Variations in Respiratory Excretion of Carbon Dioxide Can Be Used to Calculate Pulmonary Blood Flow

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Abstract

Background: A non-invasive means of measuring pulmonary blood flow (PBF) would have numerous benefits in medicine. Traditionally, respiratory-based methods require breathing maneuvers, partial rebreathing, or foreign gas mixing because exhaled CO$_2$ volume on a per-breath basis does not accurately represent alveolar exchange of CO$_2$. We hypothesized that if the dilutional effect of the functional residual capacity was accounted for, the relationship between the calculated volume of CO$_2$ removed per breath and the alveolar partial pressure of CO$_2$ would be reversely linear.

Methods: A computer model was developed that uses variable tidal breathing to calculate CO$_2$ removal per breath at the level of the alveoli. We iterated estimates for functional residual capacity to create the best linear fit of alveolar CO$_2$ pressure and CO$_2$ elimination for 10 minutes of breathing and incorporated the volume of CO$_2$ elimination into the Fick equation to calculate PBF.

Results: The relationship between alveolar pressure of CO$_2$ and CO$_2$ elimination produced an R$^2$ = 0.83. The optimal functional residual capacity differed from the “actual” capacity by 0.25 L (8.3%). The repeatability coefficient leveled at 0.09 at 10 breaths and the difference between the PBF calculated by the model and the preset blood flow was 0.62 ± 0.53 L/minute.

Conclusions: With variations in tidal breathing, a linear relationship exists between alveolar CO$_2$ pressure and CO$_2$ elimination. Existing technology may be used to calculate CO$_2$ elimination during quiet breathing and might therefore be used to accurately calculate PBF in humans with healthy lungs.

Keywords: Pulmonary blood flow; Cardiac output; Carbon dioxide elimination; End-tidal carbon dioxide

Introduction

A clinician’s ability to determine a patient’s cardiac output is critical in the assessment of cardiopulmonary health. Clinically, this measurement can be required intermittently during surgery, as well as post-operatively. Cardiac output may also be measured in research settings, but doing so with invasive methods requires expensive critical care equipment, trained personnel, a sterile environment and readily available resuscitative equipment.

Cardiac output is arguably one of the most important parameters reflecting cardiovascular health and yet its measurement is currently limited to patients with Swan-Ganz catheters in the operating room, critical and intensive care units. To date, no non-invasive method has proven itself comparable to thermodilution in accuracy, repeatability, and in physiological soundness [1, 2]. Nevertheless, the thermodilution method is plagued with limitations in clinical practice, the most important ones being associated with its invasiveness [3].

Methods for measuring cardiac output non-invasively can be classified as respiratory-based or non-respiratory-based. The latter, which includes Doppler (external, transtracheal and transesophageal), bioimpedance, and pulse contour analysis, has not yet been accepted into clinical practice because of either theoretical or practical limitations [4]. Additionally, there are some respiratory-based methods that utilize foreign gas breathing, including argon and acetylene, but these methods require a source of external gas, are impractical in many settings, and will not be dealt with in detail here [5].

The respiratory-based methods are the oldest, the most physiologically sound, and traditionally the most accepted method of cardiac output measurement. Their principles and assumptions are well understood as are their limitations, the most important of which is that they more accurately measure pulmonary blood flow (PBF) rather than cardiac output. Originally described for oxygen, Fick equation, developed in the late 1800s, is based on the measurement of elements of the mass balance across the lungs [6]. The following is the
The need for measuring CvCO
has been presented, but none has proven itself repeatable and may pose a challenge to patients with respiratory compromise [9]. Single-breath methods in PA
That method demonstrated that if a subject’s alveolar ventilation (V_A) were acutely and transiently reduced, a step change would result (once steady state is reached, V_A and VCO_2 would result from alveolar CO_2 pressure (P_ACO_2), which in turn is approximated from end-tidal CO_2 pressure (P_TOCO_2). Mixed venous pressure of CO_2 (PvCO_2) however, is difficult to obtain non-invasively, and has classically posed the biggest challenge to measurement of PBF. Respiratory maneuvers such as breathing and rapid equilibration with external reservoirs have been employed to estimate PvCO_2, but these have the disadvantage of requiring an external supply of CO_2, and may pose a challenge to patients with respiratory compromise [9]. Single-breath methods have been presented, but none has proven itself repeatable and accurate.

