Intensive Care Med (2002) 28:1470–1474
DOI 10.1007/s00134-002-1477-1

ORIGINAL

Evaluation of a noninvasive method for cardiac output measurement in critical care patients

Gastón E. Murias
Ana Villagrá
Sara Vatua
Maria del Mar Fernandez
Héctor Solar
Ana Ochagavía
Rafael Fernández
Josefina López Aguilar
Pablo V. Romero
Lluis Blanch

Received: 11 February 2002
Accepted: 26 July 2002
Published online: 4 September 2002

This study was carried out at the Intensive Care Department, Hospital de Sabadell, Corporació Parc Tauli, Sabadell, Spain.
The study was partially funded by the Fundació Parc Tauli.

G.E. Murias · H. Solar
Critical Care Center, Hospital San Martín, La Plata, Argentina

A. Villagrá · S. Vatua
M. del Mar Fernandez · A. Ochagavía
R. Fernández · J.L. Aguilar · L. Blanch (✉)
Critical Care Center, Hospital de Sabadell, Corporacio Parc Tauli, Parc Taulí s/n, 08208 Sabadell, Spain
e-mail: lblanch@cspt.es
Tel.: +34-93-7458323
Fax: +34-93-7175116

P.V. Romero
Respiratory Department, Hospital de Bellvitge, Barcelona, Spain

Abstract *Objective:* Thermodilution (TD) is the gold standard to monitor cardiac output (CO) in critical care. However, there is concern about the safety of right-ventricular catheterization. The CO_2 rebreathing technique allows noninvasive CO determination by means of the indirect Fick principle. Our objectives were: (a) to assess the accuracy of a new system of CO measurement using the CO_2 partial rebreathing method (PRCO); (b) to evaluate whether the PRCO itself may induce changes in CO. *Design and setting:* Prospective study in the intensive care department in a university-affiliated hospital. *Patients:* Twenty-two mechanically ventilated critically ill patients. *Interventions:* CO measured simultaneously by PRCO and TDCO. *Measurements and results:* PRCO and TDCO values were compared by concordance analysis. Stability of cardiac output during PRCO was evaluated by comparing the TDCO measurements before, during, and after the partial rebreathing period using analysis of variance. From a total of 79 valid sets of measurements, bias and precision was calculated at –0.18±1.39 l/min. The concordance analysis of lower and intermediate CO values (<7 l/min) yielded a bias and precision calculation of –0.07±0.91 l/min. No changes in hemodynamics were observed during the partial rebreathing period. *Conclusions:* The noninvasive partial CO_2 rebreathing technique may be an alternative method for CO determination in mechanically ventilated critically ill patients. The rebreathing maneuver alone does not induce changes in CO.

Keywords Cardiac output · Carbon dioxide rebreathing · Thermodilution · Monitoring · Hemodynamics · Critical care

Introduction

Since the introduction of the balloon-directed thermistor-tipped pulmonary artery catheter in critical care medicine in the 1970s [1] thermodilution cardiac output measurements (TDCO) have been available at the bedside. Although some inaccuracies with the method have been reported, it has become the clinical "gold standard." Nevertheless, concern about catheter safety [2, 3] surfaced soon after catheterization of the pulmonary artery was introduced, and several physicians suggested a moratorium in catheter use [4, 5, 6]. However, as recent investigations have highlighted the importance of invasive goal-directed therapy in the earliest stages of severe sepsis and septic shock [7], research and clinical testing of fast, noninvasive methods to monitor hemodynamic status in critically ill patients are necessary.

Various approaches to noninvasive critical care monitoring have been suggested. Analyses of exhaled CO_2 and rebreathing techniques have been tested for CO determination in the critical care setting. Several authors [8, 9, 10, 11] have reported the accuracy of the rebreath-

ing method for CO measurement in critically ill patients. Unfortunately, however, as this technique is technically difficult and time consuming, its routine use in the critical care arena is limited. To overcome the technical burden of this method the partial rebreathing technique for CO measurement (PRCO) has been commercially developed (NICO, Novametrix) [12]. This is an automated, noninvasive method that uses the indirect Fick principle. The monitor measures end-tidal PCO_2 ($P_{ET}CO_2$) and CO_2 production (VCO_2) in basal conditions during 50 s of partial rebreathing through an added instrumental dead space. By assuming stable hemodynamics, cardiac output is estimated from the changes induced in $P_{ET}CO_2$ and VCO_2.. Nevertheless, during the partial rebreathing period $PaCO_2$ increases in variable amounts (usually 4–5 mmHg) that could alter hemodynamics, mainly CO and systemic vascular resistance. Whether the increase in $PaCO_2$ can modify CO is not known.

