Effects of one-lung ventilation on thermodilution-derived assessment of cardiac output

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Editor's key points
- This study compared the reliability of cardiac output (CO) measurements during one-lung ventilation (OLV).
- CO measurements during OLV were more accurate using a pulmonary artery catheter compared with a transcardiopulmonary thermodilution technique.
- Both techniques reported trend values reliably during hypovolaemia and normovolaemia.

Background. Cardiac output (CO) monitoring can be useful in high-risk patients during one-lung ventilation (OLV), but it is unclear whether thermodilution-derived CO monitoring is valid during OLV. Therefore, we compared pulmonary artery (CO_{PATD}) and transcardiopulmonary thermodilution (CO_{TPTD}) with an experimental reference in a porcine model.

Methods. CO_{PATD} and CO_{TPTD} were measured in 23 pigs during double-lung ventilation (DLV) and 15 min after the onset of OLV, during conditions of normovolaemia and after haemorrhage. An ultrasonic flow probe placed around the pulmonary artery (CO_{PAFP}) was used for reference.

Results. The range of CO in these experiments was 1.5–3 litre min\(^{-1}\). Normovolaemia: during DLV and conditions of normovolaemia, the mean (95% limits of agreement) bias for CO_{PATD} compared with CO_{PAFP} was –0.05 (–0.92 and 0.83) litre min\(^{-1}\), and 0.58 (–0.40 and 1.55) litre min\(^{-1}\) for CO_{TPTD}. During OLV, the bias for CO_{PATD} remained unchanged at 0.08 (–0.51 and 0.66) litre min\(^{-1}\), P=0.15, and the bias for CO_{TPTD} increased significantly to 0.85 (0.05 and 1.64) litre min\(^{-1}\), P=0.047. Hypovolaemia: during DLV, the bias for CO_{PATD} compared with CO_{PAFP} was 0.22 (–0.20 and 0.66) litre min\(^{-1}\) and for CO_{TPTD} was 0.60 (0.12 and 1.10) litre min\(^{-1}\). There was no significant change of bias during OLV for CO_{PATD} [0.30 (–0.10 and 0.70) litre min\(^{-1}\), P=0.25] or bias CO_{TPTD} [0.72 (0.21 and 1.22) litre min\(^{-1}\), P=0.14]. Trending ability during OLV, quantified by the mean of angles \( \phi \), showed good values for both CO_{PATD} (\( \theta = 11.2 \)) and CO_{TPTD} (\( \theta = 1.3 \)).

Conclusions. CO_{TPTD} is, to some extent, affected by OLV, whereas CO_{PATD} is unchanged. Nonetheless, both methods provide an acceptable estimation of CO and particularly of relative changes of CO during OLV.

Keywords: cardiac output; hypovolaemia; intraoperative monitoring; one-lung ventilation; physiological monitoring; thermodilution
Accepted for publication: 16 January 2012

One-lung ventilation (OLV) is performed routinely during thoracic surgery\(^1\) and is usually well tolerated. Nevertheless, some of the consequences of OLV, such as increased pulmonary vascular resistance (PVR) induced by hypoxic pulmonary vasoconstriction, increased ventilation pressures, hypoxaemia, or hypercarbia, can cause haemodynamic changes, which can potentially lead to circulatory instability.\(^2\)\(^3\) Therefore, cardiac output (CO) monitoring can be a useful tool to optimize haemodynamic management in patients undergoing major thoracic surgery.\(^4\)\(^5\) CO estimation by pulmonary artery thermodilution (CO_{PATD}) using a pulmonary artery catheter or transcardiopulmonary thermodilution (CO_{TPTD}) is frequently used for this purpose during surgery and in intensive care.

However, there are a few data showing the validity of CO measurement by pulmonary artery thermodilution and transcardiopulmonary thermodilution during OLV, and these techniques have not been compared with an experimental reference standard. This reference standard is provided by an ultrasonic flow probe placed around the pulmonary artery (CO_{PAFP}) because of its high accuracy (±1–2%) and reproducibility and also its fast response.\(^6\)\(^7\)\(^8\)\(^9\) The validation of thermodilution methods is of special interest, since OLV potentially can influence the principles of these methods. This holds true in particular for CO_{TPTD}, since hypoxic pulmonary vasoconstriction in the deflated lung might have an influence on transit time and thus the contact time of the indicator with the surrounding tissue.

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leading to altered indicator concentrations over time at the site of the detection. Consequently, the validity of using thermodilution-derived CO measurements in clinical practice for monitoring and guidance of therapy during OLV is unclear.