In 1980, a novel method of calculating PBF without the need for measuring CvCO was described by Gedeon et al [9]. That method demonstrated that if a subject’s alveolar ventilation (V_A) were acutely and transiently reduced, a step change would occur, after a few breaths. At this point, assuming PBF and PvCO_2 had not changed in this short time (< 30 - 45 s), two Fick equations could be applied to the model:

Eq. 3a: PBF = VCO_2/(S × PvCO_2 - S × P_ACO_2)
Eq. 3b: PBF = VCO_2/(S × PvCO_2 - S × P_ACO_2)

where VCO_2 and P_ACO_2 are the exhaled CO_2 volumes and alveolar CO_2 pressures after a new steady state has occurred, respectively, and S is a conversion constant to content. Since PvCO_2 and PBF remain unchanged with this maneuver, these equations together yield a single equation:

Eq. 4: PBF = (VCO_2 - VCO_2')/(S × P_ACO_2' - S × P_ACO_2)

This way, a small, temporary change in V_A can be used to calculate PBF without the need for invasive monitors. This method has been proven reliable in intubated patients by multiple studies [10-12].

Creative as this method is; however, there are several limitations to it. First, the time to reach the new steady state is a function of the subject’s V_A and functional residual capacity (FRC). On average, this time is approximately 30 - 45 s, or about five breaths, which means that only two data points are used to calculate PBF before recirculation of arterial blood occurs, limiting the method’s accuracy. Second, because V_A is required to be transiently reduced, and because the normal variability of breathing creates noise in the measurement signal, this method is limited only to intubated patients. Finally, P_ACO_2 must be allowed to re-equilibrate to steady state levels before a subsequent test can be performed, which may require an additional 60 - 120 s.

Materials and Methods

Flux of CO_2 at the alveoli

The method proposed here redefines the term VCO_2 as described in Fick’s equation. According to conventional understanding, VCO_2 is defined as the excretion of CO_2 past the lips, measured with a pneumotachometer and CO_2 monitor. However, exhaled CO_2 on a breath-by-breath basis seldom reflects actual metabolic CO_2 production or pulmonary capillary excretion into the lungs [13]. Instead, an average over several breaths is required for this estimation, as the FRC acts as a reservoir for CO_2. For example, a large breath that expunges a large volume of CO_2 past the lips would incorrectly reflect a large “production” of CO_2. The Fick equation, therefore,
would be more physiologically accurate if the term VCO₂ represented the continuous flux of CO₂ from the blood into the alveoli (VCO₂A), rather than the discrete, tidal excretion of CO₂ past the lips (VCO₂M). Averaged over many breaths, VCO₂M will accurately reflect VCO₂A.

**Relationship between VCO₂A and PₐCO₂**

After redefining VCO₂ in this manner, it becomes clear that there exists a linear relationship between the flux of CO₂ out of the blood (VCO₂A) and PₐCO₂ (Fig. 1).

At steady state VCO₂A and PₐCO₂ produce a single point on this line. The slope of this line, PBF, is proportional to the PBF. A second theoretical line exists on this diagram, connecting the origin with the steady state point. This second line is described by the basic physiologic equation:

\[ \text{Eq. 5: } V_{CO₂A} = Vₐ × PₐCO₂/713 \]

where Vₐ is the alveolar ventilation - the slope of the line. It becomes clear that VCO₂A - not VCO₂M - must be applied when describing these relationships, as washout of the FRC with each breath due to normal variations in tidal volume and respiratory frequency. Preiss et al. J Clin Med Res. 2015;7(2):83-90

**Method for calculating VCO₂A**

The method described above requires calculation of the VCO₂A, the flux of CO₂ across the alveolar membrane. Calculation for VCO₂A has been described thoroughly elsewhere [13]. Briefly, a simple mass balance dictates that the flux of CO₂ into the alveoli from the blood is related to the flux of CO₂ at the mouth and the change of CO₂ stores in the lung:

\[ \text{Eq. 6: } V_{CO₂A} = VCO₂M - ΔVCO₂S \]

where VCO₂A is the alveolar flux of CO₂, VCO₂M is the flux of CO₂ at the mouth, and ΔVCO₂S is the change in lung stores of CO₂. VCO₂M is easily measured using a metabolic cart, which integrates exhaled CO₂ concentration and expiratory flow.

