REPRODUCIBILITY OF THERMODILUTION CARDIAC OUTPUT DETERMINATION IN CRITICALLY ILL PATIENTS: COMPARISON BETWEEN BOLUS AND CONTINUOUS METHOD

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ABSTRACT. Objective. A semi-continuous thermodilution method (CCO) was recently developed to measure cardiac output with less risk of bacterial contamination, fluid overload, and user-induced errors than the classical bolus technique (BCO). Previous comparison between these two methods showed negligible bias. However, large limits of agreement suggest that the two methods are not interchangeable. We hypothesized that this poor agreement may be due to differences in reproducibility. **Methods.** In 23 critically ill patients, 369 paired measurements of CCO and BCO were compared (range of cardiac outputs: 2.8 to 16 L/min). The reproducibility of BCO and CCO methods was evaluated on a sample of 205 and 209 determinations, respectively. **Results**. The comparison between the CCO and the BCO methods confirmed previous results: i.e., small bias (−0.39 L/min) and large limits of agreement (−2.06 to +1.28 L/min). Reproducibility showed no bias for either the CCO or the BCO method. Limits of reproducibility agreement between repeated determinations were approximately 50% less for CCO than for BCO method: respectively −0.87 to +0.82 L/min for the CCO method and −1.56 to +1.37 L/min for the BCO method. Consequently, the threshold necessary to ascertain that the difference between two measurements was not due to the internal variability of the method (3 × SEM) was 0.39 for the CCO method and 0.75 L/min for the BCO method. **Conclusion**. Differences in reproducibility may explain the poor agreement between the CCO and BCO methods. The better reproducibility of the CCO method allows the detection of smaller variations in cardiac output and suggests the superiority of this new method.

KEY WORDS. Critically ill, heart, cardiac output, hemodynamics, thermodilution technique, monitoring, catheterization.

INTRODUCTION

The management of critically ill patients usually requires the measurement of hemodynamic variables such as right atrial, pulmonary arterial, and radial arterial pressures, as well as arterial and mixed venous oxygen saturations [1]. This information is continuously available, but the current procedure used to measure cardiac output is based on the bolus thermodilution method (BCO). This method provides only intermittent measurements, requires time-consuming procedures and calculations, and is subject to user-induced errors due to improper injection technique. Furthermore, this method may cause fluid overload in volume-sensitive patients, and may be a cause of bacterial contamination [2]. It is possible to circumvent these problems with continuous monitoring of cardiac output,

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which may provide early information on fluid challenge, vasoactive therapy, or modifications in mechanical ventilation. Furthermore, this method can also uncover pathological modifications in hemodynamically unstable patients.

A semi-continuous thermodilution method (CCO) has been recently developed [3, 4]. This method uses a standard pulmonary artery catheter modified by the attachment of an electrically controlled right ventricular thermal filament, which adds small amounts of heat into the blood in a specific, random, on-off sequence, without any addition of volume. The heat pulses serve as the indicator and replace the traditional fluid bolus, without introduction of thermal risk [5].

Since 1992, several studies (Table 1) [4, 6–14] have compared the agreement between the BCO technique and the (CCO) technique using the method of Bland and Altman [15, 16]. These studies used the BCO technique as the reference, since this was a standard method, and more importantly because of its widespread clinical use. Except for two recent studies [13, 14], this comparison was limited to cardiac outputs below 10 L/min. All studies showed a negligible mean difference (bias) between the two methods, but large limits of agreement (0.6 to 1.7 L), clearly suggesting that the two methods are not interchangeable. However, whether one method is better than the other remains to be established. We hypothesize that this lack of agreement may be due to the difference in reproducibility between the two methods. Indeed, as shown by Stetz et al. in 1982 [17], the lack of accuracy of the BCO method compared with the standards (Fick or dye dilution) is likely to be due to its large variability. Obviously, the more repeatable method will be the more accurate [15].

The aims of the present study were to: 1) assess the agreement between the BCO and CCO methods in a large panel of critically ill patients, with a wide range of cardiac outputs, and 2) to compare the reproducibility of the two methods and determine which one is the most accurate.

