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Estimation of Errors in Determining Intrathoracic Blood Volume Using the Single Transpulmonary Thermal Dilution Technique in Hypovolemic Shock

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Background: **The transpulmonary thermal dilution technique has been widely adopted for monitoring cardiac preload and extravascular lung water in critically ill patients. This method assumes intrathoracic blood volume (ITBV) to be a fixed proportion of global end-diastolic volume (GEDV). This study determines the relation between GEDV and ITBV under normovolemic and hypovolemic conditions and quantifies the errors in estimating ITBV.**

Methods: **Nineteen pigs allocated to control (n = 9) and shock (n = 10) groups were studied. Shock was maintained for 60 min followed by volume resuscitation. The dual dye–thermal dilution technique was used to measure GEDV and ITBV ($ITBV_m$) at baseline (time 0), shock phase (30 and 90 min), and after resuscitation (150 min). The regression equations estimated from paired GEDV and $ITBV_m$ measurements under normovolemic and hypovolemic conditions were used to estimate ITBV from the corresponding GEDV, and the estimation errors were quantified. A more simplified equation, used in a commercially available clinical monitor (ITBV = 1.25 × GEDV), was then used to estimate ITBV.**

Results: **The regression equation in the control group was $ITBV_m = 1.21 \times GEDV + 99$ ($r^2 = 0.89$, $P < 0.0001$) and in the shock group at 30 and 90 min was $ITBV_m = 1.45 \times GEDV + 0.6$ ($r^2 = 0.95$, $P < 0.0001$). The 95% confidence interval for the y-intercept was relatively wide, ranging from 31 to 168 and −47 to 49, respectively, for the two equations. The equation estimated in the control group led to overestimation of ITBV and a significant ($P < 0.05$) increase in errors in the shock group at 30 and 90 min. Errors in estimating ITBV using the simplified commercial algorithm were less than 15% under normovolemic and hypovolemic conditions.**

Conclusions: **The linear relation between GEDV and ITBV is maintained in hypovolemic shock. Even though the relation between GEDV and ITBV is influenced by circulatory volume and cardiac output, the mean errors in predicting ITBV were small and within clinically tolerable limits.**

THERE is an increasing body of evidence showing that intrathoracic blood volume (ITBV) and global end-diastolic blood volume (GEDV) determined by the dye–thermal dilution technique provide a better estimate of cardiac preload than central venous pressure or pulmonary capillary wedge pressure.[1–7] The dye–thermal dilution technique also provides an estimate of extravascular lung water (EVLW), which is a useful measure of early pulmonary edema.[8,9] This technique involves the injection of cold indocyanine green dye (ICG) into the right atrium (or vena cava) followed by simultaneous recording of temperature (T) and dye–dilution curves in the abdominal aorta.[10,11] The volume of distribution of temperature and ICG between the point of injection and sampling is a function of the mean transit time (MTt) of each indicator and cardiac output (CO). With improvements in technology, it is now possible to perform online measurement of temperature and ICG concentrations using a rapid response thermistor-tipped photometric catheter placed in the upper abdominal aorta. When this catheter is positioned above the origins of the major splanchnic and renal arteries, both indicators will distribute predominantly within the fluid compartments in the chest. While the thermal bolus distributes in the entire fluid compartment (intrathoracic thermal volume [ITTV]), ICG is confined to ITBV alone because of protein binding. Therefore ITTV, ITBV, and EVLW may be measured using the following steps[12]:

$$ITTV = CO \times MTt_T, \quad (1)$$

$$ITBV = CO \times MTt_{ICG}, \quad (2)$$

$$EVLW = ITTV - ITBV. \quad (3)$$

However, the dye–thermal dilution technique, although effective, is expensive, time-consuming, and cumbersome for clinical use. This led to the development of the single transpulmonary thermodilution technique for the routine estimation of GEDV, ITBV, and EVLW in critically ill patients. The single transpulmonary thermal dilution technique uses the MTt_T to derive ITTV as described in equation 1 and the exponential down slope time of the thermodilution curve (DSt_T) to derive pulmonary thermal volume (PTV) and GEDV using the following steps[13–15]:

$$PTV = CO \times DSt_T, \quad (4)$$

$$GEDV = ITTV - PTV. \quad (5)$$

Figure 1 provides a schematic diagram summarizing the key stages of the dye–dilution technology.

