Noninvasive Partial Rebreathing Cardiac Output
for Nonintubated Subjects

by

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ABSTRACT

The conventional partial rebreathing technique for noninvasive cardiac output measurement is limited to patients with mechanical and mixed ventilation. It would be advantageous to extend monitor utility to gain access to reliable, noninvasive measures of cardiac health in settings such as intensive care units and cardiac outpatient clinics. However, the original partial rebreathing technique did not have adequate reliability for clinical use when tested on spontaneously breathing, nonintubated volunteers. Hardware and software modifications made during the course of this research led to a new means of signal acquisition and processing for cardiac output estimation so the monitor could be used on spontaneously breathing subjects.

Several challenges were anticipated for the monitoring of cardiac output during spontaneous ventilation, and corresponding solutions were developed during a testing phase with spontaneously breathing volunteers at rest. Changes were made to the patient interface so that respiratory measurements could be made from a face mask during oxygen delivery. Algorithms were altered such that the rebreathing period was shortened. The new, shorter partial rebreathing period provided sufficient data for cardiac output estimation while minimizing the uncomfortable effects of CO2 rebreathing for the subject.

Measurements from the modified noninvasive device were compared with those of an invasive reference method (thermodilution) in twenty-seven spontaneously breathing post cardiac surgery patients. Performance of the device from this clinical trial was promising. For a mean cardiac output (thermodilution) of 5.21 L/min, the bias was -0.34 L/min, the standard
deviation was 1.21 L/min (±46%), and the limits of agreement were -2.76 and 2.08 L/min. The correlation coefficient of a linear regression analysis was 0.408, while the slope was 0.875.

Following the clinical trials, additional refinements were made to face mask and algorithms in order to improve both the bias and the precision of the device. New data processing algorithms and a shorter rebreathing period were among the critical advancements. The new device was tested for safety and feasibility in an animal comparison study (during mechanical ventilation) and in a study on spontaneously breathing human volunteers. Cardiac output estimates from the new algorithm compared well with those of thermodilution in the animal study; bias was -0.059 L/min, SD was 0.58 L/min (±24%), and limits of agreement were 1.08 and -1.19 L/min. This performance is within published clinical acceptance standards for cardiac output monitoring.

It was concluded that because the performance of this device was improved compared to the original device for mechanically ventilated subjects, further development and testing on spontaneously breathing subjects is warranted. This conclusion was further supported by the results of the clinical trial and the volunteer feasibility study.
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CHAPTER 1

INTRODUCTION

1.1 Objectives

The objective of the work described in this thesis was to extend the functionality of a conventional partial CO₂ rebreathing cardiac output monitor (NICO₂, Wallingford, CT) from mechanically ventilated patients to spontaneously ventilated patients. To accomplish this, the work comprised four main goals: modify the hardware and the algorithm of the original NICO₂ so that it would be compatible with spontaneously breathing subjects; test the modified system on spontaneously breathing postoperative ICU patients; improve the modified NICO₂ device according to what was learned from the clinical studies; and conduct preliminary feasibility tests on the new NICO₂, first on mechanically ventilated patients, and then on spontaneously breathing volunteers.

1.2 Motivation

Cardiac output (C.O.), measured as the volume of blood pumped by the heart per unit of time, is an important indicator of a patient’s cardiovascular status. Knowledge of the cardiac output of a patient can help in hemodynamic evaluation and management of therapeutic interventions, and is crucial information for some critical care decisions. Indications for monitoring C.O. include: management of positive end-expiratory pressure (PEEP) and volume therapy, distinguishing between cardiogenic and noncardiogenic pulmonary edema, diagnosis of unresponsive congestive heart failure, diagnosis and monitoring of pulmonary hypertension,
major cardiac surgery, and complicated myocardial infarction.\textsuperscript{1-2} In these settings, clinicians use the cardiac output measurements as a tool for diagnosing problems or predicting trends of cardiopulmonary status.\textsuperscript{3}

Acute perioperative and postoperative cardiac morbidity affects more than 1.5 million cardiac surgical patients annually in the United States,\textsuperscript{4} and it is the leading cause of death following anesthesia and surgery. The health care costs related to cardiac morbidity and mortality are tremendous. The estimated amount spent world-wide on cardiac output monitoring equipment\textsuperscript{5} rose 17% to $97.9 million from 1997 to 1999. In addition, an estimated 7-8 million noncardiac surgical patients who are currently not monitored are at risk each year for cardiac morbidity or mortality.\textsuperscript{5} This unmonitored group of people is at risk on the basis of diagnosed cardiovascular disease (1M), two or more risk factors (2-3M), or an age over 65 (4M). Due to changing demographics and increasing numbers of noncardiac elective surgeries, this number is expected to double within the next 30 years.\textsuperscript{6,7} There is clinical interest in diagnosing and treating cardiovascular disease earlier and with less overall health care cost (i.e., with shorter hospital stays and noninvasive monitoring),\textsuperscript{5} which leads to an expectation for the cardiac output market to grow 15% annually (primarily through growth in the noninvasive segment) to reach $195 million by 2004.

Cardiac output monitoring is a vital part of the management and prevention of perioperative cardiac morbidity in these patients. However, conventional thermodilution methods for measuring cardiac output bear considerable risk. This is because many complications exist with the use of pulmonary artery (PA) catheters, including infection,\textsuperscript{8} intracardiac knotting,\textsuperscript{9} catheter perforation of the pulmonary artery causing cardiac tamponade,\textsuperscript{10} hemorrhage,\textsuperscript{11} ventricular arrhythmia,\textsuperscript{12} and complete heart block.\textsuperscript{13} In addition, use is restricted to infrequent measurements to avoid volume overloading of the patient. Another study\textsuperscript{14} showed that catheterization was associated with increased mortality and
increased resource use. In light of these concerns, the use of the thermodilution method is generally limited to patients who are at risk for perioperative cardiac morbidity and other cases of overt high risks of severe cardiovascular complications.\textsuperscript{15} Even when the risk to benefit ratio does warrant catheterization, there is evidence that the catheter should not be left in place for longer than 72 hours, as recognized by the American Society of Anesthesiologists Task Force on Pulmonary Artery Catheterization.\textsuperscript{15} Thermodilution cardiac output monitoring is used in less than 15\% of the 7-8 million at-risk surgical patients mentioned above\textsuperscript{16} and is not suitable for application outside of the operating room or intensive care unit.

Indeed, the invasive nature of this method, the resulting potential for harm to the patient, the high health care costs, and concerns regarding the precision and accuracy of this method have prompted some to seek noninvasive methods of measurement. Noninvasive methods of cardiac output estimation could be used on patients for whom the risk of an invasive method is too great. The advantages held by the noninvasive cardiac output monitors are predicted to have a large impact on health care in the future; noninvasive monitors\textsuperscript{5} comprised only 10\% of the market in 1999, but by 2004, they are expected to comprise 44\%. A cardiac output estimate could replace subjective guesswork about the patient's cardiac status with objective, quantitative information to allow earlier and more appropriate intervention.

There is a clinical need for a cardiac output monitor that is reliable, noninvasive, simple to use, and inexpensive enough for regular use. The original NICO\textsubscript{2} monitor satisfies many of the clinical needs for cardiac output monitoring. However, the technology is currently limited to use on mechanically ventilated patients. This limitation may make one reluctant to use the rebreathing monitor in the operating room in place of conventional thermodilution and subsequently have few viable alternatives for C.O. monitoring postextubation. Technological advancements could make the device available for use throughout the continuum of care to the patient, from diagnosis to surgery and from recovery to follow up treatment. The alternative
technology would not replace the conventional PA catheter completely, but could provide the health care community with safer and noninvasive choices for monitoring cardiac output.

