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

(Article begins on next page)

Original Article

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.

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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
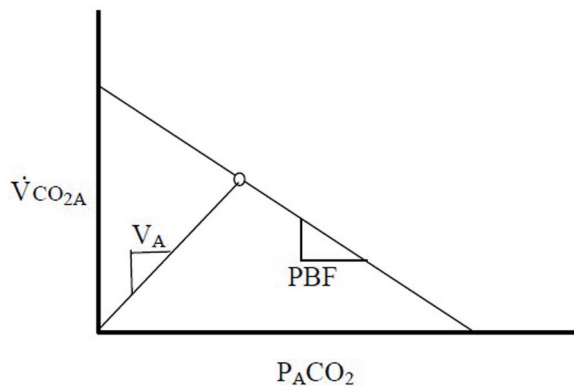
Figure 1. The relationship between VCO$_{2A}$ and P$_A$CO$_2$ is linear. The slope of this line is proportional to the pulmonary blood flow. An intersecting line can be drawn from the origin following the relationship V$_A$ = VCO$_2$ × P$_A$CO$_2$/713. The steady state point (A) for P$_A$CO$_2$ and VCO$_{2A}$ is produced by the balance of CO$_2$ diffusion into the alveoli and the flow of blood into the pulmonary capillaries.
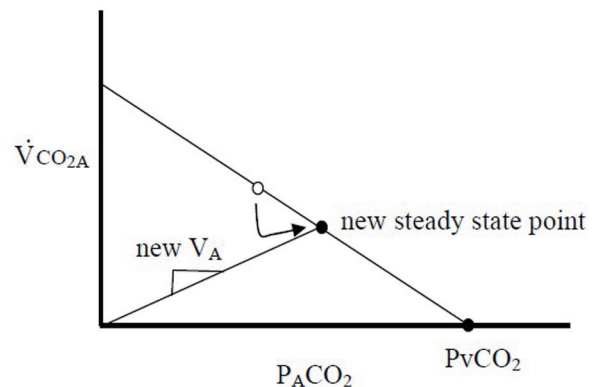

Figure 2. Gedeon's method of reducing V$_A$ for several breaths acutely increases P$_A$CO$_2$ and reduces VCO$_{2A}$ creating a new steady state point on the same line. Point A and point B can be used together to calculate the slope of the line, which is the pulmonary blood flow.

equivalent equation describing the movement of carbon dioxide (CO$_2$):

Eq. 1:   PBF = VCO$_2$/(CvCO$_2$ - CaCO$_2$)

where PBF is the pulmonary blood flow, VCO$_2$ is the metabolic CO$_2$ production, and CvCO$_2$ and CaCO$_2$ are the concentrations of CO$_2$ in the blood entering (mixed venous, v) and leaving (arterial, a) the lungs respectively. To keep the method purely non-invasive, alveolar pressure is conventionally used as a surrogate for content. The relationship between PaCO$_2$ and CaCO$_2$ is usually assumed to be linear in the physiologic range, and through previous *in-vitro*, CO$_2$ content of oxygenated blood can be estimated using the following equation [7, 8]:

Eq. 2:   Content = 4 × Pressure + 260

Generally, PaCO$_2$ is approximated from alveolar CO$_2$ pressure (P$_A$CO$_2$), which in turn is approximated from end-tidal CO$_2$ pressure (P$_{ET}$CO$_2$). 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 breathholding 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$_2$ 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 in P$_A$CO$_2$ and VCO$_2$ would result (once steady state is reached, 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$_A$CO$_2$)
Eq. 3b: PBF = VCO$_2$'/(S × PvCO$_2$ - S × P$_A$CO$_2$')

where VCO$_2$' and P$_A$CO$_2$' 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$_A$CO$_2$' - S × P$_A$CO$_2$)

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$_A$CO$_2$ 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,

Table 1. The Parameters Used in the Mathematical Model

Parameter	Error	Value
$PvCO_2$ (mm Hg)	None	50
Pulmonary blood flow (L/min)	None	6
Tidal volume (mL)	±30%	500
Respiratory frequency (/min)	None	12
FRC (L)	None	3
PBF-preset (L/min)	None	6

would be more physiologically accurate if the term VCO_2 represented the continuous flux of CO_2 from the blood into the alveoli (VCO_{2A}), rather than the discrete, tidal excretion of CO_2 past the lips (VCO_{2M}). Averaged over many breaths, VCO_{2M} will accurately reflect VCO_{2A}.