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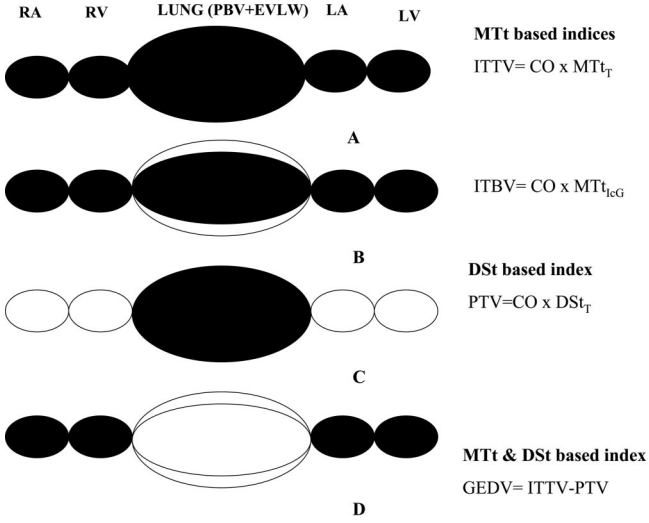

Fig. 1. Schematic diagram of the relevant fluid compartments and their derivation. Note that it is feasible to derive global end-diastolic volume (GEDV) using the temperature dilution curves alone. CO = cardiac output; DSt = down slope time; ITBV = intrathoracic blood volume; ITTV = intrathoracic thermal volume; MTt = mean transit time; PTV = pulmonary thermal volume, which includes the pulmonary blood volume and the extravascular lung water.

If ITBV is considered to be a constant proportion of GEDV, it is then possible to obtain an indirect estimate of ITBV and EVLW from the transpulmonary thermodilution curves alone. The commercially available device currently using this technology (PiCCO; PULSION; Medical Systems, Munich, Germany) uses a linear equation with a coefficient of 1.25 and an intercept of 0 to estimate ITBV from measured GEDV values:

$$\text{ITBV} = 1.25 \times \text{GEDV}. \quad (6)$$

This system has now been accepted for routine hemodynamic monitoring in many critical care units in the United Kingdom and in mainland Europe. The recent controversy related to the safety of pulmonary artery catheters in critically ill patients[16] has no doubt encouraged this shift toward other forms of hemodynamic monitoring. (The acronym PiCCO points to the fact that this system provides a *c*ontinuous estimate of *c*ardiac *o*utput using *p*ulse contour analysis, and *i*ntrathoracic blood volume and EVLW using the transpulmonary thermal dilution technique.) However, the derivation of ITBV using equation 6, a key step in the estimation of EVLW using the PiCCO system, has remained controversial ever since its introduction for measuring ITBV and EVLW in clinical monitoring. It has been argued that the relation between GEDV and ITBV may be influenced by overall volume status and CO. Furthermore, compensatory venous/arteriolar vasoconstriction in the pulmonary, systemic, and splanchnic circulations and the consequent redistribution of blood from the peripheral compartments to more central compartments may alter the numerical relation between GEDV and ITBV. These concerns have limited the acceptance of the PiCCO technology in many institutions. The current study was therefore undertaken to independently verify the numerical relation between GEDV and ITBV under normovolemic and severe hypovolemic conditions in a laboratory model of sustained shock and fluid resuscitation and to quantify the errors in using the PiCCO system under these conditions. We hypothesized that the regression equation describing the relation between GEDV and ITBV in normovolemic animals would lead to significant errors when used to estimate ITBV in animals with hypovolemic shock.

