Noninvasive Monitoring Cardiac Output Using Partial CO\textsubscript{2} Rebreathing

Brian P. Young, MD\textsuperscript{a,*}, Lewis L. Low, MD\textsuperscript{b}

Proper management of critically ill patients requires the rapid and accurate assessment of cardiac function over a wide range of disease states. Hemodynamic assessment is essential for care of these patients and ideally would be accomplished with a minimally invasive device that can provide precise measurements with few risks to the patient. Advanced cardiovascular monitoring is a prerequisite to optimize hemodynamic treatment in critically ill patients who are commonly prone to cardiocirculatory failure.\textsuperscript{1} Continuous measurement of cardiac output enables the early recognition of hemodynamic trends and allows for earlier therapeutic interventions. The most ideal cardiac output (CO) monitor should be reliable, continuous, noninvasive, operator-independent, cost-effective, and have a fast response time.\textsuperscript{1} Technology should be applicable to both the ICU and the operating room monitoring for management of the patient. Moreover, cardiac output monitoring and early fluid management interventions may translate into better outcomes and cost savings through reduced length of ICU and hospital stay.\textsuperscript{2}

Routine measurement of cardiac output has been available only since the 1970s, when Swan and colleagues\textsuperscript{3} reported that pulmonary artery catheter (PAC) insertion could be performed at the bedside with a specially designed balloon tipped catheter. Cardiac output monitoring with a PAC using the bolus thermodilution method became the de facto gold standard shortly after its introduction. Continued questions about the PAC’s effect on morbidity and mortality\textsuperscript{4} have led to an increased interest in other methods, particularly noninvasive methods for cardiac output monitoring. In particular, noninvasive carbon dioxide (CO\textsubscript{2}) Fick methods are seeing a resurgence in

\textsuperscript{a} Kern Critical Care Unit, Good Samaritan Medical Center, Legacy Health, 2282 NW Northrup Street, Suite #42, Portland, OR 97210, USA
\textsuperscript{b} Medical Specialties Division, Legacy Health, 2282 NW Northrup Street, Suite #41, Portland, OR 97210, USA
* Corresponding author.
E-mail address: byoung@lhs.org
research and clinical interest. This article reviews one such device using partial CO₂ rebreathing to determine cardiac output and its application for hemodynamic monitoring in an ICU and the operating room setting.

THEORY OF OPERATION

Adolph Fick described the first method of cardiac output estimation in 1870. This method remains the original reference standard by which all other means of determining cardiac output are evaluated. Fick postulated that oxygen uptake in the lungs is entirely transferred to the blood. Therefore, cardiac output can be calculated as the ratio between oxygen consumption (VO₂) and arteriovenous difference in oxygen (AVDO₂). The Fick principle allows substitution with a multitude of substitutes for oxygen consumption, including CO₂ clearance, and can be represented mathematically as shown in Fig. 1.

![Fig. 1. CaCO₂ content (ml/100 mL blood); CO, cardiac output; CvCO₂, mixed venous CO₂ content (ml/100 mL blood); etCO₂, etCO₂ concentration (mmHg); FiO₂, fraction of inspired oxygen; N, normal ventilation; R, rebreathing; S, slope of CO₂ dissociation curve; SpO₂, oxygen saturation obtained by pulse oximetry (%). (From Hofer CK, Ganter MT, Zollinger A. What technique should I use to measure cardiac output? Curr Opin Crit Care 2007;13(3):308–17; with permission.)](image-url)
Venous CO\(_2\) (VCO\(_2\)) can be calculated by the difference in CO\(_2\) content between expired and inspired gases. The Fick equation can then be further modified by use of a partial CO\(_2\) rebreathing technique. This involves a transitory interruption of CO\(_2\) elimination by the addition of dead space to the ventilatory circuit, which leads to a progressive increase in end-tidal CO\(_2\) (etCO\(_2\)) that approximates the mixed venous partial CO\(_2\) value.\(^7\)\(^{-10}\) This eliminates the need for a direct measurement of CvCO\(_2\) and, therefore, the need for a central venous catheter.\(^5\)\(^,\)\(^6\)\(^,\)\(^10\) The change (delta) VCO\(_2\) is then calculated by comparing normal and rebreathing values. The change (delta) in arterial CO\(_2\) (CaCO\(_2\)) content can then be approximated by the change in etCO\(_2\) multiplied by the slope of the CO\(_2\) dissociation curve (S), which is linear between 15 and 70 mmHg of partial pressure of CO\(_2\).\(^6\)\(^,\)\(^10\) Because intrapulmonary shunts can affect estimates of CO with this technique, an arterial blood sample is required to enter arterial oxygen tension values for shunt estimation. This leaves the equation as follows:

\[
\text{CO} = \frac{\Delta VCO_2}{S} \times \Delta \text{etCO}_2
\]

Combining measurements under normal and rebreathing conditions allow elimination of VCO\(_2\) content from the Fick equation and, therefore, there is no requirement for a central venous access for data input in the calculations.\(^6\)\(^,\)\(^7\)\(^,\)\(^11\)

**COMMERCIAL SYSTEMS FOR HEMODYNAMIC MONITORING USING PARTIAL CO\(_2\) REBREATHEING**

Of the partial CO\(_2\) rebreathing cardiac output monitor systems that have been developed, the NICO (Noninvasive Cardiac Output) monitor (Novametrix Medical Systems, Inc, Wallingford, CT, USA) remains the most widely deployed and studied. This technology is essentially self-contained and requires little additional training for the clinician. The NICO monitor consists of a CO\(_2\) sensor (infrared light absorption), a disposable airflow sensor (differential pressure pneumotachometer), a specific disposable rebreathing loop, and a pulse oximeter.\(^6\)\(^,\)\(^11\) The production of CO\(_2\) (VCO\(_2\), mL/min) is calculated from minute ventilation and its instantaneous CO\(_2\) content, whereas the CaCO\(_2\) (mL/100 mL of blood) is estimated (Fig. 2) from etCO\(_2\) (mmHg).

Kotake and colleagues\(^12\) have subsequently demonstrated the improved performance of the NICO monitor equipped with updated software (version 5), improving correlation of the NICO monitor to the PAC over a range of cardiac outputs. Updates to version 5.0 attenuated the effects of rebreathing introduced by the NICO monitor without compromising the accuracy of the cardiac output measurement.

Taking advantage of modern sophisticated sensor and signal processing technology, NICO uses this ratio of the change in the change in the etCO\(_2\) partial pressure, and CO\(_2\) elimination to automatically derive cardiac output that is readily available for applications in the ICU and operating room settings. CO\(_2\) production is calculated as the product of CO\(_2\) concentration and air flow during a breathing cycle and CaCO\(_2\) content is derived from etCO\(_2\) and the CO\(_2\) dissociation curve.\(^5\)\(^,\)\(^9\)\(^{-11}\) A disposable rebreathing loop allows an intermittent partial rebreathing state in cycles of 3 min. The rebreathing cycle induces an increase in etCO\(_2\) and mimics a drop in CO\(_2\) production. The obtained differences of these values are then used to calculate CO.

Good CO determination was observed as long as the NICO system was applied to intubated, mechanically ventilated patients with minor lung abnormalities and fixed ventilatory settings. Changes in VCO\(_2\) and etCO\(_2\) only reflect the amount of blood
flow that participates in gas exchange; hence, intrapulmonary shunt can affect the estimation of cardiac output by the NICO.7

**NICO VALIDATION AND LIMITATIONS**

Several animal and relatively small human subject trials have been conducted to evaluate the accuracy and precision of partial CO2 rebreathing determined cardiac output compared with PAC-derived data. Early clinical human subject evaluations of the partial rebreathing technique11,13–15 reported a relatively loose agreement (bias ± 1.8 l/min) between cardiac output measured using thermodilution and NICO. Cardiac output as determined by the NICO device in one study showed a 37% error compared with the PAC.16 However, the investigators did note a better correlation between normal-to-low cardiac output values using the NICO monitor. Several studies have shown that the indirect Fick equation is only valid when the partial CO2 is greater than 30 torr when the CO2-hemoglobin dissociation curve is linear. Subsequent studies have shown better correlation with the PAC and, therefore, there are increasing applications for the NICO device.