We designed this study to answer two questions: first, how accurate are partial rebreathing CO measurements in critical care patients receiving mechanical ventilation, and, second, does the partial rebreathing technique alter cardiac output during the measurement period because of the increase in $PaCO_2$?

Material and methods

We studied 29 critically ill patients recovering from various clinical conditions and receiving mechanical ventilation in volume-controlled mode. The study was performed at the General Intensive Care Department of the Hospital of Sabadell. The protocol was approved by the ethics committee, and informed consent was obtained from the patients' relatives. Inclusion criteria were the need for mechanical ventilation because of acute lung injury, the presence of a thermistor-tipped pulmonary artery catheter (7.5 F catheter, Baxter., Irvine, Calif., USA) for clinical indication, and hemodynamic stability during the procedure. The partial rebreathing device of the monitor (NICO with software version 2.0, Novametrix, Wallingford, Conn., USA) was placed between the Y-piece of the ventilator and the endotracheal tube. After a minimum of 30 min to allow patient stabilization, arterial and mixed venous blood samples were collected to measure shunt fraction, and PRCO was determined with the monitor using the nonaveraged form. We performed TDCO measurements (Hewlett Packard, Palo Alto, Calif., USA) with 10 ml iced DW 5% bolus randomly distributed over the respiratory cycle by using a closed circuit (Co-Set, Baxter). Measurements were performed during the basal period of the NICO monitor (three boluses), during the partial rebreathing period (two boluses), and immediately thereafter (three boluses). With each set of TDCO measurements heart rate, $P_{ET}CO_2$, and mean systemic and pulmonary artery pressures were recorded (Hewlett Packard).

During the partial rebreathing period the increment in dead space increased $P_{ET}CO_2$, while VCO_2 determination showed an artifactual reduction. The monitor measures pulmonary nonshunted capillary blood flow by using a modified indirect Fick equation [12, 13]. By adding shunted blood flow (estimated by Nunn's isoshunt curves) [14] the equipment calculates CO. Data from NICO were discarded when the monitor was unable to obtain either a stable CO_2 period or PRCO measurements.

We performed a maximum of four sets of measurements in each patient. Between measurements a minimum of 2 h was allowed. A total of 101 pairs of simultaneous measurements were performed. Twenty-two sets of measurements were discarded because the NICO monitor was unable to achieve a stable CO_2 reading. Seven patients were excluded from the study as we were unable to obtain PRCO measurements in these cases. No sets were discarded due to problems with TDCO measurements. We thus analyzed 79 sets of measurements in 22 patients (13 men, 9 women; median age 62 years, range 21–84). The median Acute Physiology and Chronic Health Evaluation II score was 17 (range 9–28).

Correlation between methods was assessed by linear regression analysis. Concordance between methods during the partial rebreathing period was determined by means of bias (mean difference between the two methods) and precision (SD of the mean difference between the two methods) [15]. The relationship between difference and mean CO measurement was assessed by the proportional difference in the CO estimation. Hemodynamic stability during the partial rebreathing period was evaluated by comparing TDCO and hemodynamic data recorded immediately before, during, and immediately after PRCO by using analysis of variance for repeated measurements. Significance was set at $p<0.05$.

