

# Pulse contour cardiac output analysis in a piglet model of severe hemorrhagic shock\*

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**Objective:** Pulse contour cardiac output (PCCO) analysis is a technique for continuous cardiac output (CO) monitoring through an arterial catheter after calibration by transpulmonary thermodilution (TPTD). Studies in adults show good correlation with pulmonary artery thermodilution (PATD) CO. Data are limited in children and patients with hemodynamic instability. The objective was to determine whether TPTD CO and PCCO analysis correlate with PATD CO in a piglet model of severe hemorrhagic shock. Mixed venous oxygen saturation ( $\text{S}\bar{\text{V}}\text{O}_2$ ) was also compared with PATD CO.

**Design:** Prospective animal study.

**Setting:** University animal research laboratory.

**Subjects:** Domesticated piglets, 24–37 kg.

**Interventions:** Hemorrhagic shock was created by graded hemorrhage in anesthetized piglets. Hemorrhage was initiated to achieve mean arterial pressure plateaus of 60, 50, 40, 30, and 20 mm Hg.

**Measurements and Main Results:** CO was measured by PATD and simultaneously with two femoral artery PCCO catheters. At each mean arterial pressure plateau, one PCCO catheter was recalibrated by TPTD; the other catheter was not recalibrated

during hemorrhage. TPTD CO, PCCO measurements from each catheter, and  $\text{S}\bar{\text{V}}\text{O}_2$  were compared with PATD CO at each mean arterial pressure level. TPTD CO and recalibrated PCCO showed excellent correlation ( $r^2 = .96$  and  $.97$ ) and small bias ( $+0.11$  and  $+0.14$  L/min), respectively, compared with PATD. Without recalibration, PCCO measurements were not accurate during rapid hemorrhage ( $r^2 = .22$ ).  $\text{S}\bar{\text{V}}\text{O}_2$  decline did not correlate as well with PATD CO ( $r^2 = .69$ ).

**Conclusions:** TPTD CO and recalibrated PCCO analysis correlate well with PATD CO in this severe hemorrhagic shock model. The mean difference is small ( $<0.15$  L/min) and is not clinically significant. With rapid changes in blood pressure or intravascular volume, PCCO is not accurate unless recalibrated by TPTD CO.  $\text{S}\bar{\text{V}}\text{O}_2$  did not correlate well with CO in this model. (Crit Care Med 2008; 36:1189–1195)

**KEY WORDS:** cardiac output; shock; hemorrhagic; monitoring; physiologic; catheterization; pulmonary artery flotation catheter; thermodilution; intensive care units; pediatric

Goal-directed hemodynamic therapy is believed to reduce morbidity and mortality in critically ill adult surgical, emergency department (ED), and inten-

sive care unit patients (1–4). Studies in children with septic shock have also demonstrated that early and aggressive fluid resuscitation, as well as therapies specifically directed at improving cardiac output (CO) and oxygen delivery, is associated with improved survival (5–7).

The use of CO as an end point for resuscitation remains a matter of debate. The pulmonary artery catheter (PAC) has been the clinical gold standard for CO measurement, but concerns regarding safety, efficacy, and cost have been raised (8–10). Use of the PAC has been limited in the pediatric intensive care and ED settings due to safety concerns and practical difficulties. Thus, critically ill children and ED patients are frequently managed without objective measures of CO.

Pulse contour cardiac output (PCCO) analysis is a newer technique that provides continuous CO measurement through an arterial catheter. Based on a modification of the Wesseling algorithm, PCCO analysis calculates beat-to-beat CO using a complex formula that incorporates the

area under the systolic time curve and aortic impedance (11). Aortic impedance is derived from a single CO determination by the transpulmonary thermodilution (TPTD) method. This involves injecting saline through any central venous catheter and calculating thermodilution CO at the thermistor-tipped PCCO arterial catheter with a modified Stewart-Hamilton equation. After calibration by TPTD CO, PCCO analysis provides continuous CO measurement based on the arterial pressure waveform alone (11). TPTD may itself be used as an independent measure of CO, as it has been shown to correlate closely with other objective CO measures and has a much lower coefficient of variation than CO derived from the PAC (5.3% vs. 10% to 20%) (12). TPTD is in fact regarded by some as the new gold standard for CO determination in children (12).

