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Qinghua Sun
Peter Rogiers
Dirk Pauwels
Jean-Louis Vincent

Comparison of continuous thermodilution and bolus cardiac output measurements in septic shock

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Q. Sun · J.-L. Vincent (✉)
Department of Intensive Care,
Erasme University Hospital,
Free University of Brussels,
Route de Lennik 808, 1070 Brussels,
Belgium
e-mail: jlvincen@ulb.ac.be
Tel.: +32-2-5553380
Fax: +32-2-5554555

P. Rogiers · D. Pauwels
Department of Intensive Care,
Middelheim General Hospital, Antwerp,
Belgium

Abstract *Objective:* To compare continuous (CCO) and bolus (BCO) thermodilution cardiac output measurement techniques over a wide range of cardiac outputs and blood temperatures in a septic sheep model. *Design and setting:* Prospective experimental study in a university intensive care laboratory. *Subjects:* Thirty-five anesthetized sheep. *Interventions:* Pulmonary artery catheters allowing measurement of CCO and BCO were placed through the external jugular vein. Cecal ligation and perforation was performed to induce septic shock. In 14 sheep two femoral venous catheters were placed and connected to a hemofiltration system to alter blood temperature. *Measurements:* CCO and BCO were measured every hour during the experiment. Three 10-ml bolus injections of iced normal saline were given through a closed injectate system and then averaged. The CCO readings were collected just before the BCO measurements. The relationship between CCO and BCO was assessed using Bland and Altman's method. *Results:* In 465 paired data the temperature ranged between 34.0° and 40.9°C, CCO between 1.4 and 17.0 l/min, and BCO between 1.1 and 17.4 l/min. There was a highly significant correlation between CCO and BCO (r=0.97). The bias (difference between CCO and BCO) was –0.19 l/min, the SD of the difference 0.45 l/min, and the limits of agreement –1.08/0.71 l/min. There were also highly significant correlations between CCO and BCO at the different temperatures (extreme values: 34.0–34.9°C, r=0.90; 40.0–40.9°C, r=0.98). *Conclusions:* Thermodilution measurements of CCO are reliable, when compared to BCO measurements, over a large range of cardiac outputs and blood temperatures.

Keywords Hemodynamic measurement · Monitoring system · Fever · Critically ill

Introduction

Accurate assessment of cardiac output is important in the management of critically ill patients. Several invasive and noninvasive methods have been proposed for the measurement of cardiac output, including the Fick method, dye and thermal dilution techniques, radionuclide angiography, electrical impedance, and echo Doppler techniques [1, 2, 3, 4, 5, 6]. The most widely accepted method for measuring cardiac output in the intensive care unit (ICU) is the thermodilution technique [7], which conventionally involves intermittent bolus cardiac output measurements (BCO). Other commonly measured variables including heart rate, blood pressure, central venous and pulmonary artery pressures, oxygen saturation, and temperature can be monitored continuously. A continuous thermodilution cardiac output (CCO) monitoring system (Vigilance, Baxter Healthcare) with a thermal filament-wrapped pulmonary artery catheter has become commercially available. The accuracy and precision of CCO has

been found to be acceptable under various conditions in a volumetric fluid flow model [8, 9], in animals [8, 10] and in patients [11, 12, 13, 14, 15, 16, 17, 18]. However, most studies have been performed over a relatively short period with one or two manipulations per day or under controlled conditions (hemodynamically stable cardiac surgical, or septic patients). In addition, blood temperature can vary widely in acutely ill patients, but the CCO technique has not been well tested over a large range of blood temperatures.

The aim of the present study was to investigate whether the accuracy and precision of the CCO technique are reliable, compared to bolus thermodilution measurements, over a wide range of cardiac output values and blood temperatures. We used a septic shock sheep model combined with hemofiltration to decrease body temperature, allowing us to compare CCO with BCO over a large range of cardiac outputs and blood temperatures.