Relationship between VCO_{2A} and P_ACO_2

After redefining VCO_2 in this manner, it becomes clear that there exists a linear relationship between the flux of CO_2 out of the blood (VCO_{2A}) and P_ACO_2 (Fig. 1).

At steady state VCO_{2A} and P_ACO_2 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:

Eq. 5: $VCO_{2A} = V_A \times P_ACO_2/713$

where V_A is the alveolar ventilation - the slope of the line. It becomes clear that VCO_{2A} - not VCO_{2M} - must be applied when describing these relationships, as washout of the FRC can confound the changes that relate these variables.

Gedeon's method aims to use two steady state VCO_{2M} points to determine the slope of the PBF line: one attained from the subject breathing at rest (where VCO_{2M} only equals VCO_{2A} if averaged over many breaths), and the second after a small change in V_A (measured after 4 - 5 breaths, when, after a transient period, VCO_{2M} is assumed to be equal to VCO_{2A}). In an extreme case, if the breath were held for 30 s and a new steady state were reached, P_ACO_2 would be equal to $PvCO_2$, or the x-intercept (Fig. 2). This method can only measure two points because after 4 - 5 breaths of breathing at a second V_A, recirculation would alter $PvCO_2$. However, if VCO_{2A} can be measured with each breath, one data point along this line could be produced with each exhalation, and the slope, PBF could be calculated with sequential breaths. Variations in VCO_{2A} are needed to explore this line, and the slope of the second line, V_A, would vary with each breath due to normal variations in tidal volume and respiratory frequency. Since VCO_{2A} likely fluctuates little during quiet breathing (as opposed to VCO_{2M}), 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, $PvCO_2$, and calculating PBF using equation 1.

Method for calculating VCO_{2A}

The method described above requires calculation of the VCO_{2A}, the flux of CO_2 across the alveolar membrane. Calculation for VCO_{2A} has been described thoroughly elsewhere [13]. Briefly, a simple mass balance dictates that the flux of CO_2 into the alveoli from the blood is related to the flux of CO_2 at the mouth and the change of CO_2 stores in the lung:

Eq. 6: $VCO_{2A} = VCO_{2M} - \Delta VCO_{2S}$

where VCO_{2A} is the alveolar flux of CO_2, VCO_{2M} is the flux of CO_2 at the mouth, and ΔVCO_{2S} is the change in lung stores of CO_2. VCO_{2M} is easily measured using a metabolic cart, which integrates exhaled CO_2 concentration and expiratory flow.

The change in lung stores of CO_2 from breath 1 to breath 2, ΔVCO_{2S}, can be described as the sum of two terms describing the change in CO_2 concentration at a constant V_A, and the change in V_A at a constant CO_2 concentration:

Eq. 7: $\Delta VCO_{2S} = V_A(P_ACO_2' - P_ACO_2)/713 + P_ACO_2'\Delta V_A$

where ΔVCO_{2S} is the change in alveolar stores of CO_2, $V_{A,1}$ is the alveolar volume at the end of breath 1, P_ACO_2 and P_ACO_2' are the fractions of CO_2 in the alveoli at the end of breaths 1 and 2, respectively and ΔV_A 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 CO_2 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. P_ACO_2 was recorded once per breath (the final P_ACO_2 value at the end of exhalation) and VCO_{2M} was calculated at the mouth during exhalation. The model was run over a period of 10 min (100 breaths), and P_ACO_2, VCO_{2M}, Vt-in and Vt-out were recorded with each breath. V_A for sequential breaths was calculated as $V_A' = V_A + $ 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.