The change in lung stores of CO₂ from breath 1 to breath 2, ΔVCO₂S, can be described as the sum of two terms describing the change in CO₂ concentration at a constant Vₐ, and the change in Vₐ at a constant CO₂ concentration:

\[ \text{Eq. 7: } ΔVCO₂S = Vₐ(\frac{PₐCO₂'} - PₐCO₂)/713 + PₐCO₂'ΔVₐ \]

where ΔVCO₂S is the change in alveolar stores of CO₂, Vₐ, is the alveolar volume at the end of breath 1, PₐCO₂ and PₐCO₂' are the fractions of CO₂ in the alveoli at the end of breaths 1 and 2, respectively and ΔVₐ is the change in alveolar volume from breath 1 to breath 2.

**Computer simulation**

For this study, a computer simulation of tidal breathing was designed to test the theory under ideal conditions using Microsoft Excel 2003 (Redmond, Washington, USA). Incremental calculations of lung CO₂ volume were made for each 0.001 min. Tidal breathing was simulated using variable inhaled and exhaled tidal volumes (±30%), allowing lung volume to return to a different FRC with each breath. Complete alveolar mixing was assumed, inspiratory and expiratory times were equal, inhalation and exhalation flows were linear, and alveolar dead-space and shunt were assumed to be minimal. PₐCO₂ was recorded once per breath (the final PₐCO₂ value at the end of exhalation) and VCO₂M was calculated at the mouth during exhalation. The model was run over a period of 10 min (100 breaths), and PₐCO₂, VCO₂M, Vt-in and Vt-out were recorded with each breath. Vₐ for sequential breaths was calculated as Vₐ = Vₐ + Vt-in - Vt-out, where Vt-in and Vt-out are inhaled tidal volume and exhaled tidal volume, respectively. Detailed parameters are outlined in Table 1.

**PₐCO₂-ave versus PₑₜCO₂**

As stated above, the diffusion of CO₂ across the alveolar membrane should form a linear relationship with the pressure of CO₂ in the alveoli. Therefore, measurements of PₑₜCO₂, a single sample taken at the end of exhalation, would be inappropriate to use in equation 3 since it reflects an end-expiration value rather than an average (PₑₜCO₂-ave). In the computer model, an average PₐCO₂ is easy to calculate, but this is not the case clinically, when PₑₜCO₂ samples are the only measurements.

### Table 1. The Parameters Used in the Mathematical Model

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<th>Error</th>
<th>Value</th>
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<td>PVCO₂ (mm Hg)</td>
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<td>50</td>
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<tr>
<td>Pulmonary blood flow (L/min)</td>
<td>None</td>
<td>6</td>
</tr>
<tr>
<td>Tidal volume (mL)</td>
<td>±30%</td>
<td>500</td>
</tr>
<tr>
<td>Respiratory frequency (/min)</td>
<td>None</td>
<td>12</td>
</tr>
<tr>
<td>FRC (L)</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>PBF-Preset (L/min)</td>
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Although not included in this table, a transient period, P₂CO₂, would vary with each breath due to normal variations in tidal volume and respiratory frequency. Since VCO₂A likely fluctuates little during quiet breathing (as opposed to VCO₂M), variability of breathing, which was once the system “noise”, therefore becomes important for measurement of PBF.

Once this line is observed over multiple breaths, PBF can be calculated by extrapolating to the x-intercept, PVCO₂, and calculating PBF using equation 1.
readily available non-invasively. To estimate $P_{A, CO_2}$-ave for a single breath using only non-invasive data, we back-calculated to the $P_{A, CO_2}$ that might exist at peak inhalation and averaged this with $P_{ET, CO_2}$. The $P_{A, CO_2}$ at peak inhalation might be estimated as:

Eq. 8: \[(\text{Volume of CO}_2\text{ in Lung at End-Exhalation} - \text{Volume of CO}_2\text{ Diffused during Exhalation} + \text{Exhaled Volume of CO}_2) \times \frac{713}{\text{Peak Alveolar Volume}}\]

Averaging this value with $P_{ET, CO_2}$ may produce a reasonable estimate of $P_{A, CO_2}$-ave which can be applied in equation 1.

**Calculation of VCO$_2$A**

VCO$_2$ was calculated using equation 6 using sequential breaths, $\Delta V_A$ was assumed to be measurable without the need for nitrogen monitors (Vt-in and Vt-out were measurable), and VA was initially assumed to be 3 L. VCO$_2$A was then calculated using equation 5. Using 10 min of breathing data, when PBF and PV$_{CO_2}$ were assumed to be in steady state, a plot of VCO$_2$A versus $P_{A, CO_2}$ was created and $R^2$ was calculated for
the line of best fit. FRC was then iterated in increments of 0.25 L from 2 L to 4 L to achieve the most optimal linear relationship between VCO$_2$A and PA$_{CO_2}$.

