Cardiac output can be measured with the transpulmonary thermodilution method in a paediatric animal model with a left-to-right shunt

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**Editor’s key points**

- This experiment aimed to validate transpulmonary thermodilution (TPTD) measurements of cardiac output (CO) in the presence of a left-to-right shunt.
- Nine lambs underwent surgical construction of aorto-pulmonary left-to-right shunt.
- TPTD CO was compared with perivascular flow around the main pulmonary artery.
- TPTD was found to be a feasible technique in the presence of left-to-right shunt.

**Background.** The transpulmonary thermodilution (TPTD) technique for measuring cardiac output (CO) has never been validated in the presence of a left-to-right shunt.

**Methods.** In this experimental, paediatric animal model, nine lambs with a surgically constructed aorta-pulmonary left-to-right shunt were studied under various haemodynamic conditions. CO was measured with closed and open shunt using the TPTD technique (COTPTD) with central venous injections of ice-cold saline. An ultrasound transit time perivascular flow probe around the main pulmonary artery served as the standard reference measurement (COMPA).

**Results.** Seven lambs were eligible for further analysis. Mean (sd) weight was 6.6 (1.6) kg. The mean COMPA was 1.21 litre min−1 (range 0.61–2.06 l min−1) with closed shunt and 0.93 litre min−1 (range 0.48–1.45 litre min−1) with open shunt. The open shunt resulted in a mean Qp/Qs ratio of 1.8 (range 1.6–2.4). The bias between the two CO methods was 0.17 litre min−1 [limits of agreement (LOA) of 0.27 litre min−1] with closed shunt and 0.14 litre min−1 (LOA of 0.32 litre min−1) with open shunt. The percentage errors were 22% with closed shunt and 34% with open shunt. The correlation (r) between the two methods was 0.93 (P<0.001) with closed shunt and 0.86 (P<0.001) with open shunt. The correlation (r) between the two methods in tracking changes in CO (ΔCO) during the whole experiment was 0.94 (P<0.0001).

**Conclusions.** The TPTD technique is a feasible method of measuring CO in paediatric animals with a left-to-right shunt.

**Keywords:** cardiac output; children; fluid therapy; hemodynamics; hypovolemic shock; left-to-right shunt; monitoring; thermodilution

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haemorrhagic shock with open and closed shunt and resuscitation with closed shunt. We also studied the possibility to track the changes in the CO.

Methods
This experiment was performed in accordance with Dutch national legislation concerning guidelines for the care and use of laboratory animals and was approved by the local ethics committee on animal research of the Radboud University Nijmegen Medical Centre (RUNMC Licence number RU-DEC 2008-117; CDL-project number 33047). Nine lambs were studied under general anaesthesia. Premedication consisted of the i.m. administration of midazolam 2 mg kg$^{-1}$ and ketamine 10 mg kg$^{-1}$ and i.v. administration of propofol 2 mg kg$^{-1}$. General anaesthesia was maintained using inhalation of isoflurane 1–1.5 vol.% and continuous i.v. administration of sufentanil 20 μg kg$^{-1}$ h$^{-1}$, midazolam 0.2 mg kg$^{-1}$ h$^{-1}$, ketamine 10 mg kg$^{-1}$ h$^{-1}$, and pancuronium 0.05 mg kg$^{-1}$ h$^{-1}$ after a loading dose of 0.05 mg kg$^{-1}$. During the experiment, continuous i.v. glucose 10% 2 ml kg$^{-1}$ h$^{-1}$ was administered. The lambs were orotracheally intubated using a 5–6 mm (inner diameter) cuffed tracheal tube (Kruse, Marslev, Denmark). The lungs were mechanically ventilated in a pressure-controlled mode using tidal volumes of approximately 10 ml kg$^{-1}$ (Datex-Ohmeda anaesthesia machine). Normocapnia, guided by capnography with the CO$_2$SMO Plus Respiratory Profile Monitor (Model 8100, Respironics, Pittsburgh, USA), was achieved by adjusting the respiratory frequency to maintain an end-tidal CO$_2$ tension of approximately 4.0 and 5.5 kPa. A servo-controlled heating mattress and an external heating lamp were used to maintain rectal temperature between 38 and 40°C. At the start of the shunt construction, anticoagulation therapy was given with unfractioned heparin with a loading dose of 100 IU kg$^{-1}$ and a continuous i.v. infusion of 50 IU kg$^{-1}$ h$^{-1}$. At the end of the experiment, the animals were killed.

