Cardiac output measurement with transpulmonary ultrasound dilution is feasible in the presence of a left-to-right shunt: a validation study in lambs

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**Editor’s key points**

- Measuring cardiac output (CO) in neonates is complex due to shunt.
- CO was measured in lambs with a surgical left-to-right aorto-pulmonary shunt, using two methods.
- Transpulmonary ultrasound dilution was reliable even with a left-to-right shunt.
- The technique may be useful in critically ill children and neonates.

**Background.** Cardiac output (CO) monitoring remains complex in newborns as most of the current technologies fail to accurately measure systemic blood flow in the presence of shunts. We validated CO measurements using transpulmonary ultrasound dilution (TPUD) in a neonatal lamb model with a left-to-right shunt.

**Methods.** Regular arterial and central venous catheters were inserted into seven lambs (3.5–8.3 kg). A surgically constructed left-to-right aorto-pulmonary Gore-Tex shunt was intermittently opened and closed, while CO was manipulated by creating haemorrhagic hypotension. CO measurements with TPUD (COtpud) were compared with those obtained by an ultrasonic transit-time flow probe positioned around the main pulmonary artery (COufp).

**Results.** We performed 72 sessions of three paired CO measurements. The mean COufp was 1.00 litre min⁻¹ (range 0.47–1.75 litre min⁻¹) and mean COtpud 1.05 litre min⁻¹ (range 0.54–1.87 litre min⁻¹). With an open shunt, the mean Qp/Qs ratio was 1.8 (range 1.3–2.6). A comparison between COufp and COtpud showed a mean bias (SD) of 0.03 (0.09) and 0.07 (0.10) litre min⁻¹, respectively, for measurements with a closed and an open shunt. The percentage error was 18% and 20% for measurements with a closed and an open shunt. Polar plot analysis showed good trending ability for both closed and open shunt groups.

**Conclusions.** TPUD is a reliable technology to measure CO in the presence of a left-to-right shunt.

**Keywords:** cardiac output; children; dilution technique, indicator; ductus arteriosus; haemodynamics; monitoring

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Reliable measurement of cardiac output (CO) remains challenging in the paediatric population.¹⁻³ Many techniques are not suitable especially in the neonate due to technical restraints, size limitations, the necessity of blood withdrawal, and possible indicator toxicity.⁴ Hence, CO is generally estimated from indirect clinical and laboratory parameters.⁵ However, these variables are considered unreliable for assessing CO.⁶ Objective CO measurements could therefore be important to newborn patients. Low CO is proven to be associated with an increased mortality in children.⁷ In preterm infants, low systemic blood flow is associated with increased risk of periventricular/intraventricular haemorrhage, impaired neurodevelopmental outcome, and increased mortality.⁸⁻¹⁰ It is plausible that CO monitoring can prevent these risks. In addition, CO monitoring could optimize cardiovascular management as CO and not low arterial pressure will be targeted to start inotropic support in these critically ill newborns.

During the period of transition, patent fetal channels influence the results of most CO measurement technologies making objective measurement even more complicated. Functional echocardiography is increasingly being used to assess CO, myocardial (dys)function, intra- and extracardiac shunts, and organ blood flow.¹¹⁻¹² However, as this method is labour-intensive and expertise in echocardiography is required, it cannot be considered as an instant bedside monitoring system. Many of the other current CO measurement techniques have not been validated in patients with shunts,¹³⁻¹⁵ with the exception of the modified carbon dioxide Fick method.¹⁶

Transpulmonary ultrasound dilution (TPUD) was introduced in 1995 to enable measurement of several
haemodynamic parameters in patients during haemodialysis. The technique was adapted for CO measurements and tested in vitro, in animals, adults, and children, using isotonic saline at body temperature as an indicator, that is injected in a low-volume extracorporeal arterio-venous (AV) tubing loop inserted between an indwelling arterial and central venous catheter. Recently, the method was validated in juvenile piglets and proven to be reproducible, accurate, and safe.

The aim of this study was to validate the accuracy and precision of the TPUD technology in a lamb model with an intermittently opened and closed left-to-right shunt under different haemodynamic conditions.