**Real-world adjustments**

To simulate real-world measurements, error was introduced into each measurement (P$_{A_{CO_2}}$, Vt-in, Vt-out, VCO$_2$M, Table 1), consistent with manufacturer specifications [14] and calculation of PBF was repeated.

**PBF comparisons**

PBF was calculated from equation 3 using two techniques: first, using known VCO$_2$A measurements directly from the model (PBF-preset), calculated using actual diffusion of CO$_2$ across the alveolar membrane, and second, using VCO$_2$M to calculate VCO$_2$A using equation 5 (PBF-calc), which represents the strategy that might be used practically in subjects. In the either case, PBF would be calculated using equation 1 where P$_{vCO_2}$ was attained by extrapolating to the x-intercept of a plot relating VCO$_2$A and P$_{A_{CO_2}}$-ave. We determined the appropriate number of breaths required for accurate measurement of PBF-calc, by increasing the number of breaths used to calculate the average PBF-calc until the repeatability was similar to that of thermodilution [15].

PBF-calc was assessed and evaluated using Bland-Altman analysis where the acceptable error was taken from prior established theory [16].

**Results**

The model for tidal ventilation produces reasonable values for P$_{A_{CO_2}}$ over 10 min of breathing. Sample oscillations in P$_{A_{CO_2}}$ and lung volume can be seen in Figure 3. VCO$_2$A tended to vary less over the course of 10 min of breathing than VCO$_2$M, as can be seen in Figure 4. When VCO$_2$A was plotted against P$_{A_{CO_2}}$-ave a linear relationship was revealed which was stronger than with P$_{ET_{CO_2}}$ (R = 0.83 versus 0.74, Fig. 5).

Iterating FRC demonstrated that small deviations from the model value produced poorer relationships between VCO$_2$A and P$_{A_{CO_2}}$ (Fig. 6). However, the optimal FRC achieved after iterating FRC was 3.25 L, which was 0.25 L (8.3%) greater than the actual FRC used in the model. Non-optimal FRCs did not significantly reduce the accuracy of the calculated PBF, but did increase its variability.

When P$_{A_{CO_2}}$-ave was used instead of P$_{ET_{CO_2}}$, the relationship was improved (R$^2$ = 0.83 versus 0.74). PBF-calc was calculated using 10 breaths at a time (see repeatability below) by extrapolating the line in Figure 3 to the x-intercept (P$_{vCO_2}$) and applied into equation 1. Using this method, the difference between PBF-preset and PBF-calc was 0.62 ± 0.53 L/min.

Figure 7 shows that the repeatability coefficient fell from 1.13 to 0.09 L/min as the number of breaths used to calculate PBF-calc increased from 2 to 30. The repeatability coefficient decreased and leveled at 0.09 when approximately 10 breaths were used to average calculation for PBF-calc. The repeatability coefficient for thermodilution is likely between 0.4 and 0.6 L/min [4, 15], which is the equivalent of using 5 - 6 breaths to average PBF-calc measurements in the proposed method.

**Figure 5.** The relationship between VCO$_2$A and P$_{A_{CO_2}}$ using end-tidal PCO$_2$ (P$_{ET_{CO_2}}$, gray squares) versus time averaged CO$_2$ across the breath (P$_{A_{CO_2}}$-ave, closed circles).
Discussion

The most common method for cardiac output measurement involves indicator dilution, normally dyes and temperature. A dye, or cold saline, is typically injected via an invasive catheter into the pulmonary artery and the temporal profile of the concentration of the dye or the temperature of the blood is measured downstream. The profile of the indicator change over time is used to calculate the cardiac output. Over the last three decades, there has been a steady improvement in the technology required to manufacture the catheters and thermistors, and to analyze the indicator curves and calculate the cardiac output [17]. In addition, the expertise to place the catheters and look after catheterized patients has become widespread.

Nevertheless, there are at least three drawbacks necessarily associated with these methods. First, pulmonary artery catheters are inherently invasive and have associated complications including damage to the carotid artery, subclavian artery and lung, air emboli, pneumothorax, malignant arrhythmias and heart block, rupture of right atrium, right ventricle and/or pulmonary capillary, local infection and septicamia, and more [3]. Second, they have many associated costs as a result of the requirement for critical care areas, equipment and personnel. Third, their accuracy is questionable, and can be less reliable and helpful as required for management of critically ill patients [18]. Despite these drawbacks, thermodilution methods continue to be widely used as less invasive alternatives are not sufficiently accurate, not sufficiently robust, or too cumbersome to perform in a large variety of clinical settings [19].

