Determination of cardiac output by ultrasound dilution technique in infants and children: a validation study against direct Fick principle

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Editor’s key points

- The minimally invasive ultrasound dilution technique (UDT) was compared with the ‘gold standard’ reference technique, the direct Fick principle, in infants and children as an alternative measure of cardiac output (CO).
- This study found a close correlation, with a coefficient $\geq 0.8$ for CO values between direct Fick principle and UDT.
- Further studies are necessary to evaluate the accuracy and limitations of UDT in specific patients.

Background. In critically ill children, monitoring of cardiac output (CO) is essential to guide haemodynamic management and facilitate cardiovascular therapy. The ultrasound dilution technique (UDT), a novel minimally invasive indicator method, was recently introduced to determine CO. We validated UDT against the ‘gold standard’ reference technique, the direct Fick principle, in infants and children.

Methods. Twenty-six children (median age: 6 yr 2 months; median weight: 19.2 kg) underwent diagnostic heart catheterization. In each child, CO was determined by the Fick principle using direct measurement of oxygen consumption and invasive oximetry. Consecutively, haemodynamically stable conditions provided; three independent measurements of CO were conducted with UDT. CO values were compared using bias and limits of agreement calculated using the Bland–Altman approach and linear regression analysis for the complete study group and for a subgroup with body weight $<20$ kg ($n=14$).

Results. The mean (standard deviation) CO values were 3.76 (1.73) litre min$^{-1}$ (range 1.38–6.97) for the direct Fick principle and 3.49 (1.72) litre min$^{-1}$ (range 1.31–7.00) for UDT. An excellent correlation ($r=0.96$) was found between both methods ($P<0.0001$). The Bland–Altman analysis demonstrated good clinical agreement with a mean bias of 0.26 litre min$^{-1}$, limits of agreement of $-0.66$ and 1.19 litre min$^{-1}$, and percentage error of 25.9%. Comparable results were obtained for patients $<20$ kg (mean bias=0.19 litre min$^{-1}$, percentage error=25.5%).

Conclusions. CO measurements by UDT agree favourably with Fick-derived CO data and both techniques were found to be equivalent and interchangeable. UDT represents a valid and applicable method for repetitive CO determinations in infants and children.

Keywords: cardiac output; children; direct Fick principle; ultrasound dilution technique

Cardiac output (CO) determines the global oxygen supply to every organ. Its assessment is reasonable in critically ill patients to guide haemodynamic management and facilitate cardiovascular therapy. Today, various techniques such as the Fick principle,\textsuperscript{1,2} pulmonary artery thermodilution,\textsuperscript{3} transpulmonary thermodilution,\textsuperscript{4} minimally invasive techniques such as electric velocimetry,\textsuperscript{4} and several other methods based on pulse contour analysis have been primarily invented for CO measurements in critically ill adults.\textsuperscript{5} However, there is still an insufficient number of studies for children that assess the validity and applicability of most techniques.\textsuperscript{6} Furthermore, many haemodynamic monitoring devices entail specific risks and limitations in children:\textsuperscript{7} higher incidences of complications, technical and size constraints, inappropriate algorithm, toxicity of indicators (lithium), inaccuracy in the presence of shunts, and thrombotic occlusion after insertion of the arterial

thermodilution catheter.\textsuperscript{5,6} In critically ill children, a safe, accurate, and reliable technique for repetitive CO measurements is required.

Recently, minimally invasive ultrasound dilution technology (UDT) has been introduced to monitor CO in children of any age and weight with pre-existing peripheral arterial (radial, ulnar, femoral, or pedal) and central venous catheters.\textsuperscript{5,7–9} This technique applies alterations of blood ultrasound velocity (normal 1560–1585 m s$^{-1}$) induced by isotonic saline (1533 m s$^{-1}$) as an indicator.\textsuperscript{7} A bolus of body temperature isotonic saline is injected into a central venous line. After transcardiopulmonary passage, a dilution curve is recorded on the arterial side using an extracorporal arteriovenous (AV) loop.\textsuperscript{8} CO is calculated from the obtained dilution curve according to the Stewart–Hamilton principle.\textsuperscript{9} CO determination by UDT was compared with ultrasound flow probes,\textsuperscript{10} pulmonary artery catheter