The correlation between the NICO and standard thermodilution was shown to be severely adversely affected in spontaneously breathing patients.17 The NICO value was inversely proportional to an etCO2 difference between pre-rebreathing and post-rebreathing. The large bias in spontaneously breathing patients is likely due to a small delta-etCO2 in spontaneously breathing patients and therefore the NICO tends to measure higher CO values in spontaneously breathing patients. To achieve optimal results with the NICO monitor, the patient should be maintained under fully controlled mechanical ventilation. Variations in ventilatory modalities, mechanically assisted spontaneous breathing, or use of this technique in patients with lung pathologies would likely affect the accuracy of the NICO monitor.

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**Fig. 2.** Experimental setup for validation of breath-by-breath CO2-elimination rate and partial CO2 rebreathing measurements. The devices in the boxes marked with dashed lines were used for the partial CO2 rebreathing experiments only. (From de Abreu MG, Quintel M, Ragaller M, et al. Partial CO2 rebreathing: a reliable technique for noninvasive measurement of nonshunted pulmonary capillary blood flow. Critical Care Med 1997;25(4):675–83; with permission.)
(increased shunt fraction) will, therefore, decrease accuracy of NICO-derived cardiac output readings.\textsuperscript{5}

Odenstedt and colleagues\textsuperscript{18} found a good correlation between NICO derived cardiac output, and cardiac output using the thermodilution technique with a pulmonary artery catheter (correlation coefficient, $r = 0.96$, within-subject correlation $r = 0.88$). They did identify a small underestimation of cardiac output by NICO of 0.04 L/min, with the limits of agreement ($\pm 2$ SD) being $-1.68$ and $1.76$ L/min. They also found that in hemodynamically unstable patients the NICO method closely followed thermodilution derived cardiac output (TDCO) in tracking changes in CO. Pulmonary shunt was underestimated by approximately 11\% compared with standard shunt calculations using arterial and mixed venous blood gases.

A case report\textsuperscript{19} suggests that CO\textsubscript{2} insufflation during laparoscopic surgery does not affect the agreement between NICO and thermodilution.

**AFFECT OF PULMONARY DISEASE**

Increased intrapulmonary shunt and poor hemodynamic stability, common in critically ill patients, are likely to alter the precision of cardiac output estimation by the NICO monitor. Changes in VCO\textsubscript{2} and etCO\textsubscript{2} only reflect the amount of blood flow that participates in gas exchange; hence, intrapulmonary shunt can affect the estimation of cardiac output by the NICO.

Because noninvasive CO measurement depends on CO\textsubscript{2} rebreathing and assumes constant dead space and mixed venous CO\textsubscript{2} content through the CO\textsubscript{2} rebreathing procedure, Tachibana and colleagues\textsuperscript{20} investigated in a prospective comparative study the effects of tidal volume ($V\textsubscript{T}$), ventilatory mode, inspired oxygen fraction ($FiO\textsubscript{2}$), and positive end-expiratory pressure (PEEP) on the accuracy of the measurement. They found that during mechanical ventilation with large constant $V\textsubscript{T}$ or during spontaneous breathing (PSV), CO measurements obtained by CO\textsubscript{2} rebreathing technique correlate with those obtained by thermodilution method and that, when minute ventilation is large, the accuracy of the CO\textsubscript{2} rebreathing technique is not affected by a selection of volume or pressure-controlled ventilation, or PSV, PEEP, or $FiO\textsubscript{2}$. However, when $V\textsubscript{T}$ and minute ventilation are reduced, the CO\textsubscript{2} rebreathing technique underreports CO.