Multiple studies in adult surgical intensive care units have shown excellent agreement between pulmonary artery thermodilution (PATD) CO and PCCO

\*See also p. 1377.

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Supported, in part, by a grant from the North Carolina Jaycees Burn Center. PICCO catheters and monitoring devices (PICCO-plus) were supplied by Pulsion Medical Systems, AG, Munich, Germany.

Dr. BA Cairns has received honoraria and grant support from Pulsion but is not a paid consultant, speaker, or advisor for the company. Pulsion did not review this article prior to submission. The remaining authors have not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0B013E31816592A3

(11, 13, 14), but few data exist for PCCO use in children. The effects of small patient size, extremely high heart rates, and abrupt changes in blood pressure on the accuracy and precision of PCCO analysis remain unclear. Of particular interest is the dependence of PCCO analysis on the TPTD determination of aortic impedance, which may be affected by the greater compliance of the child's aorta. It is unclear whether frequent recalibration by TPTD CO is necessary during dramatic hemodynamic variations in these patients.

In this study, we evaluated the use of PCCO analysis in a piglet model of severe hemorrhagic shock simulating rapid decline in blood pressure, marked intravascular volume loss, and extreme tachycardia in pediatric patients. Our primary objective was to determine the accuracy of TPTD CO and PCCO compared with PATD CO and to assess the need for recalibrating the PCCO system in the setting of rapid hemodynamic changes. Mixed venous oxygen saturation ( $S\bar{V}O_2$ ), a commonly used surrogate of CO, was also compared with PATD CO in this hemorrhagic shock model.

## METHODS

This study was approved by the Institutional Animal Care and Use Committee at the University of North Carolina. All procedures were conducted in accordance with guidelines established by the National Institutes of Health.

**Preparation.** Ten domesticated piglets from a single provider source aged 2–4 months and weighing 24–37 kg were fasted for 12 hrs before the experiment but had free access to water. Animals were anesthetized with intramuscular ketamine 500 mg followed by inhalational 5% isoflurane via a snout mask with 100% oxygen via an anesthesia apparatus (SAV 2500 and CDS 1000, Surgivet, Waukesha, WI). After endotracheal intubation, inhalational isoflurane was titrated between 2% and 4% during instrumentation to maintain adequate anesthesia. Palpebral reflexes, mandibular muscle tone, movement, motor response to graded painful stimulus, and heart rate were used to assess the depth of anesthesia. Oxygen was administered to maintain  $Pao_2 > 100$  mm Hg (13.3 kPa), and minute ventilation was adjusted to maintain  $Paco_2$  at approximately 40–45 torr (5.3–6.0 kPa). An orogastric tube was used to decompress the stomach. Electrocardiogram and end-tidal  $CO_2$  were continuously monitored (Propaq 106, Protocol Systems, Beaverton, OR). After instrumentation, isoflurane was decreased to 1% 5 mins before hemorrhage and maintained throughout the remainder of the experiment.