1.3 Review and Limitations of Current Monitors

Because cardiac output is a difficult parameter to measure, no method currently balances the ideal properties of a continuous, noninvasive measurement that is automated, operator independent, patient specific, cost effective, easy to use, and accurate for sedated and nonsedated patients of many sizes and of many cardiac output levels. Several competing methods of noninvasive cardiac output measurement techniques are currently being developed. A comparison of the clinically most commonly used methods and desirable characteristics of cardiac output monitors is shown in Table 1.1. The current monitors can be divided into three categories: invasive, minimally invasive, and noninvasive.

1.3.1 Invasive Cardiac Output Monitoring

1.3.1.1 Thermodilution. Currently, the most widely used and clinically accepted standard for cardiac output measurements is the bolus thermodilution technique (TDCO). Setup for the thermodilution technique includes the introduction of a balloon-tipped, flow directed Swan-Ganz pulmonary artery (PA) catheter. A known quantity of fluid (saline) at a known temperature is injected into the blood through the PA catheter at a specific location and the change in temperature of the blood downstream is measured and integrated. This method assumes ideal, perfect ventricular mixing of the indicator and that cardiac output does not change during the course of the measurement. The performance of the technique is extensively documented, with correlation coefficients typically between 0.8 and 0.9 when compared with other methods. The published accuracy generally varies widely (between ±3 and ±30%) because of sensitivity to noise and operator technique.
Approximately 1-2 million patients are monitored with thermodilution each year in the United States.\textsuperscript{23,24} The major disadvantage is that a skilled clinician must insert a catheter in the right heart and pulmonary artery, which is associated with considerable morbidity and mortality risks.\textsuperscript{25,26} Because the technique is associated with considerable morbidity and mortality, it is not justified to monitor all patients by using invasive pulmonary artery catheters, even if knowledge of cardiac output would be clinically valuable.\textsuperscript{14,27,28}

\subsection*{1.3.1.2 Continuous cardiac output (CCO).} CCO is a variation of the thermodilution technique that also uses a pulmonary artery catheter to deliver and record temperature changes. Instead of introducing a bolus of cool fluid to the blood, the method employs the addition of a small amount of heat. A heating filament mounted on the catheter adds heat in a pseudo-random binary sequence, and the downstream temperature is measured by a thermistor on the same catheter. The binary sequence is used to estimate the impulse response function of the system, which is used to derive the dilution curve. Cardiac output is calculated from the power level, the physiologic constants, the pseudo-random binary sequence, and the measured temperature difference.\textsuperscript{29,30} An example of this system is the Baxter Vigilance System (Baxter, Deerfield, Illinois).

In selected studies reporting the performance of the CCO systems compared to conventional TD, the bias ranges between -0.07 and 0.31 L/min, and the precision is within 1 L/min.\textsuperscript{31-34} Limits of agreement (mean difference +/- 1.96 SD) are reported to be between -2.1 and 2.0 L/min.

This system is more clinically accepted than other TD Bolus alternatives, perhaps because of the already familiar use of a catheter and the convenience of not requiring manual injections. However, several concerns are also related to the method. First, cardiac output measurements are highly averaged (3 to 6 minutes) and therefore, changes are detected only slowly. Second, body temperature changes, such as during recovery from bypass surgery and
respiration\textsuperscript{35} (0.2° C), can compete with the temperature changes initiated by the filament, adding complication to the measurement. Third, catheter placement introduces risk of infection to the patient.

1.3.1.3 Pulse contour analysis calibrated with thermodilution. The pulse contour method is based on the relationship between arterial pressure waveform measurements and stroke volume, which therefore implies a relationship to cardiac output. The stroke volume is computed as the ratio of the systolic area of the aortic pressure tracing and the vascular impedance. The vascular impedance can be estimated with empirically derived nomograms that include heart rate, age and mean arterial pressure.

An example of a device that uses this method is the PiCCO monitor by Pulsion (Cornelius, NC). This device is new, and was approved for marketing by the FDA in June, 2000. The device combines thermodilution with pulse contour analysis to provide continuous cardiac output monitoring.\textsuperscript{36} It does not require (but can be used with) a PA catheter. Instead, a central venous catheter is used for injection and a peripheral artery catheter is used for temperature curve sampling. The PiCCO device uses arterial thermodilution-calibrated pulse contour analysis to estimate continuous cardiac output. The monitor also provides physiologic variables related to volume and, using the arterial access, blood pressure and systemic vascular resistance.

This device is less invasive than conventional thermodilution. It is also considered semi-continuous, since it can provide information with each heart beat. However, the pulse contour method may not work if systemic vascular resistance or arterial compliance has changed since the calibration.\textsuperscript{36} Furthermore, the method still requires a central venous and a peripheral arterial catheter, since it cannot be calibrated without thermodilution.
1.3.2 Minimally Invasive Cardiac Output Technologies

1.3.2.1 Transpulmonary dilution. This type of method is less invasive because it eliminates the need for placing a catheter through the right heart and valves. An example of a device employing transpulmonary dilution is the Lithium Dilution Cardiac Output monitor by LiDCO Ltd (Williamsville, NY). A bolus of lithium chloride is injected through a central venous catheter, and a 3 mL sample of blood is automatically pulled from a peripheral arterial catheter (at a rate of 4 mL/min) for concentration measurements by a lithium-selective electrode. A lithium dilution curve is then constructed from the concentration measurements. Cardiac output, C.O., is calculated as:

\[
C.O. = \frac{\text{LiCl Dose} \times 60}{(\text{Area}) \times (1 - \text{PCV})},
\]

where LiCl Dose is in mmol; "Area" is the integral of the primary curve (mM.s); and PCV is packed cell volume, calculated as hemoglobin concentration (g/dl) ÷ 34. The (1-PCV) correction is needed because lithium is distributed in the plasma.

The arterial lithium dilution measurement can be made only once every 12 hours due to safety concerns. Therefore, if something were to function incorrectly, the dilution measurement could not be repeated, and the device would be unusable for 12 hours. The cardiac output measurements are made continuous by using pulse contour, which relies on the assumption that the SVR does not change in between dilution measurements. The toxicity of lithium results in contraindications for use during the first trimester of pregnancy or for patients already being treated with lithium therapy; the background lithium would prevent a sufficient signal/noise ratio. Another disadvantage is that a blood sample is required to measure packed cell volume; this categorizes the method as minimally invasive rather than noninvasive. As with all indicator dilution methods, abnormal shunts could result in erroneous cardiac output
measurements. LiDCO has found that the electrodes drift in the presence of competitive muscle relaxants, and they hope to overcome this problem.

1.3.3 Noninvasive Cardiac Output Technologies

Noninvasive cardiac output techniques are more desirable, not only because they pose fewer risks than placing a PA catheter and removing blood samples, but also because they generally require less training, less set up time, and are less painful. The main noninvasive cardiac output methods currently competing for clinical acceptance include tracheal bioimpedance, transesophageal Doppler ultrasound, and rebreathing. Each of these methods is reviewed, with special attention being paid to patient comfort, ease of use, and the ability to be used in a noncritical care environment where the patient may be only lightly sedated or not sedated.