Results

Cardiac output ranged from 1.4 to 12.7 l/min when measured with TDCO and from 1.4 to 13.4 l/min when measured with NICO. From a total of 79 sets of measurements we found a significant correlation between NICO and TDCO measurements ($R^2=0.71$, $p<0.001$; Fig. 1). The concordance analysis showed a bias and a precision calculation of –0.18±1.39 l/min and a 95% confidence interval (CI) of +2.59 to –2.95 l/min (Fig. 2A). The proportional difference in CO measurements between the methods was 46% and – 45%. To test the possible impact of a different number of measurements in each patient we repeated the agreement analysis with only the first set of measurements from each patient. We found very similar results, with a bias and precision calculation of 0.16±1.4 l/min and a 95% CI of +2.96 to –2.65 l/min.

Using a clinical decision-making approach, not all CO levels have the same meaning. Accordingly, we decided to analyze lower and intermediate CO, i.e., CO values below 7 l/min, separately. For these sets of measurements concordance analysis showed a bias and precision calculation of –0.07±0.91 l/min and 95% CI of +1.75 to –1.90 l/min (Fig. 2B).

The profile of hemodynamic measurements obtained before, during, and after the partial rebreathing maneuver is shown in Table 1. No changes in TDCO, heart

Table 1 Hemodynamic data during the PRCO measurement period before, during, and after rebreathing (*HR* Heart rate, *MAP* mean systemic arterial pressure, *MPP* mean pulmonary arterial pressure, *TDCO* thermodilution cardiac output)

	Before	During	After	*p*
HR (b/min)	90±18	91±18	91±19	0.993
MAP (mmHg)	81±11	81±12	82±15	0.839
MPP (mmHg)	28±6	29±6	29±6	0.692
TDCO (l/min)	5.9±2.3	6.1±2.4	6.2±2.4	0.740

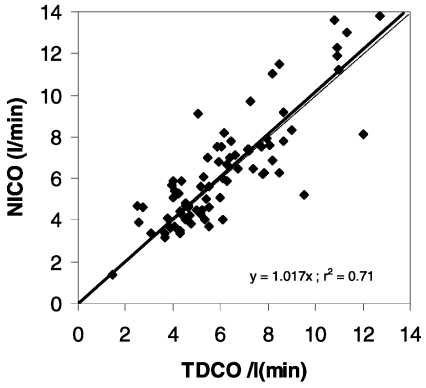

Fig. 1 Correlation plotting cardiac output determined by NICO vs. cardiac output determined by TDCO showing a significant correlation (R^2=0.71, n=79; p<0.001). *Solid line* Regression line; *dotted line* line of identity. *TDCO* Thermodilution cardiac output; *NICO* noninvasive cardiac output

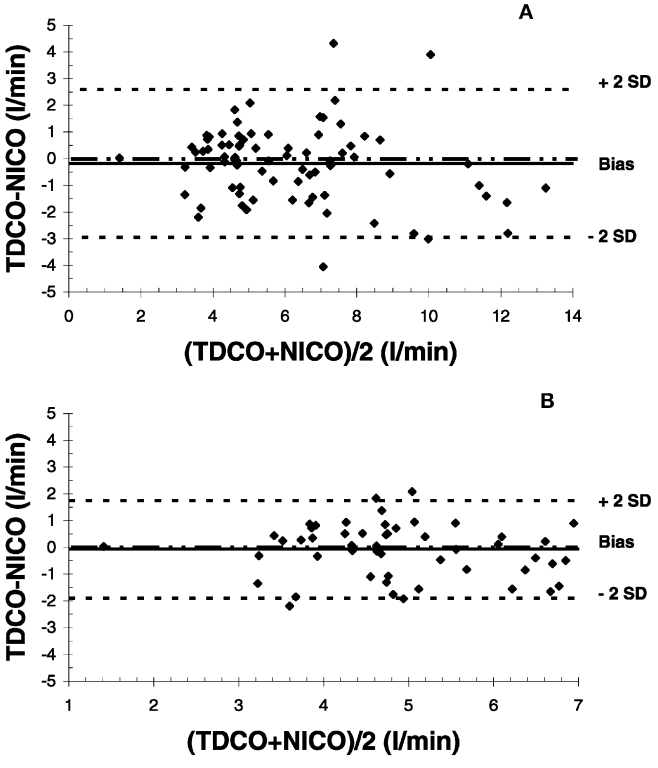

Fig. 2A, B Concordance analysis plots showing bias and agreement between TDCO and NICO. **A** Entire range of measurements. *Solid line* Bias (–0.18 l/min); *dotted lines* 95% confidence limits (±2 SD) for the bias. **B** Lower and intermediate CO values. *Solid line* Bias (–0.07 l/min); *dotted lines* 95% confidence limits (±2 SD) for the bias. *TDCO* Thermodilution cardiac output; *NICO* noninvasive cardiac output

rate, systemic, or pulmonary artery pressures were observed. $P_{ET}CO_2$ increased from 32±4.4 mmHg in the basal period to 38±4.8 mmHg (p<0.01) during the partial rebreathing period.

