REBREATHING USED FOR CARDIAC OUTPUT MONITORING
DOES NOT INCREASE HEART RATE

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Abstract
The partial rebreathing method for cardiac output determination produces short periods of elevated arterial CO₂ content. Because previous work had shown that elevated etCO₂ levels increased cardiac output, mostly due to heart rate increases, a concern was raised that the rebreathing periods could be inducing an elevated heart rate. This could also raise the cardiac output (CO), since CO = (Heart Rate) X (Stroke Volume). We studied 93 patients in the OR and the ICU who had undergone a total of 5142 partial rebreathing measurements by the NICO₂ monitor (Novametrix Medical Systems) to determine whether the heart rate was raised, even if transiently, during the monitored period. Our conclusion was that the rebreathing periods caused no detectable change in the heart rate.

Introduction
Cardiac output is a clinically important variable although it remains difficult to measure, since it is based on many interrelated factors and can vary even with respiration. Information about the level of cardiac output describes the general health of the heart and cardiovascular system and can be used by physicians to guide care, especially in critical care situations. Cardiac output is monitored clinically in about 1,000,000 patients each year with the bolus thermodilution technique. The thermodilution method, in which a bolus of cold saline is injected through a pulmonary artery (PA) catheter directly into the heart, is currently the most widely used and clinically accepted standard for measurement of cardiac output. Unfortunately, the costs associated with placement of a PA catheter are high. Because it is associated with considerable morbidity and mortality, not all patients in whom cardiac output monitoring would be valuable can be monitored by thermodilution.

A reliable method for measuring cardiac output non-invasively is desirable, especially for those patients who are at risk for peri-operative cardiac morbidity but in whom the risk-benefit ratio does not justify invasive monitoring. Non-invasive methods are also more desirable because they can be less costly and can require less set up time. A number of non-invasive methods have been introduced for clinical use, including transthoracic bioimpedance, esophageal Doppler, transesophageal echocardiography, and NICO₂ partial rebreathing.

The NICO₂ method is based on a version of the Fick equation and produces intermittent periods of elevated arterial CO₂ content. The difference in endtidal (or end-expiratory) CO₂ levels between the rebreathing and normal periods is approximately 5 mmHg. It is during this period of elevated arterial CO₂ levels that the appropriate variables for the cardiac output calculation are generated. A concern was raised that since the CO₂ levels were being elevated for the measurement, the cardiac output may have been raised by the measurement technique itself. This concern was related to previous work, including that of Eger, which stated that cardiac output was raised, mostly due to increased heart rate, when the etCO₂ was raised stepwise in six-minute increments.

To address this issue, we monitored 93 subjects in the OR and the ICU who underwent NICO₂ non-invasive cardiac output monitoring to see if we could observe a difference in the heart rate attributable to the elevated CO₂ levels.

Partial Rebreathing Non-invasive Cardiac Output Technology (NICO₂)

Our lab has developed a non-invasive CO₂ rebreathing system to measure cardiac output from the respiratory measurements of intubated patients. The NICO₂ technology has been approved by the FDA and is commercially available for use in hospitals to monitor mechanically ventilated patients. Clinical studies have shown that the NICO₂ system performs well in intubated, mechanically ventilated patients.

The method is based on a principle described by Adolf Fick in 1870. Fick postulated that the quantity of a gas such as O₂ or CO₂ entering or leaving the lungs is equal to the quantity of the gas expelled or taken up by the
blood as it flows through the pulmonary capillaries and participates in gas exchange. (Figure 1).

![Figure 1: Circulation and gas exchange](image)

That is, a mass balance equation can be used to describe how cardiac output is related to gas exchange. The conventional Fick technique based on $O_2$ has long been a standard by which other methods of determining cardiac output have been evaluated:

$$\dot{Q} = \frac{\dot{V}_{O_2 \text{ consumed}}}{C_{aO_2} - C_{\infty O_2}}, \quad \dot{V}_{O_2} \quad (1)$$

where $\dot{Q}$ is cardiac output (liters/minute), consumed is the amount of $O_2$ consumed by tissue metabolism (liters/minute), and $C_{aO_2}$ is the mixed venous $O_2$ concentration of the blood (blood flowing into the lungs in % volume) and $C_{\infty O_2}$ is the arterial $O_2$ concentration of blood flowing from the lungs (%volume).