Instrumentation
Immediately after induction of anaesthesia, the animals received a femoral artery catheter (3Fr 7 cm, PV2013L07, Pulsion, Germany), a femoral central venous catheter (5Fr 2 lumen 13 cm, Arrow, Germany) and a Pediasat Oximetry Catheter (4.5Fr 5 cm, Edwards Lifesience LLC, USA) positioned in the external jugular vein with the tip positioned in the superior vena cava. All intravascular catheters were inserted by surgical cut-down. A left-sided thoracotomy was performed and the remains of the native ductus arteriosus were ligated. A 4–6 mm paediatric shunt (Gore-Tex Vascular Grafts, Gore Medical, USA) was constructed between the descending aorta and the left pulmonary artery. Ultrasound transit time perivascular flow probes (PAX series, Transonic Systems, Ithaca, NY, USA) were placed around the main pulmonary artery (Q$_{MPA}$, probe 10 mm) to measure reference CO (CO$_{MPA}$). Two 8-mm flow probes were positioned around the descending aorta, proximal (Q$_{pre}$) and distal (Q$_{post}$) of the aorta-pulmonary shunt. The flow probes were checked for zero flow value directly postmortem. Ultrasound transit time flow probes use a two-way ultrasound technique. By calculating the difference between transit times upstream and downstream, the blood flow is measured. Care was taken to avoid air within the flow probe by applying sufficient quantities of acoustic gel. During the whole experiment, the thorax was left open, enabling opening and closure of the shunt with a clip.

Transpulmonary thermodilution
Transpulmonary thermodilution CO (CO$_{TPTD}$) was measured by injecting ice-cold saline into the jugular venous catheter. Temperature changes were detected by the thermistor-tipped catheter inserted in the femoral artery connected to a commercially available device (PiCCOplus, software version 6.0, Pulsion, Munich, Germany). We used the mean value of three bolus injections of 3 ml of ice-cold (<10°C) saline. The venous injection point was not in proximity to the arterial femoral catheter thermistor tip, thereby avoiding the cross-talk phenomenon in the case of low CO.$^{17, 18}$ Measurements were stored on a computer using specially designed software (PiCCO-Volef Data Acquisition version 6.0, Pulsion, Munich, Germany). Before a series of thermodilution measurements, the central venous catheter was flushed with 1–2 ml of ice-cold saline. Afterwards, each thermodilution measurement was visually inspected to ensure that it was technically correct.

Other measurements
We measured invasive arterial pressure and central venous pressure, electrocardiogram, heart rate, arterial oxygen saturation, end-tidal CO$_2$, respiratory frequency, tidal volume, airway pressure, and body core temperature. During CO$_{TPTD}$ measurement, all other haemodynamic variables, including CO$_{MPA}$, were recorded simultaneously with a 200 Hz sampling rate using a computer system with special biomedical registration software (Poly, Inspektor Research Systems, Amsterdam, The Netherlands). The exact time span of the thermodilution measurement was marked in the registration. The difference between CO$_{TPTD}$ and CO$_{MPA}$ was calculated using the mean value of three consecutive TPTD measurements and the mean value of CO$_{MPA}$ measurements over the same three periods. To analyse whether changes in CO$_{MPA}$ are adequately reflected by changes in CO$_{TPTD}$, we included all measurements over the entire experiment.