MATERIALS AND METHODS

Patients

Twenty-one patients admitted to the medical intensive care units of two university hospitals were included. Mean age was 62 yr. (range 35 to 83), mean SAPS (simplified acute physiology score) [18] on admission was 16 (range 7 to 25). Diagnoses were septic shock (n = 16), cardiogenic shock (n = 2), hypovolemic shock (n = 1), paraquat intoxication (n = 1), and hyperthyroidism (n = 1). All patients were on mechanical ventilation. The hemodynamic status of these patients required the placement of a pulmonary artery catheter, according to the judgement of the physician in charge. Patients with atrial fibrillation or tricuspid insufficiency were excluded. The study protocol was approved by the institutional review boards.

Methods

The quadruple lumen pulmonary artery catheter (Intellicath™ Continuous Cardiac Output Thermodilution Catheter, model PA3-H 8F, Baxter Healthcare Corporation, Edwards Critical-Care Division, Irvine, CA) is connected to a monitor (Vigilance™, Baxter Healthcare Corporation, Edwards Critical-Care Division, Irvine, CA). The system allows automatic and semi-continuous measurement of cardiac output by the thermodilution technique with heating instead of cooling of the blood. The system combines the use of the indicator dilution principle with signal-to-noise processing techniques that eliminate background thermal noise in the pulmonary artery. The heating source is a thermal filament coated with an ultra-thin polymer film and placed on the catheter wall in the region of the catheter injectate port. When the catheter is inserted into the heart, the filament is located within the right ventricle, away from the ventricular wall. Small energy signals are introduced directly into the blood in a random, on-off pattern to form the input signal, which is repeated continuously. The resulting temperature changes are detected by a distal thermistor in the pulmonary artery and form the output signal. The input and output signals are cross-correlated through a complex formula to generate a classic indicator dilution curve from which cardiac output is calculated. The system does not provide instantaneous cardiac output, but, rather, averages measurements over a 3- to 6-min period, updated every 30 sec. The technique and the theoretical background are detailed elsewhere [3, 4].

The monitor is also able to measure cardiac output by the traditional BCO method using the same catheter. In the BCO mode, when the injectate menu is operating, the CCO mode is cancelled and has to be restarted later.

Protocol

The Intellicath™ catheter was inserted, the proximal injectate port was positioned in the right atrium just above the tricuspid valve, and the position was checked

Table 1. Results of the Main Studies on Comparison Between Bolus (BCO) and Semi-continuous (CCO) Methods of Cardiac Output Measurements. Limits of Agreement are Calculated for All Studies as MD ± 1.96 SD where MD (Mean Difference) is the Bias and SD (Standard Deviation) is the SD of the Bias (Precision)

Reference	Yelderman 1992 (4)	Lichtenthal 1993 (6)	Spackman 1993 (7)	Glorieux 1994 (8)	Schmid 1994 (9)	Lichtenthal 1994 (10)	Böttiger 1994 (11)	Haller 1994 (12)	Munro 1994 (13)	Bolt 1994 (14)	Present study
BCO determination											
No. of measurements	2 to 5	NA	3	≥3	3 to 5	NA	3	NA	3	3	3
Injectate volume (mL)	10	NA	10	10	NA	NA	NA	10	10	NA	10
Injectate temperature	Room	NA	Room	Room	Cold	NA	Cold	Cold	Cold	Cold	Cold
CCO determination											
Sample	222	165	45	104	167	183	175	163	100	404	369
Range (L/min)	2.8 to 10.8	2.0 to 9.0	NA	3.4 to 10.0	3.2 to 10.8	2.0 to 8.0	2.6 to 9.8	3.8 to 15.6	5.5 to 14.0	1.6 to 16.0	2.8 to 16.0
Bias (L/min	0.02	−0.01	−0.06	NA	0.01	−0.21	0.06	0.35	0.02	0.03	−0.39
Precision (L/min)	0.54	0.59	1.00	NA	0.9	1.40	0.56	1.01	0.88	0.52	0.85
Limits of agreement (L/min)	−1.04 to 1.08	−1.17 to 1.15	−2.02 to 1.90	−0.97 to 1.26	−1.75 to 1.77	−2.95 to 2.53	−1.04 to 1.16	−1.63 to 2.33	−1.70 to 1.74	−0.99 to 1.05	−2.06 to 1.28

Underlined references are published papers.
NA: not available.

by radiograph and pressure measurement. The catheter was then connected with the Vigilance® monitor. After self-test and initialization, the CCO was measured and recorded.