**Instrumentation.** An 8-Fr oximetric pulmonary artery thermodilution catheter (Abbott Critical Care Systems, Chicago, IL) was positioned in a pulmonary artery via the right external jugular vein. This oximetric PAC was connected to a thermodilution CO device (Baxter Explorer, Edwards Lifesciences LLC, Irvine, CA). This device was calibrated to allow for continuous  $S\bar{V}O_2$  monitoring and set up for thermodilution CO measurements using 5-mL injections of room-temperature normal saline. A series of three PATD CO measurements were made at baseline. A micromanometer-tipped catheter (Millar Instruments, Houston, TX) was positioned in the aortic arch via the left brachial artery for continuous monitoring of mean arterial pressure (MAP). Both femoral arteries were cannulated with 4-Fr thermodilution PCCO catheters (Pulsioath, Pulsion Medical Systems AG, Munich, Germany). These PCCO catheters were each connected to separate monitoring devices (PiCCO-Plus Monitor v4.1.2, Pulsion Medical Systems AG, München, Germany) for comparison of continuous CO readings. The monitoring device contains all instrumentation required for TPTD CO and PCCO. A series of three TPTD CO measurements, each using 10 mL of iced normal saline ( $< 8^\circ C$ ) injected via the proximal port of the PAC, was performed to simultaneously calibrate the two PCCO catheters at baseline. One catheter was then randomly chosen for TPTD recalibration during the experimental protocol. All hemodynamic data were recorded into a computer-based data acquisition system (Polyview Data Acquisition and Analysis System, Astromed, West Warwick, RI). An 8-Fr sheath introducer (Arrow International, Reading, PA) was inserted in the femoral vein and attached to a roller pump for rapid blood withdrawal.

**Experimental Protocol.** Figure 1 shows the experimental protocol sequence. Baseline hemodynamic and oximetric measurements

were taken before initiation of hemorrhage. The animals then underwent femoral venous catheter blood withdrawal at a rate of 2 mL/kg/min over 5-min intervals to sequentially drop the MAP by 10-mm Hg increments. The rate of blood withdrawal was adjusted, if needed, to yield approximately 5 mins of hemorrhage to reach each sequential MAP level. Blood withdrawal was stopped temporarily to yield plateaus in MAP at 60, 50, 40, 30, and 20 mm Hg. The MAP was held at the target MAP  $\pm 2$  mm Hg for 5–8 mins while CO measurements and  $S\bar{V}O_2$  readings were taken. At each incremental MAP plateau, a series of three PATD CO measures were taken followed by a single TPTD CO measurement using one of the two PCCO catheter systems. The same PCCO system was used for the sequential recalibrations (R-PCCO) at each incremental MAP plateau. After baseline calibration, the other PCCO (NR-PCCO) system was not recalibrated for the remainder of the experiment. PATD CO, TPTD CO, R-PCCO, NR-PCCO,  $S\bar{V}O_2$ , and heart rate were recorded at each MAP level.

**Data Analysis.** Standard descriptive statistics, including CO means and standard deviations, were calculated for each method studied. Analysis of variance was used to compare TPTD CO, R-PCCO, and NR-PCCO with PATD CO. Regression analysis was used to correlate PATD CO to TPTD CO, R-PCCO, and NR-PCCO at each MAP level during hemorrhage. Logarithmic regression was used to compare PATD CO to  $S\bar{V}O_2$ . A  $p$  value  $< .05$  was considered significant.

Bland-Altman analysis was performed to assess bias between the PATD CO and both TPTD CO and R-PCCO. This statistical method is used for comparing two measurement techniques when neither can be considered a true gold standard (15). Bias is defined as the mean difference between two measurement techniques and represents the amount by which one technique over- or underestimates the