Transthoracic electrical impedance is one of the oldest principles used for continuous and noninvasive cardiac output measurement. Despite many years of development, reliable estimates of cardiac output have not been uniformly reported and the technique will require continued refinement before achieving widespread clinical use. Transesophageal echocardiography ultrasound relies on very expensive and sensitive sensors and image processing technology, which must be managed by a highly skilled operator. These methods are not included in this review.

1.3.3.1 Tracheal bioimpedance. This is a very new method for cardiac output measurements. For the measurement, a multi-electrode array on the cuff of an endotracheal tube injects high frequency electrical current, and the resulting voltage drop is measured. The voltage signal is thought to be related to aortic blood flow. An example of a device that uses this technology is the ECOM by Imagyn (Irvine, CA). Reported values are heart rate, stroke volume, C.O., and electrical impedance values. This monitor is still at an early stage with
respect to the engineering, regulatory process, educational effort, and marketing strategy. At this time, algorithms have been mainly developed for use in swine; algorithms for humans are in the process of being developed.

In an animal study of 10 swine, the measurements from this method were compared with transit time flow probe measurements. Linear regression analysis showed an $r^2$ of 0.77 and a slope of 0.94. The reported bias was 0.15 L/min, and the limits of agreement were –2.53 to 2.82 L/min.

Use of this device is limited to intubated patients, and among these patients, possible problems exist with over-inflated or under-inflated cuffs, since electrode contact may be lost. If multiple electrodes lose contact with the wall, the signal is lost. The signal may deteriorate with extended periods of intubation (> 24 hrs) due to accumulation of mucous between the tracheal wall and the ET cuff. Patients with stiff lungs and resultant high airway pressures will cause an under-inflated cuff to loose contact with the tracheal wall. Because of the requirement for patient intubation, use of this method is limited beyond critical care settings. Also, this method cannot be used for small pediatrics and infants since their small endotracheal tubes do not have cuffs.

1.3.3.2 Transesophageal Doppler ultrasound. This technique estimates cardiac output by measuring blood velocity in the descending aorta. To convert this to cardiac output, the following assumptions are necessary: 1) the velocity profile is known and constant; 2) maximum aortic cross-sectional area has been identified, is constant, and is of circular shape (in some devices this assumption must be accomplished with empirically derived nomograms); and 3) distribution between ascending and descending aortic blood flow is known and constant. Typically, the device assumes that 70% of the cardiac output passes through the descending aorta.
Performance of the Doppler method has recently been reported.\textsuperscript{38} In comparison with standard thermodilution, multiple regression showed a correlation coefficient of 0.96. Bland-Altman data analysis also revealed a mean difference between the techniques (bias) of −0.01 L/min and limits of agreement of 1.12 L/min. In another representative study,\textsuperscript{39} correlation coefficients between transesophageal Doppler and thermodilution, thermodilution and Fick, and transesophageal Doppler and Fick were 0.846, 0.746, and 0.811, respectively.

The CardioQ by Deltex (Branford, CT) is an example of a monitor that uses esophageal Doppler ultrasound to monitor cardiac output and other parameters related to left ventricular performance. To estimate the aortic diameter with a nomogram, the user enters patient weight, height, and age. The CardioQ software also has a mode that automatically adjusts the gain of the Doppler signal. In the past, this had to be done manually. An automatic gain might improve the consistency of cardiac output estimations.

The Hemosonics 100 by Arrow (Reading, PA) is another device that employs the same theory. In addition to the Doppler transducer, it has an M-Mode transducer for the measurement of aortic diameter and to help in the positioning of the probe. This additional capability can reduce the problems associated with the user and position dependent nature of the measurements.

The hemodynamic assessment is performed on a beat-to-beat basis, which can be a clear advantage over other methods. The method also holds the potential to infer other hemodynamic parameters, such as contractility and afterload, from the measurements. Changes observed in these variables may provide clinicians with better information for clinical decisions, such as when optimizing fluid management.

The method is noninvasive, but to tolerate the esophageal probe, the patient needs to be heavily sedated. The precise position of the transducer is critical for this technique and may require frequent adjustment, especially in the presence of motion. Anatomical differences
between a specific patient and published norm can also lead to errors. Because of these limitations, the device is not compatible with use outside of critical care environments.

1.3.3.3 NICO$_2$ rebreathing monitor. The original NICO$_2$ partial rebreathing technology uses an automated, noninvasive method that provides cardiac output measurements every three minutes. The technique is based on the well-accepted Fick principle (described in detail in Section 1.4); changes in CO$_2$ elimination and partial pressure of end-tidal CO$_2$ in response to a brief change in effective ventilation are used to measure cardiac output. In addition to noninvasive cardiac output monitoring, the NICO$_2$ technology also provides important information about respiratory function (e.g., VCO$_2$, end-tidal CO$_2$, airway resistance, respiratory compliance, etc.).

Clinical studies have shown that the noninvasive cardiac output system performs well in intubated, mechanically ventilated patients. In studies comparing the NICO$_2$, the bioimpedance and the Doppler methods with thermodilution, NICO$_2$ system showed better limits of agreement (± 28%) than either impedance (± 37%) or Doppler (± 65%).$^{40-46}$

Because it is based on an automated partial rebreathing differential Fick method, the NICO$_2$ system is noninvasive, easy to use, comfortable for the subject, and is based on commonly monitored clinical signals. Use of the monitor is contraindicated for patients with severe pulmonary disease and patients who cannot tolerate elevation of arterial CO$_2$ levels. At this stage of development, NICO$_2$ is limited to use on mechanically ventilated patients and patients with mixed ventilation. However, with shorter periods of measurement and other hardware and software modifications, it appears possible to extend the application to spontaneously ventilated patients. If the application of the technology were successfully expanded to spontaneously ventilated patients, the system would have the unique advantage over other methods of being available for monitoring throughout the continuum of care delivered to the patient.
1.4 Earlier Work with the Fick Principle and Rebreathing

1.4.1 Original CO₂-Based Direct Fick Equation for Cardiac Output Measurement

The current NICO₂ method for measurement of cardiac output is based on the steady state mass balance principle stated by Adolf Fick in 1870. Fick postulated that at steady state, the amount of O₂ transferred from the lungs to the blood is equal to the quantity of the gas gained by the blood as it flows through the pulmonary capillaries and participates in gas exchange. In more general terms, the production or uptake of an indicator gas divided by the arterial-venous gradient of that gas yields the cardiac output. The Fick equation expressed with CO₂ as the indicator gas is:

\[
\dot{Q}_t = \frac{\dot{V}_{CO₂}}{CₐCO₂ - CᵥCO₂},
\]

where \( \dot{Q}_t \) is the cardiac output in L/min, \( \dot{V}_{CO₂} \) is the rate of carbon dioxide elimination in mL/min, \( CₐCO₂ \) is the arterial carbon dioxide content in mL CO₂/liter blood, and \( CᵥCO₂ \) is the mixed venous carbon dioxide content in mL CO₂/liter blood.

The direct Fick technique has long been a standard by which other methods of determining cardiac output have been evaluated. However, in its original form, the Fick method is an invasive method that requires catheterization to sample the blood gas concentrations. Because of this the direct Fick method is not widely used clinically, although its accuracy makes it a commonly chosen method for research. A measurement with the direct Fick method requires steady state, i.e., cardiac output and metabolic rate do not change. In addition, measurement error was a challenge when this method was commonly used because the technique of measuring blood gas concentrations often contained large error. Therefore, estimations when the cardiac output was high were closer to the true value than measurements.
of low cardiac output, largely due to the larger venous-arterial gradient. Obtaining mixed venous blood samples was difficult because they were often drawn from the right atrium, where the blood returning from different parts of the body was mixing for the first time. Later, samples were also taken from the pulmonary arteries by feeding the catheter through the heart.

