Pressure recording analytical method for measuring cardiac output in critically ill children: a validation study

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Editor’s key points

- The pressure recording analytical method (PRAM) uses arterial pressure waveform analysis to continuously measure cardiac output.
- Simultaneous PRAM and transpulmonary ultrasound dilution-based measurements were made in a cohort of children.
- Comparisons of single paired measurements are presented and analysed with Bland-Altman plots.
- Polar plots are used to assess agreement of the methods in tracking changes in cardiac output.

Background. Pressure recording analytical method (PRAM) is a novel, arterial pulse contour-based method for measuring cardiac output (CO). Validation studies of PRAM in children are few, and have not assessed both absolute accuracy and ability to track changes in CO across a broad case mix. We aimed to compare CO as measured by PRAM with that using a transpulmonary dilution method in a cohort of critically ill children.

Methods. Forty-eight, mechanically ventilated children with a median (inter-quartile) weight of 10.7 (5.5–15) kg with arterial and central venous catheters in situ were studied. CO was measured simultaneously using PRAM and the comparator method, transpulmonary ultrasound dilution (UD). Measurements were repeated before and after therapeutic interventions that were intended to augment CO (e.g. fluid bolus).

Results. In total, 210 paired measurements were compared. The mean (SD) CO was 1.9 (1.2) litre min⁻¹ with UD when compared with 1.92 (0.5) litre min⁻¹ using PRAM. The mean bias was 0.02 litre min⁻¹ with wide limits of agreement: ± 2.21 litre min⁻¹, giving a percentage error of 116%. The concordance between PRAM and UD for measuring changes in CO was also poor, with only 37% of measurements falling within the pre-defined polar plot limits of ± 30°.

Conclusions. There is an unacceptably poor agreement between UD and PRAM. We do not recommend the use of PRAM for measuring CO in critically ill children with the current algorithm.

Keywords: cardiac output; monitoring; pressure recording analytical method; ultrasound dilution

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Cardiovascular organ failure is common in critically ill children.¹ ² Compared with adults, children manifest both a higher incidence of cardiovascular dysfunction, and greater variability in haemodynamic status during resuscitation; furthermore, these changes can occur rapidly.³ Early detection of cardiovascular insufficiency in high-risk patients may reduce morbidity and mortality, by guiding the timely application of appropriate therapy.⁴ ⁵ However, an accurate assessment of cardiovascular status requires advanced haemodynamic monitoring, including measurement of cardiac output (CO).⁶ ⁷ This is reinforced by the finding that CO cannot be estimated clinically, and deleterious changes in CO can precede changes in other haemodynamic variables.⁸ ⁹

Although a variety of techniques for CO measurement are available in paediatric patients, there is growing interest in novel arterial pulse wave methods based upon arterial pulse wave analysis. These have the obvious advantage of utilizing a pre-existing arterial line; in addition, not all require external calibration.¹⁰ However, concerns have been raised about the accuracy of these methods, particularly during periods of haemodynamic instability.¹¹ ¹²

Pressure recording analytical method (PRAM) is a relatively novel arterial pulse wave method of CO measurement.¹³ In contrast to other pulse contour techniques, PRAM is based primarily upon detailed morphological analysis of the pressure waveform, including identification of pulsatile and non-pulsatile systolic pressure–time areas together with an estimation of vascular impedance. There are several adult and animal validation studies of PRAM; however, there is paucity of literature regarding its use in paediatrics.¹⁴ ¹⁵

With this in mind, we aimed to validate PRAM in a heterogeneous group of critically ill paediatric patients, by comparison with a transpulmonary ultrasound dilution (UD) method for CO measurement. The latter have recently been described as approaching a gold standard for bedside paediatric measurement.¹⁶ Our aims were two-fold: first, to compare absolute values for the two techniques via the Bland–Altman analysis, and, secondly, to evaluate whether PRAM could
Methods

This prospective, single centre, observational study was conducted within a 20-bed multi-disciplinary paediatric intensive care unit (PICU). The study was approved by the regional ethics committee (South East London REC2, 10/H0802/62) and written informed consent was obtained from all parents or legal guardians.

Forty-eight, mechanically ventilated children (32 males) were enrolled during September 2010 to October 2011, of whom 78% were also receiving inotropic support. The median (inter-quartile range) age and weight were 17.0 (4.5–47.3) months and 10.7 (5.5–15) kg, respectively. The majority of patients were admitted after cardiac surgery (Table 1), and data were collected within the first 24 h after admission. Inclusion criteria included the presence of arterial and central venous lines. Children with significant valvular regurgitation, extreme haemodynamic instability, large anatomical shunts, or arrhythmias were excluded from the study.