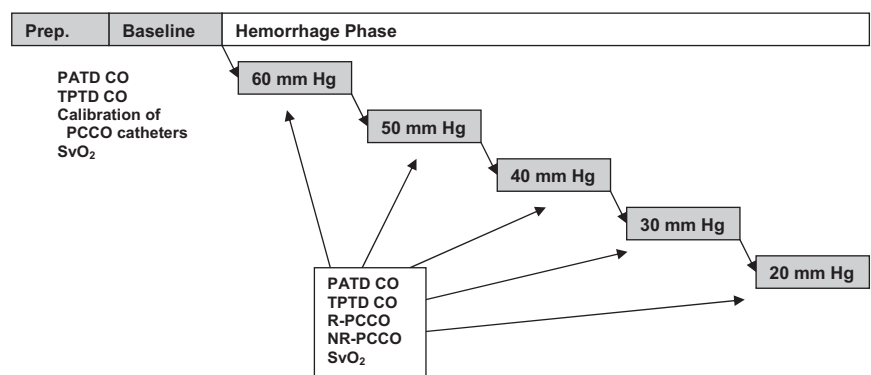


Figure 1. Experimental timeline. Following instrumentation, baseline measurements of cardiac output (CO) were made by pulmonary artery thermodilution (PATD) and transpulmonary thermodilution (TPTD). Pulse-contour cardiac output (PCCO) catheters were calibrated by TPTD. Venous blood withdrawal was then initiated to sequentially reduce mean arterial pressure (MAP) by 10-mm Hg increments. Blood pressure was maintained at each mean arterial pressure plateau to perform PATD CO and TPTD CO. These values were recorded, and the TPTD CO was used to recalibrate one of the two PCCO catheters (R-PCCO). The other catheter was not recalibrated during hemorrhage (NR-PCCO).

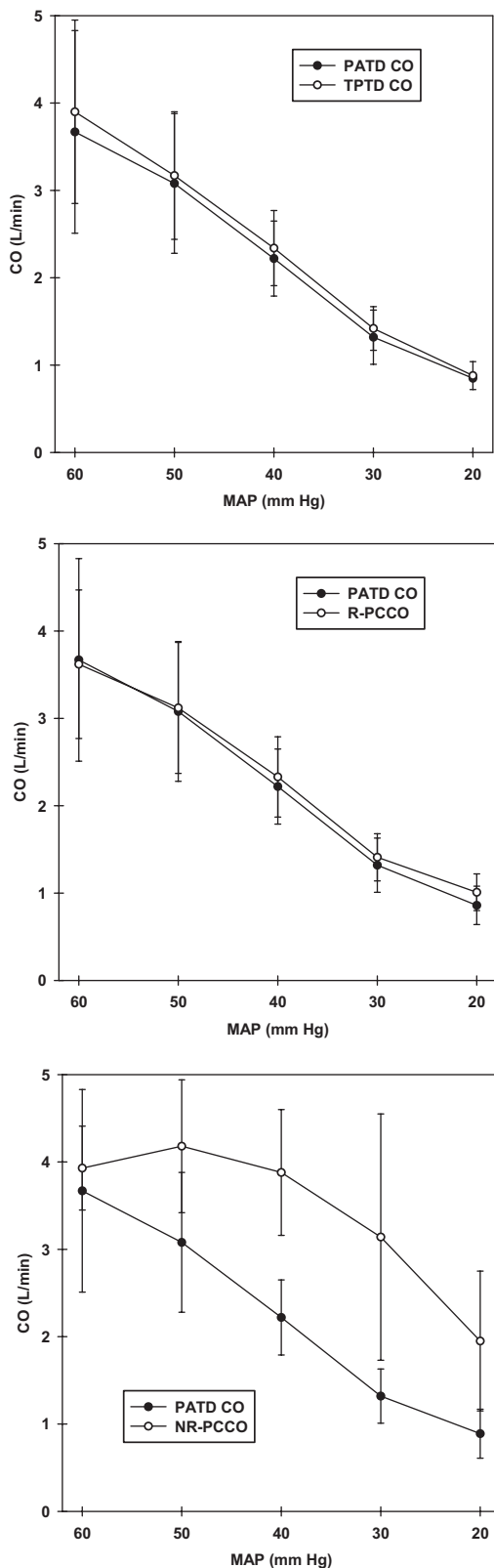


Figure 2. Cardiac output (CO) vs. mean arterial pressure (MAP). *Top*, pulmonary artery thermodilution (PATD) CO and transpulmonary thermodilution (TPTD) CO; *middle*, PATD CO and recalibrated PCCO (R-PCCO); *bottom*, PATD CO and nonrecalibrated PCCO (NR-PCCO); data are mean  $\pm$  SD (n = 10).

other. Precision is calculated as the SD of the differences between the two techniques. Upper and lower limits of agreement were calculated as the bias  $\pm$  1.96 SD.