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thermodilution,11 and transpulmonary thermodilution12 in paediatric animal models. In adults, several studies have assessed the accuracy of CO measurements by UDT vs transpulmonary thermodilution8 and pulmonary artery catheter.13 Recently, a validation study between thermodilution by the pulmonary artery catheter and UDT has been performed in children.7 Although all comparative studies showed an excellent correlation and only a small bias for CO measurements with UDT compared with reference techniques,7–12 so far UDT has never been validated against the ‘gold standard’ reference technique—the direct Fick principle—for CO measurements.

The purpose of this study was to evaluate the agreement of CO measurements by UDT with the direct Fick principle in infants and children undergoing heart catheterization.

Methods
We conducted a prospective, single-centre study in children to assess CO measurements derived by UDT vs the direct Fick principle as reference technique in a paediatric cardiac catheterization laboratory. Approval of the research protocol was obtained from the local research ethical committee (Ref: 532). Written informed consent was obtained for each child from their legal guardians, and, depending on age, the patient as well.

Patients
Children with heart defects that might influence indicator dilution methods were excluded from the study.14–19 The latter comprised children with intra- or extracardiac shunting, single ventricular circulation, significant atrioventricular or semilunar valve regurgitation, significant valvular stenosis with decompen-sated ventricle, and aortic isthmus stenosis. Finally, 26 infants and children (16 males and eight females), some with residual lesions (e.g. obstruction to ventricular outflow), underwent heart catheterization for haemodynamic evaluation for clinical decision-making or interventional purposes (Table 1). The median [interquartile range (IQR)] age was 6 yr 2 months (8 months to 17 yr 4 months) and the median weight was 19.2 (6.0–74) kg. Fourteen children (median age 3 yr 1 month (8–78 months) had a body weight <20 kg with a median weight of 12.9 (6.0–19.8) kg. Of the 26 children included, eight were sedated and spontaneously breathing room air; 18 obtained general anaesthesia with mechanical ventilation without oxygen supply (Table 1).

Direct Fick principle
Oxygen consumption (VO2) was measured by indirect calorimetry applying the Deltatrac II Metabolic Monitor (Datex, Helsinki, Finland)20 according to the manufacturer’s instructions.21 In sedated spontaneously breathing patients, an age-appropriate canopy was placed over the patient’s head and all openings were thoroughly sealed with a thin plastic wrap to avoid loss of expired gas. In anaesthetized patients, uncuffed tubes were used up to a size of 5.0; larger tubes were cuffed. Uncuffed tubes were required to seal up to 25 cm H2O inspiratory airway pressure. Air leakage was assessed by placing a stethoscope over the patient’s mouth. In the presence of any audible leak, the tube was replaced by a cuffed tube. In mechanically ventilated patients, the metabolic monitor was connected to the circuit of a Servo 300A ventilator (Maquet, Rastatt, Germany).

A minimum stabilization period of 5 min was allowed before the sample gases were used for analysis. VO2 was measured each minute and then averaged; steady-state conditions for at least 10 consecutive minutes were provided. Steady state was defined as <10% coefficient of variation (CV) for repeated measurements of VO2, <5% CV for successive determination of the respiratory quotient, and <0.3% fluctuation in inspired oxygen.72 Patients were not included in the study if they had hypoventilation with CO2 retention or did not fulfill steady-state criteria.

For oximetry, age- and size-matched arterial and venous introducer sheaths were placed into the femoral artery and vein, respectively, under local anaesthesia. Oxygen saturations were obtained from the caval veins, right atrium, pulmonary trunk, pulmonary artery, and from the aorta or femoral artery, respectively, and analysed with a co-oximeter (Hemoximeter OSM 3, Radiometer, Copenhagen, Denmark). Haemoglobin concentration was determined in the first blood sample from the femoral artery. CO values were calculated by the Fick principle using blood samples from the pulmonary trunk and femoral artery.23 Computation of CO was done by one of the contributors after the complete diagnostic or interventional catheterization was finished. This person was blinded for the results of CO measurements by UDT.

