

CARDIOVASCULAR

## Non-invasive measurement of cardiac output using an iterative, respiration-based method

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### Editor's key points

- Current non-invasive monitors of cardiac output suffer from significant practical limitations.
- A novel respiratory-based method involving sequential gas delivery to control alveolar ventilation is described and compared with bolus pulmonary artery thermodilution.
- This novel method was validated in a porcine model of liver transplantation, and is therefore a promising approach for further evaluation.

**Background.** Current non-invasive respiratory-based methods of measuring cardiac output ( $\dot{Q}$ ) make doubtful assumptions and encounter significant technical difficulties. We present a new method using an iterative approach ( $\dot{Q}_{IT}$ ), which overcomes limitations of previous methods.

**Methods.** Sequential gas delivery (SGD) is used to control alveolar ventilation ( $\dot{V}_A$ ) and  $\text{CO}_2$  elimination ( $\dot{V}_{\text{CO}_2}$ ) during a continuous series of iterative tests. Each test consists of four breaths where inspired  $\text{CO}_2$  ( $P_{I\text{CO}_2}$ ) is controlled; raising end-tidal  $P_{\text{CO}_2}$  ( $P_{E'\text{CO}_2}$ ) by about 1.33 kPa (10 mm Hg) for the first breath, and then maintaining  $P_{E'\text{CO}_2}$  constant for the next three breaths. The  $P_{I\text{CO}_2}$  required to maintain  $P_{E'\text{CO}_2}$  constant is calculated using the differential Fick equation (DFE), where  $\dot{Q}$  is the only unknown and is arbitrarily assumed for the first iteration. Each subsequent iteration generates measures used for calculating  $\dot{Q}$  by the DFE, refining the assumption of  $\dot{Q}$  for the next test and converging it to the true  $\dot{Q}$  when  $P_{E'\text{CO}_2}$  remains constant during the four test breaths. We compared  $\dot{Q}_{IT}$  with  $\dot{Q}$  measured by bolus pulmonary artery thermodilution ( $\dot{Q}_{TD}$ ) in seven pigs undergoing liver transplantation.

**Results.**  $\dot{Q}_{IT}$  implementation and analysis was fully automated, and  $\dot{Q}_{TD}$  varied from 0.6 to 5.4 litre  $\text{min}^{-1}$  through the experiments. The bias (between  $\dot{Q}_{IT}$  and  $\dot{Q}_{TD}$ ) was 0.2 litre  $\text{min}^{-1}$  with 95% limit of agreement from  $-1.1$  to 0.7 litre  $\text{min}^{-1}$  and percentage of error of 32%. During acute changes of  $\dot{Q}$ , convergence of  $\dot{Q}_{IT}$  to actual  $\dot{Q}$  required only three subsequent iterations.

**Conclusions.**  $\dot{Q}_{IT}$  measurement is capable of providing an automated semi-continuous non-invasive measure of  $\dot{Q}$ .

**Keywords:** carbon dioxide; cardiac output; monitoring; respiration

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Obtaining a measurement of cardiac output ( $\dot{Q}$ ) that is practical, accurate, non-invasive, continuous, and fully automated is highly desirable in clinical practice.<sup>1</sup> Indeed, monitoring  $\dot{Q}$  is a mandatory part of haemodynamic goal-directed therapy,<sup>2</sup> where prompt implementation can improve outcomes in high-risk patients.<sup>3,4</sup> Currently, the clinical standard for measuring  $\dot{Q}$  is bolus thermodilution ( $\dot{Q}_{TD}$ ). Unfortunately, the pulmonary artery catheter (PAC) required is invasive, with possibly life-threatening complications.<sup>5,6</sup>

The non-invasive Fick measurement of  $\dot{Q}$  (Fick  $\dot{Q}$ )<sup>7–10</sup> applies respiratory manoeuvres to determine  $\dot{Q}$ . However, despite its theoretical simplicity, Fick  $\dot{Q}$  has practical difficulties. All Fick  $\dot{Q}$  methods require two measures of steady-state arterial  $P_{\text{CO}_2}$  ( $P_{a\text{CO}_2}$ ) and  $\text{CO}_2$  elimination ( $\dot{V}_{\text{CO}_2}$ ) to calculate  $\dot{Q}$ : the first is