## RESULTS

Mean baseline CO was 4.0 L/min ( $\pm$ 1.3 L/min) by PATD and 4.13 L/min ( $\pm$ 1.6 L/min) by TPTD and PCCO ( $p$  not significant). Total blood loss during the hemorrhage protocol averaged 40 mL/kg ( $\pm$ 7 mL/kg) or approximately 50% of total blood volume. Mean heart rates increased from baseline of 107 ( $\pm$ 32 beats/min) to a maximum of 194 beats/min ( $\pm$ 27 beats/min) during the last stage of the protocol. Initiation of hemorrhage until completion of the experimental protocol required approximately 1 hr.

Incremental blood withdrawal resulted in a corresponding decline in MAP and CO (Fig. 2). TPTD CO and R-PCCO readings correlated closely with PATD CO at each MAP level ( $p < .001$ ) (Fig. 2, *top* and *middle*). NR-PCCO readings overestimated PATD CO with declining MAP by as much as 100% ( $p < .001$ ) (Fig. 2, *bottom*).

Linear regression analysis showed high correlations for both TPTD CO and R-PCCO ( $r^2 = .97$  and  $r^2 = .96$ , respectively) compared with PATD CO (Fig. 3, *top* and *middle*). The correlation between PATD CO and NR-PCCO measurements was poor ( $r^2 = .22$ ) (Fig. 3, *bottom*), and discordance became greater as CO decreased.

Finally, Bland-Altman analysis comparing PATD CO with both TPTD CO and R-PCCO demonstrated close agreement between the two methods over the wide range of CO values obtained, with a mean bias of  $0.14 \pm 2$  SD  $0.47$  L/min and  $0.11 \pm 2$  C  $0.45$  L/min, respectively (Fig. 4).

*Mixed Venous Oxygen Saturation.* Logarithmic regression analysis showed a significant correlation between PATD CO and  $S\bar{V}O_2$  ( $r^2 = .69$ ) (Fig. 5).

## DISCUSSION

This study demonstrates both the utility and limitations of TPTD and PCCO in the setting of rapidly changing hemodynamics due to acute hemorrhagic shock. Despite smaller patient size, extremely high heart rates, and substantial changes in MAP, intravascular volume, and CO, both TPTD CO and recalibrated PCCO correlated very closely with the clinical gold standard of PATD CO. TPTD CO and R-PCCO consistently overestimated the PATD CO by  $<0.15$  L/min, which is well