Neviere and colleagues\textsuperscript{21} did find that in mechanically ventilated patients with chronic obstructive pulmonary disease, cardiac output measurements by the CO\textsubscript{2} rebreathing technique might correlate closely with thermodilution ($r^2 = 0.92, P<.001$).

Increased intrapulmonary shunt and lack of hemodynamic stability, common in critically ill patients, may alter the precision of CO\textsubscript{2} estimation by the NICO. Patients with lung disease or postoperative atelectasis can contribute to decreased accuracy of the NICO measurements, a finding also experienced in a porcine model of trauma.\textsuperscript{15}

Similarly, Nilsson and colleagues\textsuperscript{14} found the reproducibility of thermodilution and CO\textsubscript{2}-rebreathing cardiac output were excellent, with coefficients of reproducibility of 0.35 l/min and 0.60 l/min. They concluded the methods are not interchangeable with the present version of the NICO. The reproducibility of the partial CO\textsubscript{2}-rebreathing technique holds promise that a sufficient accuracy may be obtained by suitable modifications of the monitor’s algorithms.

**CARDIOTHORACIC SURGERY PATIENTS**

Several studies have evaluated the use of the NICO monitor for intraoperative monitoring during cardiothoracic surgery. Botero and colleagues\textsuperscript{22} important study of patients undergoing cardiopulmonary bypass (CPB) conducted a unique evaluation
of four simultaneous cardiac output measurements techniques, including ultrasound transit-time flowmetry, which may be considered the true gold standard for cardiac output measurement. Agreement with this reference method was best for NICO and worst for continuous thermodilution, with thermodilution bolus being intermediate, raising separate questions of the appropriate standard for comparison. NICO measurements seem to agree well with thermodilution before CPB but the tendency was for NICO to underestimate CO after CPB. Crespo and colleagues evaluated the NICO device in 25 patients undergoing elective cardiac surgery and found that the agreement between the NICO and continuous cardiac output is clinically acceptable and is unaffected by etCO2. All these studies support the conclusion that the NICO monitor offers an appropriate alternative to invasive CO measurement.

Ng and colleagues examined the use of the noninvasive partial CO2 rebreathing system for cardiac output monitoring of patients undergoing thoracic surgery and one-lung ventilation. They found that the NICO device showed a tendency to underestimate CO compared with thermodilution CO at all measurement times. Although the study size was small, overall, the bias for the NICO was −0.29 L/min, and they concluded that the NICO device is still useful for monitoring during thoracic surgery. Gueret and colleagues found that during off-pump cardiac surgery the noninvasive cardiac output reliably measures cardiac output and does it more rapidly than a PAC and may be more useful to detect rapid hemodynamic changes.

**PARTIAL CO2 REBREATHEING MEASUREMENTS IN SEVERE LUNG INJURY**

Neviere and colleagues conducted a study to compare measurement of cardiac output by the CO2 rebreathing method with the thermodilution cardiac output technique in mechanically ventilated patients with acute lung injury. This prospective study evaluated patients over a wide range of cardiac index for patients with acute lung injury. There was a significant correlation between thermodilution and CO2 rebreathing methods ($r^2 = 0.82, P<.01$) and the mean difference between the CO2 rebreathing method and thermodilution was 0.05 l/min/m2, with a standard deviation for the bias of 0.38 l/min/m2. These results suggest that the CO2 rebreathing method may be a reliable noninvasive technique to determine cardiac output in mechanically ventilated patients with acute lung injury.

This finding was contradicted in a more recent study evaluating patients with acute lung injury at two levels of severity (lung injury score <2.5, group A; and >2.5, group B). Patients with acute lung failure (partial O2/FiO2 < 300) showed a poor positive correlation between the methods for the patients from groups A ($r = 0.52, P<.001$) and B ($r = 0.47, P<.001$). Errors in estimating CaCO2 content from etCO2 and situations of hyperdynamic circulation associated with dead space or increased shunt may explain these results with a greater difference between NICO and TDCO the more critical the lung injury.