Methods

Transpulmonary ultrasound dilution

TPUD is based on the difference in ultrasound velocity in blood and the indicator (isotonic saline at body temperature) and uses an extracorporeal AV loop that can be connected to any indwelling arterial and central venous catheter (Fig. 1). The AV loop is flushed with heparinized saline (1 U ml\(^{-1}\)) to prevent thrombosis. A peristaltic pump provides stable blood flow during measurement. The indicator is injected into the venous limb and a venous sensor calculates the exact amount of injected indicator and the ultrasound velocity of the used saline. An arterial sensor measures the decrease in ultrasound velocity in blood by the injected saline. An ultrasound dilution curve is obtained, from which CO is calculated using the Stewart–Hamilton equation. After two to three measurements, the loop is flushed and the pump stopped. The method has been described extensively. An ultrasonic transit-time flow probe positioned around the main pulmonary artery was used as a reference method for measurement of blood flow, which is considered the gold standard in an animal model.

Animals

This experiment was performed in accordance with Dutch national legislation concerning guidelines for the care and use of laboratory animals, was approved by the Ethical Committee on Animal Research of the Radboud University Nijmegen (RU-DEC #2008-117), and was part of a multidisciplinary CO study performed in seven random-bred lambs (3.5–8.3 kg) under general anaesthesia. Ketamine (10 mg kg\(^{-1}\)), atropine (0.03 mg kg\(^{-1}\)), and midazolam (2 mg kg\(^{-1}\)) were administered i.m. as premedication. After i.v. injection of propofol (2 mg kg\(^{-1}\)), the lambs were orotracheally intubated with a cuffed tracheal tube (ID 4–6 mm; Kruse, Marslev, Denmark) and mechanically ventilated in a pressure control mode using a Datex Ohmeda Excel 210 SE anaesthesia machine (GE Healthcare, Waukesha, WI, USA). Anaesthesia was maintained with inhalation of isoflurane (0.5–2.0 vol%) and with i.v. administration of sufentanyl (15–20 \(\mu\)g kg\(^{-1}\) h\(^{-1}\)), ketamine (10 mg kg\(^{-1}\) h\(^{-1}\)), and midazolam (0.2 mg kg\(^{-1}\) h\(^{-1}\)). The depth of anaesthesia was repeatedly assessed by pain stimuli (nose septum, corner of the mouth, and interdigital space of forepaw) and clinical parameters such as heart rate, spontaneous ventilation, and elevated arterial pressure. Anaesthetics were adapted if necessary. Pancuronium (0.02 mg kg\(^{-1}\) h\(^{-1}\) after a loading dose of 0.05 mg kg\(^{-1}\)) was administered only during thoracotomy to prevent muscle spasm due to cauterization. Ventilator settings were adjusted in order to maintain normoxaemia (\(S_{a}O_2\) 90–95%) and normocapnia (\(P_{a}CO_2\) 4.0–6.0 kPa; \(E_{CO_2}\) 4.0–6.0 kPa). A servo-controlled heating mattress and a heating radiator were used to maintain a rectal temperature between 38 \(^{\circ}\)C and 39 \(^{\circ}\)C. At the end of the experiment, the animals were euthanized with a lethal dose of pentobarbital (150 mg kg\(^{-1}\) i.v.).

Instrumentation

Immediately after induction of anaesthesia, intravascular catheters were surgically inserted. The tip of the arterial catheter (16 G 13 cm\(^{-1}\) 1.7 mm\(^{-1}\), 681002, Secalon T\textsuperscript{TM}, Becton, Dickinson and Company, Oxford, UK) was positioned in the abdominal aorta via the left femoral artery and connected to the arterial limb of the TPUD extracorporeal circuit. This circuit was primed with 1.2 ml isotonic saline. A double-lumen central venous catheter (16 G 16 cm\(^{-1}\) 1.7 cm\(^{-1}\), Arrow, Arrow International, Reading, PA, USA) was inserted via the right femoral vein with the position of the tip in the inferior vena cava. One lumen was connected to
the venous limb of the AV loop for TPUD CO measurement. The other lumen was used for administration of fluids and medication.