Materials and Methods

After institutional approval (Licence 42/1788; Home Office, Shrewsbury, United Kingdom), 19 immature female Large-White pigs (mean weight, 26.3 kg; SD, 3.3 kg) were randomly allocated to a control group (n = 9) and a shock group resuscitated with 4% succinylated gelatin (Maelor Pharmaceuticals Ltd., Wrexham, United Kingdom) (n = 10). Anesthesia was induced with halothane, oxygen, and nitrous oxide administered *via* a snout mask followed by tracheal intubation and mechanical ventilation using a volume-cycled ventilator (Blease-Brompton-Manley; Chesham, Bucks, United Kingdom) (tidal volume, 10–15 ml/kg; rate, 12–15 breaths/min). An intravenous infusion of alphaxalone-alphadolone (Saffan; Pitman-Moore, Uxbridge, United Kingdom; 15 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}) was commenced when venous access had been established. A pulmonary artery catheter (Baxter Swan-Ganz CCO/VIP, 7.5 French; Edwards Life Sciences, Irvine, CA) was sited *via* the external jugular vein using aseptic techniques. All animals received maintenance fluids (0.9% NaCl, 10 ml $\cdot$ kg^{-1} $\cdot$ h^{-1}) to replace insensible fluid loss. The dye–dilution catheter (Pulsiocath PV 2024, 4 French; PULSION) was positioned in the upper abdominal aorta *via* the femoral route. Previous studies from our laboratory in pigs of similar proportions have shown that the distance from the femoral artery to the diaphragmatic crura was approximately 38 cm. The dye–dilution catheter was therefore advanced to 36–37 cm from the point of entry into the femoral artery to ensure that the tip of the catheter was positioned just below the level of the diaphragm. At the end of instrumentation, all animals were given a rest period of 30 min. After baseline measurements (time 0), the shock group was subjected to hemorrhagic shock by removing blood at a rate of 1 ml $\cdot$ kg^{-1} $\cdot$ min^{-1} until hypovolemic shock was established. All hemodynamic measurements were repeated at this stage (30 min), and the animals were allowed to remain in shock for 60 min (90 min). During this shock phase, the presence of shock was confirmed using three of the following four predetermined endpoints:[17]

1. greater than 30% reduction in CO

2. greater than 30% reduction in mean arterial pressure
3. mixed venous oxygen saturation less than 40%
4. blood lactate concentration greater than 3 mM

At the end of the shock phase, volume resuscitation was achieved using 4% succinylated gelatin. Fluid administration was stopped when CO had been restored and was maintained above 90% of baseline values. A final set of hemodynamic measurements were then made at 150 min. The animals were killed by anesthetic overdose, the lungs were removed, and EVLW content was determined by a gravimetric method that corrects for intravascular volume.[18]

Measurement of GEDV, ITBV, and EVLWi

The dye–thermal dilution method (COLD Z-03; PULSION Medizintechnik, Munich, Germany) was used to measure GEDV, measured ITBV ($ITBV_m$), and extravascular lung water index (EVLWi) at 0, 30, 90, and 150 min. Duplicate estimates of EVLWi using a manual injection of 10 ml cold ICG (PULSION; 1 mg/ml) were made, and the numerical average of the two closest measurements was taken as the true EVLWi. If the difference in EVLWi between the duplicate injections was greater than 10%, a third injection was made in keeping with current clinical practice, and the average of two closest values was used in all subsequent calculations. At each of the four time points, other hemodynamic variables, including heart rate, pulmonary artery thermodilution, transpulmonary thermodilution, and mean arterial pressure were also recorded.

Cardiac Output and Mean Arterial Pressure

The Vigilance continuous CO monitor (Baxter Healthcare Ltd., Deerfield, IL) was used to measure continuous CO and intermittent thermodilution CO. Continuous CO measurements were stopped at the four time points when cold ICG was injected for CO, GEDV, and $ITBV_m$ measurements. Continuous CO measurements were used to control the volume of blood loss and adequacy of fluid resuscitation only and were not used in any of the subsequent statistical analyses. Arterial pressure was transduced directly from the side arm of the aortic cannula. The pressure signals were acquired and stored in a personal computer using standard signal processing equipment and software (CED 1902, CED1401 and Spike 2; Cambridge Electronics Design, Cambridge, United Kingdom).

Statistical Analyses

The relation between GEDV and $ITBV_m$ in control and shock groups was first estimated using linear regression analyses where the correlation coefficients and y-intercepts were compared using 95% confidence intervals (CIs). Hemodynamic variables were analyzed using analysis of variance for repeated measurements (general linear model; SPSS 9.0; SPSS Inc., Chicago, IL). Significant factors were further compared using 95% CIs of estimated means at each of the four stages. Statistical significance was defined as $P < 0.05$ (two sided). Bland-Altman plots and within-subject correlation were used to compare the different measures of CO and measured/estimated ITBV.[19,20] Because all data were normally distributed, mean (SD) values were used as summary statistics.