Therefore, the aim of this experimental animal study was to assess the validity of CO measurements by pulmonary and transcardiopulmonary thermodilution during OLV in two different haemodynamic conditions. We chose normovolaemia and hypovolaemia to represent a wide variation in CO and compared the data with an experimental reference of measurement by a pulmonary artery flow probe.

**Methods**

The study was approved by the local governmental commission on the care and use of animals. Twenty-three domestic pigs were studied. The animals received care in compliance with the ‘Guide for the Care and Use of Laboratory Animals’ (National Institutes of Health publication No. 86–23, revised 1996).

**Anaesthesia and instrumentation**

Twenty-three German domestic (Landrace) pigs in overt good health with a body weight of 35–40 kg were studied. The animals were allowed to fast overnight and premedicated with an i.m. injection of ketamine (10 mg kg$^{-1}$), azaperone (4 mg kg$^{-1}$), midazolam (0.5 mg kg$^{-1}$), and atropine sulphate (1 mg). An i.v. access was established in an ear vein and anaesthesia was maintained by continuous infusion of fentanyl (0.05 mg kg$^{-1}$ h$^{-1}$) and propofol (10 mg kg$^{-1}$ h$^{-1}$). Thereafter, tracheotomy and placement of a tracheal tube (8.5 mm) were performed. After securing the airway, a pancuronium (0.1 mg kg$^{-1}$) was injected i.v. to facilitate surgical preparation. The lungs were ventilated using a five-lead ECG and pulse oximetry. The lungs were ventilated using volume-controlled ventilation (Zeus, Drägermedical®, Germany), using tidal volumes 10 ml kg$^{-1}$; inspiration:expiration ratio 1:1.6; PEEP 5 cm H$_2$O, and inspiratory oxygen fraction 0.5). During OLV, tidal volumes were reduced to 6 ml kg$^{-1}$. End-expiratory $P_{CO_2}$ was maintained at 5.3–6 kPa by adjusting ventilatory rate. An i.v. infusion of saline was infused at a rate of 13 ml kg$^{-1}$ h$^{-1}$ to maintain hydration. The animals were placed in the supine position for catheter placement and surgical preparation. An 8.5 Fr central venous catheter was introduced into the right internal jugular vein for drug and fluid administration, and for central venous pressure measurement. An introducer sheath (8.5 Fr) was placed into the right external jugular vein and pulmonary artery catheter (7 Fr, Intra Special Catheters®, Germany) advanced for $CO_{PARD}$ measurement and for the measurement of mean pulmonary artery pressure (mPAP) and PVR. Further, another introducer sheath (8.5 Fr) was placed into the left external jugular vein for volume withdrawal. Finally, a thermistor-tipped catheter (5 Fr, PICCO Catheter, Pulsion®, Munich, Germany) was placed into the femoral artery for detection of transcardiopulmonary thermodilution. All introducer sheaths and the central venous catheter were placed surgically by direct preparation of the relevant vessel, except the femoral arterial catheter, which was placed percutaneously. Body temperature was measured using the arterial catheter and kept constant by the use of warming blankets and pre-warming of infusions, if required.

After thoracic skin incision, a median sternotomy was performed. After preparation of mediastinal tissue and surgical haemostasis, the pericardium was incised longitudinally in the midline and tacked to the chest wall. Mediastinal fatty tissue was dissected by monopolar electric scalpel, and pulmonary artery and the ascending aorta were exposed. A perivascular ultrasonic flow probe (18 mm, Medistim®, Norway) was placed around the pulmonary artery for reference CO measurement. A sufficient amount of acoustic gel was placed between pulmonary artery and flow probe to avoid any air hindering the accurate flow probe measurement.

**Measurements and experimental protocol**

Normovolaemia was established by the infusion of hetastarch colloids 5 ml kg$^{-1}$ (Voluven 130/0.4 6%, Fresenius Kabi®, Germany) at intervals of 5 min until stroke volume variation (SVV) measured by arterial pulse contour analysis (PICCO$_2$, Pulsion) was below 10%. The measurement protocol was then started and the first measurements were performed during double-lung ventilation (DLV) and normovolaemia (M1). All pulmonary and transcardiopulmonary thermodilution measurements were assessed by three sequential central venous injections of 10 ml of cold saline solution (<8 °C) randomly given throughout the respiratory cycle via the central venous port of the pulmonary artery catheter. All thermodilution curves were examined, and measurements were accepted if none of the three consecutive values differed by more than 10% from the mean. Simultaneously to every thermodilution measurement, CO of the flow probe was recorded using EMKA software (EMKA Technologies®, Paris, France). PVR was calculated by the formula PVR (dyn s cm$^{-5}$) = ($P_{A_{mean}}$ – $PCWP$) × $CO^{-1}$ × 80 using pulmonary artery catheter parameters.