1.4.2 Indirect Fick Method: Total Rebreathing

Rather than using a catheter to directly measure mixed venous and arterial CO2 content, these values can be estimated noninvasively from the respiratory gases; this is termed the indirect Fick method. An example of an indirect Fick method is the total rebreathing technique in which end-tidal CO2 partial pressure (PETCO2) is monitored during both normal breathing and total rebreathing periods. The PETCO2 can be related to the blood concentration with the CO2 dissociation curve. In the numerous variants of the total rebreathing method, the common objective is to allow the subject to rebreathe until the CO2 accumulates or reaches a plateau, such that mixed venous CO2 content can be estimated. During rebreathing, equilibrium is reached, and the partial pressure of CO2 in the end pulmonary capillary blood can be assumed to be equal to the partial pressure of CO2 in the alveoli; the CO2 elimination from the lungs approaches zero (VCO2 ≈ 0). The normal breathing period is used to estimate the arterial CO2 content.

In the total rebreathing indirect Fick method, the noninvasive variables are expressed in terms of alveolar instead of arterial blood gas concentrations. When alveolar or end-capillary CO2 content (CaCO2) is used in the Fick equation rather than arterial CO2 content, the pulmonary capillary blood flow (QPCBF) (i.e., the nonshunted blood flow that participates in gas exchange) is measured instead of cardiac output (Q):

where $\dot{Q}_{PCBF}$ is the pulmonary capillary blood flow (the part of the cardiac output actually participating in the gas exchange in the lungs), $\dot{V}CO_2$ is the rate of carbon dioxide elimination in mL/min, $C_ACO_2$ is the alveolar carbon dioxide content in mL CO$_2$/liter, and $C_vCO_2$ is the mixed venous carbon dioxide content in mL CO$_2$/liter. Note that the diffusion gradient is typically adequate for end-capillary and alveolar CO$_2$ to equilibrate.

The total cardiac output can be calculated from $\dot{Q}_{PCBF}$ by estimating the fraction of cardiac output bypassing the lung (shunt fraction) and adding it to $\dot{Q}_{PCBF}$:

$$\dot{Q}_t = \dot{Q}_s + \dot{Q}_{PCBF},$$

where $\dot{Q}_t$ is the total cardiac output in L/min, $\dot{Q}_s$ is the portion of the cardiac output in L/min that bypasses the blood gas exchange surfaces in the alveoli of the lungs, called the intrapulmonary shunt blood flow, and $\dot{Q}_{PCBF}$ is the pulmonary capillary blood flow in L/min.

The total rebreathing method was often applied to healthy subjects with high cardiac outputs (i.e., as in during exercise). Because the normal shunt fraction for a healthy adult is only about 5 percent of the total cardiac output, the $\dot{Q}_s$ component was typically ignored.

Problems with the total rebreathing techniques include the need for patient cooperation during breathing, including special rhythms and breath holding, the need to breathe from a bag with CO$_2$ accumulating, and the requirement of steady state equilibrium during the measurement.
1.4.3 Differential Fick Partial Rebreathing Method

The differential Fick partial rebreathing method is a variation of the traditional rebreathing methods. Like the indirect Fick method, it uses both normal breathing and rebreathing periods, as well as the respiratory gases. In contrast to traditional rebreathing methods, the differential partial rebreathing method eliminates the need to know mixed venous CO₂ content and can be used with ventilated patients where patient cooperation is not always possible. The partial rebreathing technique employs a differential form of the Fick equation to calculate cardiac output, wherein the ratio of the change in the numerator and the denominator during a brief change in effective ventilation denotes the cardiac output level.

The partial rebreathing method described by both Gedeon and Capek calls for adding a serial dead space to the breathing circuit to temporarily alter effective ventilation. Measurements of the V̇CO₂ and C₄CO₂ are made during both normal and rebreathing periods. This method requires that the patient inhale only some of the air that was previously exhaled.

Because the cardiac output is assumed to remain the same within the measurement cycle, the indirect Fick equations for the rebreathing and nonrebreathing periods can be set to be equal:

\[
\dot{Q}_{PCBF} = \frac{\dot{V}CO_{2N}}{C_vCO_{2N} - C_ACO_{2N}} = \frac{\dot{V}CO_{2R}}{C_vCO_{2R} - C_ACO_{2R}},
\]

where R is rebreathing and N is nonrebreathing, \(\dot{Q}_{PCBF}\) is the pulmonary capillary blood flow, \(\dot{V}CO₂\) is the volume of CO₂ excreted by the lungs per minute and \(C_ACO₂\) and \(C_vCO₂\) are the alveolar and mixed venous CO₂ contents, respectively. Equation 1.5 can be rearranged to obtain:

\[
\dot{Q}_{PCBF} = \frac{\dot{V}CO_{2N} - \dot{V}CO_{2R}}{(C_vCO_{2N} - C_ACO_{2N}) - (C_vCO_{2R} - C_ACO_{2R})}.
\]
Because of the relatively large size of the CO₂ stores in the body and the slow time constant of the CO₂ stores relative to the length of time of rebreathing, it can be assumed that the mixed venous CO₂ content does not change during a brief change in effective ventilation (\(C_{v}CO_{2R} = C_{v}CO_{2N}\)). Equation 1.6 can then be reduced to:

\[
Q_{PCBF} = \frac{\Delta V}{\Delta C_{A}CO_{2}} ,
\]  

(1.7)

where \(\Delta V = \dot{V}CO_{2N} - \dot{V}CO_{2R}\) and \(\Delta C_{A}CO_{2} = C_{A}CO_{2N} - C_{A}CO_{2R}\).

If partial pressure of end-tidal CO₂ (\(P_{ETCO2}\)) measured at the mouth is corrected for alveolar dead space, it can be assumed to be equal to alveolar CO₂ partial pressure which is in equilibrium with partial pressure of CO₂ in the end capillary blood. Equation 1.7 can then be written as:

\[
Q_{PCBF} = \frac{\Delta VCO_{2}}{S \Delta P_{ETCO2}} ,
\]  

(1.8)

where \(S\) is the slope of the CO₂ dissociation curve in mL CO₂/liter blood/mmHg.

To summarize the assumptions necessary for the differential Fick partial rebreathing technique, cardiac output and \(C_{i}CO_{2}\) do not change during the measurement period and \(Vd/Vt\) is constant. The performance (Table 1.2) of partial CO₂ rebreathing has been studied extensively.\(^{41-46, 52, 53, 56-68}\)
1.5 The Noninvasive Cardiac Output (NICO₂) Technology

In its original form, the NICO₂ system was developed to measure cardiac output in intubated patients using an automated CO₂ differential Fick partial rebreathing technique. Clinical research to date shows sufficient accuracy and reliability of NICO₂ cardiac output measurements in intubated, mechanically ventilated subjects, where regular breathing patterns are exhibited and the good seal of the endotracheal tube is achieved. Setup time for the noninvasive device is less than 5 minutes.