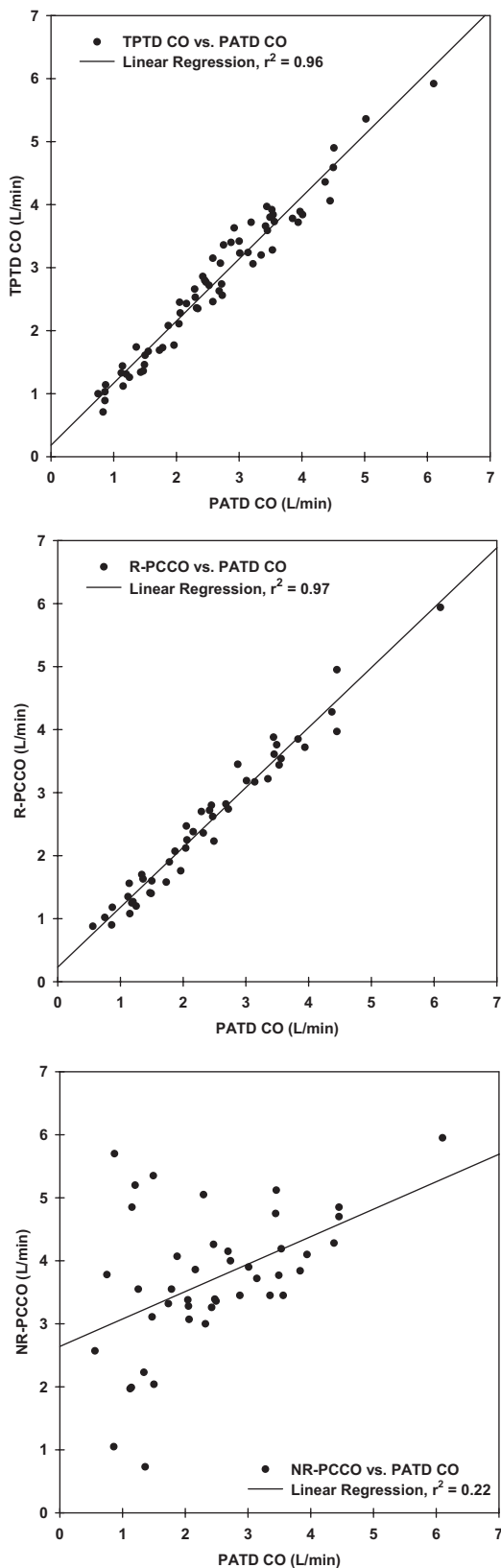


Figure 3. Linear regression of cardiac output (CO) measurement techniques. *Top*, transpulmonary thermodilution (TPTD) CO vs. pulmonary artery thermodilution (PATD) CO; *middle*, recalibrated PCCO (R-PCCO) vs. PATD CO; *bottom*, nonrecalibrated PCCO (NR-PCCO) vs. PATD CO.

less than the 15% variation considered clinically acceptable when comparing consecutive PATD CO determinations (16). The single SD of approximately 0.24 L/min also represents clinically acceptable variation. In this model we observed less variation for TPTD CO and R-PCCO, with narrower mean bias and smaller SD, than shown in adult clinical studies comparing PCCO analysis to PATD CO (11, 13, 14).

No previous studies have examined PCCO under the extreme conditions of hemorrhagic shock. This study demonstrated that rapid blood loss with a substantial (>20%) drop in MAP can result in markedly inaccurate PCCO readings unless recalibration with TPTD CO is performed. Clinically, the frequency required to yield accurate PCCO readings would vary on an individual patient basis, although sudden changes in excess of 20% may be a reasonable threshold for recalibration. In extremely unstable cases, we have confirmed that TPTD CO can be used independently to guide therapy. It is important to note that newer versions of PCCO analysis software (PiCCO-Plus version 5.01, Pulsion Medical Systems AG, Munich, Germany) have attempted to correct this problem and could obviate the need for recalibration during major hemodynamic changes.

*Clinical Significance of Cardiac Output Monitoring.* Diminished CO with inadequate tissue oxygen delivery increases mortality (2, 7, 17), and survivors of critical illness tend to have higher CO and oxygen delivery (18). Therapies directed at improving CO and oxygen delivery improve outcomes in a variety of clinical situations (1, 2, 4, 6, 7).

PATD has long been the standard technique for measuring CO in adults. However, multiple studies suggest increased morbidity, mortality, and cost associated with PAC use (8–10, 19, 20). PAC use is, in part, operator dependent, and operator error may account for some of the increased adverse events (21). In children, the literature suggests that PACs substantially increase the risk of thrombosis and infection when compared with standard central venous catheters (22). Arrhythmias, knot formation, and pulmonary artery rupture are other potential complications. PAC insertion and maintenance can also be time consuming and technically difficult. Because of these technical and safety concerns, PACs are uncommon in pediatric intensive care and are rarely used in the ED.