Ultrasound dilution technique
The detailed set-up (Fig. 1) and principles of UDT have been described elsewhere.9 All measurements were performed in triplicate with the COstatus® monitor (Transonic System Inc., Ithaca, NY, USA). During the measurements, the obtained indicator dilution curves were visually validated for their quality and morphology by one of the authors. One single measurement was excluded due to a missing recirculation hump. In four patients the monitor excluded one single measurement (abnormal injection curve (n=2), error message ‘Use saline at body temperature’ and ‘Repeat’ due to an abnormal indicator dilution curve). In those five patients, one single further measurement was additionally conducted. Finally, the results of three measurements were averaged. For further information about the principles of UDT and the excluded measurements, refer to the Supplementary material.

Study protocol
Cardiorespiratory status was continuously monitored to ensure all parameters were in a physiological, age-specific range during the measurements. Providing steady-state conditions, haemodynamic measurements for the direct Fick principle were performed ~20–40 min after induction of anaesthesia and before first angiography. Directly upon completion of oximetry, consecutive measurements with UDT followed. In order to ensure sequential comparison of the two methods, haemodynamically stable conditions (no movement of the patient, no change in the patient’s level of consciousness,
Table 1  Patient characteristics. Baseline characteristics of patients, including age in yr and months, height, weight, gender, diagnosis, residual heart defect while performing CO measurements, and mechanical ventilation (MV), are shown. AS, aortic stenosis; BWG, Bland–White–Garland syndrome; DORV, double-outlet right ventricle; LPA, left pulmonary artery; LVOTO, left ventricular outflow tract obstruction; PHT, pulmonary hypertension; PS, pulmonary stenosis; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; VSD, ventricular septal defect.