Discussion

The results of the present study show a good correlation between CO measurements with thermodilution and with the NICO apparatus. Nevertheless, the wide confidence intervals might reduce the possibility of direct substitution of TD for the new partial rebreathing method. An additional issue demonstrated in this study is that the NICO rebreathing maneuver did not induce any detectable changes in cardiac output.

The NICO monitor was first tested in animals [12, 16] and later in patients after cardiac surgery [17, 18]. Results are controversial but encouraging. In the critical care setting there are some limitations to the partial rebreathing technique to measure CO. First, in nonparalyzed patients the increase in instrumental dead space usually induces an increase in patient's respiratory rate to maintain $PaCO_2$, thereby reducing the magnitude of the signal, which limits the monitor's ability to detect changes in $P_{ET}CO_2$ and VCO_2. Second, noise is increased by respiratory pattern irregularities that produce unstable $P_{ET}CO_2$ and VCO_2. This reduction in signal-to-noise ratio could impair monitor accuracy. Third, additional CO not calculated with the Fick equation due to shunt fraction is estimated from pulse oxymetry and inspired oxygen content [12].

A strong limitation of research in this field is the lack of a true gold standard. Clinical use has confirmed TDCO at this site, but limitations of the method are well known [19, 20, 21, 22, 23, 24]. However, as a "clinical gold standard," TDCO offers physicians information for medical decision making. Any alternative method under evaluation must provide information similar to that obtained by means of the gold standard method. When there is a lack of agreement in this scenario, it is not always clear which method is correct and which is not. To minimize the likelihood of TDCO inaccuracies we used 10-ml boluses of iced DW 5% to increase signal magnitude and randomly distributed the bolus injection throughout the respiratory cycle to have a more representative value of the mean cardiac output [20, 25]. We used a closed circuit to minimize problems related to inhomogeneities in injectate temperature [26], and three TDCO boluses in each period were also averaged. A NICO measurement includes a 60-s basal time, a 50-s rebreathing time and a 70-s stabilization time. However, the 50-s rebreathing time was not long enough to perform three TDCO measurements, and consequently only two could be carried out. Therefore TDCO accuracy in this period may be diminished [27]. Moreover, elevation in minute ventilation induced by the increment of instrumental dead space during NICO measurement could have added thermal noise and further impaired TDCO reproducibility [28]. However, the fact that mean and standard deviation did not differ between measurements performed before, during, and after the partial rebreathing period

markedly reduces the likelihood of substantial TDCO inaccuracies. The results of the present study showed a good correlation between CO measurements with thermodilution and with the NICO apparatus. As with other authors [18], we also found less agreement between NICO and TDCO at higher CO. This could be explained in three different ways. First, at a higher cardiac output, the area under the thermodilution curve is small and signal-to-noise ratio is impaired. This might occur even if measurements are not biased. Second, during PRCO monitoring a short sudden change in instrumental dead space is induced. For a given increase in instrumental dead space (as predicted by the indirect Fick equation), signal magnitude (end-tidal and arterial PCO_2 difference) decreases as CO increases [10], resulting in precision impairment. Third, under conditions of elevated cardiac output the venous-arterial PCO_2 difference narrows, increasing the experimental error of measurement. In fact, at higher CO states both methods could be less accurate and agreement between them would worsen.

Random error tends to cancel out when repeated measurements are performed, thus improving accuracy [29, 30]. However, when a measurement is averaged, the monitor's response time and its ability to detect a sudden change in the monitored variable worsens. A major advantage of continuous or near-continuous monitoring is that it instantly alerts physicians to changes in a patient's state. The sooner a change is detected, the earlier treatment can be modified. Accordingly, we decided to test the device in the nonaveraged mode because, although the accuracy of the method is not enhanced, response time is improved.