For technical reasons, direct measurement of the shunt flow is not possible; therefore, shunt flow was calculated as the difference between Q$_{pre}$ and Q$_{post}$. The Q$_p$/Q$_s$ ratio was calculated using the following equation:

$$\frac{Q_p}{Q_s} = \frac{[Q_{MPA} + (Q_{pre} - Q_{post})]}{Q_{MPA}}$$

In open shunt conditions, we included only measurements with a $Q_p/Q_s$ ratio of >1.5.
Protocol

The CO measurements were performed during three phases of the experiment as shown in Figure 1. The aorta-pulmonary shunt was alternately opened and closed with a clip. The haemorrhage was performed by three periods of withdrawal of blood from the venous catheter to obtain a decrease in mean arterial blood pressure of 10 mm Hg each step. After the haemorrhagic phase, the shunt remained closed and the animals were resuscitated with three fluid challenges of 20 ml kg$^{-1}$ of either homologous whole blood transfusion or hydroxyethyl starch (HES) 130/0.4 6% (Voluven$^\text{TM}$), depending on the haemoglobin content of the blood, analysed after each volume loading. Blood transfusions were stopped as soon as the initial haemoglobin content was reached.

In case of serious haemodynamic insufficiency at the time of the experiment, a continuous infusion of epinephrine was administered to prevent the animal from dying.

Statistical analysis

Comparison between absolute values of CO$_{\text{TPTD}}$ and CO$_{\text{MPA}}$ and changes in CO was performed using correlation statistics (Pearson correlation) after confirming normal distribution of the data. In addition, data were analysed using the method described by Bland and Altman.$^{19}$ As the number of measurements per animal did not vary (1 × 12, 6 × 13), we did not correct for the repeated measurements. The difference between the two methods (bias) was calculated by subtracting the value of CO$_{\text{MPA}}$ from CO$_{\text{TPTD}}$. The bias was plotted against the mean CO [(CO$_{\text{MPA}}$+CO$_{\text{TPTD}}$)/2]. The limits of agreement (LOA) were calculated by multiplying the standard deviation (sd) of the bias with 1.96. The percentage error was calculated using the following formula: (1.96 × sd of the bias)/mean CO$_{\text{MPA}}$ × 100%, using mean CO$_{\text{MPA}}$ as being the reference.$^{20}$ The coefficient of variance (CV) of the CO was calculated as sd being the percentage of the mean of all the CO measurements of each technique and lamb separately. Calculations and data management were performed using Excel for Windows (Office 2007, Microsoft, Seattle, WA, USA). Statistical calculations were performed with MedCalc (Med-Calc Software, Mariakerke, Belgium).

Results

One lamb died during the surgical procedure because of an intractable bleeding before the first measurement was performed. In another lamb, the aorta-pulmonary shunt was

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Table 1 Characteristics, haemodynamic parameters, and procedures of each lamb separately. CO$_{\text{MPA}}$, cardiac output measured by perivascular flow probe around the main pulmonary artery

<table>
<thead>
<tr>
<th>Lamb no.</th>
<th>Weight (kg)</th>
<th>Age (days)</th>
<th>Shunt size (mm)</th>
<th>Mean shunt flow (litre min$^{-1}$)</th>
<th>Mean Q$<em>{p}$/Q$</em>{s}$ ratio [range]</th>
<th>Mean CO$_{\text{MPA}}$ closed shunt (litre min$^{-1}$)</th>
<th>Mean CO$_{\text{MPA}}$ open shunt (litre min$^{-1}$)</th>
<th>Mean MAP (mm Hg) [range]</th>
<th>Total blood withdrawal (ml kg$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.5</td>
<td>12</td>
<td>4</td>
<td>0.7</td>
<td>1.9 [1.7–2.1]</td>
<td>0.87</td>
<td>0.80</td>
<td>46 [36–54]</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>6.2</td>
<td>5</td>
<td>6</td>
<td>0.6</td>
<td>1.6 [1.3–1.8]</td>
<td>1.23</td>
<td>0.98</td>
<td>40 [29–53]</td>
<td>21</td>
</tr>
<tr>
<td>3</td>
<td>8.7</td>
<td>10</td>
<td>6</td>
<td>0.9</td>
<td>1.7 [1.6–1.8]</td>
<td>1.65</td>
<td>1.31</td>
<td>44 [35–58]</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>6.4</td>
<td>11</td>
<td>6</td>
<td>0.6</td>
<td>2.0 [1.4–2.4]</td>
<td>1.06</td>
<td>0.67</td>
<td>34 [25–51]</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>7.3</td>
<td>28</td>
<td>6</td>
<td>0.7</td>
<td>1.6 [1.3–1.8]</td>
<td>1.49</td>
<td>1.19</td>
<td>43 [32–54]</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>7.7</td>
<td>28</td>
<td>6</td>
<td>0.6</td>
<td>1.6 [1.4–1.9]</td>
<td>1.15</td>
<td>1.00</td>
<td>55 [47–115]</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>6.4</td>
<td>29</td>
<td>6</td>
<td>0.8</td>
<td>2.4 [2.1–2.6]</td>
<td>0.93</td>
<td>0.61</td>
<td>46 [33–53]</td>
<td>22</td>
</tr>
</tbody>
</table>
insufficient with a maximum $Q_p/Q_s$ ratio of 1.2. Data from this lamb were excluded from the study. As a result, seven lambs with a mean (SD) body weight of 6.6 (1.6) kg and age of 17.6 (10.3) days were included. The mean COMPA with a closed shunt was 1.21 litre min$^{-2}$ (range 0.61–2.06 litre min$^{-2}$) and with an open shunt 0.93 litre min$^{-2}$ (range 0.48–1.45 litre min$^{-2}$). Haemodynamic data for each individual lamb are shown in Table 1. The open shunt resulted in a mean $Q_p/Q_s$ ratio of 1.8 (range 1.6–2.4) with a mean aorta-pulmonary shunt flow of 0.7 litre min$^{-1}$ (range 0.6–0.9 litre min$^{-1}$).