A left-sided thoracotomy was performed and a non-stretch, thin-walled vascular graft (internal diameter 4–6 mm, Gore-Tex®, W.L. Gore and Associates Inc., AZ, USA) was inserted between the descending aorta and the left pulmonary artery. After a loading dose of heparin (100–120 IU kg⁻¹), a continuous infusion of heparin (50–100 IU kg⁻¹ h⁻¹) was used to prevent shunt thrombosis. Adequately sized perivascular ultrasonic transit-time flow probes (PAX series, Transonic Systems Inc., Ithaca, NY, USA) were used to measure blood flow in the main pulmonary artery (COufp) and proximal (QAOpre) and distal (QAOpost) to the aorto-pulmonary shunt on the descending aorta. We chose to place the flow probe around the main pulmonary artery and not the ascending aorta as this latter (i) does not include the coronary blood and (ii) does not measure true systemic flow in the presence of a left-to-right shunt. A flow probe positioned around the main pulmonary artery (proximally to the shunt insertion) measures right ventricular output which reflects the systemic blood flow in the absence of an intracardiac shunt, irrespective of a potential left-to-right aorto-pulmonary shunt.

Before each TPUD measurement, the adequacy of signal strength of the flow probes was checked. The flow probes were checked for zero value directly post-mortem.

**Experimental protocol**

After a 15 min stabilization period, the study protocol was started (Fig. 2). During the experiment, the aorto-pulmonary shunt was intermittently closed and opened fully by (un)clamping. CO was manipulated by creating haemorrhagic hypotension by gradually withdrawing blood, therefore decreasing the mean arterial pressure by 10 mm Hg over a period of ~5 min. After each intervention, one session of TPUD measurements—consisting of three consecutive injections with 1.0 ml kg⁻¹ isotonic saline—was performed.

We used biomedical data acquisition software (Poly, Inspextor Research Systems BV, Amsterdam, The Netherlands) to store COufp, QAOpre, and QAOpost with a 200 Hz sampling rate. The difference between COtpud and COufp was calculated using the mean value of three consecutive TPUD measurements and the mean value of the three corresponding intervals measured by the flow probe. The Qp/Qs ratio was calculated as (COufp + QAOpre - QAOpost)/COufp.

**Statistical analysis**

A Bland and Altman plot was used to assess agreement between the two methods of CO measurement (for groups with a closed and an open shunt). The mean bias was defined as the mean difference between COufp and COtpud. The mean bias was plotted against the mean CO [(COufp + COtpud)/2]. Precision was represented by limits of agreement (LOA). LOA were calculated by the bias ± 1.96 × SD of the bias. As the number of measurement sessions per animal was almost identical, we did not correct for repeated measurements. The percentage bias was calculated as 100 × (mean bias/mean COufp). The percentage error was calculated as 100 × (1.96 × SD bias/mean COufp) as proposed by Critchley and Critchley. The coefficient of variation (CV) for both measurement methods was calculated as 100 × (SD per session/mean CO per session). The variance of the TPUD method and the reference method was also expressed as the coefficient of error (CE) and calculated as (SD per session/mean CO per session)²/3 with 3 the number of measurements in one session, as described by Cecconi and colleagues. Mean bias (with 95% confidence interval) and LOA were also calculated for COtpud based first on the initial injection of saline and, respectively, the mean of the first two and all three injections in one session for the groups with a closed and an open shunt. The differences in bias and percentage error between measurements with a closed and an open aorto-pulmonary shunt were analysed using the Mann–Whitney test. A value of 0.05 was chosen as the level of significance. A polar plot was used to analyse the agreement in CO trend monitoring between

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**Fig 2** Study protocol. Circles indicate the timing of three consecutive paired CO measurements.
the two methods as described by Critchley and colleagues. The distance from the centre of the plot (vector) represents the mean change in CO. The angle with the horizontal (0° radial) axis represents disagreement. The less the disagreement between CO measurements, the closer the data pairs will lie along the horizontal radial axis. Good trending is defined when the data are situated within the 10% boundaries.

SPSS 16.0.01 for Windows® (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The polar plot was created with SigmaPlot for Windows version 7.1 (Systat Software, Inc., San Jose, CA, USA).

Results
Table 1 shows the characteristics of the study population. The native ductus arteriosus was found to be closed in all animals.

