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


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 × GEDV + 99 (r^2 = 0.89, P < 0.0001) and in the shock group at 30 and 90 min was ITBV_m = 1.45 × 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 two equations 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 steps12:

1. ITTV = CO × MTt_{T},
2. ITBV = CO × MTt_{ICG},
3. EVLW = ITTV − ITBV.

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 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 steps13–15:

1. PTV = CO × DSt_{T},
2. GEDV = ITTV − PTV.

Figure 1 provides a schematic diagram summarizing the key stages of the dye-dilution technology.
catheters in critically ill patients has no doubt encour-
aged this shift toward other forms of hemodynamic mon-
itoring. (The acronym PiCCO points to the fact that this
system has now been accepted for routine hemo-
dynamic monitoring in many institutions. The current study was
therefore undertaken to independently verify the numer-
cal relation between GEDV and ITBV under normovol-
emic 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 hy-
povolemic shock.

Materials and Methods

After institutional approval (Licence 42/1788; Home
Office, Shrewsbury, United Kingdom), 19 immature fe-
male 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,
oxxygen, and nitrous oxide administered via a
snout mask followed by tracheal intubation and mechan-
cal 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 (Saf-
fan; Pitman-Moore, Uxbridge, United Kingdom; 15 mg ·
kg⁻¹ · 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 technique. All animals received maintenance
fluids (0.9% NaCl, 10 ml · kg⁻¹ · h⁻¹) to replace insen-
sible 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 base-
line measurements (time 0), the shock group was sub-
jected to hemorrhagic shock by removing blood at a rate of
1 ml · kg⁻¹ · min⁻¹ until hypovolemic shock was estab-
lished. 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 ml of 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 (ITBVm), 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 ITBVm 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 ITBVm 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 ITBVm 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 (ITBVe; ITBV estimated indirectly using a regression equation) was compared against ITBVm, 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 ITBVm 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” (ITBVe) 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 ITBVm and ITBVe 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/ITBVm 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 ITBVe for each of the animal in the shock group. The difference between ITBVm and ITBVe was expressed as a percentage of ITBVm, ((ITBVm - ITBVe)/ITBVm $\times 100$) and used as the percent prediction error at each of the time points. When this approach is adopted, the quantitative relation between ITBVm 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 ITBVm/GEDV values from the shock group at 30 and 90 min only. Values from 9 animals in the shock group (18 pairs of GEDV/ITBVm at 30 and 90 min) were used to derive the regression equation to be used in the
tenth animal (and the process repeated for all 10 animals) in keeping with the out-of-sample prediction technique. 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 was defined as \[ \frac{(\text{ITBV}_m / \text{ITBV}_{\text{PiCCO}}) / \text{ITBV}_m \times 100} \]

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 indexed to body weight (ITBVm). 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 ITBVm 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

\[ \text{ITBV}_m = 1.21 \times \text{GEDV} + 99 \]  

(7)

Table 1. Hemodynamic Variables for Control and Shock Groups

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

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 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 % ErrorPiCCO refer to the percentage errors when ITBV was derived from GEDV using equation 7 or equation 6, respectively, compared with ITBVm.

% Error = [(ITBVm – ITBV) / ITBVm] x 100; % ErrorPiCCO = [(ITBVm – ITBVPiCCO) / ITBVm] x 100

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

$$\text{ITBV}_m = 1.3 \times \text{GEDV} + 58 \quad (8)$$

($$r^2 = 0.92, P < 0.0001; 95\% \text{ CI for slope, 1.1 to 1.5 and 95\% CI for y-intercept, } -33 \text{ to } 150).$$

The regression equation obtained in the shock group under hypovolemic conditions at 30 and 90 min was

$$\text{ITBV}_m = 1.45 \times \text{GEDV} + 0.6 \quad (9)$$

($$r^2 = 0.95, P < 0.0001; 95\% \text{ CI for slope, 1.3 to 1.6 and 95\% CI for y-intercept, } -47 \text{ to } 49).$$

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/ITBVm values only provided a more accurate estimate of ITBV in the shock group at 30 and 90 min (mean bias, 12.9%; 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. We compared alternate measures of ITBV, i.e., ITBVm 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
ITBV is preserved in hypovolemic shock (fig. 3; r² = 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 ITBVt 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 ITBVt 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). Consequentially 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

(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 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). 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

Anesthesiology, V 103, No 4, Oct 2005

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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. Kuntscher et al. have shown in a previous clinical study that involved a small group of patients with septic shock. However, this early study used an older technology based on off-line measurement of ICG using an external dye densitometer. Wickerts et al. 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. 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. 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 vasconstriction may lead to a reduction in transit time and consequentially underestimation of GEDV and ITBV. None of the above three studies, 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. 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.

The authors thank Tim Riney, B.S., and Hazel Marshall, B.Sc. (Senior Technicians, MRC Trauma Group, University of Manchester, Manchester, United Kingdom), for their help in conducting these experiments, and Malachy O. Columb, F.R.C.A. (Consultant Anesthesiologist, South Manchester University Hospitals, Withenshaw, Manchester, United Kingdom), for statistical advice.

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9. Withenshaw, Manchester, United Kingdom), for statistical advice.