To compare CCO and BCO measurements, every 6 hours the CCO value was noted. Immediately after this, warm solution was removed from the catheter, and then a rapid series of three ice-cold solution boluses were given. A 10-ml ice-cold 5% dextrose solution was injected using a closed-injected delivery system (CO-Set®, Baxter Edwards, Critical-Care) with in-line temperature measurement. Thermodilution curves were always plotted to detect artifacts. The BCO values were obtained by averaging at least three measurements randomly within the respiratory cycle. The average BCO value was then compared with the value obtained immediately before CCO. During the study period, there was no change in the mechanical ventilation parameters or in any therapeutical intervention.

To evaluate the reproducibility of the two methods, a second CCO value was obtained immediately after the series of boluses and compared with the first CCO value. The first and the third BCO values were also compared in this manner.

Statistical analysis

The paired data were plotted and the line of identity on which all points would lie if the two methods gave exactly the same results was drawn. Agreement between CCO and BCO measurements was assessed by the method of Bland and Altman [15,16]. The bias is the mean difference (MD) between the two methods of measurement and represents the systematic error; bias is compared to ideal null bias (paired t-test, a P-value < 0.05 was considered significant). Precision (the SD of the bias) is representative of the random error or variability between the two techniques. MD ± 1.96 SD are the limits of agreement. If the limits of agreement are smaller than the threshold of clinical relevance, the two methods may be considered in agreement, and therefore interchangeable.

The reproducibility of the BCO and CCO methods were first analyzed according to Stetz et al. [17]: the standard error of the mean (SEM) is the basis for predicting reproducibility. SEM is derived by dividing the standard deviation of repeated measurements by the square root of the number of measurements (two for both BCO and CCO). SEM is characteristic of the variability for each method or instrument. SEM may also be used to determine for each method the threshold required to differentiate two values of CCO: a variation