Materials and methods

This study was approved by our institutional review board for animal care. Care and handling of the animals were in accord with National Institutes of Health guidelines. We studied 35 mature female sheep (weight 30.0±3.6 kg) which developed septic shock induced by cecal ligation and perforation. After endotracheal intubation under intramuscular injection of 40 mg xylazine (Bayer, Germany) and 150 mg ketamine (Ketalar, Warner-Lambert, Ireland) the sheep were anesthetized with a 3-ml infusion of the mixture of midazolam (Dormicum, Hoffmann-La Roche, Switzerland) and fentanyl (Janssen Pharmaceutica, Beerse, Belgium), using an infusion pump (Perfusor secura, Braun, Melsungen, Germany), and mechanically ventilated with a mixture of air and oxygen (Servo ventilator 900B, Siemens-Elema, Solna, Sweden). The inhaled oxygen fraction was adjusted to maintain arterial blood oxygen saturation above 98%. Muscle paralysis was obtained by pancuronium bromide at an initial dose of 0.15 mg/kg, followed by a continuous infusion of 0.075 mg/kg per hour. Respiratory rate was 12 breaths/min, and tidal volume was adapted to keep end-tidal PCO_2 (47210A Capnometer, Hewlett-Packard, Waltham, Mass., USA) between 28 and 38 mmHg. The left forepaw vein was used for the intravenous administration of midazolam, fentanyl, and pancuronium bromide. The right forepaw vein was catheterized for intravenous infusion of fluids. Through the right external jugular vein a 7.5-F gauge thermal filament-wrapped, flow-directed, pulmonary artery catheter (93A-439H-7.5F, Baxter Edwards Critical-Care, Irvine, Calif., USA) was placed under guidance of pressure waves (Sirecust Monitor 404, Siemens, Davis, Calif., USA). Through a midline laparotomy the cecal and ileocecal junctions were identified, and all of the cecum to within 5 cm of the ileocecal valve was devascularized. The distal cecum was eventually ligated with no. 2 silk. After making a 1-cm perforation in the cecal tip, spillage of fecal material (about 30 ml) into the peritoneal cavity was encouraged and the compromised bowel returned to the right lower quadrant. The abdomen was then closed with a running suture of 0 Dexon. No antibiotics were given at any time. In 14 sheep two venous catheters were placed through femoral veins and connected with a hemofiltration machine (Baxter BM11A and 14, Baxter Deutschland, Unterschleissheim, Germany) for continuous venovenous hemofiltration to decrease body temperature. Temperature was allowed to alter naturally with no manipulation of the substitution fluid. Intravenous fluid maintenance for the surgical procedure was about 1000 ml Ringer's lactate (Baxter).

After surgical preparation the sheep were allowed to stabilize for 30 min before the first measurement was taken. The sheep were infused with Ringer's lactate or 6% hydroxyethyl starch solution (130/0.4, or 200/0.5, Fresenius), titrated to keep the pulmonary artery occlusion pressure constant. As septic shock developed slowly over a period of about 10 h after the induction of peritonitis, there were no abrupt changes in pulmonary artery occluded pressure that required rapid fluid resuscitation. CCO and BCO measurements were repeated every hour throughout the experiments.

A computer system (Vigilance, Baxter software 5.02E, Irvine, Calif., USA) was used to measure cardiac output automatically. The system provides average measurements over a 3- to 6-min period with continuously updated (about every 60 s), time-averaged, cardiac output values. An ice-cold saline solution (10 ml) was injected at end-inspiration [19] within 2–3 s using a closed-injectate delivery system (CO-Set, Baxter) with in-line temperature measurement. Before measuring cardiac output, warm saline solution in the catheter was removed. The equipment for BCO measurement was the same as for CCO measurement by the intermittent bolus technique. Thermodilution curves were always plotted to detect artifacts. Each time three BCO measurements were performed, and the averaged value was taken as the BCO to compare with the CCO value (the average CO of the preceding 3–6 min) shown on the screen exactly before BCO measurement.

Linear regression was performed. To compare CCO and BCO measurements, bias (the mean difference between the two methods) was calculated to evaluate the systematic error between two methods [20]. Precision (the SD of the bias) is representative of the random error or variability between the different techniques [21]. The limit of agreement is defined by ±2 SD [20]. The relative error (expressed in %) was defined as 100×([BCO measurement minus CCO measurement]/BCO measurement). A p value less than 0.05 was considered as statistically significant.