1.5.1 Mainstream Gas Sensors

The NICO₂ mainstream sensors use nondispersive infrared (NDIR) absorption and dual wavelength ratiometric-single beam optics to detect CO₂. The measurement range is 0-150 mmHg (0-20 kPa). The response time is less than 60 ms. Accuracy is 2 mmHg for readings between 0 and 40 mmHg, 5% of the reading for the range of 41-70 mmHg, and 8% of the reading for CO₂ in the range of 71-150 mmHg.

The airflow during respiration is monitored with a differential pressure sensor. The flow range of the flow sensor is 2-180 L/min at a barometric pressure of 760 mmHg, room air, 35°C. The flow sensor accuracy is the greater of 3% of the reading or 0.5 L/min.

The flow and CO₂ signals are sampled at 100 Hz with a resolution of 0.1 L/min for flow and 0.1 mmHg for PETCO₂. The NICO₂ monitor computes ĊCO₂ as the product of the integrated flow and CO₂ signals and displays ĊCO₂ and PETCO₂ data on a breath-to-breath basis.

1.5.2 Pulse Oximeter

The reusable pulse oximeter can measure blood oxygen saturation levels from any digit. A separate attachment can be used to measure saturation of the blood at the ear lobe.
The oximeter calculates SpO₂ with a two-second average and is accurate within 2% for oxygenation levels of 80-100%.

1.5.3 Pneumatic Valve

During mechanical ventilation, the NICO₂ rebreathing valve assembly is connected between the patient's breathing circuit (at the wye piece) and the patient's endotracheal tube. The NICO₂ rebreathing valve contains a dual diaphragm and is pneumatically controlled, such that a return spring keeps the valve in the nonrebreathing position unless pneumatic positive pressure is applied (See Figure 1.1). The NICO₂ 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 inserts the adjustable deadspace (150-450 mL) in the breathing circuit serially between the wye piece of the breathing circuit and the endotracheal tube connected to the patient. This causes the patient to rebreathe a portion of previously exhaled CO₂. By the end of the inspiratory period, the subject is inhaling fresh air. Therefore, the subject is only rebreathing part of the previously exhaled CO₂. Partial rebreathing does not require patient cooperation and has only a small impact on ventilation.

1.5.4 Measurement Cycle

Each NICO₂ 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 (Figure 1.2). During rebreathing, the increase in inhaled CO₂ due to rebreathing causes a reduction in the CO₂ volume eliminated from the lung (decrease in ̇VCO₂) and a corresponding increase in alveolar and arterial CO₂ tension (increase in PACO₂ and ṖETCO₂). The changes in the respiratory signals can be seen in a signal vs. time plot (Figure 1.3).
In the original NICO₂ monitor, which was developed specifically for mechanical ventilation, baseline values for \( \dot{V}CO₂ \) and \( PETCO₂ \) are calculated as the average of a group of samples taken 27 seconds before the start of the rebreathing process. During rebreathing, values for \( \dot{V}CO₂ \) and \( PETCO₂ \) are calculated as the average of the samples taken during the last 25 seconds of the rebreathing period. These average values are chosen because they are the plateau points of the signal during the rebreathing and nonrebreathing periods. The regularity of mechanical ventilation aids in the identification of the plateaus in the signal at baseline and rebreathing levels. Using the Fick equations, the changes in \( PETCO₂ \) and \( \dot{V}CO₂ \) are then used to calculate the pulmonary capillary blood flow (\( Q_{PCBF} \)).

Alternatively, \( PETCO₂ \) can first be converted to pulmonary end-capillary concentration of carbon dioxide (\( Cc'CO₂ \)) with the following CO₂ dissociation curve equation\(^{52}\):

\[
Cc'CO₂ = 175 * \ln(1 + 0.1933 * P_ACO₂) 
\]

(1.9)

where \( P_ACO₂ \) is approximated by \( PETCO₂ \) and is measured in mmHg. The resultant value of \( Cc'CO₂ \) is measured in mL CO₂/L blood. The two signals (\( \dot{V}CO₂ \) and \( Cc'CO₂ \)) can then be plotted against each other (Figure 1.4). In this case, the negative value of the slope of the line formed by the data points collected during one measurement cycle represents the pulmonary capillary blood flow (\( Q_{PCBF} \)). This is because there is a linear relationship between \( \dot{V}CO₂ \) and \( Cc'CO₂ \) as described by the Fick equation (Equation 1.2). In other words, when a ventilation change such as rebreathing is initiated, \( \dot{V}CO₂ \) drops dramatically because much of the previously exhaled CO₂ is again inhaled. With more rebreathing breaths, this slowly leads to a lower diffusion gradient for CO₂ in the alveoli and therefore a slowly raising CO₂ content in the blood. If total rebreathing were accomplished, the \( \dot{V}CO₂ \) and \( Cc'CO₂ \) signals would continue to follow the line of slope \(-Q\) until no CO₂ would move from blood to alveoli (\( \dot{V}CO₂ = 0 \))
mL/breath). At this point, the line of slope $-\dot{Q}$ intercepts the x-axis and represents the venous blood CO$_2$ content, since the alveolar CO$_2$ content is the same as venous.

### 1.5.5 Shunt correction accuracy

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 (F$_{IO2}$) values and the average blood oxygen saturation values (Sp$_{O2}$), determined noninvasively by a pulse oximeter$^{70}$. Cardiac output is then calculated from $\dot{Q}_{PCBF}$ and shunt fraction (Equation 1.4).

The limited accuracy of pulse oximetry Sp$_{O2}$ measurements (±1-2%) and the steep oxygen tension saturation curve (especially for Sp$_{O2} > 95\%$) may lead to inaccuracies in the estimates of noninvasive 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. It was previously shown that these noninvasive estimates of intrapulmonary shunt compare well with invasive estimates.$^{71}$ An accuracy of ± 20% in the estimation of shunt fraction is sufficient to ensure that the error in the estimation of cardiac output$^{71}$ is less than ±5%.

### 1.6 Overview of this Thesis

The objective of this study was to modify the original NICO$_2$ system for use on spontaneously ventilated subjects. Both the hardware and the software were modified to accomplish this objective since they had first been specifically designed for mechanically ventilated subjects. The hardware was modified to accommodate nonintubated subjects during oxygen delivery. The software was modified by adding new data analysis parameters, shortening the rebreathing periods, and employing a new calculation algorithm. The hardware and software changes taken together would provide patient comfort, improved performance,
and ease of use of a noninvasive monitor unique in its capacity to be used on awake, spontaneously ventilated subjects.

In the first part of the study, several challenges to monitoring spontaneously ventilated patients were anticipated and met. These challenges included: 1) face mask leaks, preventing reliable $\text{PETCO}_2$ and $\dot{\text{VCO}}_2$ measurements; 2) spontaneous breaths, which are much more irregular than mechanical breaths; and 3) variability in effective end-expiratory lung volume, causing wildly varying functional residual capacity from one breath to the next and associated changes in gas measurements unrelated to cardiac output.

The patient interface of the NICO$_2$ cardiac output monitor was improved so that it could accommodate spontaneously breathing patients. Commercially available face masks and mouthpieces were evaluated for suitability in signal acquisition. An oxygen delivery system was developed which would not hamper concurrent mainstream gas monitoring. The suggested volume and length of time of rebreathing required for an acceptable signal to noise ratio were also investigated. The newly enhanced rebreathing system was tested for feasibility of use in awake, nonintubated volunteers. The feasibility tests would examine the plausibility and reproducibility of measurements and the effect of rebreathing on spontaneous ventilation, patient comfort, anxiety, and blood oxygen saturation.