A total of 72 sessions (with each three measurements) were performed and analysed. The mean \( CO_{up} \) was 1.00 litre \( \text{min}^{-1} \). With the shunt closed, \( CO_{up} \) ranged from 0.61 to 1.75 litre \( \text{min}^{-1} \) (mean 1.10 litre \( \text{min}^{-1} \)), with the shunt open from 0.47 to 1.46 litre \( \text{min}^{-1} \) (mean 0.91 litre \( \text{min}^{-1} \)). The mean \( CO_{tpu} \) was 1.05 litre \( \text{min}^{-1} \). With the shunt closed, \( CO_{tpu} \) ranged from 0.61 to 1.87 litre \( \text{min}^{-1} \) (mean 1.13 litre \( \text{min}^{-1} \)), with the shunt open from 0.54 to 1.51 litre \( \text{min}^{-1} \) (mean 0.98 litre \( \text{min}^{-1} \)). With the shunt open, the mean \( Qp/Qs \) ratio was 1.8 (1.3–2.6).

The Bland–Altman plot for the combined measurements with open and closed shunts is shown in Figure 3. The mean bias was 0.05 litre \( \text{min}^{-1} \) with a precision (1.96 \( \times \) SD) of 0.19 litre \( \text{min}^{-1} \). The mean bias (SD) was 0.03 (0.09) and 0.07 (0.10) litre \( \text{min}^{-1} \) for measurements with closed and open shunts, respectively. LOA were ±0.18 and ±0.20 litre \( \text{min}^{-1} \) for measurements with closed and open shunts, respectively, resulting in a percentage error of 18% and 20%, respectively. The percentage bias was 2.8% for measurements with the closed shunt and 6.8% for measurements with the open shunt. The CV for \( CO_{tpu} \) measurements with the closed shunt was 3.3% and for measurements with the open shunt 4.6%. The CV for \( CO_{up} \) measurements was 1.5% for both closed and open shunts.

<table>
<thead>
<tr>
<th>Lamb</th>
<th>Weight (kg)</th>
<th>Number of sessions</th>
<th>Mean ( CO_{up} ) (range) (litre ( \text{min}^{-1} ))</th>
<th>Mean ( MAP ) (range) (mm Hg)</th>
<th>Mean ( Qp/Qs ) (range)</th>
<th>Total blood withdrawal (ml kg ( ^{-1} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.5</td>
<td>11</td>
<td>0.86 (0.65–0.99)</td>
<td>0.79 (0.52–0.89)</td>
<td>30–70</td>
<td>1.9 (1.8–2.1)</td>
</tr>
<tr>
<td>2</td>
<td>6.2</td>
<td>10</td>
<td>1.19 (0.83–1.58)</td>
<td>1.41 (0.75–1.41)</td>
<td>27–55</td>
<td>1.6 (1.3–1.8)</td>
</tr>
<tr>
<td>3</td>
<td>8.3</td>
<td>10</td>
<td>1.51 (1.27–1.75)</td>
<td>1.28 (1.10–1.46)</td>
<td>33–65</td>
<td>1.7 (1.6–1.9)</td>
</tr>
<tr>
<td>4</td>
<td>6.4</td>
<td>10</td>
<td>0.83 (0.61–0.99)</td>
<td>0.66 (0.47–0.75)</td>
<td>25–52</td>
<td>1.9 (1.4–2.3)</td>
</tr>
<tr>
<td>5</td>
<td>7.3</td>
<td>10</td>
<td>1.37 (1.15–1.59)</td>
<td>1.15 (0.91–1.31)</td>
<td>27–55</td>
<td>1.6 (1.4–1.8)</td>
</tr>
<tr>
<td>6</td>
<td>7.7</td>
<td>10</td>
<td>1.06 (0.88–1.23)</td>
<td>0.93 (0.82–1.00)</td>
<td>37–104</td>
<td>1.6 (1.4–1.8)</td>
</tr>
<tr>
<td>7</td>
<td>6.4</td>
<td>11</td>
<td>0.88 (0.67–1.11)</td>
<td>0.67 (0.49–0.80)</td>
<td>30–64</td>
<td>2.4 (2.1–2.6)</td>
</tr>
</tbody>
</table>
The CE for COtpud measurements with the closed shunt was 1.9% and for measurements with the open shunt 2.6%. We noticed no significant correlation between bias and shunt fraction ($r^2=0.03$), mean arterial pressure ($r^2=0.03$), weight ($r^2=0.02$), and heart rate ($r^2=0.02$).