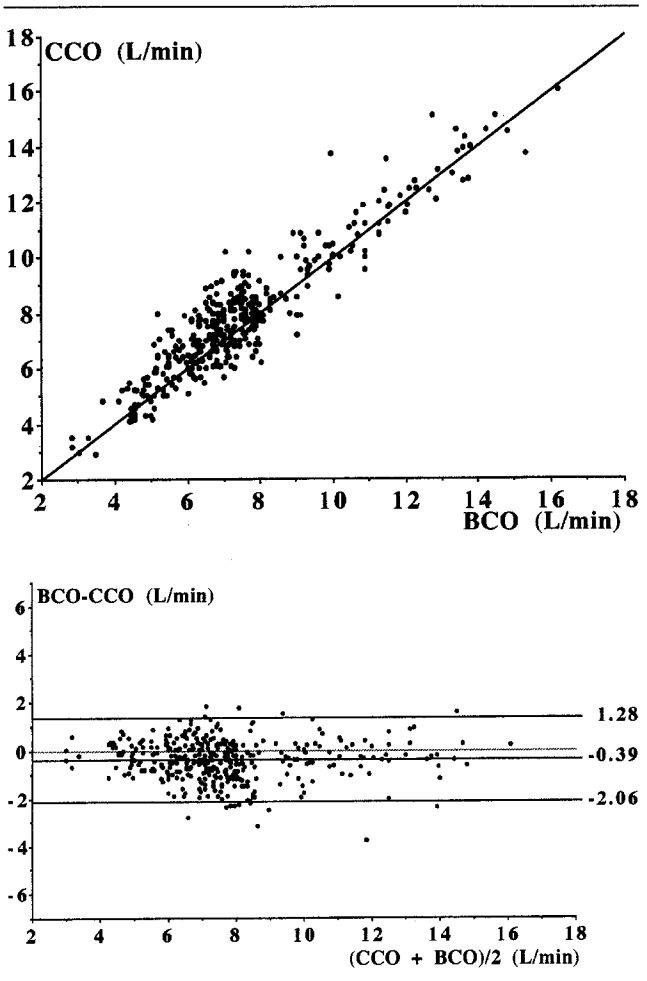

Fig 1. Comparison between semi-continuous method (CCO) and bolus method (BCO) of cardiac output determination by thermodilution (n = 369 paired determinations). On the upper graph are represented the paired determinations and the line of identity. On the lower graph are represented the mean (X-axis) and the differences (Y-axis) of the paired determinations. The dotted line represents the line of identity. Solid lines are the bias and the limits of agreement between the two methods.

of three SEM is needed to be confident that two values of cardiac output are different.

Reproducibility of both CCO and BCO was also analyzed according to Bland and Altman [15, 16]: We used the CO measurements before and after the series of bolus injections for CCO. Similarly, the first and third measurements of BCO were used as paired data.

RESULTS

No particular complications or difficulties were noted during catheter insertion or measurement. Two patients had a core temperature higher than 40 °C, and CCO determination was temporarily interrupted. No deleterious effects were noted in terms of thermal change and no data were eliminated before analysis. Data obtained by CCO ranged from 2.90 to 16 L/min (mean 7.87 L/min), and those obtained by BCO ranged from 2.80 to 16 L/min (mean 7.48 L/min).

Agreement

The comparison between the two methods is shown in Figure 1. Mean values obtained by the CCO method were higher than those obtained by the BCO method; bias was −0.39 L/min and was different from ideal null bias ($P < 0.001$). SD of the difference (precision) was 0.85 L/min and the limits of agreement between the two methods were −2.06 and +1.28 L/min.

Reproducibility

The reproducibility of the BCO and CCO methods was evaluated on a sample of 205 and 209 determinations, respectively; SEM was 0.25 L/min and O.13 L/min, respectively. Therefore, the threshold required to consider two measurements as different (i.e., not due to the variability of the method) was 0.75 L/min and 0.39 L/min for the BCO and CCO methods, respectively. Bland and Altman analysis [15, 16] (Figure 2) showed negligible bias, which was not statistically different from the ideal null bias ($P > 0.1$) (−0.02 L/min, and −0.09 L/min) for both the BCO and CCO methods. The limits of agreement were −1.56 to +1.37 L/min for the BCO method and approximately half as much for the CCO method (−0.87 to +0.82 L/min).

DISCUSSION

The main result of this study, which has not been shown previously, is that repeated measures of CCO showed less variability than BCO. As a result, the threshold required to differentiate two values for cardiac output is half as much for the CCO method compared with the BCO method (0.39 vs. 0.75 L/min). This point is of clinical importance because the CCO method may provide more sensitive information in hemodynamically unstable patients or during therapeutical interventions.

