultrasound (CEUS) has been proposed as a minimally-invasive, alternative method for blood volume measurement. With CEUS, transpulmonary indicator dilution curves are obtained with a small amount of ultrasound contrast agent (UCA) injected in a peripheral vein. In a previous experimental study, we demonstrated that volume estimation with CEUS in in vitro conditions was accurate and showed excellent agreement with volume estimation by thermodilution.⁸⁻¹¹ Moreover, we demonstrated the clinical feasibility of pulmonary blood volume (PBV) measurements with CEUS in patients.⁸⁻⁹ However, comparison of CEUS with TPTD is currently lacking. In this study, we therefore aimed to investigate the agreement between volumes obtained by UCA-dilution and TPTD in an in vitro setup as well as in a pilot study in patients.
Methods

In vitro setup

The agreement of volumes derived from TPTD and UCA-dilution was tested in an in vitro setup as previously described. The setup consisted of a network of tubes - mimicking the pulmonary vessels - connected to a roller pump (Cobe Stoeckert multi-flow bloodpump, Stoeckert Instruments, Munich, Germany) (Fig. 1). Degassed water was used as transport medium and the in- and out-flow tubes were submerged in a water-filled basin at 37°C. A transesophageal (TEE) probe X7-2t (Philips Healthcare, Andover, MA, USA) was also submerged in the water-filled basin to optimize the acoustic impedance while insonifying the tubes. In the outflow tube a 5 F thermistor-tipped catheter, PV2015 (Pulsion Medical Systems, Munich, Germany) was positioned at the point where the ultrasound beam intercepted the inflow and outflow tubes. With each measurement, a syringe with 20 ml of 4°C saline and 0.2 ml SonoVue® (Bracco SpA, Milan, Italy) was injected into the inflow tube through an injection point consisting of a single lumen central venous line (Blue flextip catheter, Arrow®, Reading, PA, USA) and an injectate temperature sensor PV4046 (Pulsion Medical Systems, Munich, Germany). This SonoVue® dose ensures a linear relationship between concentration and measured acoustic intensity, which is essential for application of the indicator dilution theory.

The injectate temperature sensor and the PicCO® catheter were connected via an interface cable to the PicCO® plus monitor (Pulsion Medical Systems, Munich, Germany), which was connected to a computer. Data were accessible with PicCO®-Win software (Pulsion Medical Systems, Munich, Germany). After a thermodilution measurement, the software provided time, cardiac output (CO), GEDV, ITBVTH, extravascular lung water (EVLW), mean transit time (MTT), and down-slope time (DST).

The volume of the network between the ultrasound interception points was varied to create different system-volumes, namely 890, 718, 530, and 356 ml. All tubes were isolated with polyethylene covers (Climaflex®, NMC, Eynatten, Belgium) preventing heat loss and the hydrodynamic circuit was open to avoid indicator recirculation. The flow generated by the roller pump was varied between 1 and 4 litres min⁻¹ in increments of 0.5 litre min⁻¹ and controlled by a flow sensor (Flow controller ARS 260, Biotech, Vilshofen, Germany) positioned at the end of the circuit.

The TEE probe made cross-sectional B-mode images of the inflow and outflow tubes (Fig. 2). The ultrasound scanner (iE33, Philips Healthcare, Andover, MA, USA) used harmonic imaging,
2.7–5.4 MHz, to increase the signal-to-noise ratio (SNR) for UCA, with a low mechanical index (MI) of 0.2 to reduce microbubble destruction. The other settings were dynamic range of 50 dB, general gain at 60%, frame rate of 27 Hz, and image depth of 8 cm. The B-mode images were stored in an uncompressed format and two regions of interest (ROIs) were drawn in each cross-sectional tube image using commercially available software (QLAB 8, Philips Healthcare, Andover, MA, USA) (Fig. 2A). The passage of SonoVue along the tubes was registered and acoustic indicator dilution curves (IDCs) were extracted from the ROIs. These acoustic IDCs were fitted by the local density random walk (LDRW) model using MATLAB 2009b (The Mathworks, Natick, MA, USA) as this model provides the best least square error fit to the IDC and a physical description of the dilution process. The MTT of UCA between the inflow and outflow tubes was directly derived from the parameters of the fitted acoustic IDCs. Volumes (ITBVUC) were calculated as the product of the flow measured by the ARS 260-flow controller and the difference in MTT between the two curves.