The polar plot (Fig. 4) shows good trending in every group as most of the data points lie inside the limits of good agreement (i.e. 10% ± 0.1 litre min⁻¹ as mean CO=1.0 litre min⁻¹). Table 2 shows the mean bias and LOA between COufp and COtpud based first on the initial injection of saline and, respectively, the mean of the first two injections and all three injections for measurements with closed and open shunts. With additional injections, we noticed a slight, but not significant improvement in both the accuracy (bias) and the precision.

**Discussion**

Our study shows that CO can reliably be measured using the TPUD in an animal model with a left-to-right shunt.

CO was measured within a large range of Qp/Qs (1.3–2.6). With an open (left-to-right) shunt, accuracy and precision decreased in comparison with measurements with a closed shunt. Although almost statistically significant, the increased bias was not of any clinical relevance as the bias percentage was still low. The altered accuracy is the result of a change in the dilution curve in the presence of a left-to-right aorto-pulmonary shunt (Fig. 5A and B). The initial height of the curve is somewhat lower as a smaller amount of indicator reaches the arterial sensor during the first pass. However, the downslope is slurred, wider, and asymmetric due to the shunt circulation. The indicator that has shunted from the aorta through the shunt to the pulmonary artery appears later in the curve as it reaches the sensor in a delayed way. The primary curve—representing the dilution curve that would have been produced in the absence of shunt circulation—is calculated by the COstatus software (Fig. 5C). The principle of the software algorithm is to define the optimal segment for extrapolation that can eliminate the influence of indicator recirculation. If the elimination is accurate, agreement between the dilution technique measurements and the flow probe measurements should be close. The overestimation of CO in the presence of a left-to-right shunt in our study is possibly due to a somewhat larger elimination of indicator recirculation performed by the algorithm from the COstatus. Comparison with other methods is hampered. Reports using lithium dilution (LidCO) excluded patients with shunts as CO measurements were not reliable.13 14 Transpulmonary thermodilution (TPTD) is widely used and accepted to measure CO in adults and older children, but literature about the influence of shunts is scarce.36 37 A recently published article shows that measuring CO in lambs with a left-to-right shunt is feasible.31

Our results also showed a subtle decrease in precision in the presence of a shunt. However, this finding is not significant and to our opinion merely based on coincidence. Despite this small decrease in precision, the percentage error for measurements with open shunt was within the acceptable range of <30% as proposed by Critchley and Critchley33 and used by others.34–39 The percentage error in other paediatric, adult, and animal studies (in patients with higher ranges of CO and without shunts) with the TPTD technique varies from 9.5% to 31.4%.3

**Table 2** Mean bias and LOA between COufp and COtpud based first on the initial injection of saline and, respectively, the mean of the first two injections and all three injections for measurements with a closed and an open shunt. *No significant difference between closed and open shunt (P>0.05). **No significant difference between 1, 2, and 3 injections (P>0.05). LOA, limits of agreement

<table>
<thead>
<tr>
<th></th>
<th>Closed shunt**</th>
<th>Open shunt**</th>
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<tbody>
<tr>
<td></td>
<td>1 injection</td>
<td>2 injections</td>
</tr>
<tr>
<td>Bias (litre min⁻¹)*</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>LOA (litre min⁻¹)*</td>
<td>± 0.22</td>
<td>± 0.18</td>
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</table>

Fig 4 Polar plot representing the changes in CO measured with TPUD cardiac output with a left-to-right shunt

Fig 5 Polar plot representing the changes in CO measured with TPUD cardiac output with a left-to-right shunt. The angle with the horizontal (0° radial) axis represents the mean change in CO. The distance from the centre of the plot (vector) represents the mean change in CO. The primary curve—representing the dilution curve that would have been produced in the absence of shunt circulation—is calculated by the COstatus software (Fig. 5C). The principle of the software algorithm is to define the optimal segment for extrapolation that can eliminate the influence of indicator recirculation. If the elimination is accurate, agreement between the dilution technique measurements and the flow probe measurements should be close. The overestimation of CO in the presence of a left-to-right shunt in our study is possibly due to a somewhat larger elimination of indicator recirculation performed by the algorithm from the COstatus. Comparison with other methods is hampered. Reports using lithium dilution (LidCO) excluded patients with shunts as CO measurements were not reliable.13 14 Transpulmonary thermodilution (TPTD) is widely used and accepted to measure CO in adults and older children, but literature about the influence of shunts is scarce.36 37 A recently published article shows that measuring CO in lambs with a left-to-right shunt is feasible.31