Technical considerations

The average of three determinations for BCO for the

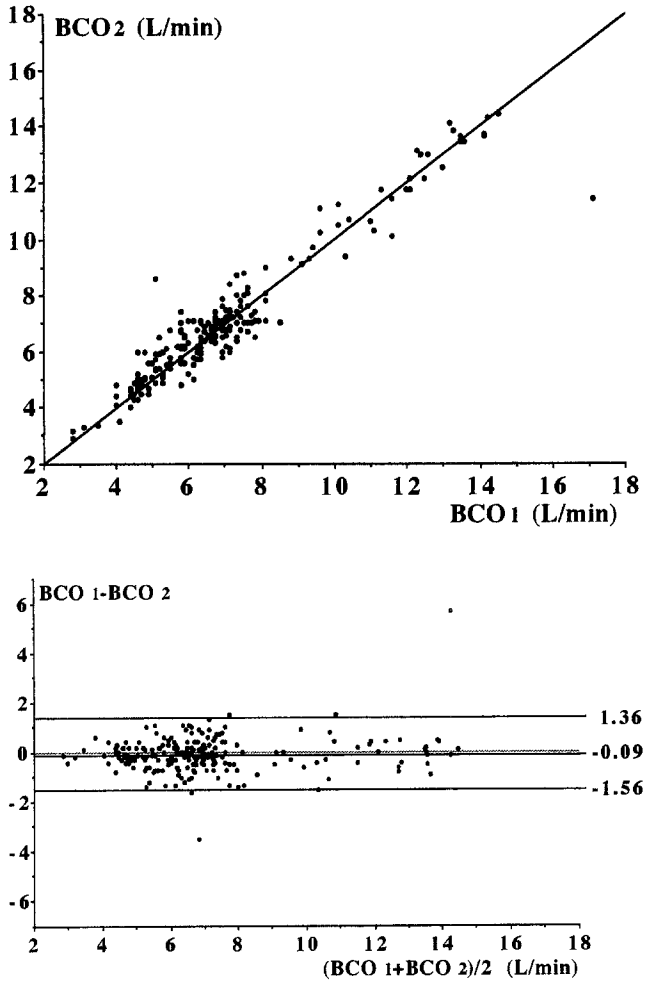

Fig 2. Reproducibility of the bolus (BCO) method of cardiac output determination (n = 205 paired determinations). On the upper graph are represented the first (X-axis) and the second (Y-axis) determinations and the line of identity. On the lower graph are represented the mean (X-axis) and the differences (Y-axis) between the first and the second determination. The dotted line is the line of identity; solid lines are the bias and the limits of agreement between the repeated measurements.

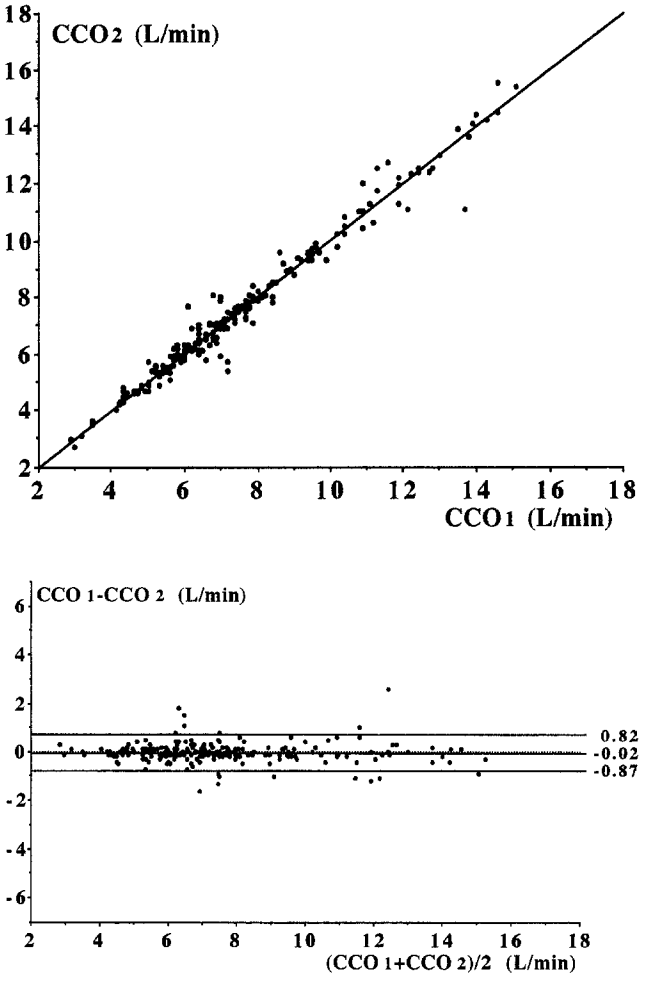

Fig 3. Reproducibility of the semi-continuous (CCO) method of cardiac output determination (n = 209 paired determinations). On the upper graph are represented the first (X-axis) and the second (Y-axis) determinations and the line of identity. On the lower graph are represented the mean (X-axis) and the differences (Y-axis) between the first and the second determinations. The dotted line is the line of identity, solid lines are the bias and the limits of agreement between the repeated measurements. Comparison with Figure 2 shows in both cases negligible bias, but smaller limits of agreement and, thus, less variability for the CCO method.