In the clinical ICU trial undertaken as part of this research, which involved twenty-seven awake, recently extubated spontaneously breathing human subjects, the measurements of the modified NICO$_2$ system were compared with those from a reference standard (thermodilution). This clinical trial also served as a respiratory data collection period. The author oversaw the data collection for this study. The data were later replayed and reanalyzed for further algorithm development. With these data, new challenges to monitoring spontaneously ventilated subjects were identified.
In response to the clinical data, a colleague refined the NICO$_2$ algorithm. Additional data processing and algorithm techniques were investigated to address the challenges ascertained from the results of the patient study. A new component of the algorithm was developed to compensate for irregular tidal volume and decreased signal to noise levels.

Statistics used to evaluate the performance of the device in the clinical trial included Bland-Altman plots and linear regression. Device modification decisions were based on evaluation by standard statistics methods such as average, average difference, and standard deviation.
REFERENCES


44. Watt RC, Loeb RG, Orr JA. Comparison of a new non-invasive cardiac output
technique with invasive bolus and continuous thermodilution. *Anesthesiology.* 1998;89(3A):A536.


70. Haryadi DG. *Partial CO2 Rebreathing Indirect Fick Technique for Non-Invasive Measurement of Cardiac Output.* [dissertation]. Salt Lake City, UT: Department of Bioengineering, University of Utah [pending].


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<th>Desirable Characteristics</th>
<th>Bioimpedance</th>
<th>Thermo-dilution</th>
<th>Doppler</th>
<th>Original NICO₂</th>
<th>Proposed NICO₂</th>
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<td>Sedation not required</td>
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<td>●</td>
<td>●</td>
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<tr>
<td>Intubation not required</td>
<td>● †</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
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<tr>
<td>Estimates reproducible within 1 L/min</td>
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<td>●</td>
<td>●</td>
<td>●</td>
<td>● †</td>
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<tr>
<td>Short setup time</td>
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<td>●</td>
<td>●</td>
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<td>●</td>
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† Depends on the method application
‡ Requires more testing
# Table 1.2

Twenty-Two Studies Reporting the Performance of the Partial CO₂ Rebreathing Techniques

<table>
<thead>
<tr>
<th>Ref</th>
<th>Method</th>
<th>Subjects</th>
<th># of samples</th>
<th>TDco Range L/min</th>
<th>Correl. Coeff. r</th>
<th>Bias L/min</th>
<th>Precision L/min</th>
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<td>53</td>
<td>Hyperhypoventil.</td>
<td>5 dogs, 6 patients</td>
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<td>0.5-6.5</td>
<td>NR</td>
<td>NR</td>
<td>20%</td>
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<td>57</td>
<td>Switched SerialDS</td>
<td>25 dogs</td>
<td>6</td>
<td>2.5-5.0</td>
<td>NR</td>
<td>NR</td>
<td>8%</td>
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<td>56</td>
<td>DS for 8 breaths</td>
<td>14 dogs</td>
<td>NR</td>
<td>2.14</td>
<td>0.94</td>
<td>0.17</td>
<td>CV=12%</td>
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<td>Switched serial DS</td>
<td>29 patients</td>
<td>329</td>
<td>0.70</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>58</td>
<td>Oleic acid lavage</td>
<td>16 dogs</td>
<td>458</td>
<td>1.5-7.5</td>
<td>0.91</td>
<td>0.01</td>
<td>0.51</td>
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<td>Hyper/hypoventil. Switched SerialDS</td>
<td>40</td>
<td>4.0</td>
<td>0.40</td>
<td>-0.12</td>
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<tr>
<td>60</td>
<td>Rebreathing</td>
<td>6 pigs</td>
<td>64</td>
<td>1.5-11.5</td>
<td>0.92</td>
<td>-0.13</td>
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<td>80</td>
<td>1.8-8.9</td>
<td>0.81</td>
<td>-0.14</td>
<td>0.77</td>
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<td>2.7-10.9</td>
<td>0.54</td>
<td>-1.69</td>
<td>1.90</td>
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<td>272</td>
<td>1.8-13.5</td>
<td>0.92</td>
<td>NR</td>
<td>0.96</td>
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<td>-1.1</td>
<td>0.62</td>
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<td>0.21</td>
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<tr>
<td>42</td>
<td>Oleic acid lavage</td>
<td>4 dogs</td>
<td>41</td>
<td>1.8-6.5</td>
<td>0.83</td>
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<td>44</td>
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<td>46</td>
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<td>69</td>
<td>0.85</td>
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<td>65</td>
<td>Switched serial DS</td>
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<td>48</td>
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<td>NR</td>
<td>0.11</td>
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NR=Not Reported  CV=Coefficient of Variation  
DS=Dead Space  y=rebreathing cardiac output, x=TDco
Figure 1.1. The NICO₂ pneumatic rebreathing valve assembly manufactured by Novametrix Inc.
Figure 1.2. One three minute measurement cycle.
Figure 1.3. Typical change in carbon dioxide elimination and end-tidal CO₂ signals during one three minute rebreathing cardiac output measurement.
Figure 1.4. Mechanical ventilation with one partial rebreathing cardiac output measurement with the original NICO\(_2\) monitor. Note that if the method had been total rebreathing, the production of CO\(_2\) at the mouth (\(\dot{V}_{CO_2}\)) would have decreased to zero (denoted with the triangle) along the line of slope -Q. In this case, \(\dot{Q}_{PCBF} = 4.36\) L/min.
CHAPTER 2

PREPARATION FOR CLINICAL STUDIES

Because of difficulties with inconsistent ventilation, the original NICO2 system was designed for mechanically ventilated patients and patients with mixed breathing. Several challenges were anticipated for the modification of the original monitor for spontaneously ventilated patients. This chapter reports the hardware and software alterations made to the device in preparation for the subsequent clinical study.

2.1 Introduction

In its original configuration, the NICO2 monitor was developed for mechanically ventilated patients who have regular breathing patterns. During mechanical ventilation, tidal volume and respiratory rate may be constant for a matter of hours. The ventilator controls inspiratory and expiratory pauses, inhalation rate, and inspired gases. Thus, the respiratory signal is quite reliable and free of many artifacts. When partial rebreathing is initiated, ventilatory drive by the patient does not affect the measurement. This allows the signal to be very predictable during and following partial rebreathing maneuvers.

Mixed breathing is largely controlled by the ventilator, but occasional patient respiratory efforts and assisted breaths may be inserted in between the mechanical breaths. Algorithm refinements to the original NICO2 made the cardiac output (CO) estimations reliable despite this small amount of irregularity in the respiratory signals.

In contrast to mechanical and mixed ventilation, spontaneous ventilation is irregular. The recorded data can include sighs, coughs, snoring, and talking. Inspiratory and expiratory
pauses, rates, and volumes may change with each breath. A large breath may be followed by a small breath, or small and big breaths can even be divided among several inspiratory and expiratory periods. These changes in ventilation are based primarily on carbon dioxide and secondarily on oxygen levels in the blood. Because a spontaneously breathing subject adjusts ventilation to control CO₂ and O₂, a long rebreathing period may cause the body to counteract the rebreathing maneuver by increasing ventilation.