Derivation of Estimated ITBV and Percent Estimation Error

Because CO is a common factor in the derivation of $ITBV_m$ and GEDV, the regression plots are likely to be influenced by mathematical coupling between these two parameters. An alternative approach was therefore also used in data analysis whereby estimated ITBV ($ITBV_e$: ITBV estimated indirectly using a regression equation) was compared against $ITBV_m$, and prediction errors at the four stages were compared using repeated-measures analysis of variance. The linear regression equation estimated using 32 pairs of measured $ITBV_m$ and GEDV values from 8 animals in the control group was applied to the 4 GEDV measurements in the ninth animal to obtain the corresponding "estimated ITBV" ($ITBV_e$) for the ninth animal in the control group. This process was repeated for each of the nine animals in the group, allowing a total of 36 comparisons between $ITBV_m$ and $ITBV_e$ within the control group. The regression equation developed using this technique is not influenced by data from the animal in which the equation would be put to use. This out-of-sample prediction technique is in the spirit of the "leave-one-out" cross-validation technique.# [21] The equation from all the GEDV/$ITBV_m$ measurements from the entire control group (36 pairs of measurements; 9 animals and 4 sets of readings per animal) was then applied to the GEDV measurements in the shock group to obtain the corresponding $ITBV_e$ for each of the animal in the shock group. The difference between $ITBV_m$ and $ITBV_e$ was expressed as a percentage of $ITBV_m$ ($[(ITBV_m - ITBV_e)/ITBV_m] \times 100$) and used as the percent prediction error at each of the time points. When this approach is adopted, the quantitative relation between $ITBV_m$ and GEDV under normovolemic conditions is imposed on the shock group even at 30 and 90 min when the animals were in shock. The percent errors for the shock group at 30 and 90 min were therefore corrected using a second set of regression equations estimated from $ITBV_m$/GEDV values from the shock group at 30 and 90 min only. Values from 9 animals in the shock group (18 pairs of GEDV/$ITBV_m$ at 30 and 90 min) were used to derive the regression equation to be used in the

http://vision.eng.shu.ac.uk/neural/FAQ/FAQ3.html#A_cross. Accessed May 7, 2005.

Table 1. Hemodynamic Variables for Control and Shock Groups

	0 min	30 min	90 min	150 min
	Baseline	Shock Phase		After Resuscitation
Heart rate, beats/min				
C	155 (33)	148 (34)	132 (28)	128 (26)
S	146 (29)	187 (34)	190 (45)*	152 (33)
Mean arterial pressure, mm Hg				
C	92.7 (23.2)	89.1 (17.9)	88.4 (21.5)	82.8 (20.7)
S	89.2 (13.8)	43.9 (10.9)*	43.6 (14.1)*	57.2 (18.7)*
Cardiac output, l/min				
C	3.6 (1.0)	3.8 (1.1)	3.5 (0.8)	3.5 (0.8)
S	4.2 (1.0)	2.4 (0.4)*	2.2 (0.9)*	4.4 (1.5)
Stroke volume, ml				
C	23.4 (6.7)	26.3 (7.5)	27.7 (7.9)	28.7 (8.6)
S	29.5 (6.6)	13.0 (2.8)*	11.4 (4.4)*	28.2 (8.5)
Pulmonary capillary wedge pressure, mm Hg				
C	5.0 (2.8)	5.6 (4.1)	5.4 (3.9)	6.6 (2.4)
S	6.6 (1.4)	3.4 (2.3)	3.7 (1.9)	8.2 (4.1)
ITBVi, ml/kg				
C	25.0 (2.9)	24.2 (2.2)	23.2 (2.9)	25.3 (4.2)
S	25.1 (3.1)	15.4 (3.8)*	15.3 (5.5)*	22.5 (5.6)
GEDVi, ml/kg				
C	17.2 (1.8)	17.0 (1.7)	16.2 (1.9)	17.5 (2.1)
S	17.7 (2.5)	10.6 (2.8)*	10.4 (3.5)*	16.2 (4.6)
EVLWi, ml/kg				
C	5.2 (1.3)	6.1 (1.1)	6.3 (0.9)	5.1 (0.9)
S	5.8 (1.2)	5.8 (1.6)	5.8 (1.4)	6.3 (1.9)
% Error				
C	3.4 (1.8)	3.6 (2.2)	4.8 (3.6)	4.3 (3.3)
S	3.2 (1.8)	13.2 (6.2)*	12.8 (9.1)*	5.3 (3.2)
% $Error_{PiCCO}$				
C	13.6 (4.3)†	10.0 (3.2)†	12.5 (4.7)†	13.2 (4.8)†
S	11.7 (2.4)†	13.8 (3.6)†	13.8 (4.5)†	10.4 (3.1)†

Data are presented as mean (SD) of all relevant hemodynamic variables during the experiment.