Thermodilution acquired volumes were calculated using CO, MTT, and DSt according to the PICCO algorithm. The estimated CO and MTT of the thermal indicator are multiplied to determine the thermal distribution volume between the injection site and the thermistor: intrathoracic thermal volume (ITTV). Thermal distribution of cold saline is within the vessel and in the surrounding tissue; therefore, ITTV comprises of ITBV and EVLW. The DSt estimated between 85 and 45% of the peak temperature represents the time constant of the largest mixing compartment. More precisely, it is the time required by the indicator to pass the pulmonary circulation and can be used to estimate the pulmonary thermal volume (PTV).

Fig 2 (A) Cross-sectional B-mode images of the inflow and outflow tubes obtained by an iE33 ultrasound scanner in the water-filled basin at pump flow of 2 litre min⁻¹ and a true volume of 530 ml. Two regions of interest are drawn in the inflow and outflow tube. At the bottom of the figure, the acoustic dilution curves are presented. They represent the acoustic intensity over time in the selected region of interest. (B) Four chamber view with harmonic imaging; ice-cold SonoVue is injected via a central venous line and passage through the four heart chambers is acquired with an iE33 TEE-probe. Two regions of interest are drawn in the right atrium and left atrium resulting in acoustic intensity over time signals, which are presented at the bottom of the figure. (C and D) The acoustic intensity dilution curves (A-IDC) of the above-presented B-mode images, both fitted by the LDRW model. The red and yellow lines are the measured A-IDCs, corresponding to panel (A and B). The green and pink curves are the fitted IDCs of the inflow tube and right atrium, and outflow tube and left atrium, the green and pink dotted vertical lines express the MTT of each IDC.
In the in vitro setup we investigated the agreement between ITBV\textsuperscript{UCA} and ITTV, as we expect the ITTV to correlate to the ITBV\textsuperscript{UCA} minus the volume between the injection point and the point where the ultrasound beam intercepts the inflow tube; this was 159 ml. We also investigated the agreement between ITBV\textsuperscript{UCA} and PBV by TPTD, as the PBV is consistent with the intravascular part between the right ventricle and left atrium in patients. The UCA SonoVue\textsuperscript{®} consists of microbubbles which stay intravascular and does not extravasate outside the vessels like cold saline.

Patients

Patients were participating in a follow up study that examined the effect of cardiac resynchronization therapy in cardiac surgery patients with impaired LVEF on ITBV.\textsuperscript{14} This study was approved by the Institutional Review board of the Catharina hospital Eindhoven (ISRCTN90330260). Patients scheduled for elective coronary artery bypass grafting surgery were included after written informed consent was obtained. Patients were aged 18 yrs and above, had an ejection fraction $\leq$ 35%, sinus rhythm, QRS duration over 130 ms and left bundle branch block pattern. Patients with preoperative atrial fibrillation, a myocardial infarction within the past three months, a history of gastric or oesophageal disease and allergy to sulphur-hexafluoride were excluded.

Measurement protocol

After induction of anaesthesia, all patients received a 8.5 F central venous catheter (DM- 12853, Arrow\textsuperscript{®}, Reading, PA, USA) in the right jugular vein. The medial lumen was connected to the injectate temperature sensor (PV4046, Pulsion Medical Systems, Munich, Germany). The Pulsiocath 5 F termostat-tipped catheter, PV2015L20A (Pulsion Medical Systems, Munich, Germany), was placed in the femoral artery. Both the injectate sensor and Pulsiocath were connected to the PICCO\textsuperscript{®} monitor (Pulsion Medical Systems, Munich, Germany). For UCA-dilution, a TEE probe X7-2t, connected to an iE33 ultrasound scanner (both, Philips Healthcare, Andover, MA, USA) was placed in the esophagus.

Measurements were performed during the operation except during cardiopulmonary bypass time. At least three measurements were done before and after cardiopulmonary bypass. Each measurement consisted of a simultaneous ultrasound registration and TPTD by injecting a double indicator: 20 ml ice-cold saline with 0.2 ml SonoVue\textsuperscript{®}. Injection of the indicator through the injectate temperature sensor automatically started the TPTD measurement on the PICCO\textsuperscript{®} monitor. Thermodilution data were stored on a personal computer connected to the monitor using PICCO\textsuperscript{®}-Win software. The MTT, DST, CO, and ITTV were registered. GEDV is the end-diastolic volume of the four heart chambers and is given as the difference between ITTV and PTV. The ITBV\textsuperscript{TH} is calculated according to the simplified equation: $1.25 \times \text{GEDV}$, which is used in the PICCO\textsuperscript{®} software.\textsuperscript{15} The EVLW is calculated by subtracting the ITBV\textsuperscript{TH} from the ITTV. Finally, PBV is calculated by subtracting the EVLW from the PTV.