Calculations of the CV are shown for each technique per lamb in Table 2. The median CV for the TPTD technique and flow probe (MPA) was 6% (min. 0% and max. 33%) and 1% (min. 0% and max. 6%), respectively. An example of a change in the thermodilution curve induced by opening the shunt is shown in Figure 2. The shunt opening induced a $Q_p/Q_s$ ratio of 1.8. The measurement results are shown in Table 3. The increase in mean transit time (MTt) was almost half the increase in down slope time (DSt): 52 and 92%, respectively. The influence of the $Q_p/Q_s$ ratio on the change in MTt and DSt is shown in Figure 3. The inverse correlation between the percentage changes of $Q_p/Q_s$ and CO is shown in the same figure ($r = -0.84; P < 0.0001$).

Differences between the COTPTD and the COMPA with a closed and open shunt are shown in Figure 4A and B, respectively. The higher number of paired CO measurements in Figure 4B is explained by the fact that during the resuscitation phase the shunt remained closed. The mean bias was 0.17 litre min$^{-1}$ (LOA 0.27 litre min$^{-1}$) with the shunt closed and 0.14 litre min$^{-1}$ (LOA 0.32 litre min$^{-1}$) with an open shunt. The bias was not influenced by epinephrine administration or the magnitude of the $Q_p/Q_s$ ratio (not shown). The Spearman’s coefficient of rank correlation (rho) between the shunt ratio ($Q_p/Q_s$) and the difference

### Table 2 Coefficient of variation (CV) in cardiac output (CO) measurements of each lamb separately. Mean CO$_{TPTD}$, mean CO of all transpulmonary thermodilution; MPA, main pulmonary artery measurements

<table>
<thead>
<tr>
<th>Lamb no.</th>
<th>Mean CO$_{TPTD}$ (litre min$^{-1}$)</th>
<th>SD</th>
<th>CV (%)</th>
<th>Mean CO$_{MPA}$ (litre min$^{-1}$)</th>
<th>SD</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.90</td>
<td>0.05</td>
<td>5</td>
<td>0.84</td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1.19</td>
<td>0.08</td>
<td>7</td>
<td>1.13</td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1.65</td>
<td>0.12</td>
<td>7</td>
<td>1.52</td>
<td>0.02</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0.98</td>
<td>0.07</td>
<td>8</td>
<td>0.91</td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>1.51</td>
<td>0.09</td>
<td>6</td>
<td>1.37</td>
<td>0.01</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>1.50</td>
<td>0.18</td>
<td>12</td>
<td>1.09</td>
<td>0.02</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>1.06</td>
<td>0.08</td>
<td>8</td>
<td>0.81</td>
<td>0.01</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 3 The values of transpulmonary thermodilution (TPTD) measurements of cardiac output (CO), MTt (time interval between the moment of injection and time of appearance of half of the amount of injectate at the detector), DST (extrapolated decay of the curve), EVLW (extravascular lung water, and GEDV (global end diastolic volume) with a closed and open shunt in lamb 1, graphically shown in Figure 2