In critical care the PRCO technique for CO monitoring has three limitations uncommon in the anesthesia scenario. First, the technique involves a moderate increase in $PaCO_2$ during the rebreathing period that precludes its use in patients with intracranial hypertension. Second, the device requires stable CO_2 elimination for a reliable CO measurement, precluding its use in spontaneously breathing patients in whom tidal volume is variable. Our patients were not paralyzed and were breathing in assisted mandatory ventilation, and therefore minute ventilation could be changed when instrumental dead space increased during the partial rebreathing period. In this situation $P_{ET}CO_2$ becomes unstable and impairs signal-to-noise ratio. In our study 22 of 101 measurements were discarded because the NICO monitor could not obtain a stable CO_2 reading. Nonetheless, none of these patients showed any clinical or hemodynamic signs of intolerance to the rebreathing period. Third, the PRCO method measures only the nonshunted fraction of the cardiac output. Since shunt fraction, hemoglobin content, hemoglobin P50, arterial CO_2 partial pressure, and the difference between arterial and mixed venous O_2 contents might be altered in critically ill patients, miscalculations of estimated shunt fraction by the NICO device could also occur.

A compelling issue in monitoring is the avoidance of any modification in the monitored variable induced by the measuring technique itself. During PRCO measurements, for a given minute ventilation, $PaCO_2$ usually increases up to 6 mmHg while mixed venous PCO_2 basically remains unchanged. Hemodynamic changes related to acute changes in CO_2 levels are well documented [31]. Consequently, to test whether transient increases in $P_{ET}CO_2$ could induce a bias in the measurement we measured TDCO immediately before, during, and immediately after the partial rebreathing period. No changes were found in CO, heart rate, or systemic and pulmonary arterial pressures secondary to the slight and brief increase in $PaCO_2$. To our knowledge, this issue has not been addressed in previous studies.

In conclusion, the NICO monitor provides a near-continuous, automated, and totally noninvasive method for CO measurement in the critical care setting. NICO offers an alternative to invasive CO measurement that could be further improved with new software developments. Nevertheless, the lack of pulmonary vascular pressure determination precludes the replacement of the pulmonary artery catheter in a substantial proportion of critically ill patients.

Acknowledgement The authors thank Novametrix for their technical support.

References

1. Ganz W, Donoso R, Marcus HS, Forrester JS, Swan HJ (1971) A new technique for measurement of cardiac output by thermodilution in man. Am J Cardiol 27:392–396
2. Gore JM, Goldberg RJ, Spodick DH, Alpert JS, Dalen JE (1987) A community-wide assessment of the use of pulmonary artery catheters in patients with acute myocardial infarction. Chest 92:721–727
3. Connors AF Jr, Speroff T, Dawson NV, Thomas C, Harrell FE Jr, Wagner D, Desbiens N, Goldman L, Wu AW, Califf RM, Fulkerson WJ Jr, Vidaillet H, Broste S, Bellamy P, Lynn J, Knaus WA (1996) The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. JAMA 276:889–897
4. Robin ED (1985) The cult of the Swan-Ganz catheter. Overuse and abuse of pulmonary flow catheters. Ann Intern Med 103:445–449
5. Robin ED (1987) Death by pulmonary artery flow-directed catheter. Time for a moratorium? Chest 92:727–731
6. Dalen JE, Bone RC (1996) Is it time to pull the pulmonary artery catheter? JAMA 276:916–918
7. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345:1368–1377