The ultrasound settings were harmonic imaging at 2.7–5.4 MHz, frame rate of 27 Hz, MI 0.2, and linear post-processing. The digital loops were recorded in a standard four chamber view with a maximum loop-time of 180 seconds to acquire the right atrium (RA) and left atrium (LA) UCA indicator dilution curves (UCA-IDCs). The acoustic intensity evolution over time of the UCA-IDCs was measured by drawing ROIs in the RA and LA, using Qlab 8 software for acoustic quantification (Fig. 2a). These IDCs were fitted by the LDRW model (Fig. 2b) as mentioned in the in vitro section. The difference in MTT ($\Delta$MTT) between LA and RA was derived by model fitting and subtraction, and the ITBV\textsuperscript{UCA} was calculated by multiplying $\Delta$MTT by the CO assessed by thermodilution, measured simultaneously by PICCO\textsuperscript{®}.

As described above, the agreement between the ITBV\textsuperscript{UCA} and the PBV was assessed, as the PBV is the closest to the anatomical volume assessed by ITBV\textsuperscript{UCA} in patients.

Statistical analysis

GraphPad Prism version 5.03 (GraphPad Software, San Diego, CA, USA) statistical software was used for all statistical analysis. In both the in vitro and in vivo datasets, the distribution of the volume-data was assessed using the D’Agostino-Pearson normality test. All normally distributed parameters are expressed as mean (SD) and differences were calculated using Student’s unpaired t-tests. Non-parametric data are expressed as median (25th, 75th percentiles) and assessed for differences using the Mann-Whitney U-tests. For all tests, a $P$ value $<0.05$ was considered as significant. The relation between ITTV, PBV, ITBV\textsuperscript{UCA} in vitro and true volumes was analysed by linear regression. The level of agreement between ITTV, PBV, ITBV\textsuperscript{UCA} and true volumes of the in vitro setup was determined with Bland-Altman analysis.\textsuperscript{16} In patients, PBV and ITBV\textsuperscript{UCA} were compared by regression analysis. Bland-Altman analysis was used to analyse the agreement between PBV and ITBV\textsuperscript{UCA} and was corrected for repeated measures using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium).\textsuperscript{17}

Results

In vitro comparison of TPTD vs UCA-dilution

A total of 73 simultaneous UCA-dilution and TPTD measurements were performed at different volumes and flows. Both ITTV and PBV showed good correlation with the true volumes, $r_s=0.96$ (95% CI, 0.93–0.97; $P<0.0001$) for ITTV, and $r_s=0.96$ (95% CI, 0.93–0.97; $P<0.0001$) for PBV. ITBV\textsuperscript{UCA} showed excellent correlation with the true volumes with a correlation coefficient $r_s=0.97$ (95% CI, 0.95–0.98; $P<0.0001$) (Fig. 3a).

Bland-Altman analysis of the TPTD volumes and true volumes revealed a bias of 499 ml (limits of agreement 176–821 ml) for ITTV and –380 ml (limits of agreement of –88 – –672 ml) for the PBV. ITBV\textsuperscript{UCA} Bland-Altman analysis yielded a bias of –42 ml (limits of agreement of –103–18 ml) (Fig. 3b). When comparing the measured volumes by UCA-IDC and PBV by TPTD, the bias was –338 ml (limits of agreements of –90 – –585 ml). In detail, Bland-Altman...
analysis showed that TPTD largely overestimated the true volumes at higher volumes. This trend between bias and volume was not observed for UCA derived volumes (Fig. 3B).

In vivo comparison of PBV by TPTD and ITBV by UCA–dilution

Patient characteristics and the demographic data are presented in Table 1. 17 patients were enrolled; one patient was excluded because of inadequate TPTD data acquisition. In each patient, at least 2 simultaneous loops were performed with echocardiography and TPTD, before and after cardiopulmonary bypass.