* Significantly different from the corresponding baseline values; repeated-measures analysis of variance, $P < 0.05$. † Significantly greater error when compared with errors in deriving $ITBV_e$ using equation 7 (control group at 0, 30, 90, and 150 min; shock group at 0 and 150 min) or equation 9 (shock group at 30 and 90 min).

C = control group; EVLW = extravascular lung water; GEDV = global end-diastolic volume; ITBV = intrathoracic blood volume; S = shock group. EVLWi, GEDVi, and ITBVi refer to the respective values indexed to body weight; Error and % $Error_{PiCCO}$ refer to the percentage errors when ITBV was derived from GEDV using equation 7 or equation 6, respectively, compared with $ITBV_m$.

% Error = $[(ITBV_m - ITBV_e)/ITBV_m] \times 100$; % $Error_{PiCCO} = [(ITBV_m - ITBV_{PiCCO})/ITBV_m] \times 100$

tenth animal (and the process repeated for all 10 animals) in keeping with the out-of-sample prediction technique.[21] Finally, the PiCCO algorithm (equation 6) was used to obtain $ITBV_{PiCCO}$ in both groups of animals and compared against $ITBV_m$ using Bland-Altman plots. Percent $error_{PiCCO}$ was defined as $[(ITBV_m - ITBV_{PiCCO})/ITBV_m] \times 100$.

Results

The mean weights for both groups were similar (control group, 26.8 [3.0] kg; shock group, 27.8 [3.8] kg). Gravimetrically determined EVLWi data were available in only 15 animals and ranged between 5.9 and 12.2 ml/kg (mean, 8.4 ml/kg; SD, 2.1 ml/kg). In these animals, the percentage EVLW detected by the dye–thermal dilution technique was approximately 80% of lung water determined by the gravimetric method. In the shock group, the shock phase was associated with a significant reduction in CO, stroke volume, and mean arterial pressure at 30 and 90 min ($P < 0.05$). The above changes were, as expected, accompanied by a significant reduction ($P < 0.05$) in GEDV indexed to body weight (GEDVi) and $ITBV_m$ indexed to body weight ($ITBVi_m$). The hemodynamic variables for both groups during the entire experiment are summarized in table 1. The relation between CO measurements obtained by pulmonary artery thermodilution and transpulmonary thermodilution in shock is of considerable clinical interest and is summarized in figure 2.

The correlation between GEDV and $ITBV_m$ for control and shock groups are summarized in figure 3. The regression equation obtained using all the 36 pairs of measurements in the control group was

$$ITBV_m = 1.21 \times GEDV + 99 \quad (7)$$

($r^2 = 0.89$, $P < 0.0001$; 95% CI for slope, 1.1–1.4 and 95% CI for y-intercept, 31–168). The regression equation

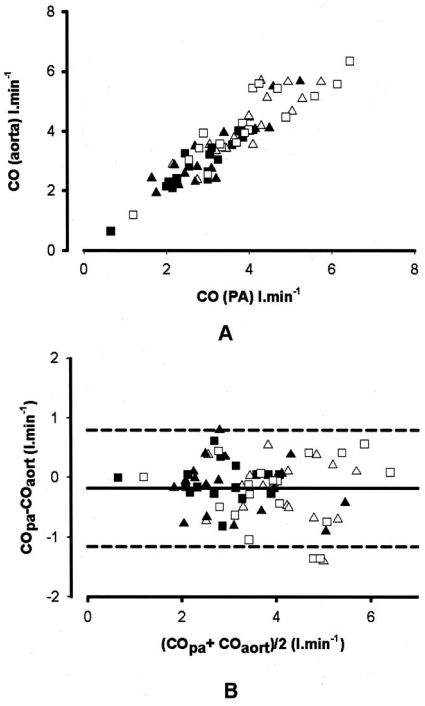

Fig. 2. Comparison between cardiac output (CO; l/min) measurements obtained by pulmonary artery thermodilution (CO_{pa}) and transpulmonary thermodilution (CO_{aort}) using within-subject correlation (*A*) and Bland-Altman plot (*B*) (within-subject correlation $r^2 = 0.95$; bias = −0.21 and SD = 0.51). The bias of −0.21 indicates that transpulmonary thermodilution systematically overestimates CO. *Open triangles* = time 0; *closed triangles* = 30 min; *closed squares* = 90 min; *open squares* = 150 min.