P_ACO_2-ave versus $P_{ET}CO_2$

As stated above, the diffusion of CO_2 across the alveolar membrane should form a linear relationship with the pressure of CO_2 in the alveoli. Therefore, measurements of $P_{ET}CO_2$, 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 (P_ACO_2-ave). In the computer model, an average P_ACO_2 is easy to calculate, but this is not the case clinically, when $P_{ET}CO_2$ samples are the only measurements
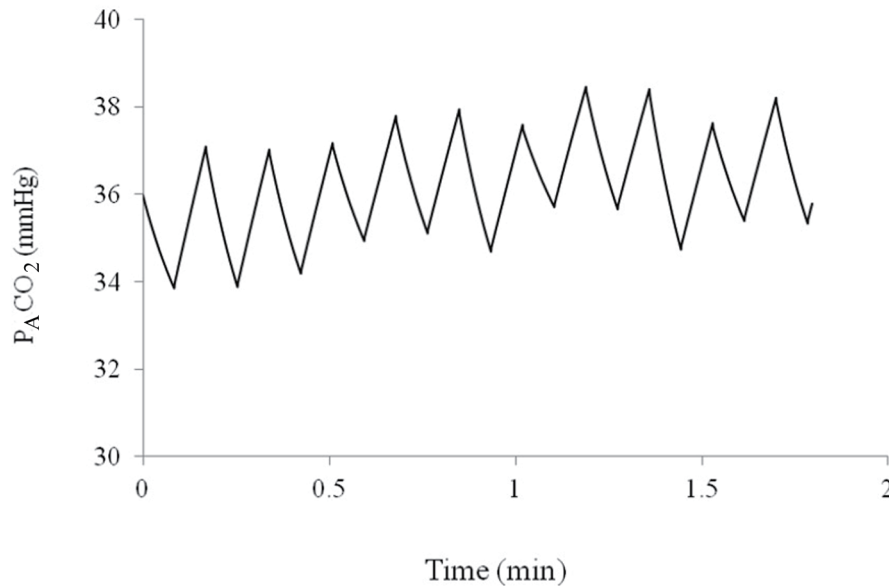
Figure 3. Alveolar partial pressure of CO_2 over a period of 2 min as predicted by the computer model.

readily available non-invasively. To estimate P_ACO_2-ave for a single breath using only non-invasive data, we back-calculated to the P_ACO_2 that might exist at peak inhalation and averaged this with $P_{ET}CO_2$. The P_ACO_2 at peak inhalation might be estimated as:

Eq. 8:   (Volume of CO_2 in Lung at End-Exhalation - Volume of CO_2 Diffused during Exhalation + Exhaled Volume of CO_2) × 713/Peak Alveolar Volume

Averaging this value with $P_{ET}CO_2$ may produce a reasonable estimate of P_ACO_2-ave which can be applied in equation 1.

Calculation of VCO_{2A}

VCO_{2S} was calculated using equation 6 using sequential breaths, ΔV_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_{2A} was then calculated using equation 5. Using 10 min of breathing data, when PBF and $PvCO_2$ were assumed to be in steady state, a plot of VCO_{2A} versus P_ACO_2 was created and R^2 was calculated for