Afterwards, OLV was initiated using a 5 Fr endobronchial blocker (CookMedical, Bloomington, IN, USA) placed into the left main bronchus under bronchoscopic guidance to achieve deflation of the left lung. After an equilibration period of 15 min, measurements were repeated (M2). OLV was terminated and DLV was re-established. After another 15 min for equilibration, hypovolaemia was induced by withdrawal of 20 ml kg$^{-1}$ of blood over 30 min. Subsequently, measurements were repeated (M3) and again OLV was implemented. After 15 min, measurement M4 was carried out. After completion of measurements, the animals were killed by fast injection of 50 mmol KCl during deep anaesthesia.

**Statistical analysis**

Data were analysed using SigmaPlot 12 (Systat Software Inc., San Jose, CA, USA) and GraphPad Prism 5 (GraphPad Software, La Jolla, CA, USA). Power analysis revealed that 22
animals were necessary to detect a relevant CO bias of 0.55 between DLV and OLV (power 0.8, α error rate 0.05, two-tailed test). The Kolmogorov–Smirnov test was used to assess the distribution of the data. Variables are expressed as mean (so) when normally distributed. Student's t-test was performed for corresponding bias comparison between measurements during DLV and OLV. The bias was calculated by subtracting CO_PATD from CO_PAFP and CO_TPTD, respectively. Student’s t-test was also used for comparison of the bias during DLV and OLV. The relationship of CO_PATD and CO_PAFP and of CO_TPTD and CO_PAFP was quantified using linear regression analysis, and the strength of agreement was analysed using the concordance correlation coefficient (CCC) according to Lin.12 Based on the line of identity (y=x).8 Furthermore, for comparison of CO_PATD and CO_TPTD with the reference CO_PAFP, analysis according to Bland and Altman was used, giving bias (precision) and limits of agreement [bias (1.96 precision)].13 14 The percentage error was calculated as limits of agreement divided by (mean CO_PAFP + mean CO_PATD)/2 or (mean CO_PAFP + mean CO_TPTD)/2, respectively. Considering a precision of 20% of the thermodilution methods and a precision of the flow probe of 2% respectively. Student’s t-test. The Kolmogorov–Smirnov test was used to assess the distribution of the data. Variables are expressed as mean (standard deviation). *P<0.05 compared with values during DLV.

### Cardiovascular measurements

CO values during this study were between the range 1.5 and 3 litre min⁻¹. During normovolaemia and DLV, there was a close agreement of CO_PATD with CO_PAFP (CCC=0.83), whereas the agreement between CO_TPTD with CO_PAFP was less (CCC=0.66). During OLV, the agreement for CO_PATD was even higher (CCC=0.89), but for CO_TPTD it decreased to 0.51. During OLV, the regression line showed the equation CO_PATD=0.254+0.935×CO_PAFP for CO_PATD and CO_TPTD=0.398+(1.164×CO_PAFP) for CO_TPTD.

During conditions of normovolaemia, the institution of OLV did not change the bias for CO_PATD compared with CO_PAFP (Table 2). The Bland–Altman analysis showed an overestimation of CO by CO_TPDT, this overestimation increased further after OLV, reflected by a significant increase in the bias (Fig. 1). The percentage error decreased after OLV for both CO_PATD and CO_TPTD, showing an acceptable accuracy (percentage error 20–25%) of both methods during OLV.

During hypovolaemia with DLV, the agreement of CO_PATD with CO_PAFP was CCC=0.70 and for CO_TPTD and CO_PAFP, CCC was 0.42. After institution of OLV, the agreement for CO_PATD with CO_PAFP remained unchanged (CCC=0.72), but the agreement decreased for CO_TPTD with CO_PAFP (CCC=0.38). During OLV, the regression line was described by CO_PATD=0.238+(1.039×CO_PAFP) for CO_PATD, and for CO_TPTD the equation for regression line was CO_TPTD=0.204+(1.306×CO_PAFP).

Bias compared with CO_PAFP did not change statistically significantly for CO_PATD and CO_TPTD after OLV (Table 2). Again, the overestimation of CO was greater by transpulmonary thermodilution than by pulmonary artery thermodilution. However, overall accuracy was acceptable in hypovolaemia for both methods (percentage error 20–25%) (Fig. 2).