The irregular nature of spontaneous ventilation rendered the original NICO₂ cardiac output estimations inconsistent. With the normal deviations in the respiratory pattern, the PETCO₂ and V̇CO₂ signals were altered, such that they were not necessarily indicative of the cardiac output, but rather of the changes in ventilation and various components of the lung physiology, including anatomic dead space and diffusion of the gases during differing inspiratory pause lengths. The standard deviation of an average V̇CO₂ of 405 mL/min was 215 mL/min, while an average PETCO₂ of 38.5 mmHg had a standard deviation of 5.5 mmHg.

This chapter describes the hardware and software alterations made to the original system in preparation for the subsequent clinical patient study. The foreseen challenges to signal acquisition in spontaneously ventilated subjects fell into three main categories: patient interface, irregular signal, and lower percentage of inspired oxygen levels (room air is 21% oxygen, compared to typical ventilator settings of 70%). These changes were needed to assure adequate oxygenation and to improve signal acquisition during spontaneous respiration so that cardiac output estimates could be more reliably made from irregular spontaneous ventilation signals.

2.2 Patient Interface: Mask vs. Mouthpiece

2.2.1 Introduction

In preparation for the preliminary volunteer studies and subsequent algorithm development, the choice of an appropriate patient interface had to be made. The best options
for measurements on spontaneously breathing subjects were a mouthpiece and a face mask. Advantages of the mouthpiece potentially included a better expiratory gas signal to noise ratio and a smaller deadspace. Advantages of the mask potentially included more patient comfort during the measurement, the ability to swallow (absence of a nose clip), a better fit for more face shapes, less cooperation required from the patient, and the ability to monitor both mouth and nasal ventilation, as in during sleep. It was proposed that the clinician could have the flexibility to use either attachment, the mask or the mouthpiece, as determined by the needs of the patient. This would require that the monitor be capable of detecting which attachment was in place. In addition, it was important to know whether the mouthpiece and masks could be used interchangeably to measure mainstream $P_{ETCO2}$ accurately. The purpose of these studies was to determine whether one type of interface must be used rather than the other, or whether either type of attachment would be acceptable.

### 2.2.2 Materials and Methods

Following IRB approval and informed subject consent, two healthy, spontaneously breathing volunteers were monitored alternatively with a small face mask, a small mask together with a nose clip, a medium mask, a medium mask with a nose clip, a mouthpiece with a nose clip, and a nose clip with no extra attachment. The nose clip was used together with the face masks to observe whether the deadspace estimations could be improved by reducing the mixing induced by nasal breathing. The mask type in these studies was a disposable medium adult anesthesiology face mask with inflation valve and hook ring (Sims, Smiths Industries, Fort Myers, FL). Each attachment was directly attached to a NICO$_2$ sensor. The NICO$_2$ monitor was used to measure the $P_{ETCO2}$ and estimate the deadspace of each of the attachments. This is done with a single breath $F_{ECO2}$ vs. volume curve (Figure 2.1), the area under which ($A + p$) can be summed for all the breaths in a minute to calculate $\dot{V}CO_2$ in mL/min. Airway deadspace ($Vd$) is estimated from the start of expiration to the point in a single breath $F_{ECO2}$ vs.
volume plot where the area under the curve (p) is equal to the area between the waveform and the asymptotic line drawn at the maximum level of $FECO_2$ (q).

In a second phase of the study, subjects were monitored with a single medium adult mask and NICO$_2$ sensor. A Datex anesthesia monitoring system, the Capnomac Ultima (Division of Instrumentarium Corp., Helsinki, Finland) was used to measure the reference PETCO$_2$ values at various positions near the patient’s mouth. These positions were at the NICO$_2$ sensor window, at the distal end of the NICO$_2$ rebreathing assembly, parallel with the subject’s teeth, and at the distal end of the face mask deadspace. Because there are small errors associated with the measurements of each monitor, the numbers from the NICO$_2$ monitor were adjusted to match those of the Datex monitor when the Datex probe was at the same position as the NICO$_2$ sensor window. This was the zero point of the values for the comparisons in this study, and all subsequent NICO$_2$ measurements were adjusted by this amount. The PETCO$_2$ values were recorded during nonrebreathing periods and at the end of 50 second partial rebreathing periods.

2.2.3 Results

The NICO$_2$ monitor did not consistently estimate the deadspace, even when mixing within the deadspace was minimized with a nose clip. The deadspace measurement results are shown in Table 2.1. The monitor could therefore not detect which attachment, the mouthpiece, small mask, or medium mask, was in place.

End-tidal CO$_2$ measurements were not observed to change when different attachments were in place, and all PETCO$_2$ measurements were within the manufacturer specification limits for accuracy (less than two mmHg difference at 0-40 mmHg) when compared to the Datex measurements.

In the second phase of the study, the two monitors recorded the same $\Delta$PETCO$_2$ initiated by each of the rebreathing maneuvers. The average difference between the fixed position
mainstream NICO$_2$ and the variable position sidestream Datex P$\text{ETCO}_2$ measurements was 0.48 mmHg with a standard deviation of 0.35 mmHg.

2.2.4 Discussion

For cardiac output estimation by the NICO$_2$ rebreathing algorithm, it is less important whether the absolute P$\text{ETCO}_2$ measurement is accurate; it is very important to measure the change in P$\text{ETCO}_2$ accurately. The fixed-position NICO$_2$ sensor satisfactorily measured the same rebreathing-induced $\Delta$ P$\text{ETCO}_2$ as the Datex probe, which was placed in several different positions close to the mouth. Neither the mouthpiece nor the face mask was found to be substantially better than the other for measurement of P$\text{ETCO}_2$ in these tests.

Making two types of patient interfaces available to the clinician would introduce an extra level of complication to the data analysis portion of the work. It was hoped that the monitor could detect which attachment was in place so the two groups could be separated from each other during analysis if necessary. Because the NICO$_2$ monitor did not distinguish between the tested attachments based on measurements of deadspace or end-tidal CO$_2$, it was necessary to choose one type of attachment for the future clinical studies. The face mask performed well for P$\text{ETCO}_2$ measurements on the volunteers, and since it offered more advantages in comfort and fit over the mouthpiece, it was decided to pursue the face mask as the preferred attachment for future studies.

2.3 Face Mask Selection

2.3.1 Introduction

Face masks are widely used throughout medical practice. For the purpose of a clinical cardiac output data collection and comparison trial, it was decided to choose one of the commonly available commercial face masks rather than developing a new mask.
2.3.2 Materials and Methods

Commercially available masks were researched, evaluated, and the best one chosen. The desired criteria were as follows: comfortable fit for most people, low airway resistance to minimize work of breathing, good seal with the face that minimizes leaks during both inspiration and expiration, low deadspace compared to V_T, low price, widely available, able to capture both nasal and oral respiratory signals, easy to wear when sick or sleepy, quick and easy to strap on or hold in place, and useful even on people with facial trauma or beards. Local physicians were asked to contribute their opinions and experience during the evaluation process. An internet and product catalog search was performed. Following this search, the best masks were tried on for comfort and to test the quality of the seal formed.

2.3.3 Results

Based on the decision criteria, the commonly used anesthesiology face mask with inflation valve and hook ring (Sims, Smiths Industries, Fort Myers, FL) was chosen for subsequent clinical studies (Figure 2.2). This mask had the advantages of being widely available, comfortable, forming a leak-free seal with most faces quite easily, being cheaper than many other masks, and being available in small, medium, and large adult and pediatric sizes. The deadspace of the face mask was approximately 100-150 mL when the appropriately sized mask was placed on the subject’s face. The anesthesiology face mask had an air-filled membrane encircling the perimeter of the mask. This membrane was inflatable and, when pressed against the face, formed a virtually leak-free seal. A head strap could be used to hold the mask in place. The NICO_2 sensor could be easily attached directly to the mask to obtain respiratory measurements.