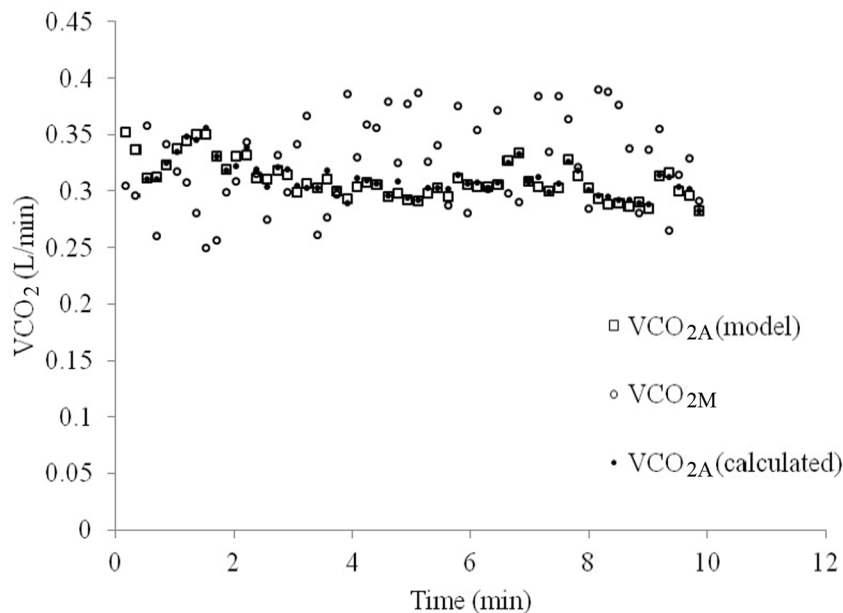**Figure 4.** VCO_2 over time as measured at the mouth (VCO_{2M}, open circles), as pre-set by the model (VCO_{2A}-model, open squares) and as calculated using the proposed method (VCO_{2A}-calculated, closed circles).
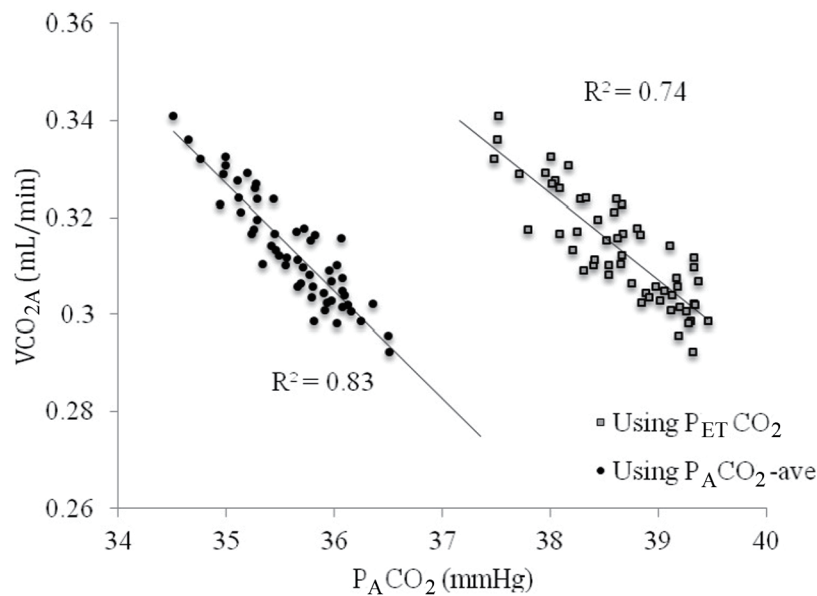
Figure 5. The relationship between VCO_{2A} and P_ACO_2 using end-tidal PCO_2 ($P_{ET}CO_2$, gray squares) versus time averaged CO_2 across the breath (P_ACO_2-ave, closed circles).

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_{2A} and P_ACO_2.

Real-world adjustments

To simulate real-world measurements, error was introduced into each measurement (P_ACO_2, Vt-in, Vt-out, VCO_{2M}, 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_{2A} measurements directly from the model (PBF-preset), calculated using actual diffusion of CO_2 across the alveolar membrane, and second, using VCO_{2M} to calculate VCO_{2A} 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 $PvCO_2$ was attained by extrapolating to the x-intercept of a plot relating VCO_{2A} and P_ACO_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_ACO_2 over 10 min of breathing. Sample oscillations in P_ACO_2 and lung volume can be seen in Figure 3.