### Trending ability

In order to evaluate the ability of CO_PATD and CO_TPTD to detect changes in CO during OLV, the relative changes (ΔCO_PATD and ΔCO_TPTD) between CO in conditions of normovolaemia and hypovolaemia were compared with those measured by

### Results

The mean (so) body weight of the animals was 36.0 (5.6 kg). CO was not affected by OLV neither measured by pulmonary artery or transcardiopulmonary thermodilution nor by direct flow measurement using the flow probe (P>0.05). PVR and mPAP increased significantly after OLV in both normovolaemia and hypovolaemia (Table 1).

### Table 1 Cardiovascular data in DLV and OLV during normo- and hypovolaemia.

<table>
<thead>
<tr>
<th></th>
<th>Heart rate (beats min⁻¹)</th>
<th>mAP (mm Hg)</th>
<th>mPAP (mm Hg)</th>
<th>PVR (dyne s cm⁻¹)</th>
<th>CO_PATD (litre min⁻¹)</th>
<th>CO_TPTD (litre min⁻¹)</th>
<th>CO_PAFP (litre min⁻¹)</th>
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<tr>
<td><strong>Normovolaemia</strong></td>
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<tr>
<td>DLV (M1)</td>
<td>73.4 (14.8)</td>
<td>75.1 (14.9)</td>
<td>18.7 (2.9)</td>
<td>331 (150)</td>
<td>2.90 (0.78)</td>
<td>2.86 (0.74)</td>
<td>3.48 (0.88)</td>
</tr>
<tr>
<td>OLV (M2)</td>
<td>76.8 (14.3)</td>
<td>67.8 (12.9)</td>
<td>24.8* (3.4)</td>
<td>512* (149)</td>
<td>2.74 (0.65)</td>
<td>2.81 (0.67)</td>
<td>3.59 (0.85)</td>
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<tr>
<td><strong>Hypovolaemia</strong></td>
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<tr>
<td>DLV (M3)</td>
<td>97.8 (22.0)</td>
<td>44.4 (6.9)</td>
<td>14.9 (1.9)</td>
<td>436 (105)</td>
<td>1.66 (0.37)</td>
<td>1.89 (0.38)</td>
<td>2.27 (0.44)</td>
</tr>
<tr>
<td>OLV (M4)</td>
<td>106.8 (25.3)</td>
<td>45.2 (9.9)</td>
<td>21.3* (3.5)</td>
<td>670* (196)</td>
<td>1.67 (0.41)</td>
<td>1.97 (0.47)</td>
<td>2.39 (0.58)</td>
</tr>
</tbody>
</table>
direct flow probe measurements (ΔCOPAfp). CCC was high for both ΔCOPATD (CCC=0.87) and ΔCOTPTD (CCC=0.87). The regression line for ΔCOPATD was ΔCOPATD=0.230+1.003×ΔCOPAfp. The regression line for ΔCOTPTD is described by ΔCOTPTD=0.071+1.191×ΔCOPAfp. The mean θ angle made by ΔCO vectors and the line of identity (y=x) was θ=11.2° for pulmonary artery thermodilution and θ=1.3° for transcardiopulmonary thermodilution, reflecting a very good trending ability for both methods. Polar plots show the θ angle as the angle between the ΔCO vector and the polar axis. Furthermore, the polar plots demonstrate that all data were within the range of 0.5 litre min⁻¹, representing a reliability to follow changes in values (trending ability) (Fig. 3). Although trending ability is high for both methods,
the polar plot for $\Delta CO_{TPTD}$ underlines that the data are more dispersed, indicating less agreement with the transcardiopulmonary thermodilution method.

**Discussion**

This is the first study to compare CO measured by pulmonary and transcardiopulmonary thermodilution to CO measured...
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by an experimental reference (pulmonary artery flow probe) during OLV. Our results revealed that CO\textsubscript{PATD} is less affected by OLV than CO\textsubscript{TPTD}, which showed a significant increase in bias after the onset of OLV in normovolaemia, representing a normal range of values for CO. Furthermore, the agreement of CO\textsubscript{PATD} with CO\textsubscript{PAPF} was unaffected by OLV, whereas the agreement for CO\textsubscript{TPTD} with CO\textsubscript{PAPF} decreased after the onset of OLV in both normovolaemia and hypovolaemia. Although CO\textsubscript{TPTD} was generally overestimated and CO\textsubscript{PATD} was overestimated during OLV and hypovolaemia, bias and precision were in the acceptable range for both methods during all conditions.\textsuperscript{15} The percentage error was also within an acceptable range (20–25%). Nonetheless, during DLV and normovolaemia, the percentage error was 30% for both thermodilution methods; this can be explained by two outlying measurements. Both methods also showed high agreement to the reference in detection of haemodynamic changes during OLV, that is, changes in actual CO, here induced by acute haemorrhage.

