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RELIABILITY OF CONTINUOUS PULSE CONTOUR CARDIAC OUTPUT MEASUREMENT DURING HEMODYNAMIC INSTABILITY

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Johansson A, Chew M. Reliability of continuous pulse contour cardiac output measurement during hemodynamic instability.
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ABSTRACT. Objective. Arterial pulse contour analysis is gaining widespread acceptance as a monitor of continuous cardiac output (CO). While this type of CO measurement is thought to provide acceptable continuous measurements, only a few studies have tested its accuracy and repeatability under unstable hemodynamic conditions. We compared continuous CO measurement using the pulse contour method (PCCO) before and after calibration with intermittent transpulmonary thermodilution cardiac output (TpCO). **Method.** We compared the two methods of CO measurements in 15 Landrace pigs weighing 20–25 kg in an experimental model of sepsis. Nine pigs were given an infusion of *E. coli* lipopolysacchride (LPS), and six pigs acted as controls. PCCO values before and after calibration ($PCCO_1$ and $PCCO_2$ respectively) were registered, and their errors relative to TpCO measurements were compared. **Results.** The mean coefficient of variation for repeated PCCO measurements was 6.85% for the control group, and 13.99% for the endotoxin group. The range of TpCO was 1.01–3.15 L/min. In the control group the bias ±2SD was 0.11 ± 0.53 L/min (TpCO vs $PCCO_1$) and -0.02 ± 0.38 L/min (TpCO vs $PCCO_2$). In the endotoxin group, the agreement was poor between TpCO and $PCCO_1$, 0.08 ± 1.02 L/min. This improved after calibration (TpCO vs $PCCO_2$) to 0.01 ± 0.31 L/min. **Conclusions.** In hemodynamically stable pigs, both pre- and post-calibration PCCO measurements agreed well with the intermittent transpulmonary thermodilution technique. However, during hemodynamic instability, and pre-calibration PCCO values had wide limits of agreement compared with TpCO. This was reflected by larger coefficients of variation for PCCO in hemodynamic instability. The error of PCCO measurement improved markedly after calibration, with bias and limits of agreement within clinically acceptable limits.

KEY WORDS. heart, cardiac output, measurement techniques, pulse contour analysis, measurement techniques, thermodilution, anesthesia, sepsis

INTRODUCTION

Hemodynamic monitoring and treatment of hemodynamic instability are fundamental tasks in intensive care. Cardiac output (CO) is regarded one of the most important hemodynamic determinants of tissue oxygen delivery, and is often used to guide volume and vasopressor therapy. CO is traditionally measured by the bolus thermodilution technique with a pulmonary artery catheter (PAC), and is considered the clinical gold standard. However, practical disadvantages and risks associated with the PAC catheter, along with a lack of evidence for improved outcome [1–3], have contributed to its infrequent

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use. The PiCCO (Pulsion Medical Systems, Germany) device which uses pulse contour analysis for continuous cardiac output measurement is gaining clinical acceptance. Pulse contour cardiac output (PCCO) is calculated by measuring the area under the systolic arterial pressure waveform. The same device is also able to measure intermittent transpulmonary thermodilution cardiac output (TpCO) against which PCCO is calibrated. TpCO has been investigated against the clinical gold standard of bolus thermodilution, and seems to provide reliable CO measurements [4–12].

Hemodynamic changes often dominate the clinical picture in the septic patient, and it is here that monitoring is often necessary in order to guide treatment. While PCCO has been validated in intensive care settings [4–12], few studies have validated its use in hemodynamically unstable patients [13–16], specifically in septic shock. These studies have had variable conclusions. Our own clinical experience of this method in hemodynamically unstable patients in the Intensive Care Unit (ICU) is that there are considerable differences between measurements made pre- and post-calibration.

The aim of this study was to evaluate the reliability of pulse contour (PCCO) cardiac output measurements in an experimental model of septic shock. We wanted specifically to test the repeatability of the PCCO method in this setting and to see if there were any significant improvements in the accuracy of PCCO measurements after calibration against transpulmonary thermodilution.

METHODS AND MATERIALS

This study was approved by the Swedish National Board for Animal Experimentation and conforms to the guidelines laid out in the Guide for the Care and Use of Laboratory Animals from the National Research Council.