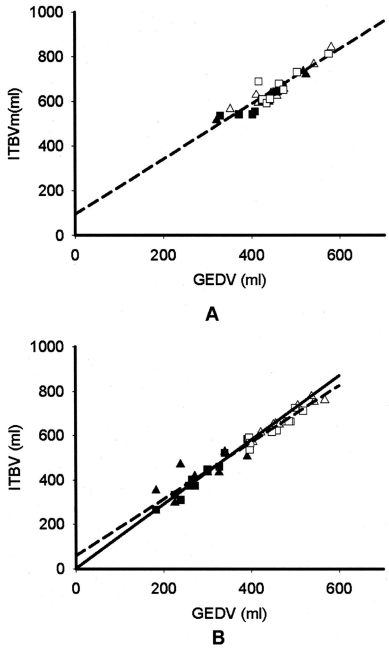

Fig. 3. (*A*) Correlation plot showing the relation between end-diastolic blood volume (GEDV) and measured intrathoracic blood volume ($ITBV_m$) in the control group ($ITBV_m = 1.21 \times GEDV + 99$; $r^2 = 0.89$, $P < 0.0001$; 95% confidence interval [CI] for slope, 1.1–1.4 and 95% CI for y-intercept, 31–168). (*B*) Shock group under normovolemic (*open triangles and squares* with the correlation line shown as *interrupted line*: $ITBV_m = 1.3 \times GEDV + 58$; $r^2 = 0.92$, $P < 0.0001$; 95% CI for slope, 1.1 to 1.5 and 95% CI for y-intercept, −33 to 150) and hypovolemic conditions (*shaded triangles and squares* with the correlation line shown as a *solid line*: $ITBV_m = 1.45 \times GEDV + 0.6$; $r^2 = 0.95$, $P < 0.0001$; 95% CI for slope, 1.3 to 1.6 and 95% CI for y-intercept, −47 to 49). The differences between the slopes and intercepts of the three equations are not statistically significant.

obtained in the shock group under normovolemic conditions (at 0 and 150) minutes was

$$ITBV_m = 1.3 \times GEDV + 58 \quad (8)$$

($r^2 = 0.92$, $P < 0.0001$; 95% CI for slope, 1.1 to 1.5 and 95% CI for y-intercept, −33 to 150). The regression equation obtained in the shock group under hypovolemic conditions at 30 and 90 min was

$$ITBV_m = 1.45 \times GEDV + 0.6 \quad (9)$$

($r^2 = 0.95$, $P < 0.0001$; 95% CI for slope, 1.3 to 1.6 and 95% CI for y-intercept, −47 to 49). The 95% CIs for the y-intercept were very wide, and consequently the differences between the y-intercepts in equations 7, 8, and 9 were not statistically significant ($P > 0.05$). The family of regression equations developed within the control group using the leave-one-out cross-validation strategy provided an accurate estimate of ITBV in the control group (mean bias, 0.9%; SD, 4.2%), and the mean percent prediction error was less than 5% at all four time points (table 1). In the shock group, however, equation 7 resulted in overestimation of ITBV at 30 and 90 min, and consequently, the percent prediction error was significantly greater ($P < 0.05$) than the corresponding errors at 0 and 150 min (table 1). However, the family of equations developed using the shock-phase GEDV/$ITBV_m$ values only provided a more accurate estimate of ITBV in the shock group at 30 and 90 min (mean bias, 5.4%; SD, 4.6%). The distribution of errors at the four time points for both groups are summarized in figure 4. Even though the PiCCO equation significantly underestimated ITBV ($P < 0.01$; control group: mean bias, 12.9%; SD, 4.3%; shock group: mean bias, 12.2%; SD, 3.9%), the percent prediction errors were similar and less than 15% in both groups at all four stages of the experiment (table 1).