comparison between CCO and BCO was used. No value was discarded so that the method could be evaluated in its original form. Due to the known variability of this method [17], values that differ by more than 0.5 or 0.6 L/min are usually rejected in clinical practice, based on the investigator's judgement. This practice limits the effects of the variability, but leads to an undetermined number of measurements and a variable delay between the three measurements finally selected. During this delay, cardiac output may change, especially in critically ill patients under mechanical ventilation or in those receiving fluid challenge and/or inotropic drugs. For all of these reasons, in order to have a standardized protocol of measurements, we took the mean of three values at random times during the respiratory cycle.

To compare the reproducibility of the BCO and the CCO determination, we used the first and the third value for the BCO method. This was done to minimize the effect of time. In addition, the first and the third values of the BCO measurement were the closest values to the CCO measurements, which took place just before and after the BCO measurements. We did not rule out the effect of time between the measurements; however, if it did exist, this effect was less favorable for the CCO

method because the delay between the two measurements was greater.

Comparison between BCO and CCO determinations

Since 1992, numerous studies have compared BCO and CCO measurements. The results are summarized in Table 1. Only one recent study [14] and ours involve a large number of measurements (404 and 369, respectively) and a large range of cardiac outputs (1.6 to 16 L/min).

In all of the studies [4, 6–14], the bias was small and was positive or negative depending on the study. These results are not surprising because the technique of measurement is basically the same in the two methods, differing only by software designated to limit variability.

All of the limits of agreement (i.e., bias ± 1.96 SD) are reported on the last two lines of Table 1 and show that our results are in the range of the others. The limits of agreement are considered acceptable and, therefore, the methods are interchangeable when they do not exceed a threshold of clinical relevance. Such a threshold is difficult to define and none of the previous studies attempted to do so. However, in clinical practice, it is difficult to consider that the differences, as large as −2.06 L/min or +1.28 L/min, found in our study are negligible. Therefore, it seems that the two methods are not interchangeable, and, as pointed out by Bland and Altman [15, 16], "when the old method is the more variable one, even a new method that is perfect will not agree with it." Consequently, we hypothesized that this poor agreement could be due to differences in reproducibility between the two methods.

Reproducibility of the BCO and CCO methods

The large variability of the BCO method has been known since the study by Stetz et al. in 1982 [17]. This variability is due to variations in the technique of injection and in cardiac blood flow during the ventilatory cycle. The CCO method has the important advantage in clinical practice of providing semi-continuous data. It further reduces the variability to near 50%. This reduction is achieved partly because the CCO method is independent of the investigator and the technique of injection, and so it integrates the data over 3 to 6 minutes, smoothing out the dynamic changes (such as the influence of the ventilator settings), and partly because of the calculations that improve the signal-to-noise ratio. These calculations use the addition of several "responses" to a periodically repeated stimulation, represented here by the repeated pattern of changes in temperature. Such a technique is well-known in neurological testing for the measurement of evoked potentials.

The reproducibility may also be assessed by the calculation of two or three SEM [17]: the results confirm that the reproducibility of the CCO method is twice as good as that of the BCO method. We chose 3 SEM as the variation needed to consider two measurements as different for both methods. Consistent with the findings of Stetz et al. [17], we found that this threshold was 0.75 L/min for BCO and 0.39 L/min for CCO. This is of great importance in clinical settings, where the alterations in cardiac output under therapeutic intervention are more significant than the determination of an isolated value. For example, if, after introducing an inotropic agent in a patient with cardiogenic shock, the same variation of 0.6 L/min is significant in one case and not in another, we can suppose that medical strategies would be quite different in these two cases.

In summary, the large limits of agreement between the CCO and BCO methods of thermal dilution cardiac output determination suggest that the two methods are not interchangeable, likely because of the difference in reproducibility. However, the bias between the two methods is negligible and according to Bland and Altman [15, 16], the CCO method, which has less variability, is preferable. Furthermore, the CCO method allows detection of smaller variations in cardiac output compared with the BCO method, and in clinical practice is likely to be of better quality and usefulness than the BCO method.

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