Fifteen Landrace pigs weighing 20–25 kg were included in the experimental protocol. After pre-medication with xylazine 1 mg/kg and azaperone 2 mg/kg IM, anesthesia was induced using Sodium Thiopentone 5 mg/kg IV. The animals were intubated and ventilated with a volumetric Servo 900C ventilator (Siemens-Elema™, Sweden). Anesthesia was maintained using high dose fentanyl (50–100 mcg/kg/h) and midazolam (0.25 mg/kg/h). Body temperature was controlled to avoid hypothermia, using a warming blanket (Gaymar Meditherm, Orchard Park, NY, USA). Intravenous fluids (Ringer Acetate) were infused at a constant rate of 10 ml/kg/h throughout the experiment.

Nine pigs were randomized to an infusion of bacterial lipopolysaccharide endotoxin (*E. coli* 0111:B4, 3,000,000 EU/mg, Sigma-Aldrich) 2 μ/kg/h for 6 h (endotoxin group), and six pigs served as controls (control group). In order to maintain hemodynamic instability, catecholamines were not used to stabilize the circulation during the procedure.

Monitoring

In all pigs, a 4-French gauge thermistor-tipped PiCCO catheter (Pulsiocath PV2014L, Pulsion Medical Systems, Germany) was inserted in the left carotid artery, and connected to the PiCCO System (version 4.1) for clinical monitoring of arterial pressure (AP), arterial blood gases, PCCO and TpCO measurements. A triple lumen central venous catheter (CVC) was inserted into the left internal jugular vein for infusion of fluids and venous blood gas measurements.

Experimental procedure

The pulse contour device was calibrated after the surgical procedure by the mean values of three successive TpCO measurements and hourly thereafter. These were performed by injection of 10 mL cold saline solution, at a temperature of <10°C, via the CVC. To avoid variation between operators, the same person performed the injections. A variation of less than 15% between the triplicate measurements was defined to be acceptable.

Intermittent TpCO measurements were obtained at specific times during the study period: after the induction of anesthesia and surgical procedure (T0), subsequently hourly measurements were made (T1–T6) with start of the bacterial endotoxin infusion at T1. At each time point a single set of hemodynamic measurements was collected. Pulse Contour cardiac output measurements were recorded as an average over 30 s, immediately before ($PCCO_1$) and after ($PCCO_2$) TpCO measurements (i.e. pre- and post-calibration). HR, MAP and CVP were recorded immediately before $PCCO_1$. Arterial and venous blood was drawn for blood gas analysis also before $PCCO_1$.

Statistical evaluation

Normality was tested for using the Kolmogorov–Smirnov method. All results are expressed as mean (SD) for parametric data or median (interquartile range) for non-parametric data. Hemodynamic changes over time were tested for using ANOVA for repeated measures (on ranks for non-parametric data). The *t*-test or Mann–Whitney

rank sum test was used to identify differences between the two groups. The agreement between TpCO and PCCO was analyzed using the Bland–Altman method (17,18). To test the differences between $PCCO_1$, and $PCCO_2$ the paired *t*-test or the Wilcoxon signed rank test was used, with a Bonferroni correction applied for multiple testing. As a measure of repeatability, we calculated the coefficient of variation (CoV) between two repeated PCCO measurements using the method given in Bland et al. All statistical analyses were performed using SigmaStat (Systat, Chicago, USA).

RESULTS

Pigs given endotoxin were more hemodynamically unstable than control pigs. They developed systemic hypotension, a more negative base excess and decreases in central venous oxygenation which were significant over time, and which differed significantly from the control group (Table 1). Cardiac output remained stable in the control group, whereas in the endotoxin group it increased at $t = 2$ and $t = 3$ before returning towards baseline values, consistent with the hyperdynamic phase often described in human septic shock (Figure 1). The maximal change in TpCO was $19.0 \pm 5.6\%$ in the control group and $46.4 \pm 14.8\%$ in the endotoxin group.

Four animals in the endotoxin group died prior to the end of the experiment from endotoxic shock. Ninety-five sets of PCCO and TpCO measurements were obtained. No adverse effects related to the PiCCO catheter were observed and no data were rejected.

The ranges for CO measurements in the control group were 1.30–3.30 L/min for $PCCO_1$, 1.35–3.13 for $PCCO_2$ and 1.39–3.10 for TpCO. There were no significant changes in cardiac output over time. CO measurements ranged from of 0.86 to 3.08 L/min for $PCCO_1$, 0.95 to 3.33 L/min for $PCCO_2$ and 1.01 to 3.15 L/min for TpCO in the endotoxin group. There were significant changes over time detected using Repeated Measures ANOVA for TpCO and $PCCO_2$ ($p = 0.02$ and $p = 0.03$, respectively). There was a statistically significant difference between $PCCO_1$ and $PCCO_2$ at $t = 2$ ($p = 0.04$) and $t = 6$ ($p = 0.03$) for the endotoxin group (Figure 1).