Discussion

In the current study, we used the volume of distribution of ICG between the right atrium and upper abdominal aorta (immediately below the level of the diaphragm) as the standard measure of ITBV.[10,11] We compared alternate measures of ITBV, *i.e.*, $ITBV_c$ derived indirectly as a linear function of calculated GEDV, under normovolemic and hypovolemic conditions against this standard measure to estimate prediction errors. Our results confirm that the linear relation between GEDV and

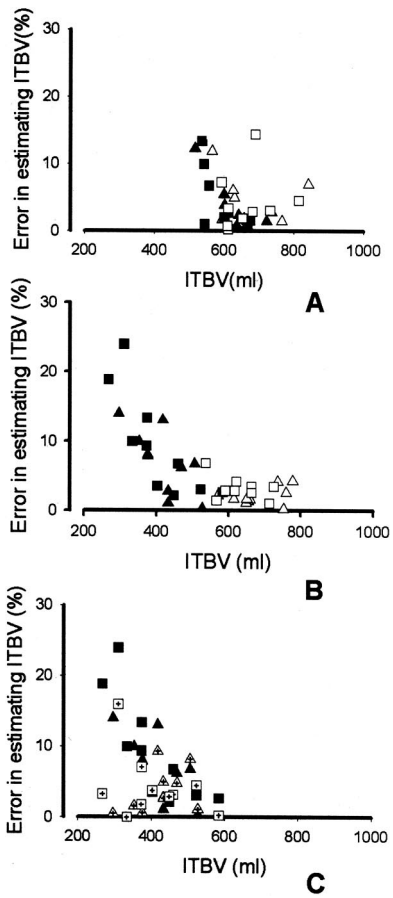

Fig. 4. (*A*) Distribution of percent prediction error in estimating intrathoracic blood volume (ITBV) in group C using equation 7. (*B*) Distribution of percent error in estimating $ITBV_e$ for group S showing the significant increase in error at 30 and 90 min (*open triangles* = time 0; *shaded triangles* = 30 min; *shaded squares* = 90 min; *open squares* = 150 min). (*C*) Percent error in group S at 30 and 90 min using equation 7 compared with "corrected errors" when $ITBV_e$ was estimated using equation 9 (*shaded triangles* = errors at 30 min; *dotted triangles* = corrected errors at 30 min; *shaded squares* = errors at 90 min; *dotted squares* = corrected errors at 90 min). Percent prediction error refers to $[(ITBV_m - ITBV_e)/ITBV_m] \times 100$.

ITBV is preserved in hypovolemic shock (fig. 3; $r^2 = 0.95$, $P < 0.0001$). However, the precise numerical relation and the corresponding regression equations relating to the two variables are influenced by circulatory volume and CO as illustrated by the wide 95% CI in the y-intercepts for equations 7, 8, and 9 (fig. 3). The significant increase in prediction errors when $ITBV_e$ during the shock phase was derived from the equation developed in the control group under normovolemic conditions (table 1) confirms this inherent dependence on circulatory volume and CO. The clinical relevance of this small but statistically significant effect of circulatory volume/CO on the numerical relation between GEDV and $ITBV_m$ and its relevance to clinical monitoring using the PiCCO system requires further clarification.

Although the prediction errors using the PiCCO equation were significantly greater than with equation 7 or 9, the overall errors were less than 15% in both groups (table 1). The correlation coefficient of 1.25 in the PiCCO algorithm is between the two coefficients determined in the two study groups (equations 7 or 9, control group: 1.21; shock group: 1.45). Furthermore, by not incorporating the y-intercept, the PiCCO equation (ITBV = 1.25 × GEDV) eliminates one of the main sources of variation related to circulatory volume/CO. Consequently, the mean bias was similar in the control and shock groups (control: mean bias, 12.9%; SD, 4.3%; shock: normovolemia; mean bias, 10.7%; SD, 3.2%; hypovolemia; mean bias, 12.2%; SD, 3.9%), and no significant changes in percent prediction error were seen in the shock group during the four stages of the experiment (table 1). Because uncertainties due to extraneous factors such as CO or circulatory volume are usually more important in clinical monitoring, the strategy adopted by the PiCCO system seems sound and clinically meaningful.