It is important to realize that owing to the use of an animal model and the size of the animals, the range of CO measured in our study was between 1.5 and 3 litre min\textsuperscript{-1}. This range does not correspond exactly to normal values in healthy humans, but are consistent with the low values sometimes seen in clinical practice. Therefore, these data are most relevant to low values of CO and the effect of therapeutic interventions. Hence, given the precision, we found that the use of both thermodilution methods is considered an adequate tool for monitoring and decision-making during OLV, both in normovolaemia and in hypovolaemia.

Earlier studies showed that the results of CO measurement were higher when measured by transcardiopulmonary thermodilution than by pulmonary artery thermodilution.\textsuperscript{16–18} This phenomenon was explained by the slowing of heart rate after fast injection of the cold thermooindicator. This temporarily reduced heart rate has a lower impact on CO measurement by transcardiopulmonary thermodilution, since with this method, the thermal indicator travels longer, and more cardiac cycles are included, when compared with pulmonary artery thermodilution. In our study, CO\textsubscript{TPTD} was estimated as being higher than CO\textsubscript{PATD} during both DLV and OLV. However, we found that overestimation of CO by transcardiopulmonary increases significantly during OLV in normovolaemia (representing a normal range of CO). This confirms the hypothesis that transcardiopulmonary thermodilution is, to some extent, affected by OLV. This can be explained by induction of hypoxic pulmonary vasoconstriction in the deflated lung, potentially trapping thermooindicator in the deflated lung and consequently reducing the amount or rate of indicator arriving at the detection site. A reduced amount of thermooindicator at the detection site leads to a smaller area under the thermodilution curve. Since the area under the thermodilution curve is inversely related to the CO, according to the Stewart–Hamilton equation, overestimation of CO measurement by transcardiopulmonary thermodilution during OLV would become plausible.\textsuperscript{19} Of course, CO measurement by pulmonary artery thermodilution would not be affected by OLV since measurement takes place in the pulmonary artery before the blood passes through the lung. However, the most clinically important finding is that relative changes of CO, as induced here by haemorrhage, were detected reliably and with comparable accuracy by both methods, representing an adequate trending ability. This ability to reflect trends is arguably the most crucial clinical information required from CO monitoring. There is only one experimental study evaluating thermodilution-derived CO measurement during OLV. Hüter and colleagues compared CO\textsubscript{TPTD} with CO\textsubscript{PATD} during OLV in a comparable animal model. They also found higher CO measured by transcardiopulmonary thermodilution than by pulmonary artery thermodilution. They also found a good correlation between these two methods.\textsuperscript{20} However, they could not answer the question of the accuracy of thermodilution during OLV, since they did not compare their results with an experimental gold standard.

We recognize some limitations of our study. For practical reasons, we performed OLV of the right lung, excluding the (smaller) left lung from ventilation, since pigs do have an accessory upper lobe branch for the right upper lobe: this complicates OLV and makes it less reliable for experimental purposes. The relative proportions of the left to right lung are ~3–4; so the effects of OLV could have been even more distinct if the right lung would have been excluded. Nonetheless, we consider the effects achieved by exclusion of the left lung as adequate. In humans, this effect should be similar since the human right lung is also bigger than the left lung. During surgery, when OLV is needed, a lateral thoracotomy is usually performed with open pleura and lateral positioning of the patient. This leads to gravitational pooling of blood to the ventilated lung. In our experimental study, we had to perform a midline thoracotomy for safe surgical placement of the pulmonary artery flow probe. This was inevitable, since the pulmonary artery blood flow and not the blood flow in the aorta should serve as reference for CO measurement, because measurement of CO in the ascending aorta is falsified by blood drainage into the coronary arteries. Further, the choice of anaesthetic technique—total i.v. anaesthesia as in our study—and factors such as choice of premedication and pre-existing lung pathology could have influenced the extent of hypoxic pulmonary vasoconstriction and consequently the impact on thermodilution techniques. However, although circumstances of the experimental setting are not one to one comparable with the clinical setting, we believe that our results basically reflect the impact of OLV on pulmonary and transcardiopulmonary thermodilution.

In conclusion, pulmonary artery thermodilution monitoring of CO was less affected by OLV than transcardiopulmonary thermodilution. Nonetheless, both methods appear to be viable tools for measurement of CO during OLV, especially with regard to the detection of changes in CO.

Declaration of interest

A.E.G. and D.A.R. are members of the Medical Advisory Board of Pulsion Medical Systems.
Funding
This study was solely funded by departmental sources.

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