Transpulmonary UD technique

Transpulmonary UD (CO-Status™; Transonic Systems, Ithaca, NY, USA) is an indicator dilution method. It utilizes an extracorporeal arterio-venous (AV) loop and two reusable ultrasound sensors: one on each side of the loop. A roller pump provides a constant blood flow rate in the AV loop. Normal saline (0.5–1 ml kg⁻¹, max 20 ml) at body temperature is used as an indicator. The transit times of the ultrasound beam crossing the extracorporeal tube change when saline is injected, in proportion to the amount of dilution of blood by the saline (the typical ultrasound velocities through 0.9% saline and blood are 1533 and 1580 m s⁻¹, respectively), which are used to calculate CO via the Stewart–Hamilton equation.¹⁸ This is an accurate and validated technique for measurement of CO in children and paediatric animal models.¹⁹–²¹ The theory and in vitro validation of this technique is reported in detail by Krivitski and colleagues.²²

Pressure-recorded analytical method

PRAM (Mostcare®; Vytech Health®, Padova, Italy) is a minimally invasive continuous (beat to beat) monitoring system utilizing a form of pulse contour analysis. Measurement involves connecting the pre-existing arterial line to the PRAM monitor via a standard disposable pressure transducer (Edwards Lifesciences, Irvine, CA, USA) and a dual-output electronic module (Agilent Technologies, Germany). One output is fed into the standard bedside monitor, while the other is connected to the PRAM monitor. All the arterial pressure tracings were checked beforehand to exclude artifact. The ECG was monitored to confirm sinus rhythm. A detailed description of the PRAM technology is found elsewhere.²³

Study protocol

Measurements were made as soon as possible after patients were admitted to the PICU (all within 24 h of admission). Baseline patient characteristic and physiological data were collected at the time of CO measurement. The sequence of CO measurements is shown in Figure 1.

Paired UD and PRAM measurements were made as follows: two consecutive UD measurements were made, and the dilution curves inspected. If the shape of the injection or dilution curves were unsatisfactory (Fig. 2), or if the variation between the two measurements was >20%, a third measurement was obtained. The readings were then averaged. This process typically took 3–5 min. PRAM measurements could not be obtained exactly at the same time, as the UD measurements required interruption of the arterial line. Thus, we averaged the continuous CO from PRAM for 3 min before and after the time corresponding to the UD measurements. Thus, a complete set of comparative measurements took ~10 min. Heart rate was monitored continuously and non-invasive arterial pressure measurement performed every minute to ensure haemodynamic stability during this 10 min period.

We performed repeated comparisons (as above) when patients received therapies likely to augment CO, such as fluid bolus administration or initiation of vasoactive medications. By taking repeated measurements on patients, we were also able to assess the ability of PRAM to track changes in CO.

Statistical methods

Values for CO are reported as mean (SD). Repeatability of each technique is reported via the coefficient of variation (standard deviation/mean, expressed as a percentage). Agreement between the two methods for measuring absolute values of CO was quantified using the Bland–Altman analysis.²⁴ The bias was defined as the mean difference between the two methods (PRAM minus UD). Limits of agreement were calculated as the mean bias (1.96 SD of the bias), adjusted for multiple measurements per patient.²⁴ The percentage error was calculated as (1.96 SD of the bias/mean of the reference

Table 1 Patient diagnostic characteristics. VSD, ventricular septal defect; TCPC, total cavopulmonary connection; AVSD, atrioventricular septal defect; TOF, tetralogy of Fallot; TAPVD, total anomalous pulmonary venous drainage

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-cardiovascular surgery</td>
<td>42 (87.5)</td>
</tr>
<tr>
<td>VSD</td>
<td>10</td>
</tr>
<tr>
<td>TCPC</td>
<td>8</td>
</tr>
<tr>
<td>AVSD</td>
<td>3</td>
</tr>
<tr>
<td>TOF</td>
<td>3</td>
</tr>
<tr>
<td>TAPVD</td>
<td>5</td>
</tr>
<tr>
<td>Others</td>
<td>13</td>
</tr>
<tr>
<td>Respiratory</td>
<td>2 (4.2)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>4 (8.3)</td>
</tr>
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</table>


method). We stipulated that the acceptable limits of agreement should be up to ±18%. This was derived using animal data from de Boode and colleagues,21 who demonstrated a combined precision error for UD and surgically placed flow probes of 13.9%. Assuming a precision of ~5% for flow probes yields a likely precision for UD as 13% ($\sqrt{13.9^2 - 5^2}$).25 If we stipulate that PRAM should be at least as accurate as UD, we thus expect an upper limit for the combined limits of agreement of ±18%.