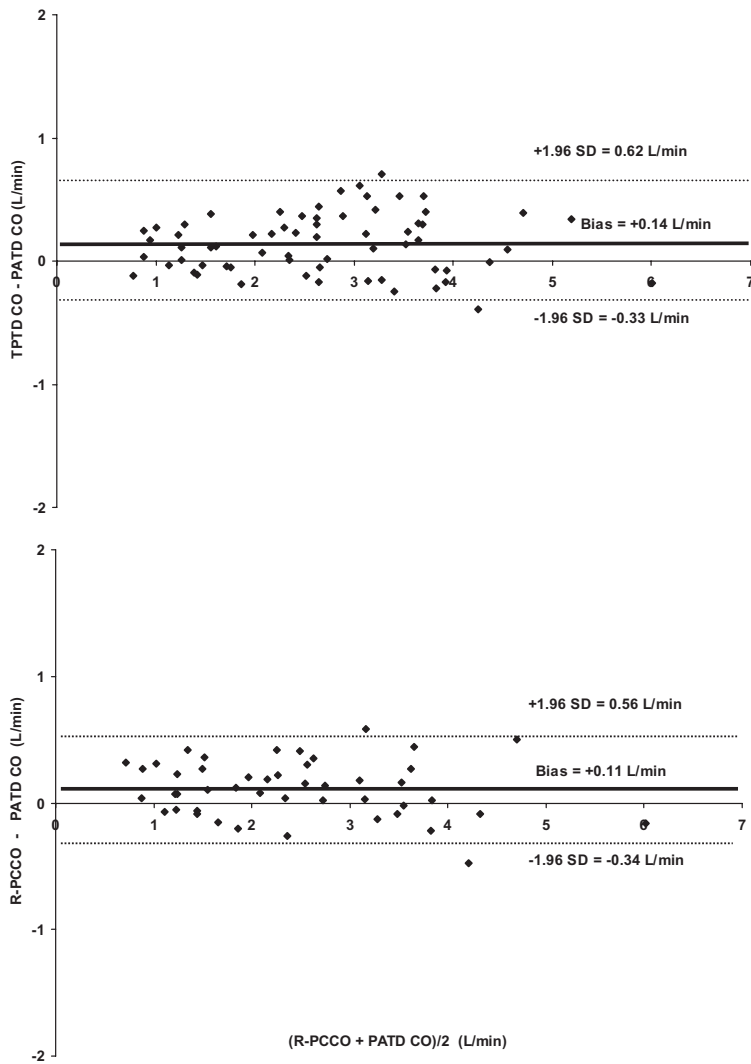


Figure 4. Bland-Altman analysis. *Top*, transpulmonary thermodilution (TPTD) cardiac output (CO) vs. pulmonary artery thermodilution (PATD) CO; *bottom*, recalibrated pulse-contour analysis CO (R-PCCO) vs. PATD CO.

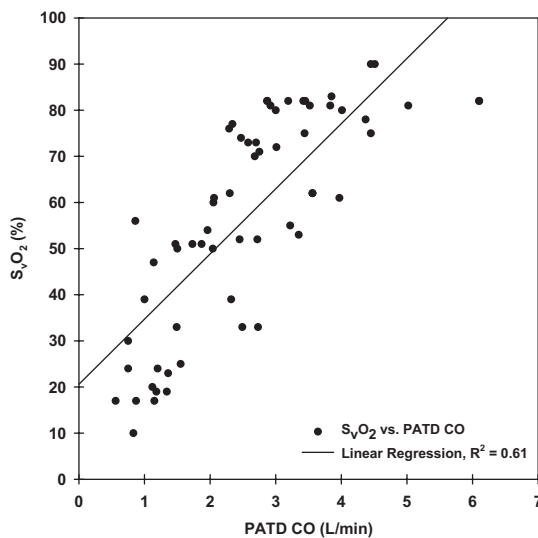


Figure 5. Linear regression analysis of mixed venous oxygen saturation ( $S_{vO_2}$ ) vs. pulmonary artery thermodilution (PATD) cardiac output (CO).

*Clinical Significance of Pulse Contour Analysis.* PCCO analysis was originally described in 1974, but it has only recently been refined and validated for clinical use (11). Several studies in adult cardiovascular surgical intensive care units have found excellent agreement between PCCO analysis and PATD CO (11, 13, 14). Studies of TPTD CO, the calibration technique for PCCO, have also revealed good correlation with both Fick and PATD CO in children (23, 24).