A total of 86 measurements were performed. The median PBV was 356 ml (IQR 306–418 ml) and the median ITBV\text{UCA} was 685 ml (IQR 567–771 ml). The correlation between the PBV and the ITBV\text{UCA} was $r_s = 0.69$ (95% CI, 0.55–0.79; $P$, 0.0001). Bland-Altman analysis for repeated measures revealed a bias of $-323$ ml with limits of agreement ranging from $-69$ to $-578$ ml (Fig. 4).\textsuperscript{17}

**Discussion**

The present study investigated the agreement between ITBV measured by UCA-dilution and ITTV as well as PBV, measured by TPTD, both in an \textit{in vitro} setup and in patients. In the \textit{in vitro} setup, ITBV\text{UCA} showed an excellent agreement over the whole range of true volumes and flows of the setup, while a considerable bias was noted in the thermodilution derived volumes especially at the lower flows and higher volumes.

In patients, a good correlation was found between the ITBV\text{UCA} and PBV by TPTD. However, a large bias was found, with ITBV\text{UCA} being nearly twice as large as PBV by

![Fig 3](http://bja.oxfordjournals.org/)

**Table 1** Patient characteristics and preoperative data. Data are presented as number (n), mean (sd), and percentages. ASA, American Society of Anaesthesiologists classification system; LVEF, left ventricular ejection fraction; COPD, Chronic Obstructive Pulmonary Disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (n)</th>
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<tr>
<td>Male/female (n)</td>
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<tr>
<td>Age (yr)</td>
<td>66 (47–80)</td>
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<tr>
<td>Weight (kg)</td>
<td>81 (14)</td>
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<tr>
<td>Height (cm)</td>
<td>172 (9)</td>
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<tr>
<td>ASA classification</td>
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<tr>
<td>Hypertension, n (%)</td>
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</tr>
<tr>
<td>LVEF (%)</td>
<td>32 (7)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>4 (24)</td>
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<tr>
<td>COPD, n (%)</td>
<td>3 (18)</td>
</tr>
<tr>
<td>Hypercholesterolaemia, n (%)</td>
<td>11 (65)</td>
</tr>
<tr>
<td>QRS duration (ms)</td>
<td>127 (30)</td>
</tr>
</tbody>
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thermodilution. Here, ITBV_{UCA} is defined as the intravascular volume between the right atrium and left atrium; we therefore expect to find a bias corresponding to the average right ventricular volume. The results from the in vitro setup are in line with previous observations, where UCA-dilution was used next to thermodilution using thermistor equipped high fidelity pressure wires. Also in this study, a small bias was found between the UCA-dilution acquired volumes and the true volumes. Correspondingly, a large bias was also found for ITTV acquired volumes with an overestimation especially at higher volumes. Likewise, Mischi and coworkers found a high correlation between the UCA-dilution volumes and the true volumes in another in vitro setup with a continuous flow pump. The ITTV estimated volumes, in this study, were corrected for the volume between the injection point and the interception of the ultrasound beam at the inflow tube, which is not an explanation for the overestimation. As in the previous study, the overestimation of the volumes can be explained by loss of indicator (heat) to the surroundings. In a corresponding study in patients where intrathoracic compartments were measured by ultrasound dilution in an extracorporeal arteriovenous loop and PICCO\textsuperscript{®}, the GEDV by PICCO\textsuperscript{®} overestimated the corresponding ultrasound dilution acquired total end-diastolic volumes.

On the other hand, the PBV by thermodilution underestimated the true volume; this can partly be explained by the algorithm. Single TPTD used Newman’s ‘slope-volume method’ to estimate the PTV. However, Newman’s model assumes instantaneous mixing in a single compartment, which is not a realistic assumption in the pulmonary circulation and in the adopted in vitro setup; in fact, precise anatomic boundaries probably cannot be assigned. As MTT measurements by thermodilution depend on flow and on diffusion of heat through two compartments, measurement errors may occur easier; cold saline is an indicator that diffuses both in the intravascular and extravascular compartments. Therefore, especially for low CO and high EVLW, significant errors in the measurement of MTT and thus EVLW may occur.