VCO_{2A} tended to vary less over the course of 10 min of breathing than VCO_{2M}, as can be seen in Figure 4. When VCO_{2A} was plotted against P_ACO_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_{2A} and P_ACO_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_ACO_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 ($PvCO_2$) 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.
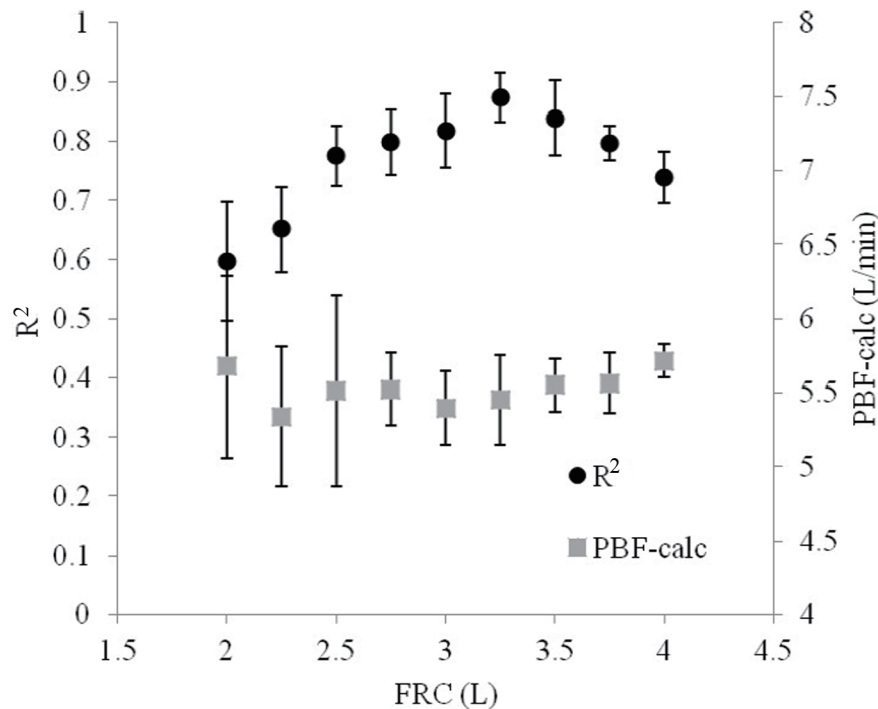
Figure 6. The R^2 statistical parameter relating VCO_{2A} to P_ACO_2 varies depending on the original estimate of FRC. As the initial guess of FRC is increased, R^2 reaches a peak, optimum point and then falls.

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 septicaemia, 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 $PvCO_2$ 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_ACO_2. Its principles are grounded in basic physiology, and its application may extend beyond that of PBF measurement. Since P_ACO_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 measureable 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.
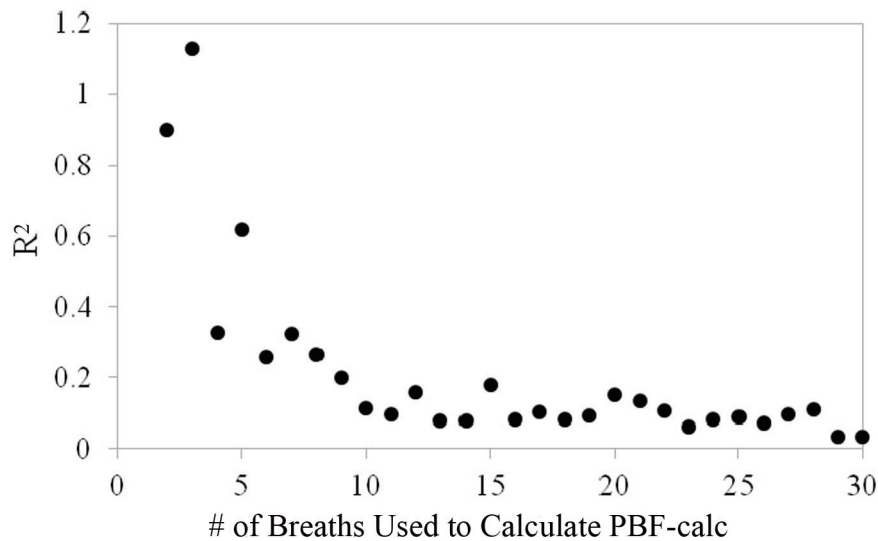
Figure 7. As few as two breaths can be used to calculate PBF but its reliability is increased as more breaths are incorporated into the calculation. Precision reaches a plateau at about 8 - 10 breaths.

This model assumes that all exhaled gas had participated in exchange of CO_2 with the blood. P_ACO_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, $P_{ET}CO_2$ would underestimate P_ACO_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_ACO_2 and VCO_{2A}. Still, deviations of $P_{ET}CO_2$ from P_ACO_2 may also be due to incomplete breaths during exhalation and not alveolar deap space per se. This also impacts the calculation for P_ACO_2-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, $P_{ET}CO_2$, VCO_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

Conflict of Interest

The authors report no conflicts of interest.

Source(s) of Support

funds.

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