executed during a baseline period of stable ventilation and the second is executed after a perturbation in ventilation from the baseline state. In order to be valid, the second measurements must be obtained after the  $P_{a\text{CO}_2}$  and  $\dot{V}_{\text{CO}_2}$  have stabilized, but before the changes in  $P_{a\text{CO}_2}$  re-circulate to the lung. As the re-circulation time is short compared with the time it takes for  $P_{a\text{CO}_2}$  and  $\dot{V}_{\text{CO}_2}$  to stabilize, it is impossible to obtain a valid second measurement because during this short time, equilibrium between the pulmonary capillaries and alveoli does not occur.<sup>11</sup> In addition,  $P_{a\text{CO}_2}$  is estimated from end-tidal  $P_{\text{CO}_2}$  ( $P_{E'\text{CO}_2}$ ). While  $P_{E'\text{CO}_2}$  can provide a suitable estimate of  $P_{a\text{CO}_2}$  in healthy lungs, this approximation is not reliable where significant ventilation/perfusion ( $V/Q$ ) inequalities exist. Lastly, Fick  $\dot{Q}$  methods measure only the portion of  $\dot{Q}$  that perfuses

alveoli and participates in gas exchange. Blood flow through intrapulmonary shunts ( $\dot{Q}_s$ ) cannot be detected by Fick  $\dot{Q}$ .

We describe a novel method ( $\dot{Q}_{IT}$ ) that overcomes the re-circulation limitation of previous Fick  $\dot{Q}$  measures, using a series of short iterative tests. The reliability of  $\dot{Q}_{IT}$  is enhanced by pairing it with our previously developed technique of sequential gas delivery (SGD), allowing precise measures of  $\dot{V}_{CO_2}$  and more definitive estimates of  $P_{aCO_2}$  from  $P_{E'CO_2}$ . However, like previous Fick  $\dot{Q}$  methods,  $\dot{Q}_{IT}$  does not measure  $\dot{Q}_s$ . We present its theoretical derivation, a description of its implementation, and a proof-of-concept study comparing  $\dot{Q}_{IT}$  with  $\dot{Q}_{TD}$  in a porcine liver transplant model.

## Methods

### The Fick equations

Fick  $\dot{Q}$  is based on the mass balance principle: during any steady state, the  $O_2$  and  $CO_2$  exchange between pulmonary capillary blood and alveolar air is equal to the gas exchange between alveolar air and the environment.  $CO_2$  is used as a tracer because, unlike  $O_2$ , the relationship between  $CO_2$  tension and  $CO_2$  content in whole blood is virtually linear.<sup>12</sup>

As equation (1) shows,  $\dot{V}_{CO_2}$  can be expressed in terms of  $\dot{Q}$ , the difference between mixed venous and arterial  $CO_2$  tensions ( $P\bar{V}_{CO_2} - P_{aCO_2}$ ) and the slope of the  $CO_2$  dissociation curve ( $S$ ).<sup>13</sup> Non-invasive end-tidal  $P_{CO_2}$  ( $P_{E'CO_2}$ ) usually substitutes for  $P_{aCO_2}$ , ignoring any inequalities, which nevertheless can be quite significant [equation (2)].

$$\dot{V}_{CO_2} = \dot{Q} \times S \times (P\bar{V}_{CO_2} - P_{aCO_2}) \quad (1)$$

$$\dot{V}_{CO_2} = \dot{Q} \times S \times (P\bar{V}_{CO_2} - P_{E'CO_2}) \quad (2)$$

For the differential Fick (DF) method,<sup>13</sup>  $\dot{V}_{CO_2}$  and  $P_{E'CO_2}$  are measured at baseline and during a reduction in alveolar ventilation ( $\dot{V}_A$ ). Assuming  $CO_2$  production remains constant during the test,  $\dot{V}_A$  reduction results in an increase in  $P_{aCO_2}$  to a new steady state. The Fick mass balance equations for each of the baseline and test states are shown in equation (3a and b), where B and T superscripts refer to baseline and test states, respectively. Assuming  $P\bar{V}_{CO_2}$  is the same as baseline after the step reduction in  $\dot{V}_A$ , and assuming the test phase is completed before re-circulation, these two Fick equations are solved for  $\dot{Q}$ : the DF equation [equation (4)].

$$\dot{V}_{CO_2}^B = \dot{Q} \times S \times (P\bar{V}_{CO_2} - P_{E'CO_2}^B) \quad (3a)$$

$$\dot{V}_{CO_2}^T = \dot{Q} \times S \times (P\bar{V}_{CO_2} - P_{E'CO_2}^T) \quad (3b)$$

$$\dot{Q} = \frac{\dot{V}_{CO_2}^B - \dot{V}_{CO_2}^T}{S * (P_{E'CO_2}^T - P_{E'CO_2}^B)} \quad (4)$$