Agreement between the two methods for tracking changes in CO ($\Delta$CO) was quantified using polar plots.17 This methodology is illustrated briefly in Figure 3, and in more detail elsewhere.26 After exclusion of data points representing small changes in CO (i.e. vectors <10% of the mean CO, equating to changes of <0.2 litre min$^{-1}$ in our study), we quantified tracking in two ways. First, acceptable calibration was defined as an angular mean bias of less than ±5°.17 Secondly, we reported the percentage of data points lying within radial limits of ±30° from the polar axis. This area should contain more than 95% of the data points if the test method is able to track changes in CO accurately (based upon a reference method precision of 20%).17

Statistical analyses were performed using Stata v11 (StataCorp., TX, USA), Microsoft Office Excel 2007, and polar plots were created using Sigmaplot 8.02 for Windows (Systat Software, Inc., San Jose, CA, USA).

Results
A total of 210 paired measurements using UD and PRAM were compared in 48 children. Six children had two comparisons, three had three comparisons, 21 children had four, and 18 patients had between five and eight comparisons. No child had more than eight comparisons. Repeated measurements on the same patient were made for the following reasons: fluid bolus (84%), administration of a vasoactive agent (8%), and extubation (8%).

The mean CO with UD was 1.9 (1.2) litre min$^{-1}$ when compared with 1.9 (0.5) litre min$^{-1}$ using PRAM. For cardiac index, the values were 3.8 (1.3) and 4.2 (1.8) litre min$^{-1}$ m$^{-2}$ for UD and PRAM, respectively (mean cardiac index is higher than CO because the majority of patients exhibit a body surface area <1.0 m$^2$). The mean (so) coefficient of variation for UD was 5.7 (6%). To quantify haemodynamic stability across each measurement epoch, we also calculated the coefficient of variation for PRAM (by comparing the mean readings of each 30 s epoch, including both pre- and post-UD

![Fig 1 Study protocol. UD, ultrasound dilution; PRAM, pressure recording analytical method. The numbers 1, 2, and 3 refer to the first, second, and third UD measurements, respectively.](image1)

![Fig 2 Abnormal UD curves. (A) An inadequate saline indicator injection demonstrated by a double humped blue curve instead of a smooth and narrow curve. Also, the indicator curve (pink) is appearing before the injection curve (blue) terminates. (B) An unsatisfactory UD curve (pink). Two abnormalities are present: (i) a large ‘double hump’ seen on the down slope, indicative of significant anatomical shunt; and (ii) an unstable continuation of the indicator curve (green) which moves below the baseline.](image2)
readings: this gave a mean (SD) coefficient of variation of 9.1 (6.2%).

The Bland–Altman analysis (Fig. 4) gave the mean bias of 0.02 litre min\(^{-1}\), with wide limits of agreement of +2.21 litre min\(^{-1}\) and a percentage error of 116%. The Bland–Altman plot suggested the presence of a systematic error, with PRAM over-reading at lower CO and under-reading at high CO (Fig. 4, \(r = 0.69\))

Since CO is a measure of total flow, which is influenced by patient size, we repeated the analysis after normalization to body surface area (i.e. cardiac index) to see if the error was influenced by high or low flow states. Here, the mean bias was 0.95 litre min\(^{-1}\) m\(^{-2}\) with very wide limits of agreement of ±5.78 litre min\(^{-1}\) m\(^{-2}\), and an overall percentage error of 143% (Fig. 5). This suggested a different type of systematic error, heteroscedasticity, which persisted even after log transformation (data not shown).

The polar plots demonstrated a poor ability of PRAM to track changes in CO (Fig. 6). On average, PRAM followed the change in CO (mean angular deviation from polar axis of 5.4\(^\circ\)); however, only 36.6% of measurements fell within the polar limits of ±30\(^\circ\).

**Discussion**

Our results demonstrate poor agreement between PRAM and UD, both in terms of measuring absolute CO (percentage error 116%) and tracking changes in CO (36.6% of measurements falling within polar limits). Our findings are at odds with the other two paediatric studies using PRAM. Calamandrei and colleagues\(^{14}\) compared PRAM with Doppler echocardiography in 48 children in a general PICU setting. They reported a mean bias of 0.12 litre min\(^{-1}\), with limits of agreement of ±0.65 litre min\(^{-1}\), giving a percentage error of 25%. Ricci and colleagues compared PRAM with pulmonary artery thermodilution in 25 cardiovascularly stable patients undergoing diagnostic cardiac catheterization. Here, the mean bias and limits of agreement were 0.2 (0.94) litre min\(^{-1}\), with a calculated percentage error of 45%\(^{15}\).