Technical and safety concerns associated with PACs make a less invasive alternative for CO monitoring desirable, particularly where CO monitoring is seldom used, such as in the pediatric intensive care unit or the ED. In children, clinician estimation of CO correlates poorly with objective measures of CO (25, 26). PCCO requires central venous and arterial catheters, which are commonly used in pediatric critical care and in the ED. In both the pediatric intensive care unit and ED, a simple and continuous measure of CO could lead to earlier and more precise diagnosis and treatment of critically ill patients. After placement of the PCCO arterial catheter and a central venous catheter, TPTD and PCCO calibration can be readily performed by nursing staff as needed and requires only a few minutes. The thermistor-tipped arterial catheter can be used as any standard arterial cannula for blood pressure measurement and blood sampling.

PCCO analysis offers the advantage of continuous CO monitoring while eliminating the need for intracardiac catheterization. PCCO analysis also provides other volumetric data that may be helpful in targeting fluid therapy. Two of these measures derived from TPTD, global end-diastolic volume and intrathoracic blood volume, have been shown in adults and children to better predict volume responsiveness than pulmonary artery occlusion pressure and central venous pressure (27–30). The PCCO system also provides continuous stroke volume variation, which also may be superior to standard measures of preload (31, 32).

Several disadvantages of the PCCO analysis system include the risks of proximal or central arterial catheterization and the inability to measure pulmonary artery pressure or pulmonary artery occlusion pressure. Also, intracardiac shunts diminish the accuracy of TPTD CO calibration, potentially limiting the utility of PCCO analysis in patients with unrepaired congenital heart disease.

The need for TPTD CO recalibration that we observed may be due to changes in aortic impedance that occur during rapid blood loss. It is unclear how necessary recalibration might be in other profound hemodynamic derangements, such as cardiogenic shock, arrhythmias, or septic shock. TPTD CO, the technique used to calibrate PCCO analysis, is itself an accurate measure of CO that can be used independently. However, during periods of less rapid change in MAP (<20%), the ability to quickly detect changes in CO and promptly evaluate response to therapy is a major advantage of the PCCO technique.

We have also shown that while  $S\bar{V}O_2$  correlates with PATD CO during hemorrhagic shock, this correlation is weaker than for PCCO analysis. Furthermore, changes in  $S\bar{V}O_2$  lag behind changes in CO during hemorrhage. These findings suggest that  $S\bar{V}O_2$  may be less sensitive to early changes in global perfusion than PCCO.

**Limitations.** We chose to compare PCCO analysis with PATD CO, which is the clinical gold standard for CO measurement. It is not, however, a true gold standard and is susceptible to variation between measurements due to a variety of factors, such as cardiorespiratory interactions and correct catheter placement. A more precise CO measurement technique might yield different results. We have also not studied the other valuable hemodynamic and volumetric data that are obtained through the PCCO system. A detailed analysis of the performance of these variables would aid greatly in understanding the clinical utility of PCCO in critically ill children. The results observed in this hemorrhagic shock study may not be applicable to other pathophysiological states, such as disorders with associated myocardial dysfunction.

## CONCLUSIONS

This study demonstrates that PCCO analysis, when recalibrated by TPTD CO during major hemorrhage and acute changes in MAP, correlates extremely well with PATD CO in a piglet model of hemorrhagic shock. In the setting of large (>20%) changes in blood pressure and intravascular volume, PCCO readings can be markedly inaccurate if not recalibrated. TPTD CO and PCCO analysis are both accurate alternatives to PATD CO, especially in areas like the pediatric in-

tensive care unit and the ED. Currently available software modifications have addressed these issues and may reduce the need for recalibration in critically ill children.

$S\bar{V}O_2$ , a commonly used surrogate of CO, is less reliable in this model of hemorrhagic shock. Clinical studies of PCCO analysis are warranted to determine the safety and utility of this technique in the pediatric critical care and ED settings.

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