Results

A total of 465 pairs of cardiac output measurements were obtained in the 35 sheep (Table 1). BCO ranged from 1.1 to 17.4 l/min and CCO from 1.4 to 17 l/min; the comparison data are plotted in Fig. 1. The bias of all measurements was –0.19 l/min and the 95% confidence limits (±2 SD) were –1.08/0.71 l/min (Fig. 2). Although relative differences in CO were greater at relatively low

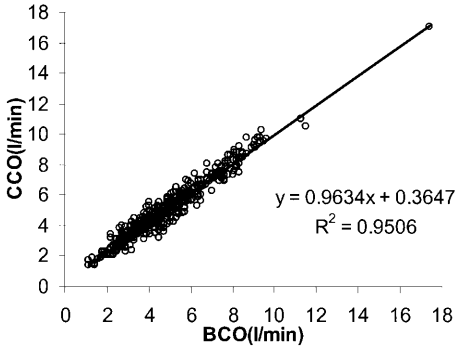

Fig. 1 Linear regression of CCO vs. BCO measurements

Table 1 Agreement of CCO with BCO measurement

	Pairs of cardiac output	Range of BCO (l/min)	Bias (l/min)	SD of bias	Bias ±2 SD	Relative error (%)	*r*
Total	465	1.1–17.4	–0.19	0.45	–1.08/0.71	0.04	0.97
BCO<5 l/min	271	1.1–4.9	–0.20	0.08	–0.35/-0.05	0.05	1.0
BCO≥5 l/min	194	5–17.4	–0.17	0.15	–0.47/0.13	0.03	1.0
34.0–34.9°C	10	1.3–4.3	–0.06	0.43	–0.92/0.80	0.02	0.90
35.0–35.9°C	23	1.6–7.6	+0.13	0.54	–0.95/1.21	0.03	0.93
36.0–36.9°C	28	1.1–6.3	–0.15	0.55	–1.23/0.96	0.03	0.91
37.0–37.9°C	89	1.4–9.1	–0.25	0.44	–1.12/0.63	0.05	0.97
38.0–38.9°C	89	1.4–9.2	–0.25	0.47	–1.18/0.68	0.05	0.97
39.0–39.9°C	94	2.2–17.4	+0.20	0.48	–1.17/0.77	0.04	0.98
40.0–40.9°C	132	1.4–9.4	–0.17	0.36	–0.89/0.54	0.03	0.98

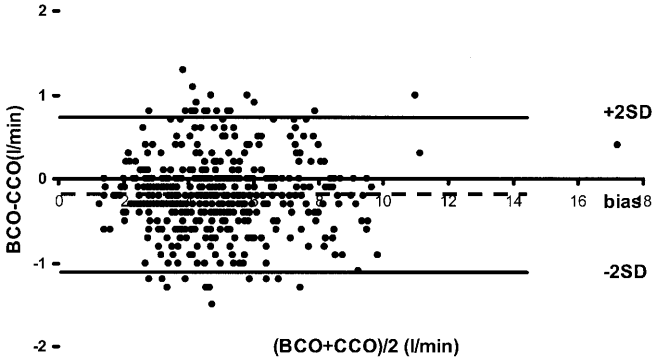

Fig. 2 Bias and variance between CCO and BCO. Mean and 95% confidence intervals are shown

CO values (Fig. 1), agreements were similar when values were grouped for cardiac output higher or lower than 5 l/min (Table 1). The CO measurements were separated into nine groups, to evaluate whether the CCO measurement technique produced reliable results over a wide range of temperatures. CCO measurements agreed closely with BCO measurements across a wide range of temperatures from 34.0° to 40.9°C.