<table>
<thead>
<tr>
<th>Number</th>
<th>Age (yr; months)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Gender (m/f)</th>
<th>Diagnosis</th>
<th>Residual heart defect</th>
<th>MV (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8 yr 11 months</td>
<td>173</td>
<td>33</td>
<td>f</td>
<td>Primary PHT</td>
<td>PHT</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>12 yr 1 months</td>
<td>150</td>
<td>45</td>
<td>m</td>
<td>DORV (Fallot type) after corrective surgery using pulmonary conduit</td>
<td>Moderate pulmonary conduit stenosis</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>12 yr 2 months</td>
<td>152</td>
<td>38</td>
<td>m</td>
<td>D-TGA after arterial switch operation</td>
<td>Pulmonary artery bifurcation stenosis</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>0 yr 9 months</td>
<td>68</td>
<td>6</td>
<td>m</td>
<td>Primary PHT</td>
<td>PHT</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>3 yr 4 months</td>
<td>100</td>
<td>19.8</td>
<td>f</td>
<td>TOF after corrective surgery</td>
<td>Moderate LPA stenosis</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>6 yr 4 months</td>
<td>118</td>
<td>16</td>
<td>m</td>
<td>PS after corrective surgery using pulmonary conduit</td>
<td>Moderate pulmonary conduit stenosis and mild regurgitation</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>11 yr 6 months</td>
<td>158</td>
<td>46</td>
<td>f</td>
<td>BWG after corrective surgery</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>2 yr 3 months</td>
<td>88</td>
<td>10.5</td>
<td>m</td>
<td>D-TGA with VSD and PS, Rastelli operation using pulmonary conduit</td>
<td>Severe pulmonary conduit stenosis, peripheral pulmonary artery stenosis</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>17 yr 6 months</td>
<td>177</td>
<td>74</td>
<td>f</td>
<td>Cardiomyopathy</td>
<td>None</td>
<td>No</td>
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<tr>
<td>10</td>
<td>0 yr 8 months</td>
<td>72</td>
<td>8.6</td>
<td>m</td>
<td>Valvular AS</td>
<td>Severe valvular AS</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>1 yr 3 months</td>
<td>77</td>
<td>11</td>
<td>m</td>
<td>D-TGA after arterial switch operation</td>
<td>Supravalvular PS</td>
<td>Yes</td>
</tr>
<tr>
<td>12</td>
<td>3 yr 8 months</td>
<td>100</td>
<td>14.6</td>
<td>f</td>
<td>Patent ductus arteriosus after catheter closure</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>6 yr 0 months</td>
<td>118</td>
<td>21</td>
<td>m</td>
<td>Severe valvular AS, Ross procedure</td>
<td>Mild regurgitation of neoaortic valve, mild pulmonary conduit stenosis/regurgitation</td>
<td>Yes</td>
</tr>
<tr>
<td>14</td>
<td>15 yr 5 months</td>
<td>181</td>
<td>64.9</td>
<td>m</td>
<td>Atrioventricular canal defect</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>15</td>
<td>3 yr 9 months</td>
<td>96</td>
<td>12.7</td>
<td>m</td>
<td>Hypertrophic obstructive cardiomyopathy</td>
<td>Moderate LVOTO</td>
<td>Yes</td>
</tr>
<tr>
<td>16</td>
<td>3 yr 11 months</td>
<td>108</td>
<td>16</td>
<td>m</td>
<td>TOF after corrective surgery</td>
<td>Hypoplastic LPA</td>
<td>Yes</td>
</tr>
<tr>
<td>17</td>
<td>14 yr 1 months</td>
<td>153</td>
<td>55</td>
<td>m</td>
<td>D-TGA with VSD and PS, Rastelli operation using pulmonary conduit</td>
<td>Moderate pulmonary conduit stenosis</td>
<td>Yes</td>
</tr>
<tr>
<td>18</td>
<td>16 yr 6 months</td>
<td>183</td>
<td>59</td>
<td>m</td>
<td>TOF after corrective surgery</td>
<td>Mild pulmonary regurgitation</td>
<td>No</td>
</tr>
<tr>
<td>19</td>
<td>1 yr 7 months</td>
<td>82</td>
<td>10.5</td>
<td>m</td>
<td>DORV (Taussig–Bing syndrome) after Kawashima intraventricular repair</td>
<td>Mild LVOTO</td>
<td>No</td>
</tr>
<tr>
<td>20</td>
<td>2 yr 9 months</td>
<td>92</td>
<td>12</td>
<td>m</td>
<td>D-TGA with VSD and LVOTO, Rastelli operation using pulmonary conduit</td>
<td>Peripheral pulmonary artery stenosis</td>
<td>Yes</td>
</tr>
<tr>
<td>21</td>
<td>6 yr 6 months</td>
<td>119</td>
<td>18.5</td>
<td>m</td>
<td>Suspected coronary artery fistula</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>22</td>
<td>10 yr 2 months</td>
<td>134</td>
<td>33.5</td>
<td>f</td>
<td>Suspected pulmonary artery fistula</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>23</td>
<td>15 yr 9 months</td>
<td>171</td>
<td>72</td>
<td>m</td>
<td>TOF after corrective surgery using pulmonary conduit</td>
<td>Moderate pulmonary conduit stenosis</td>
<td>No</td>
</tr>
<tr>
<td>24</td>
<td>13 yr 8 months</td>
<td>159</td>
<td>59</td>
<td>f</td>
<td>Subvalvar AS</td>
<td>Moderate subvalvular AS</td>
<td>No</td>
</tr>
<tr>
<td>25</td>
<td>2 yr 11 months</td>
<td>84</td>
<td>13</td>
<td>f</td>
<td>DORV (Fallot type) after corrective surgery using pulmonary conduit</td>
<td>Mild pulmonary conduit stenosis</td>
<td>Yes</td>
</tr>
<tr>
<td>26</td>
<td>3 yr 10 months</td>
<td>93</td>
<td>18.2</td>
<td>m</td>
<td>Valvular PS</td>
<td>Moderate valvular PS</td>
<td>Yes</td>
</tr>
</tbody>
</table>
heart rate, and arterial pressure) were necessary during and between the measurements. Otherwise, patients were not included in the study.