Bland Altman analysis for the control group revealed a bias ±2SD between $PCCO_1$ and TpCO of 0.11 ± 0.53 L/min ($5.7 \pm 23.9\%$), and -0.02 ± 0.38 L/min ($-0.13 \pm 16.7\%$) between $PCCO_2$ and TpCO. For the endotoxin group the respective values were 0.08 ± 1.02 L/min ($4.0 \pm 55.9\%$) for $PCCO_1$ vs TpCO and 0.00 ± 0.31 L/

Table 1. Heart rate (HR), mean arterial pressure (MAP), base excess (BE) and central venous oxygen saturation ($ScvO_2$) in control (C) and endotoxin-treated (E) pigs

		T0	T1	T2	T3	T4	T5	T6	*p* within group)
HR	C	68(63–87)	71 (67–78)	70 (66–82)	76 (74–82)	88 (77–94)	87 (81–104)	88 (81–99)	<0.001
	E	50 (47–55)	80 (56–93)	93 (74–118)	108 (80–141)	98 (77–131)	109 (94–118)	105 (94–112)	0.004
P(CvsE)		0.02	NS	NS	NS	NS	NS	NS	
MAP	C	89 (78–98)	91 (77–97)	89 (79–98)	86 (78–88)	86 (78–91)	82 (79–84)	81 (74–83)	NS
	E	77 (72–91)	73 (63–79)	67 (52–77)	72 (53–82)	57 (37–73)	50 (30–73)	61 (38–71)	0.04
P(CvsE)		NS	NS	0.022	0.035	0.001	0.004	0.038	
BE	C	6.9 (4.4–7.2)	4.9 (4.3–6.2)	4.8 (4.5–6.6)	4.5 (4.0–6.9)	5.5 (4.4–6.6)	5.2 (4.0–7.2)	5.3 (3.9–6.9)	NS
	E	6.8 (5.7–7.5)	4.0 (1.8–6.6)	3.2 (1.1–4.3)	2.5 (−3.8–3.6)	0.2 (−5.3–2.7)	0.8 (−3.1–1.6)	1.0 (−0.7–2.0)	<0.001
P(CvsE)		NS	NS	0.021	0.022	0.008	0.008	0.015	
$ScvO_2$	C	65.2 (55.6–67.5)	62.8 (55.3–63.3)	57.5 (56.5–60.8)	58.7 (56.8–60.0)	52.1 (48.9–56.2)	55.6 (55.0–60.1)	50.7 (49.4–56.7)	NS
	E	64.1 (55.5–67.7)	53.1 (50.8–62.0)	52.1 (46.5–69.5	44.9 (34.7–56.2)	30.2 (19.2–43.4)	35.8 (33.1–37.3)	32.4 (27.9–36.1)	0.027
P(CvsE)		NS	NS	NS	0.043	0.008	0.004	0.004	

Data are given as median values (interquartile range). *p*-Values for within group changes over time as well as between group differences (CvsE) are given.

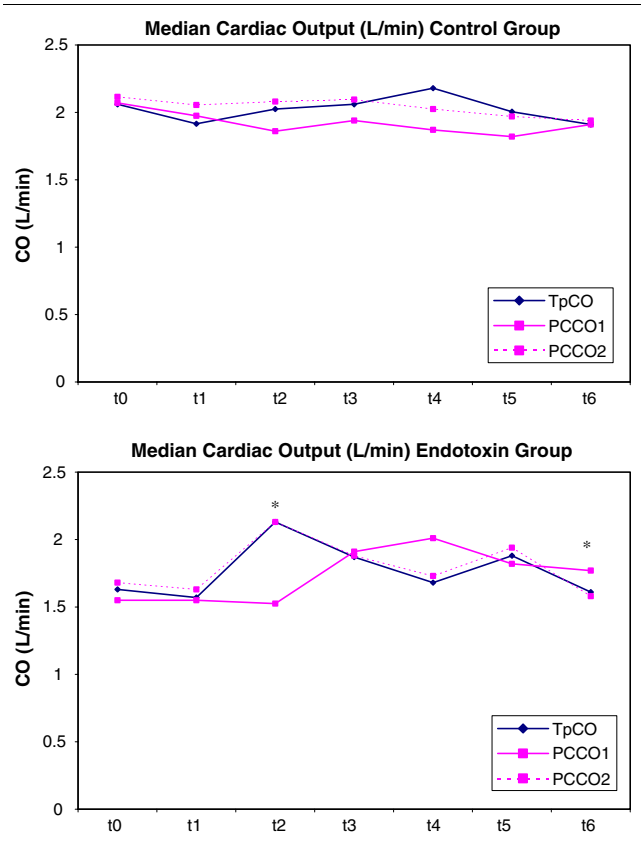

Fig. 1. Time course of cardiac output in control and endotoxin groups, measured using transpulmonary thermodilution (TpCO) and PCCO pre-calibration ($PCCO_1$) and post-calibration ($PCCO_2$). $\star p < 0.05$ for $PCCO_1$ vs $PCCO_2$.