The DF avoids the difficulty of measuring  $P\bar{V}_{CO_2}$ , however DF has acknowledged limitations.<sup>11 14</sup> First, it erroneously assumes that any gradient between  $P_{E'CO_2}$  and  $P_{aCO_2}$  remains constant and so affects both states equally. However, changes in alveolar gas concentrations during the test also change the gradients between  $P_{aCO_2}$  and  $P_{E'CO_2}$ . Secondly, there is

insufficient time for  $P_{E'CO_2}^T$  to attain its new equilibrium before re-circulation, a limitation that applies to all Fick  $\dot{Q}$  techniques.<sup>11 15 16</sup> Finally, measuring  $\dot{V}_{CO_2}^T$  is technically challenging. We address all three issues by introducing SGD and an iterative approach.

### Sequential gas delivery

The core of the iterative method is the ability to precisely control  $\dot{V}_A$  by using an SGD breathing circuit.<sup>17 18</sup> In brief, the SGD circuit is configured with a non-rebreathing valve, an expiratory gas reservoir, and an inspiratory gas reservoir supplied by a flow-controlled gas blender. A one-way valve between the expiratory gas reservoir and the inspiratory limb enables re-breathing of previously expired gas at the end of inspiration to the extent that minute ventilation exceeds fresh gas flow to the circuit. Because exhaled gas has already equilibrated with pulmonary blood, it provides no gradient for gas exchange, and is 'neutral'. The blender gas flow is the only gas potentially available for gas exchange, regardless of minute ventilation, and therefore  $\dot{V}_A$  is equal to the blender gas flow, which is known precisely (to the accuracy of the gas blender). [When the  $P_{CO_2}$  of the inspired gas is  $>0$ , the flow of inspired gas can be conceptually divided into fresh gas and 'neutral' gas:  $\dot{V}_A = \text{total gas flow} (1 - P_{ICO_2}/P_{aCO_2})$ .<sup>17</sup> The partial pressure of  $CO_2$  in inspired gas ( $P_{ICO_2}$ ) is also known from the gas blender settings, and  $P_{E'CO_2}$  can be measured accurately by capnography;  $\dot{V}_{CO_2}^B$  and  $\dot{V}_{CO_2}^T$  are then known [equation (5a and b)].

$$\dot{V}_{CO_2}^B = \frac{\dot{V}_A \times (P_{E'CO_2}^B - P_{ICO_2}^B)}{PB} \quad (5a)$$

$$\dot{V}_{CO_2}^T = \frac{\dot{V}_A \times (P_{E'CO_2}^T - P_{ICO_2}^T)}{PB} \quad (5b)$$

Dividing by  $PB$  (barometric pressure corrected for the presence of water vapour) converts partial pressures into fractional concentrations.

The important advantage of SGD for measuring  $\dot{Q}$  is that first, it enables precise setting of alveolar ventilation (and thus  $\dot{V}_{CO_2}$ ) through control of fresh gas flow. Secondly, to the extent that rebreathed gas enters alveolar dead space, it brings gas concentrations closer to those of normally perfused alveoli and reduces ventilation-perfusion heterogeneity in the lung,<sup>19</sup> enabling end-tidal gas to better reflect alveolar gas,<sup>19</sup> and arterial blood gas.<sup>20-23</sup> As a result, sources of error for the parameters used to measure  $\dot{Q}$  ( $\dot{V}_{CO_2}^B$ ,  $\dot{V}_{CO_2}^T$ ,  $P_{aCO_2}^B$ , and  $P_{aCO_2}^T$ ) are reduced.

### Iterative approach

We use an iterative approach to address the inability to establish a new equilibrium  $P_{aCO_2}$  after a step change in  $\dot{V}_{CO_2}^T$  before re-circulation. After establishing a baseline steady state,  $P_{E'CO_2}$  is raised by an arbitrary amount (about 1.33 kPa; 10 mm Hg) by delivering a bolus of  $CO_2$  during inspiration, and the resulting  $P_{E'CO_2}$  ( $P_{E'CO_2}^{T0}$ ) is noted. Thereafter, a  $P_{ICO_2}$  ( $P_{ICO_2}^T$ ) is calculated to maintain (clamp)  $P_{E'CO_2}$  at the level of  $P_{E'CO_2}^{T0}$  for the

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