<table>
<thead>
<tr>
<th>Shunt</th>
<th>CO$_{TPTD}$ (litre min$^{-1}$)</th>
<th>MTt (s)</th>
<th>DST (s)</th>
<th>EVLW (ml)</th>
<th>GEDV (ml)</th>
<th>MAP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed</td>
<td>0.95</td>
<td>8.9</td>
<td>4.8</td>
<td>61</td>
<td>65</td>
<td>55</td>
</tr>
<tr>
<td>Open</td>
<td>0.83</td>
<td>13.5</td>
<td>9.2</td>
<td>113</td>
<td>59</td>
<td>46</td>
</tr>
</tbody>
</table>

Fig 2 Transpulmonary thermodilution curves of lamb 1 with a closed and open shunt during stable haemodynamics.

Fig 3 The percentage change in the shunt ($Q_p/Q_s$) ratio compared with the percentage change in mean transit time (MTt; solid circle) and down slope time (DSt; open square) with an open and closed shunt. The linear correlation is $r = 0.95$ ($P < 0.001$) for the MTt and $r = 0.96$ ($P < 0.0001$) for the DSt. The inverse correlation between the percentage change of $Q_p/Q_s$ and CO (open triangle) is $r = -0.84$ ($P < 0.0001$).
between CO values by the two techniques was −0.2 (95% CI 0.392 to 0.00646; P=0.057). The percentage errors were 22% with a closed shunt and 34% with an open shunt. The correlation coefficient between the two methods was 0.93 (P<0.001) with a closed shunt and r=0.86 (P<0.001) with an open shunt.

The correlation between the two methods in tracking changes in CO (ΔCO) for the whole experiment was r=0.94 (P<0.0001) (Fig. 5).

Discussion

For the first time we demonstrate that the TPTD CO measurement is feasible in the presence of a significant left-to-right shunt. There was a significant correlation r=0.94 (P<0.0001) between the two methods in tracking changes of CO including the results over the whole experiment. The experiment order made it impossible to separate the results for tracking changes of CO merely in the open situation.

The precision of TPTD for measuring CO with a closed shunt is in agreement with earlier studies from our group with a percentage error well within the acceptable limits of 30% as described by Critchley and Critchley.6 20 However, the percentage error for measuring CO with an open shunt was significantly larger (34 vs 22%). This can be explained by the lower CO with an open shunt condition and the increased LOA. Probably the shunt flow itself may cause this measurement error. The longer passage time of the thermal indicator in the extra circuit may cause a loss of indicator by diffusion into the surrounding tissue resulting in an overestimation of the CO.

The calculations of CV of the CO measurements show more deviations with the TPTD method compared with the flow probe (MPA) technique (Table 2). The low CV values of our reference technique (flow probe) confirm the assessment
of CO measurements in stable conditions. The measurements by the TPTD method fluctuated more during the same time interval, which explains the difference in agreement between the two methods, although it is not possible to deduce from these calculations, which measurement contains the true value.

We used the flow through the main pulmonary artery as the reference value of the systemic blood flow. We consider this the only valid reference method, because shunt flow entered the pulmonary circulation distal to the measurement site and it also includes the coronary blood flow. The descending aortic blood flow distal from the shunt does not represent systemic blood flow, as it excludes the blood going to the upper part of the body and the coronary arteries.

CO\textsubscript{TPTD} measurement in the presence of a left-to-right shunt has, to our knowledge, not been validated before although the technique was described in several case reports.\textsuperscript{21, 22} Silove and colleagues measured systemic CO by thermal (room temperature) dilution technique in paediatric patients with a left-to-right shunt and compared the results with the reference Fick method.\textsuperscript{23} Measuring the output of the left and right ventricles separately, the issue of recirculation was circumvented. The relation between the outputs of the two ventricles correlated closely to the $Q_p/Q_s$ ratio based on the Fick method.