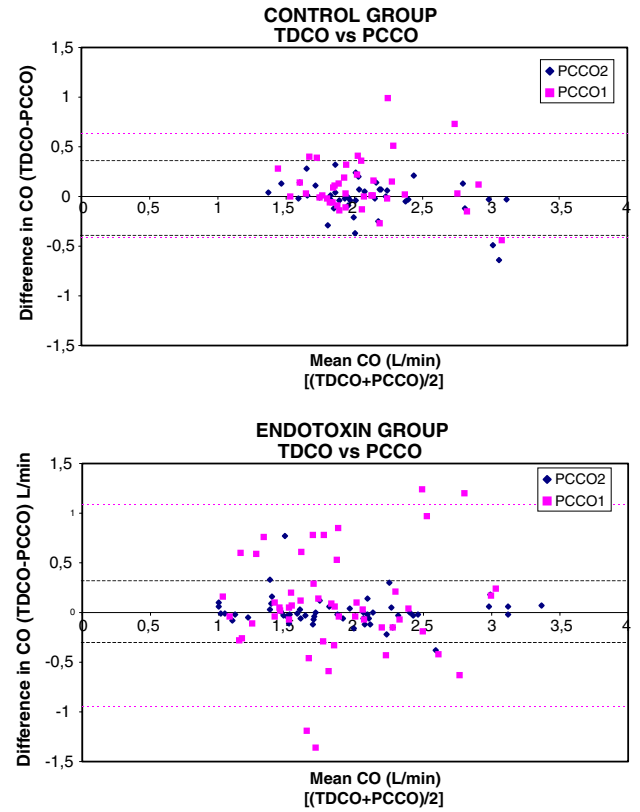

Fig. 2. Bland Altman plots for the differences between TDCO and PCCO pre-calibration ($PCCO_1$) and post-calibration ($PCCO_2$), for control and endotoxin groups.

min ($0.89 \pm 18.9\%$) for $PCCO_2$ vs TpCO (Table 2 and Figure 2).

The coefficients of variation for repeated PCCO measurements ($PCCO_1$ and $PCCO_2$) are shown in Table 3.

DISCUSSION

Our results demonstrate that CO measurement with a continuous arterial pulse contour technique (PCCO) agrees well with the intermittent transpulmonary ther-

Table 2. Mean difference ±2SD and 95% confidence intervals of the mean difference for $PCCO_1$ and $PCCO_2$ vs TpCO for control and endotoxin groups, given as absolute values and %

	Mean difference	$PCCO_{1\text{-TDCO}}$	$PCCO_{2\text{-TDCO}}$
Control group (hemodynamically stable)	Absolute (L/min)	0.11 ± 0.53	-0.02 ± 0.38
	95% CI (L/min)	0.03–0.19	−0.08–0.04
	Relative (%)	$5.7 \pm 23.9\%$	$-0.13 \pm 16.7\%$
	95% CI (%)	2.1–9.3%	−2.6–2.4%
Endotoxin group (hemodynamically unstable)	Absolute (L/min)	0.08 ± 1.02	0.00 ± 0.31
	95% CI (L/min)	−0.06–0.22	−0.04–0.04
	Relative (%)	$4.0 \pm 55.9\%$	$0.89 \pm 18.9\%$
	95% CI	−3.5–11.5%	−1.6–3.4%

Table 3. Coefficients of variation (CoV) calculated as standard deviation of repeated PCCO measurements ($PCCO_1$ and $PCCO_2$) divided by their mean, expressed as %

	T0	T1	T2	T3	T4	T5	T6	Mean
Control	10.72	6.88	6.60	7.63	6.51	4.56	5.06	6.85
Endotoxin	5.51	19.80	27.50	12.68	19.02	12.02	1.39	13.99

CoV for each sampling time as well as their mean are given.

modilution technique (TpCO) in the hemodynamically stable control group. The coefficient of variation (CoV) for repeated PCCO measurements, carried out pre- and post-calibration against TpCO was 6.85% (range 4.56–10.72%) in this group. During hemodynamic instability induced by endotoxin infusion however, the CoV increased to 13.99% (range 1.39–27.50%). This variability is also reflected in pre-calibration ($PCCO_1$) measurements which showed wide limits of agreement compared to TpCO. The reliability PCCO measurements improved markedly post-calibration ($PCCO_2$), as demonstrated by their narrower limits of agreement.