Unfortunately, in its original form, the Fick method is an invasive method requiring catheterization to determine the blood gas concentrations ($c_{aO_2}$; $c_{vO_2}$) and $V_{CO_2}$. The original Fick equation can be modified to require only non-invasively measured variables$^{21-24}$. This is done by expressing the Fick principle in terms of alveolar ($A$) instead of arterial ($a$) blood gas concentrations and by measuring $CO_2$ elimination rather than $O_2$ uptake:

$$\dot{Q}_{PCBF} = \frac{\dot{V}_{CO_2 \text{ produced}}}{C_{TCO_2} - C_{ACO_2}}, \quad (2)$$

where $PCBF$ is the pulmonary capillary blood flow (the part of the cardiac output actually participating in the gas exchange), $V_{CO_2}$ is the volume of $CO_2$ excreted by the lungs per minute and $C_{ACO_2}$ and $C_{VCO_2}$ are the alveolar and mixed venous $CO_2$ contents, respectively. Cardiac output can be calculated from $PCBF$ by estimating the fraction of cardiac output bypassing the lung (shunt fraction).

The alveolar $CO_2$ concentration can be determined non-invasively by monitoring the endtidal $CO_2$ partial pressure in the expired gas and relating it to the blood concentration through a $CO_2$ dissociation curve. Before inserting the values in the Fick equation, the non-invasive measurements of $CO_2$ elimination and $C_{ACO_2}$ must be corrected. There are two reasons for this correction. First, the lung retains some gas, even after complete expiration (functional residual capacity). Second, some regions of the lung do not participate in the gas exchange (dead space). The NICO$_2$ algorithm can compensate for these effects.

To eliminate the need to know mixed venous $CO_2$ content, we use a partial rebreathing technique. A pneumatically driven valve temporarily adds a serial dead space to the circuit so that the patient inhales a portion of the previously exhaled $CO_2$. Partial rebreathing does not require patient cooperation and has only a small impact on ventilation. The arterial $CO_2$ content rises in response to this change in ventilation, and this induced change is used together with the amount of $CO_2$ produced to calculate cardiac output.

The NICO$_2$ system estimates shunt fraction based on blood oxygen saturation ($SpO_2$) data from the non-invasive pulse oximeter and on concentration of inspired oxygen (FiO$_2$). The limited accuracy of pulse oximetry measurements of $SpO_2$ (1-2%) and the steepness of the oxygen tension-saturation curve (especially for $SpO_2 > 95\%$) may lead to inaccuracies in the estimates of non-invasive shunt fraction. In most cases, the shunt fraction is very small, so even a large relative error in the estimate of shunt fraction leads to a small error in cardiac output. An accuracy of up to $±20\%$ in the estimation of shunt fraction is sufficient to ensure that the error in the estimation of cardiac output is less than $±5\%$.$^{12}$

Clinical studies have shown that the non-invasive cardiac output NICO$_2$ system performs well in intubated, mechanically ventilated patients, in whom regular breathing patterns and the good seal of the endotracheal tube provide optimal conditions for the NICO$_2$ system. A MEDLINE search compared the NICO$_2$ technique with bioimpedance and Doppler methods. Bias and precision statistics were used to determine limits of agreement with thermodilution (two standard deviations of the difference
from thermodilution / mean cardiac output) for each method. The proposed NICO$_2$ system showed better limits of agreement (± 28%) than either impedance (± 37%) or Doppler(± 65%).$^{13-19}$

**The NICO$_2$ valve assembly**

The NICO$_2$ valve assembly (Figure 2) is connected between the patient's breathing circuit (at the Y-piece) and the patient's endotracheal tube. The NICO$_2$ monitor controls the operation of the pneumatic valve by application of positive pressure. In its default position, the pneumatic valve causes gas from the breathing circuit to bypass the adjustable deadspace. When actuated, the pneumatic valve places the adjustable deadspace (150-450 ml) serially in the breathing circuit between the Y piece of the breathing circuit and the endotracheal tube connected to the patient. This causes the patient to rebreathe a portion of previously exhaled CO$_2$. The increase in inhaled CO$_2$ due to rebreathing causes a reduction in the CO$_2$ volume eliminated from the lung (decrease in VCO$_2$) and a corresponding increase in alveolar and arterial CO$_2$ tension (increase in P$_{ACO2}$ and P$_{etCO2}$).

**The Rebreathing Cycle**

Each NICO$^2$ measurement cycle lasts 3 minutes, and is comprised of a 60 second baseline period, a 50 second rebreathing period, and a 70 second recovery period. The resulting changes in VCO$_2$ and PetCO$_2$ are shown in Figure 3. The flow and CO$_2$ signals are sampled at 100 Hz with a resolution of 0.1 L/min for flow and 0.1 mmHg for PCO$_2$. The NICO$_2$ monitor computes and displays VCO$_2$ and PetCO$_2$ data on a breath-to-breath basis. Baseline values for VCO$_2$ and PetCO$_2$ are calculated as the average of a group of samples taken 27 seconds before the start of the rebreathing process. During rebreathing, values for VCO$_2$ and PetCO$_2$ are calculated as the average of the samples taken from 25 to 50 seconds into the rebreathing period.