There are a number of potential reasons for the discrepancy between our results and these studies, including the
use of different reference methods for CO, case mix, and different cardiovascular profiles.

Reference methods

We used UD as the reference method, which, although a novel technique, has been shown to be accurate in small patients. In a piglet model using pulmonary artery flow probes as the reference method (a true gold standard), de Boode and colleagues\(^{21}\) showed that the percentage error for UD was 27% (mean CO 0.96 litre min\(^{-1}\)). Similar accuracy (percentage error 24%) was shown in another swine model, using pulmonary artery thermodilution as the reference.\(^{27}\) In 28 children undergoing cardiac catheterization, Crittendon and colleagues\(^{19}\) compared UD with pulmonary artery thermodilution, again yielding a similar percentage error of 25.4%. We have no reason to suspect that UD is any less accurate in our study; this is further supported by our low coefficient of variation (5.7%).

Case mix and cardiovascular profiles

Our patient population contained potentially important differences to both prior paediatric studies. Ours was comprised primarily of children post-cardiac bypass, a group not represented in either previous study.\(^ {14, 15}\) Our median patient age was approximately half that of Ricci and colleagues (2 vs 4 yr). Despite having a similar age to that of Calamandrei and colleagues, our median CO was \(\sim\) 30% lower (1.9 vs 2.7 litre min\(^{-1}\)), suggesting a low flow state, as is typically seen post-cardiac surgery. We have no information on vasoactive agent usage between the three studies, but these are likely to be very different given the differing case mix.

Our results do agree with recent adult studies. Paarmann and colleagues\(^ {28}\) compared PRAM with pulmonary artery thermodilution in 23 adult patients on the first postoperative day after cardiac surgery. They reported an error of 87% with wide limits of agreement of \(\pm\) 4.53 litre min\(^{-1}\). Blais and colleagues,\(^ {29}\) in a study involving 35 adult patients, compared PRAM with transthoracic echocardiography at baseline and after volume expansion. They showed a bias of \(-0.1\) litre min\(^{-1}\) and limits of agreement of \(1.9\) to \(-2.1\) litre min\(^{-1}\) with the percentage error of 34% at the baseline. Similar to our results, they also demonstrated PRAM to be unable to accurately track changes in CO (concordance rate of 60%).

Our study has several possible limitations. First, PRAM CO was not measured precisely at the same time as UD. Instead, PRAM readings were averaged 3 min before and after the time corresponding to the UD measurement. This was because the arterial line connection to the PRAM was interrupted during measurement of CO using UD. However, we believe that this is unlikely to have compromised our results due to unexpected haemodynamic instability, as the entire measurement period was brief (typically <10 min), PRAM readings were averaged pre- and post-UD, and the average coefficient of variation for PRAM from each measurement period was 9.1 (6.2%), which infers haemodynamic stability. The coefficient of variation for UD was 5.7 (6%), which is in agreement with another study.\(^ {10}\)

Secondly, we did not measure the arterial line dampening coefficient while using PRAM. This represents a potentially important limitation, as both under- and over-dampening have recently been shown to adversely affect the ability of PRAM to estimate CO.\(^ {31}\) However, we are currently undertaking a follow on study evaluating factors that may affect the accuracy of the PRAM algorithm, which includes measurement of the dampening coefficient.

Fig 5 Bland–Altman analysis for cardiac index as measured by transpulmonary UD and PRAM.

Fig 6 Polar plot demonstrating agreement between transpulmonary UD and PRAM for tracking changes in CO. The small, blue-shaded circle indicates the zone of exclusion, whereby changes in CO are too small to assess accurately. Hence data points lying within this circle are disregarded. Elsewhere, good agreement in tracking change in CO is measured by the proportion of data points falling within the polar limits of \(\pm\) 30° (bold, blue dotted lines) from the polar axis.
A final point to consider is that there may be inherent limitations with the use of continuous pulse contour methods unique to the paediatric population. These methods typically estimate stroke volume from the arterial pressure waveform taking into consideration vascular properties such as impedance, compliance, and peripheral vascular resistance. However, paediatric studies have shown that these vascular properties may be age-dependent, and can change rapidly during the course of illness.\textsuperscript{3} \textsuperscript{32} \textsuperscript{33} Furthermore, measuring small values in tiny children may push these devices towards their limits of accuracy.

\section*{Conclusion}

We found an unacceptable lack of agreement between UD and PRAM for measurement of paediatric CO in critically ill patients. PRAM was also not able to track changes in CO accurately when compared with the UD method. Hence, we do not recommend the use of PRAM for measuring CO in critically ill children with the current algorithm.

\section*{Declaration of interest}

None declared.

\section*{Funding}

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PRAM for measuring CO


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