A left-to-right shunt prolongs the indicator pathway by recirculation. Broadbent and colleagues described in 1954 the typical alterations in the peripheral (transpulmonary) dye dilution curve of a centrally located left-to-right shunt in 16 subjects with a patent ductus arteriosus.\textsuperscript{24} They showed a decrease in the maximal dye concentration and a prolongation of the disappearance time of the curve. We confirmed these findings in our experiment (Fig. 3).

The distortion of the TPTD curve can also be quantified by calculating the MT\textsubscript{t} and DST as shown in Table 3. MT\textsubscript{t} is the time interval between the moment of injection and time of appearance of half of the amount of the injectate at the detector and DST describes the extrapolated decay of the curve. Dye dilution studies showed a relationship between the concentration curve and presence and magnitude of a shunt.\textsuperscript{24, 25} As shown in Figure 3, our study revealed a significant correlation between $Q_p/Q_s$ and changes in MT\textsubscript{t} and DST. Therefore, MT\textsubscript{t} and DST related to CO may be useful for quantifying the magnitude of the shunt.

The presence of a shunt also affects the measurement of the global end-diastolic volume (GEDV) and extravascular lung water (EVLW). As DST increases with greater magnitude compared with MT\textsubscript{t}, the pulmonary thermal volume (PTV) will increase more than the intrathoracic thermal volume (ITTV). Therefore, GEDV will decrease and EVLW will increase. This has been confirmed in clinical patients.\textsuperscript{22} These results show that in cases of a left-to-right shunt, volumetric variables such as GEDV and EVLW are inaccurate.

The commonly used techniques for CO evaluation in the presence of a left-to-right shunt are arterial and venous oximetry and transthoracic echocardiography. Unfortunately, these techniques are either invasive, or need trained and experienced personnel. Recent studies of other (non-invasive) methods such as the modified carbon dioxide Fick method and electric velocimetry show promising results but need further research.\textsuperscript{26, 27} In our opinion, the TPTD method is a valuable alternative. Although the precision is less with an open shunt, the ability to track changes in CO is clinically acceptable.

Our study has several limitations. First, we only studied a limited number of animals. Secondly, although this experiment was carefully controlled, we cannot be sure that the model adequately reflects the human situation. Thirdly, it was not possible to close the shunt consistently for 100% in all animals, which is of minor importance for our study. Still we cannot rule out that the measurements in the closed shunt situation were influenced by residual shunt flow, although the results of TPTD for measuring CO with a closed shunt correlated well with the reference method and were in agreement with earlier studies from our group.

Fourthly, we introduced an uncertain amount of inaccuracy by using a syringe of 10 ml to determine 3 ml injections. It is advisable to choose the size of syringes for the volume of indicator. Fifthly, the experiment required the frequent opening and closing of the shunt. As a result it was not possible to study consecutive haemodynamic changes (after fluid therapy, for instance) with the shunt left open. Sixthly, this model resembles the situation with a patent ductus arteriosus with a unidirectional left-to-right blood flow. In the case of a bi-directional or mainly right-to-left shunt blood flow, these results will be different.
In conclusion, our study shows that CO measurement using the TPTD technique is feasible in the presence of a centrally located left-to-right shunt. However, volumetric values such as GEDV and EVLW are strongly influenced by and dependent on the amount of shunt flow.

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Conflict of interest

None declared.

Funding

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Appendix

Calculation of EVLW and GEDV:

\[ \text{ITTV} = \text{CO} \times \text{MTt} \times 1000/60 [\text{ml}] \]

\[ \text{PTV} = \text{CO} \times \text{DSt} \times 1000/60 [\text{ml}] \]

\[ \text{GEDV} = \text{ITTV} – \text{PTV}[\text{ml}] \]

\[ \text{ITBV} = \text{GEDV} \times 1.25 [\text{ml}] \]

\[ \text{EVLW} = \text{ITTV} – \text{ITBV}[\text{ml}] \]

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