In patient 12, transcatheter patent ductus arteriosus closure with concomitant angiography was performed before CO measurement. After definitive closure of the patent ductus arteriosus and exclusion of any residual shunt, an oximetry with consecutive UDT measurement followed.

Statistical analysis

Measurements were analysed with GraphPad Prism 5 software (GraphPad Software, Inc., San Diego, CA, USA). Values for CO by UDT were calculated as the mean of three single measurements. Data for CO of both methods were compared by linear regression analysis. Bias and limits of agreement mean bias ± 2 standard deviations (SD) were calculated as per the Bland–Altman approach. Percentage error for comparison of the entire CO was calculated as 2 SD of bias divided by the mean CO of both methods. Additionally, a percentage error for each set of the data was calculated for CO parameters according to Shoemaker and colleagues as follows:

\[
\text{Mean difference (\%)} = \frac{100}{n} \times \sum_{i=1}^{n} \frac{|\text{CO}_{\text{Fick}} - \text{CO}_{\text{UDT}}|}{0.5 \times (\text{CO}_{\text{Fick}} + \text{CO}_{\text{UDT}})}
\]

where \(\text{CO}_{\text{Fick}}\) and \(\text{CO}_{\text{UDT}}\) are CO measurements by direct Fick and UDT, respectively, and \(n\) is the number of patients. Critchley and Critchley recommended this approach for the comparison of values collected over a large physiological range. A percentage error < 30% for all comparisons was defined as the criterion for clinical acceptability. To assess the accuracy of UDT regarding CO measurements in smaller children like infants, toddlers, and preschoolers, all preceding statistical analyses were also performed for the subgroup of patients with a body weight < 20 kg. To further demonstrate the repeatability of UDT, the CV was calculated as SD divided by the mean for a single measurement and expressed in percentage as mean (SD) for all measurements.

Results

Twenty-six children (18 males and eight females) underwent heart catheterization for haemodynamic evaluation, including CO measurements by the direct Fick principle and UDT (Table 1). CO by direct Fick (\(\text{CO}_{\text{Fick}}\)) ranged from 1.38 to 6.97 [mean (SD) 3.76 (1.73)] litre min\(^{-1}\), whereas CO by UDT (\(\text{CO}_{\text{UDT}}\)) ranged from 1.31 to 7.00 [mean 3.49 (1.72)] litre min\(^{-1}\). A significant correlation \((r=0.96; P<0.0001)\) was observed between both methods (\(\text{CO}_{\text{UDT}}=0.96 \times \text{CO}_{\text{Fick}} - 0.17\)) (Fig. 2a). The Bland–Altman analysis between \(\text{CO}_{\text{Fick}}\) and \(\text{CO}_{\text{UDT}}\) (Fig. 2b) showed a mean CO of 3.62 (1.72) litre min\(^{-1}\) for both methods, 95% limits of agreement of −0.66 and 1.19 litre min\(^{-1}\), and a mean difference of 0.26 litre min\(^{-1}\) with an SD of the difference of 0.47 litre min\(^{-1}\) (Fig. 2b). The percentage error all the data (2 SD of bias/mean CO of both methods) was 25.9% and for each set of data was 11.5 (7.5%). The mean CV for UDT was 5.1 (2.3)%.

In patients \(n=14\) with a body weight < 20 kg, the mean CO < 20 kg obtained by Fick (\(\text{CO}_{\text{Fick, <20kg}}\)) was 2.46 (0.74) (range 1.38−3.70) litre min\(^{-1}\) and the mean CO < 20 kg derived from UDT (\(\text{CO}_{\text{UDT, <20kg}}\)) was 2.27 (0.71) (range 1.31−3.96) litre min\(^{-1}\) (figure not shown). Linear regression analysis demonstrated an excellent correlation between both techniques with a coefficient of \(r=0.91 (P<0.0001)\) in this subgroup. The Bland–Altman approach revealed a mean CO < 20 kg of both methods of 2.36 (0.72) litre min\(^{-1}\), a good clinical agreement with 95% limits of agreement of −0.39 and 0.79 litre min\(^{-1}\) and a mean difference of 0.19 litre min\(^{-1}\) with an SD of the difference of 0.30 litre min\(^{-1}\). The percentage error of entire data (2 SD of bias/mean CO < 20 kg of both methods) was 25.5% and for each set of data was 11.7 (7.9)%.
Discussion