An animal study by Gama de Abreu and colleagues looked at the performance of the partial CO2 rebreathing technique with systematical modulation of cardiac output to achieve hypodynamic, normal, and hyperdynamic states. Their results showed that although pulmonary capillary blood flow is underestimated during hyperdynamic cardiac output states and high alveolar dead spaces, the performance of the partial CO2 rebreathing technique was improved with arterial blood gas sampling and an algorithm that took into account the effects of nonequilibration of end-tidal partial pressure of CO2 (PetCO2). Such an algorithm may prove useful under moderately increased alveolar dead space and normal to hypodynamic cardiac output states.
Rocco and colleagues\textsuperscript{30} conducted a small study investigating patients with high and low pulmonary shunt fractions. They found that the partial CO\textsubscript{2} rebreathing technique is reliable in measuring cardiac output in non-postoperative critically ill patients affected by diseases causing low levels of pulmonary shunt, but underestimates it in patients with shunt higher than 35%.

**NICO IN PEDIATRIC AND GERIATRIC AGE GROUPS**

Levy and colleagues\textsuperscript{31} concluded that NICO is clinically acceptable in children with a body surface area of more than 0.6 m\textsuperscript{2} and a tidal volume greater than 300 mL, whereas discrepancies with thermodilution were more important in smaller patients. Botte and colleagues\textsuperscript{32} evaluated 21 mechanically ventilated children, weighing greater than 15 kg, in stable respiratory and hemodynamic condition. CO values obtained with this technique were in agreement with those obtained with Doppler echocardiography. Although NICO evaluation has yet to be completed in children in unstable respiratory and hemodynamic conditions, this would seem to be a reasonable endeavor for future investigations.

Yoshie\textsuperscript{33} evaluated the NICO device in patients over 65 years of age scheduled for elective lower abdominal or surface surgery. They found that, although cardiac output measures were most reliable when the arterial pressure was above 100 mmHg, there was no statistical relationship between arterial pressure and cardiac output in all measurements. They found that age, blood pressure level, history of hypertension, and body structure affected cardiac output measurements, but that the NICO values were useful to monitor cardiac output in this age population cohort.

**HIP SURGERY PATIENTS**

Gueret and colleagues\textsuperscript{34} specifically looked at the use of the partial CO\textsubscript{2} rebreathing monitor for monitoring patients undergoing repeat total hip replacements. They found a small perioperative bias with the NICO device and a slight underestimation of cardiac output when compared with the PAC. The bias was smaller when mean cardiac output was below 3L/min. An additional finding was that core temperature between 34.4\textdegree{}C and 37.6\textdegree{}C had no influence on the differences.

**OTHER APPLICATIONS**

Other investigators have proposed using noninvasive cardiac monitoring in the emergency department evaluation of patients for early identification of shock and the optimization of organ donation.\textsuperscript{35} The NICO system seems well suited for such applications and these authors await further publication of such studies.

**SUMMARY**

Compared with conventional cardiac output methods, the partial CO\textsubscript{2} rebreathing technique is noninvasive, can easily be automated, and can provide real-time and continuous cardiac output monitoring.\textsuperscript{10,36} Large outcome studies using monitoring devices such as the NICO for hemodynamic optimization are still lacking. The advantages and limitations of this technique is unique and may yet find a specific niche in which its advantages are be decisive. Partial CO\textsubscript{2} rebreathing derived cardiac output measurement does not seem ready to replace the PAC which remains unique in providing pressures (right atrial, pulmonary artery, and pulmonary “wedged”), and venous oxygen saturation in addition to cardiac output. These parameters are still extremely useful for the management of some of the most severely ill patients.\textsuperscript{8} No
single method stands out or renders the others obsolete. By making cardiac output easily measurable, however, these techniques should all contribute to improvement in hemodynamic management.1

REFERENCES