Discussion

Many efforts have been made to measure cardiac output continuously, but no routine method provides satisfactory results in terms of accuracy, ease of use and minimal invasiveness. The accuracy of echo Doppler and bioimpedance techniques is still controversial [14]. CCO measurement provides a method to measure cardiac output continuously in critically ill patients. In the CCO system a safe [9] level of heat is transferred to the blood by a computer-controlled thermal filament mounted on a modified standard Swan-Ganz catheter without the need for calibration. This technique has several advantages over BCO. First, accurate measurement of BCO depends on several factors, including constant injection, technique of injection, temperature and the volume of the injectate bolus, the speed of the injection, and timing of the indicator injection within the respiratory cycle [19, 22, 23, 24, 25, 26]; the CCO technique can avoid these shortcomings. Second, important and rapid changes in cardiac output may be lost in the critically ill patient during the interval between successive BCO measurements; CCO is displayed continuously. Third, quite large amounts of additional fluid may be needed to obtain frequent BCO measurements; no additional fluid is needed for CCO measurement. Finally, repeated manipulations and fluid injection increase the risk of infections in BCO measurement; CCO eliminates the need for such manipulations.

Since the initial experimental and clinical data from Yelderman and coworkers [8] the CCO technique has undergone investigation in animals and critically ill patients. Table 2 compares CCO with BCO measurements in animal and clinical studies. The bias and precision is not always consistent among the clinical studies, ranging from excellent [11, 14, 18] to acceptable [27] agreement. Most of these studies did not consider changes in body temperature. Boldt et al. [14] compared 404 pairs of CCO with BCO in 35 patients and found that CCO is accurate in the critically ill patient. They also observed that increased temperature did not influence the agreement of CCO and BCO measurement from 58 pairs of cardiac output measurements with rectal temperatures higher than 39°C. Bottiger et al. [18] studied 22 cardiac surgical patients with 286 data points and reported a high correlation between CCO and BCO at different time points of the ICU stay. The correlation between CCO and BCO was not affected by the change in blood temperature from 33.2° to 39.6°C.

As in the studies by Haller et al. [17] and Boldt et al. [14], we used the same pulmonary artery catheter to obtain both CCO and BCO. Haller et al. [17] performed bolus determinations of cardiac output in 12 patients using the conventional thermodilution technique and simultaneously using the indocyanine green dye dilution technique, compared with CCO. They regarded CCO mea-

Table 2 Comparison of CCO versus BCO measurement (*n* number of subjects, – not available)

Reference	Subjects	*n*	Data sets	Bias (l/min)	Precision (l/min)	*r*	Range of cardiac output (l/min)	Range of temperature reported (°C)
Yelderman et al. [8]	Sheep	7	227	–0.16	0.52	0.97	1.5–13.2	Around 40
Yelderman et al. [12]	Patients	54	222	+0.02	0.53	0.94	2.8–10.8	–
Haller et al. [17]	Patients	12	140	+0.35	1.01	0.95	3.8–15.6	–
Munro et al. [13]	Patients	9	100	+0.02	0.87	0.87	6–17	–
Boldt et al. [14]	Patients	35	404	+0.03	0.52	–	1.6–16	>39
Hogue et al. [16]	Patients	25	91	+0.41	0.82	–	2–6	–
Bottiger et al. [11]	Patients	30	540	–0.02	0.59	0.87	2–10	–
Bottiger et al. [18]	Patients	22	286	–0.05	0.56	0.92	2–10	33.2–39.6
Jakobsen et al. [28]	Patients	20	231	+0.31	0.85	0.90	2.5–14.9	–
Jacquet et al. [29]	Patients	23	173	–0.01	0.69	0.92	1.6–11.3	–
Le Tulzo et al. [30]	Patients	23	369	–0.39	0.85	–	3–16	–
Schmid et al. [31]	Patients	56	668	0.00–0.36	0.70–0.90	0.81–0.90	3–11	–
Zollner et al. [27]	Patients	20	240	+0.52	1.29	0.89	3.1–18.4	–
Present study (software 5.02E)	Sheep	35	465	–0.19	0.45	0.97	1.1–17.4	34.0–40.9

surement using the thermodilution technique as reasonably accurate. Yelderman et al. [8] compared CCO with BCO measurements in 7 sheep and obtained similar results to our study. However, the body temperature of the sheep in this study was around 40°C, and the authors were unable to determine whether the agreement was influenced by changes in body temperature. In our present study the agreement between CCO and BCO was consistent over a wide range of body temperatures between 34.0° and 40.9°C and during the whole septic shock experiment lasting more than 24 h. We thus regard CCO measurement as suitable not only in elective surgical conditions but also in critical conditions at any body temperature.

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