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This study shows that the ultrasound dilution technique is one of the first technologies that can reliably measure CO in the presence of a significant left-to-right shunt. But as Cecconi and colleagues stated, the 30% margin may lead to erroneous conclusions if the precision of the reference technique is not included. The CE of our reference method was 0.9%. The CE of TPUD was 2.6% for measurements with the open shunt and 1.9% for measurements with the closed shunt. This implies that TPUD is about 2.3 times less precise than our reference method. In our opinion, this is still very acceptable in clinical practice because (i) TPUD is compared with the gold standard for CO measurement with excellent precision and (ii) CE is equal to or lower than in other studies using TPTD in children, even in the presence of a shunt.

In this study, we also compared changes in COup and COpd during haemorrhage because not only the absolute CO measurement, but also the capability to track changes in CO make a technique more valuable for clinical use. As shown in Figure 4, all data pairs—except one—were situated within the 10% boundaries. This makes the TPUD a reliable device to measure small changes in CO, even in the presence of a shunt.

The TPUD technique has many benefits: it uses a non-toxic indicator at body temperature, which implies no (thermal) loss of indicator during the measurement period. There is also no loss of sampled blood, because all blood is redirected to the patient. Set-up time is 6 min; results are shown 1 min after injection. Changes in cerebral blood flow, cerebral blood volume (measured by near infrared spectroscopy), heart rate, and arterial pressure during subsequent actions required for TPUD measurements were not clinically relevant in an animal model. This is especially important regarding the use of this method in newborn infants who are at risk for intracranial haemorrhage as a result of fluctuations in cerebral blood flow. TPUD does not require specially designed catheters and can be connected to any indwelling catheter (peripheral arterial catheter, umbilical catheters, central venous catheter) used in critically ill neonates. Thrombosis of the AV loop has not been reported. A possible limitation of the TPUD technique is fluid overload when used repeatedly (especially in neonates) as this method requires repetitive injections with isotonic saline. In order to prevent this fluid overload, de Boode and colleagues advised to perform two consecutive measurements (instead of the three advised measurements by the manufacturer), unless the difference between the two measurements exceeds 10%. We confirmed that with additional injections, no clinically or statistically relevant improvement in accuracy and precision is seen, also in the group with the open shunt (Table 2). Currently, the TPUD method only provides intermittent CO measurements. Continuous CO monitoring is only available in a prototype. Invasive arterial pressure measurement is not possible during the 5–6 min period of CO measurements with TPUD.

TPUD is to our opinion a feasible method to use in newborns, including preterm infants. Vena cava superior flow measurements are nowadays a substitute for systemic blood flow in the neonatal intensive care. However, intensive training to optimize measurements is necessary, and even with experienced observers, there is a large inter- and intra-observer variability. Unlike the TPTD method, TPUD uses an indicator at body temperature. Although CO measurements are feasible in the presence of a left-to-right shunt with TPTD, the results are less precise than with TPUD. Especially, the necessity for a dedicated catheter makes the use of TPTD less attractive in newborn infants as this catheter cannot be used in children smaller than 3.5 kg.

Our study has some limitations. First, we used only a small number of animals. Secondly, possible interatrial shunting through a patent foramen ovale (PFO) was not ruled out. This phenomenon is often seen in neonates with a (moderate to large) patent ductus arteriosus. The presence of a PFO can alter the effect of a ductus arteriosus by decompressing the left atrium. The right ventricular output then might consequently be higher than the left ventricular output.
Although no echocardiographic studies were done, no large PFO was expected as $Q^{Ao pr e}$ was significantly higher than $C O_{pf}$ with an open shunt.

We conclude that measuring CO with TPUD is reliable in neonatal lambs in the presence of a significant left-to-right shunt covering a wide range of CO. This makes the TPUD technique a promising method to measure CO not only in critically ill children, but also in neonates, even during the transition from fetal to neonatal circulation.

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Conflict of interest

None declared.

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