The changes in PetCO$_2$ and VCO$_2$ are then used to calculate that part of the cardiac output that participates in gas exchange (pulmonary capillary blood flow (Q$_{PCBF}$)). The percentage of cardiac output bypassing the lung (shunt fraction) is determined based on Nunn's iso-shunt plots from the inspired O$_2$ fraction (FiO$_2$) values and the average blood oxygen saturation values (SpO$_2$), determined non-invasively by a pulse oximeter. Cardiac output is then calculated from Q$_{PCBF}$ and shunt fraction.

![Typical Waveforms](image)

**Figure 3:** Typical change in carbon dioxide elimination and end-tidal CO$_2$ during the rebreathing cycle.

**Methods**

**Data Collection:**

The partial rebreathing cardiac monitor (NICO$^2$, Novametrix Medical Systems) was used continuously on 93 patients in the OR (n = 50) and the ICU (n = 43). Each of the patients was intubated and mechanically ventilated...
throughout the measurement period. Patients in the OR were fully anesthetized under general anesthesia, while those in the ICU were less deeply anesthetized as they recovered from surgery. During each of the cases, the information about the etCO₂ and heart rate was automatically stored on a laptop for later analysis.

**Data Analysis:**

Theoretically, the response of the heart rate to the elevated etCO₂ levels could differ according to how deeply anesthetized the patient is, and therefore the OR and ICU sample groups were analyzed separately.

Each recorded three minute rebreathing cycle was subdivided into 30 six-second intervals. The heart rate and etCO₂ levels recorded during the baseline interval (I₀) were compared to levels before, during, and after the 50 second rebreathing period. For each cycle, differences in the heart rate and etCO₂ were calculated for |I₂ - I₁| and |I₄ - I₃|, where Δ (seconds) between intervals = TDA₀ and TDB₀, respectively. To account for the possibility of underlying trends in the heart rate, the Δt between the intervals being compared was set to be equal (TDA₀ = TDB₀). Thus, for each cycle, there were two resultant ΔHR and ΔetCO₂ values with respect to baseline (I₀). If the rebreathing were causing a change in the heart rate, one would expect to see a difference in HR for I₂ or I₄ - I₀ but not for I₀ - I₁ or I₀ - I₃.

This process of generating values for ΔHR and ΔetCO₂ was repeated for Δt’s from 14 to 60 seconds while the I₀ was held constant so that the entire 3 minute cycle period was evaluated. This was done to check whether there was a delay in the response of the heart rate to elevated CO₂ levels such that it occurred after rebreathing was completed.

To test whether the differences measured were significantly different, a second part of the evaluation was necessary. The same data was again evaluated with the procedure outlined above, but all intervals occurred during the baseline (non-rebreathing) period. This set of data was considered to be the control data which describes the inherent variation in the respiratory signals and heart rate during non-rebreathing periods. The student’s t-test was used to determine whether the sample and control values were significantly different from one another for each set of Δt’s where TDA₀(sample) = TDA₀(control) and TDB₀(sample) = TDB₀(control). Standard deviations, averages, and averages of differences were also calculated.

**Results**

A total of 5142 measurement cycles from 50 patients in the OR and 43 patients in the ICU were examined. In the OR, an average increase in etCO₂ of 5.1 mmHg had a corresponding average decrease in the heart rate of 0.24 beats/min. The standard deviations were 3.0 mmHg for etCO₂ and 5.5 beats/min for heart rate. The sample and control groups were found to be statistically different (p<0.05) from each other for etCO₂ but not for HR.

In the ICU, and average increase of 7.8 mmHg in etCO₂ levels corresponded to a heart rate decrease of 0.34 beats/min, with standard deviations of 3.1 mmHg and 6.8 beats/min, respectively.

**Discussion**

We compared baseline heart rates to rebreathing time periods and other periods throughout the cycle to examine whether the heart rate was changed, but did not find statistically significant differences (at a 0.05 significance level). The variability in the heart rate was so large that the standard deviation was much larger than any observed differences in heart rate. This is an important point clinically, as some doctors are under the impression that elevated etCO₂ levels produced by the NICO₂ could increase HR.

We observed that the heart rate actually decreased by less than one beat per minute, but this value was so small compared to the variability that there is really no change. This is in contradiction to the results found in the literature. One explanation for this contradiction could be that the etCO₂ was elevated in our method for only 50 seconds, while in the literature, etCO₂ was elevated for six minutes. During the shorter time period of rebreathing used by NICO₂ we did not observe a difference in heart rate caused by increases in etCO₂ and have concluded that the concerns related to the possible increases in heart rate do not affect NICO₂ performance.

It was somewhat surprising that the HR did not change in the ICU patients. This could have been due to remaining effects of anesthesia or because there is really no induced change during a short partial rebreathing period. This issue should be tested further in spontaneously breathing, awake subjects.

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References