8. Franciosa JA (1977) Evaluation of the CO_2 rebreathing cardiac output method in seriously ill patients. Circulation 55:449–455
9. Neviere R, Mathieu D, Riou Y, Guimez P, Renaud N, Chagnon JL, Wattel F (1994) Carbon dioxide rebreathing method of cardiac output measurement during acute respiratory failure in patients with chronic obstructive pulmonary disease. Crit Care Med 22:81–85
10. Davis CC, Jones NL, Sealey BJ (1978) Measurements of cardiac output in seriously ill patients using a CO2 rebreathing method. Chest 73:167–172
11. Blanch L, Fernandez R, Benito S, Mancebo J, Calaf N, Net A (1988) Accuracy of an indirect carbon dioxide Fick method in determination of the cardiac output in critically ill mechanically ventilated patients. Intensive Care Med 14:131–135
12. Jaffe MB (1999) Partial CO2 rebreathing cardiac output – operating principles of the NICO system. J Clin Monit 15:387–401
13. Capek JM, Roy RJ (1988) Noninvasive measurement of cardiac output using partial CO2 rebreathing. EEE Trans Biomed Eng 35:653–661
14. Benatar SR, Hewlett AM, Nunn JF (1973) The use of iso-shunt lines for control of oxygen therapy. Br J Anaesth 45:711–718
15. Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet I:307–310
16. Maxwell RA, Gibson JB, Slade JB, Fabian TC, Proctor KG (2001) Noninvasive cardiac output by partial CO2 rebreathing after severe chest trauma. J Trauma 51:849–853
17. Nilsson LB, Eldrup N, Berthelsen PG (2001) Lack of agreement between thermodilution and carbon dioxide-rebreathing cardiac output. Acta Anaesthesiol Scand 45:680–685
18. Heerden PV van, Baker S, Lim SI, Weidman C, Bulsara M (2000) Clinical evaluation of the non-invasive cardiac output (NICO) monitor in the intensive care unit. Anaesth Intensive Care 28:427–430
19. Synder JV, Powner DJ (1982) Effects of mechanical ventilation on the measurement of cardiac output by thermodilution. Crit Care Med 10:677–682
20. Stevens JH, Raffin TA, Mihm FG, Rosenthal MH, Stetz CW (1985) Thermodilution cardiac output measurement. Effects of the respiratory cycle on its reproducibility. JAMA 253:2240–2242
21. Driscoll A, Shanahan A, Crommy L, Foong S, Gleeson A (1995) The effect of patient position on the reproducibility of cardiac output measurements. Heart Lung 24:38–44
22. Harris AP, Miller CF, Beattie C, Rosenfeld GI, Rogers MC (1985) The slowing of sinus rhythm during thermodilution cardiac output determination and the effect of altering injectate temperature. Anesthesiology 63:540–541
23. Elkayam U, Berkley R, Azen S, Weber L, Geva B, Henry WL (1983) Cardiac output by thermodilution technique. Effect of injectate's volume and temperature on accuracy and reproducibility in the critically Ill patient. Chest 84:418–422
24. Bazaral MG, Petre J, Novoa R (1992) Errors in thermodilution cardiac output measurements caused by rapid pulmonary artery temperature decreases after cardiopulmonary bypass. Anesthesiology 77:31–37
25. Delhaas T, Mook GA, Zijlstra WG (1992) Respiration and measurement of cardiac output by thermodilution and central or peripheral dye dilution. J Appl Physiol 73:1047–1051
26. Nelson LD, Anderson HB (1985) Patient selection for iced versus room temperature injectate for thermodilution cardiac output determinations. Crit Care Med 13:182–184
27. Jansen JR, Versprille A (1986) Improvement of cardiac output estimation by the thermodilution method during mechanical ventilation. Intensive Care Med 12:71–79
28. Wessel HU, James GW, Paul MH (1966) Effects of respiration and circulation on central blood temperature of the dog. Am J Physiol 211:1403–1412
29. Chatburn RL (1995) Measurement theory: accuracy issues in monitoring. In: Critical care monitoring: from pre hospital to the ICU. Mosby Yearbook, St. Louis, pp 17–42
30. Levine RL, Sadovnikoff N (1995) Principles of biological signals. In: Levine RL, From RE (eds) Critical care monitoring: from pre hospital to the ICU. Mosby Yearbook, St. Louis, pp 3–16
31. Mas A, Saura P, Joseph D, Blanch L, Baigorri F, Artigas A, Fernandez R (2000) Effect of acute moderate changes in PaCO2 on global hemodynamics and gastric perfusion. Crit Care Med 28:360–365