Three potential limitations of the current study require emphasis. First, because CO is a common parameter in the derivation of GEDV and ITBV, the two measurements are mathematically coupled. The effects of mathematical coupling are bound to distort any observation based on a direct comparison between the regression equations when the common factor (CO) is subject to major changes during the course of the study. Our conclusions are therefore based primarily on "prediction errors" on comparing measured and estimated ITBV. In this context, the leave-one-out cross-validation technique provides a robust strategy by ensuring that the regression equation applied to any given animal is not influenced by values from the same animal.# Second, the relation between GEDV and ITBV was evaluated under normovolemic and extreme hypovolemic conditions. We estimated blood volume on the basis of 75 ml/kg based on previous studies in our laboratory[22] and the volume of blood removed from each animal (mean, 39%; SD, 11% of estimated blood volume) varied to achieve the predetermined endpoints of shock. This degree of hypovolemia is likely to be recognized and corrected before EVLW measurements become relevant in clinical management. The fact that, even under such extreme conditions, the PiCCO algorithm was robust enough to predict ITBV with an overall error of less than 15% is reassuring. Third, volume of distribution measured using the dye–dilution technique refers to the respective volume from the point of injection (right atrium or superior vena cava) to the point of sampling (upper abdominal aorta just below the level of the diaphragm).[10,11,13] Consequently the term *global end-diastolic volume* is a misnomer because it does not equate to the volume of blood in the four cardiac chambers alone. Nevertheless, this term has been used extensively in published literature, and we have retained its use in our study to maintain consistency. The basic premise, however, is that ITBV can be derived indirectly from a closely related

central blood volume. Whether this central blood volume should be referred to as global end-diastolic volume, as suggested in current literature and by the manufacturer (PiCCO; PULSION; Medical Systems, Munich, Germany), remains controversial and should be addressed by an appropriate consensus group.

The study also shows that CO determined by transpulmonary thermodilution compared favorably with pulmonary artery thermodilution technique during the four stages of the experiment (fig. 2). These findings therefore confirm the view that transpulmonary thermodilution technique provides a reliable alternative to the pulmonary artery thermodilution technique to measure CO. Previous investigators have reported similar findings in other clinical conditions such as subarachnoid hemorrhage, sepsis, and major burns and in patients undergoing heart transplantation.[3,23,24] Our findings in a large animal model of hemorrhagic shock add to the current body of evidence in this area. Estimates of EVLW based on the single thermal dilution technique have been shown to be significantly different from the corresponding estimates based on dye–thermal dilution technique in a previous clinical study that involved a small group of patients with septic shock.[25] However, this early study used an older technology based on off-line measurement of ICG using an external dye densitometer. Wickerts *et al.*[26] have shown that off-line measurement of ICG concentration can introduce significant errors in the estimation of EVLW due to phase delays between temperature and ICG–dilution curves. In a more recent study in patients with major burns (mean body surface area, 46%; range, 26–67%), Kuntscher *et al.*[27] have shown that ITBV estimated by the single thermal dilution technique has only a weak correlation ($r = 0.37$) with ITBV determined by the dye–thermal dilution technique. It is widely acknowledged that uniform pulmonary perfusion is an essential prerequisite for the estimation of EVLW using the dye–dilution principles. Using an experimental model of regional pulmonary hypoperfusion, Schreiber *et al.*[28] have shown that estimates of GEDV and ITBV may also be perfusion dependant and suggested that an increase in mean pulmonary transit velocity due to vasoconstriction may lead to a reduction in transit time and consequently underestimation of GEDV and ITBV. None of the above three studies,[25,27,28] however, provide any quantitative data on the numerical relation between GEDV and ITBV in hypovolemic states. In a previous study, we have shown that the numerical relation between GEDV and ITBV was not affected significantly by the presence of acute lung injury and small changes ($<$ 10%) in total blood volume.[15] We have explored this issue further in the current study and have demonstrated that although the presence of larger volume deficits does influence this relation between GEDV and ITBV significantly, the resultant errors were generally small ($<$ 15%) and within clinically tolerable limits. These findings should be taken into account when the single thermal dilution technique is applied for research purposes where a more accurate estimate of ITBV may be required. The limited nature of the current study and the relatively small sample size unfortunately precludes any formal subgroup analyses to identify cohorts of animals where prediction errors exceed 15%. We believe that this issue can be addressed meaningfully only through a larger clinical study dealing with a mixed critically ill population. It is also necessary to point out that the applications of the PiCCO system extend far beyond the estimation of ITBV/EVLW alone, and these other facets of the PiCCO technology are beyond the scope of our work and have not been commented on.

In summary, this study demonstrates that the linear relation between GEDV and ITBV is maintained in severe hypovolemic shock. Even though the exact numerical relation between GEDV and ITBV is influenced by CO and circulatory volume, the overall errors in predicting ITBV from measured GEDV were small and within clinically tolerable limits. The correlation coefficient of 1.25 and an intercept of 0 used in the PiCCO algorithm overcomes some of the variations related to CO and circulatory volume and consequently provides a relatively robust clinical measure of ITBV and EVLW.

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