In this study, a new non-invasive method of measuring PBF is introduced based on principles that are already accepted in medicine. The Fick method for measuring PBF is well established and is considered one of the most accurate techniques available. Until recently, however, the Fick technique could only be performed using blood samples despite numerous attempts to measure \( P_{vCO_2} \) non-invasively. The method of creating a step-change in \( V_A \) is the only validated non-invasive Fick method of cardiac output measurement without a special maneuver required by the patient, but can only be used on patients ventilated by a mechanical ventilator, uses only two breaths for measurement ETC. If a spontaneously breathing patient is made to rebreathe previously exhaled gas, the minute ventilation will tend to increase in order to increase the volume of air entering the lungs for gas exchange. The method presented here would require no maneuver on the part of the subject, and no foreign or compressed gases.

The method outlined here describes an original relationship between \( VCO_2 \) and \( P_{A-CO_2} \). Its principles are grounded in basic physiology, and its application may extend beyond that of PBF measurement. Since \( P_A-CO_2 \) relates directly to \( VCO_2 \) given a specific set of conditions, other variables that may influence these parameters such as alveolar dead space, may be measurable as well.

There are several practical limitations of this method. First, this strategy for measuring PBF could not be achieved without a perfect, air-tight seal around the mouth, nose, or face. Any air lost would reduce the accuracy of \( Vt-in, Vt-out \), or \( VCO_2M \). This may be inconvenient or impossible for some patients, depending on the presence of facial hair, anomalous anatomy, or trauma.
As few as two breaths can be used to calculate PBF but its reliability is increased as more breaths are incorporated into the calculation. Precision reaches a plateau at about 8 - 10 breaths.

This model assumes that all exhaled gas had participated in exchange of CO\(_2\) with the blood. \(P_{A\text{CO}_2}\) may vary depending on differences in ventilation-to-perfusion matching throughout the lung [2, 20]. If some exhaled gas originated from alveolar dead space, \(P_{ET\text{CO}_2}\) would underestimate \(P_{A\text{CO}_2}\) and as a result, PBF-calc would overestimate PBF. The significance of this was not quantified in this study, but theoretically, it is possible that iterations of alveolar dead space estimates can be coupled with the estimates of FRC to provide an optimal relationship between \(P_{A\text{CO}_2}\) and \(V_{CO_2A}\). Still, deviations of \(P_{ET\text{CO}_2}\) from \(P_{A\text{CO}_2}\) may also be due to incomplete breaths during exhalation and not alveolar dead space per se. This also impacts the calculation for \(P_{A\text{CO}_2\text{-ave}}\), which will also be affected by all of the above.

In this study, 10 min of breathing were permitted to achieve initial FRC estimate. At this point, it is unclear why the ideal FRC produced from the iterative process differed from that used in the model. Nevertheless, its impact on PBF-calc was marginal. Furthermore, the purpose of this extended period of breathing was to demonstrate the principle rather than practicality. Follow-up studies in humans will be required to further explore this strategy.

The real-world error in measuring Vt, \(P_{ET\text{CO}_2}\), \(V_{CO_2}\) was based on products currently available for purchase. These will vary depending on the manufacturer and may improve in the future, making this method more practical.

The accuracy of this method for measuring PBF was similar to others that have been proposed [15]. The repeatability demonstrated that 10 breaths were needed for optimal accuracy, a time slightly greater than would be required for a complete test of thermodilution (about 30 s) depending on respiratory frequency. However, one advantage of the proposed method in this respect is that measurements for PBF are continuous, and no time is needed for “reset”, as may be needed to washout indicator from the pulmonary artery for thermodilution.

Finally, whereas the accuracy of other respiratory-based non-invasive methods may be diminished by respiratory fluctuations, the proposed method is enhanced by large changes in tidal volume and respiratory frequency. It may even be suggested that a subject ought to be encouraged to take deep breaths, or sigh to exaggerate the variability of quiet tidal breathing.

**Conclusion**

The study we describe here is safe, theoretically sound, and demonstrates acceptable accuracy and repeatability. It represents a potential advancement towards measurement of important cardiopulmonary parameters that may be clinically important in the management of both outpatients and those in-hospital. Further studies in humans are required to quantify and evaluate its strengths and limitations.

**Acknowledgement**

None.

**Conflict of Interest**

The authors report no conflicts of interest.

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