CO is the core variable of cardiovascular performance and reflects global tissue perfusion and concomitant oxygen delivery. In critically ill patients, CO monitoring is an essential parameter for haemodynamic management and facilitates cardiovascular therapy. Therefore an accurate measurement of CO is an inevitable prerequisite.

In the present study, we compared CO obtained by the direct Fick principle with CO values of the recently introduced UDT in infants and children in a cardiac catheterization laboratory. The direct Fick principle was chosen as the reference method since it is the established standard for CO measurements. However, several practical limitations exist for application of the direct Fick principle in CO measurement and the rate of potential errors might therefore be high during the procedure. In our study, the accuracy of the Fick principle and concomitant oxygen uptake measurement was assured by several considerations: oxygen uptake was directly measured for each individual patient with a metabolic monitor validated for children. Air leaks were carefully avoided and no oxygen was supplied. Furthermore, we performed a reliable sampling of arterial and venous blood and applied strict criteria for steady state for both oxygen consumption and haemodynamic conditions encompassing the period of CO measurements with the Fick principle and consecutive UDT. We utilized the mixed venous oxygen saturation for CO calculation by the Fick principle instead of the central venous oxygen saturation as a surrogate marker. Any disturbance of the mixed venous oxygen saturation by the existence of any shunt was thoroughly excluded.

Applying these conditions, we found a close correlation with a coefficient 0.8 for CO values between the direct Fick principle and UDT. According to Critchley and Critchley, we used the Bland–Altman approach for further comparison of CO between both methods. These authors predefined a percentage error of up to ± 30% for interchangeability of two different methods for CO measurement. Over a wide range of CO values (1.38–6.97 litre min−1), we found the limits of agreement to be well below the requested 30%, with a percentage error of 25.9% and 11.5 (7.5)%, respectively, for each set of data, and only a small bias of 0.26 litre min−1. Similar results were found for the subgroup of smaller children with a body weight <20 kg. These results indicate the equivalence and interchangeability of CO measured by UDT with corresponding CO determined by the ‘gold standard’ Fick principle for children of any age and weight. Similar to Saxena and colleagues, we found a small CV around 5%, indicating a good repeatability of UDT.

Recently, Floh and colleagues compared UDT against a Fick equation in children after cardiac surgery. The authors found a small mean bias, but in contrast to our study, a large percentage error of 97% between both methods. CO was calculated via the Fick equation by dividing the measured oxygen consumption by the difference between the arterial and central venous oxygen content. However, especially after cardiac surgery, several other studies have shown a significant difference between both central venous and mixed venous oxygen saturations. Additionally, there is a permanent fluctuation of systemic and regional oxygen homeostasis and an increased oxygen extraction in the perfusion area of the inferior caval vein, leading to an overestimation of the mixed venous oxygen saturation by using the superior caval vein saturation. After surgery, often there are some residual interatrial left-to-right shunts that may interfere with central venous oxygen saturation. Those shunts were not completely excluded. Furthermore, the authors did not define strict steady-state criteria for oxygen consumption measurements. One could argue that their study might exhibit several limitations and therefore may not fulfil the criteria for a validation study using the direct Fick principle.

The correlation and agreement between CO measured by direct Fick and UDT in our investigation were consistent with a previously published validation study in children comparing CO by UDT with another reference technique (pulmonary...
artery catheter). In contrast to our trial, the latter study included children with structurally normal hearts who were almost 2 yr older in the median and with a body weight about 10 kg higher. In summary, the previous study and our results for children and several studies in adults all demonstrate that the novel UDT determines CO in all patients with clinically acceptable accuracy and precision.