In addition, the volumes measured with UCA-dilution correspond to volumes previously reported in literature. Using dye dilution technique during right and left heart catheterization Roy and co-authors noted that the pulmonary circulation was on average 211 ml m\textsuperscript{-2}. The same study showed that in patients with mitral valve insufficiency, pulmonary volumes closely matched the clinical signs of pulmonary congestion ranging from exertional dyspnoea (mildly elevated PBV, i.e. 266 ml m\textsuperscript{-2}) to nocturnal dyspnoea (severely elevated PBV, i.e. 478 ml m\textsuperscript{-2}). These ranges of PBV are in agreement with other studies with rheumatic heart disease and congestive heart failure and studies with radionuclide imaging. Interestingly, the volumes by UCA-dilution (average ITBV_{UCA} – indexed of 355 ml m\textsuperscript{-2}) seem more in this range with respect to this patient category with decreased EF and widened QRS-duration. To the best of our knowledge, PBV by PICCO\textsuperscript{®} has never been evaluated. The mismatch of the PBV by TPTD and those of other studies may challenge the PBV measurements derived from PICCO\textsuperscript{®}.

As discussed previously, in in vitro conditions we observed for the TPTD volume estimations an inverse relation between volume and bias suggesting that PBV measurements underestimate especially at larger volumes. Interestingly, in patients, we found a similar inverse relation between volume and bias, which seems to confirm that the limitations of TPTD may also apply in the in vivo measurements. However, whether blood volume estimations with UCA-dilution provide more reliable results in patients needs to be addressed in future studies.

This study has some limitations. The volumes in the in vitro setup where not completely matched, as PICCO\textsuperscript{®} uses a single catheter technique with an algorithm to calculate the intrathoracic compartment using the DST. We tried to minimize

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Fig 4 (a) Correlation between the PBV by PICCO\textsuperscript{®} and ITBV_{UCA} by UCA-dilution in patients. Solid line is the line of regression. (b) Bland–Altman plot for repeated measures of the PBV measured by TPTD and ITBV_{UCA} in patients; Solid line is the mean difference (bias); dotted lines are limits of agreement [bias (1.96 SD)].
the bias for PICCO\textsuperscript{R} by applying a correction, but the difference was too large and the bias was not constant. In our pilot study, the patient number is low and our patient population had a low EF with widened QRS duration. The UCA-dilution used the LA and RA for measuring the ITBV\textsuperscript{UCA} because of shadowing as a result of the intra-atrial septum over the right ventricle; this yields a difference comparing this volume to the actual PBV between the LA and pulmonary artery.

Future studies should be aimed at validating ITBV\textsuperscript{UCA} in patients with preserved LV EF and compare the results with heart failure patients. Also, future analyses should include assessment of trending accuracy, as relative changes are often clinically more important than absolute values. Second, in radiology, a strong correlation was found between pulmonary transit time by cardiac magnetic resonance imaging (CMR) and different heart failure parameters such as: LV diastolic function, N-terminal pro-B-type natriuretic peptide, LV volumes and, inversely, with LV ejection fraction.\textsuperscript{27,28} Validating this relationship with UCA-dilution would be of interest to confirm the value of our technique with echocardiography. Third, PICCO\textsuperscript{R} s DSt, underestimates the volumes both in vitro and in vivo; these volumes should be evaluated using double catheter techniques with an indicator, which is more bound to the intravascular compartment, like dye dilution. Finally, automatic MTT derivation from any ROI in the cavity and reliability tests should be obtained to make it clinically accessible.

In conclusion, we investigated the agreement between ITBV measurements using PICCO\textsuperscript{R} and UCA-dilution technique. UCA-dilution had the lowest bias in vitro. Although in patients, the observed differences in PBV between the two methods were relatively large, the UCA-dilution estimated volumes are more in line with the reported normal range of the PBV measured by dye-dilution or radionuclide imaging in literature. This novel minimally-invasive technique using echocardiography and UCAs deserves further investigation as it could provide an additional clinical tool for estimation of cardiac preload and LV function at the bedside.

**Authors’ contributions**
I.H.: performed in vitro data collection, in vivo data collection, performed data analysis, statistics, and wrote the manuscript.
M.S.: generated the protocol, administered the protocol at the local Medical ethical committee, included patients, and reviewed manuscript.
H.A.: performed data analysis and reviewed manuscript.
A.B.: advised on statistical analysis and reviewed the manuscript.
H.K.: performed in vivo measurements, and reviewed the manuscript.
M.M.: performed in vitro data collection, developed the general user interface for fitting the IDC, performed data analysis, and reviewed the manuscript.

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**Declaration of interest**
A.B. is a member of the associate editorial board of the British Journal of Anaesthesia.

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