In the endotoxin group, the limit of agreement between $PCCO_1$ and TpCO was unacceptably high, ± 1.02 L/min, representing a difference of 55.9% between the two types of measurements. After calibration, the agreement between $PCCO_2$ and TpCO was better, 0.00 ± 0.31 L/min, representing an improvement in the limits of agreement to 18.9%. In contrast, calibration did not play a significant role in PCCO measurements in hemodynamically stable animals, where only a small bias and close limits of agreement ($PCCO_1$ vs TpCO 0.11 ± 0.53 L/min ($5.7 \pm 23.9\%$) and $PCCO_2$ vs TpCO -0.02 ± 0.38 L/min ($-0.13 \pm 16.7\%$)) were observed both before and after calibration respectively.

For any system of hemodynamic monitoring, it is important that precise and reliable measurements can be made especially within the setting of hemodynamic instability. While PCCO has been validated in intensive care settings [4–7, 9–12], surprisingly few studies have validated its use in hemodynamically unstable patients [13–16], and specifically in septic shock.

Rödig and colleagues demonstrated that phenylephrine-induced changes in systemic vascular resistance significantly affected PCCO measurements in a group of cardiac surgical patients [13]. They suggested that after marked changes in systemic vascular resistance, the PiCCO device should be recalibrated. Scheurholz et al. evaluated the reliability of PCCO in porcine septic shock and concluded that PCCO was reliable without recalibration up to 5 h after the induction of septic shock [14]. It is notable however that within this 5-h period, there were no significant changes in hemodynamic status in the subjects. Beyond 5 h however, when significant changes in mean arterial pressure and heart rate occurred, the data showed large biases and limits of agreement between calibrated and non-calibrated CO values. On the other hand, Gödje et al. evaluated unstable post-cardiac surgical patients with >20% change in CO, and found reproducible results with PCCO compared to transpulmonary thermodilution, without recalibration of the device (16). In the study by Irlbeck et al. the bias ±2SD between PCCO and TpCO was 0.09 ± 1.7 L/min, corresponding to a limits of agreement of ±23.9% (15). Irlbeck noted that this error improved to ±15.7% by additional recalibration. Our results are consistent with these findings.

The finding that repeated PCCO measurements showed poorer repeatability (larger CoV) during haemodynamic instability is not unexpected. The question of how much measurement error is acceptable is based not only on statistical measures but clinical relevance also. One might argue that a CoV of 6.85% seen in the haemodynamically stable control group is clinically acceptable, whilst a CoV of 13.99% seen in the endotoxin group is unacceptable. We note that the CoV was worst at T2 (27.50%), with a statistically significant difference between the $PCCO_1$ and $PCCO_2$, coinciding with the hyperdynamic phase of septic shock.

We found that PCCO values post-calibration ($PCCO_2$) were clearly more closely related to TpCO measurements, compared to values pre-calibration ($PCCO_1$). This is also an expected finding since the pulse contour method requires calibration against TpCO in order to adjust for differences in arterial impedance. However, we found the difference in pre- and post-calibration to be of a magnitude that warrants some concern, particularly given that one is most reliant on continuous CO measurements during hemodynamic instability, that few publications have addressed this issue, and that in the clinical setting, the PiCCO device is usually calibrated only every eighth hour or when there is a change in SVR of ≥20%.

There were several limitations in this study. It is possible that a larger sample size as well a more unstable hemodynamic profile may have revealed further differences between the groups. Even though no statistically significant differences were seen between the groups for sampling times other than T2 and T6, there is a possibility that due to the conservative nature of the Bonferroni

correction applied for multiple analyses, we may have missed a true difference between $PCCO_1$ and $PCCO_2$ measurements.

PCCO was calibrated against transpulmonary thermodilution, which despite its current clinical acceptance, remains an imperfect gold standard. This is reflected in the 19% maximal deviation in cardiac output in the control group, when they should have been close to zero. Although the effects of anesthesia may account for some of this difference, it is likely that inherent errors in TpCO measurement itself have played a role. We would like to emphasize however, that it was not the intention of this study to compare TpCO with PCCO. TpCO measurements were included here to give an idea of the magnitude of error incurred by PCCO.

This study shows that pulse contour cardiac output should be recalibrated during sepsis-induced hemodynamic instability. With recalibration, PCCO measurements made during hemodynamic instability are as precise as those during hemodynamic stability.

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