Especially for children, the novel UDT offers a promising option, as it is applicable to any age and weight. It is operator-independent and can easily be performed by nurses. UDT applies normothermic isotonic saline as a non-toxic indicator and uses the already existing central venous and peripheral arterial catheters at any location (radial, ulnar, femoral, or pedal). Injection of the indicator and conduction of the measurement itself did not provoke any clinically relevant alterations in cerebral and systemic haemodynamics or oxygenation as previously shown in an animal model. Additionally, UDT provides the opportunity to identify shunts, quantify their magnitude, and measure CO in the presence of left-to-right shunts. Analysis of the dilution curve also offers the opportunity to assess volumetric parameters such as central blood volume (CBV) (total blood volume of the thorax), total end-diastolic volume (TEDV) (sum of all end-diastolic volumes of the atria and ventricles), and active circulating volume (ACV) (blood volume in which isotonic saline mixes within 1 min). There is growing evidence from clinical studies in children that CBV and TEDV might be more indicative for cardiac preload and intravascular volume status than cardiac filling strains such as central venous or pulmonary capillary wedge pressure and that ACV as a potential indicator of cardiac afterload strongly correlates with systemic vascular resistance. However, a few possible limitations of UDT exist: during the period of CO measurement (up to a maximum of 5–6 min), invasive arterial pressure is absent, although this short period can easily be compensated for by continuous measurement of non-invasive arterial pressure. Repetitive CO measurements with UDT bear the risk of fluid overload with isotonic saline, especially in newborns and infants. To minimize this problem, de Boode and colleagues suggested conducting only two instead of three measurements as long as the variation between the two consecutive measurements is ≤10%. Our findings of a small CV for UDT support this approach.

So far, UDT neither provides continuous CO monitoring by pulse contour analyses nor determination of extravascular lung water, although a prototype comprising both options has recently become available.

Owing to ethical concerns, it was not justifiable to perform cardiac catheterization on healthy children with structurally normal cardiac anatomy. Most of the children recruited in our study suffered from congenital heart disease with minor residual lesions. They underwent heart catheterization for haemodynamic evaluation for diagnostic or interventional reasons. Children with a relevant heart defect (intra- or extracardiac shunts, univentricular circulation, haemodynamic significant atrioventricular or semilunar valve regurgitation, significant valvular stenosis, aortic isthmus stenosis, etc.) that might have an influence on the indicator dilution technique were thoroughly excluded a priori from the study. Some of the children exhibited a valvular or outflow tract obstruction/stenosis, which has been shown to have no impact on dilution methods as long as the ventricles, as in all of our cases, were compensated. Although all children had been carefully examined beforehand, one cannot exclude any minor interference of the residual heart defects with the results of the study.

Independent of the actual study, we also measured CO by UDT in several patients with severe atrioventricular or semilunar valvar regurgitation and found a good correlation and agreement with the Fick principle (data not shown). However, as there exist some controversial studies regarding the applicability of indicator dilution techniques in general for CO measurements in these patients, we excluded these patients as we set up the study design. Further examinations will be necessary to evaluate the accuracy and limitations of indicator techniques in patients with severe valvular regurgitation.

Conclusion

We found a close, clinically acceptable agreement and correlation between CO measurements by UDT and the ‘gold standard’ direct Fick principle in children. This investigation demonstrates that both methods are equivalent and interchangeable in determining CO. Further studies are necessary to evaluate the accuracy and limitations of UDT in those patients—not now excluded—with heart defects having a potential influence on indicator dilution curves like intra- or extracardiac shunts or severe regurgitation.

Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.

Authors’ contribution

M.B., H.K., and H.B. designed the study. M.B., M. Baustert, V.P., C.M.H., and H.B. were responsible for patient assessment, enrolment, and requested informed consent from the parents or legal guardians. S.S., C.M.H., and H.B. performed the heart catheterization. M.B., M. Baustert, and V.P. conducted CO measurements with UDT. M.B. and M. Baustert did the statistical analyses. All authors contributed to the interpretation of the results, the writing and critical review of the manuscript.

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**Declaration of interest**

None declared.

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