2.3.4 Discussion

Although the face mask chosen had many advantages, a main disadvantage was that it was rather large and made the apparatus appear much more bulky than necessary when it was
placed on the subject. The large deadspace volume of the mask occasionally made some volunteers feel like they needed to breathe more rapidly or with larger tidal volumes than normal. It was decided that despite this disadvantage, this mask was the best mask available for the clinical trials.

2.4 Amount of Rebreathing

2.4.1 Introduction

In preparation for the subsequent clinical studies, the rebreathing system was tested on healthy, spontaneously breathing volunteers. It was known that a small percent of rebreathing (less than approximately 40% of the average breath size) was typically enough to obtain an acceptable signal to noise ratio and cardiac output estimate for mechanically ventilated subjects, but it was not clear how the system originally designed for intubated patients would perform on spontaneously ventilated patients. Furthermore, it was known that the respiratory signal of the spontaneously breathing subject was much more irregular than that of the mechanically ventilated patient. This section of the chapter presents the effect of differing amounts of rebreathing on the quality of the acquired signal and the resultant cardiac output estimate. A small percent of rebreathing, a large percent of rebreathing, and total rebreathing were tested. In addition, these trials were used to develop, in part, the final protocol for the clinical study.

2.4.2 Small Percent Rebreathing

2.4.2.1 Materials and methods. Following IRB approval and informed subject consent, four healthy volunteers were instructed to complete approximately 60 minutes of cardiac output monitoring and data collection during spontaneous respiration through the face mask selected in section 2.3. The face mask was an anesthesiology face mask (Sims, Smiths Industries, Fort Myers, FL) and was tightly secured with a head strap. The rebreathing volume was set to approximately 200 mL and was introduced automatically for 50 seconds every three
minutes by the original NICO\textsubscript{2} monitor. The data collection took place automatically with the NICO\textsubscript{2} monitor during this period, and the data were later analyzed off-line. A reusable pulse oximeter (Novametrix Medical Systems, Wallingford, CT) was affixed to the index finger. Noninvasive blood pressure, NICO\textsubscript{2} cardiac output values, and SpO\textsubscript{2} were also manually recorded every three minutes. During the study, volunteers watched a movie as a distraction from the study.

The protocol was broken into three phases. First, for 20 minutes, the volunteers lay supine on a hospital bed with the head raised approximately 30 degrees. Then they stood next to the bed for 20 minutes. During the third period of twenty minutes, the volunteers performed light exercise, consisting of stepping onto and then off of a two-inch step.

2.4.2.2 Results. Motion artifact was present in the pulse oximeter and respiratory signals during the light exercise portion of the study. The exercise motion also caused mask leaks and incorrect CO\textsubscript{2} measurements. The data from this portion of experiments was therefore eliminated.

During each of the first two periods, the blood pressure did not trend up or down for any of the subjects monitored. Average blood pressure, cardiac output, and SpO\textsubscript{2} values, as well as the corresponding standard deviations for each subject are shown in Table 2.2.

The respiratory data obtained from the spontaneously ventilated subjects was much more variable and less predictable than the data recorded during cases with mechanical ventilation. In these tests, the percent of rebreathing was determined to be 20 to 33 percent, depending on the tidal volume. From the CO\textsubscript{2} and V\textsubscript{CO}\textsubscript{2} signals, it appeared that a small percent of rebreathing was not enough to cause a change in V\textsubscript{CO}\textsubscript{2} and CO\textsubscript{2} to make a good cardiac output estimation. In some cycles, the baseline signal before and after rebreathing was quite stable, which aided in making a reasonable cardiac output estimation. However, the estimations for each individual were not consistent. None of the cycles showed the preferable PETCO\textsubscript{2} plateau during rebreathing, and end-tidal CO\textsubscript{2} was only increased by an average of 2.32 mmHg with a standard deviation of 0.85 mmHg. The signal was so poor during most cycles
that it was very difficult to distinguish the rebreathing periods from the nonrebreathing periods; the standard deviation of the baseline PETCO₂ signal was 0.97 mmHg. An example of the ŐCO₂ versus PETCO₂ plot is shown in Figure 2.3.

2.4.2.3 Discussion. There was too much motion artifact introduced during exercise to collect meaningful data, so the exercise portion of subsequent data collection protocols was postponed until the device had been further developed for spontaneously breathing subjects.

Since no cardiac output comparison method was available for the healthy volunteers, the other variables such as blood pressure had to be used to describe the general clinical picture. The blood pressure did not change in any of the subjects tested, so it was deduced that cardiac output was probably not changing drastically during the study periods. Therefore, the estimates from the NICO₂ should not have been changing drastically over the course of the measurement period.

The quality of the respiratory signal was also manually studied since the data rejection algorithm had not been improved to analyze spontaneous breaths. It was observed that the small percent of rebreathing was too easily overcome by the changes in ventilatory drive response displayed by the spontaneously breathing volunteers. This was because with each large breath, the subjects inspired a copious amount of fresh air, which diluted the amount of rebreathing so that very little change in either end-tidal CO₂ or ŐCO₂ was achieved during the rebreathing maneuver. The amount of change in the signal initiated by rebreathing was much smaller than the changes inherent in the signal during most spontaneous breaths. Therefore, a larger percent of rebreathing was necessary to achieve meaningful cardiac output estimations.

2.4.3 Large Percent Rebreathing

2.4.3.1 Materials and methods. Following IRB approval and informed subject consent, seven volunteers were instructed to watch a video during approximately 60 minutes of cardiac output monitoring and data collection. Volunteers were spontaneously breathing while wearing the previously selected face mask and NICO₂ sensor. The face mask was snugly
secured with a head strap. The rebreathing volume was set to approximately 450 mL (approximately 60% of the tidal volume of most breaths) and was introduced automatically for 50 seconds every three minutes by the NICO2 monitor. A reusable pulse oximeter was affixed to the index finger. The NICO2 monitor automatically collected the respiratory data during this period, and the data were later analyzed off-site. Blood pressure, cardiac output, and SpO2 values were also manually recorded every three minutes. For the first 35-45 minutes, the volunteers lay in the supine position with the upper body elevated thirty degrees. The remaining 15 minutes were spent standing in place next to the bed.

Following the data collection period, the information was examined for consistency, signal clarity, sources of noise, and potential for repeatable cardiac output estimations. Different periods during rebreathing and before and after rebreathing were used to calculate the cardiac output. With spreadsheet software, cardiac output was manually calculated, and the best periods for consistent calculation determined.

2.4.3.2 Results. The results for the manually recorded values, blood pressure, cardiac output, and SpO2, are shown in Table 2.3. An excessive amount of motion artifact was present in the CO2 signal during the standing phase of the study, requiring this portion of the data to be eliminated from analysis.

The change in the end-tidal CO2 signal initiated by rebreathing was 4.82 mmHg with a standard deviation of 0.81 mmHg. The baseline PETCO2 signal had a standard deviation of 0.54 mmHg. A recognizable plateau in the end-tidal CO2 signal was observed during rebreathing. The data appeared to be more regular than the data obtained during the small percent rebreathing study (Section 2.4.2). Some cycles in this data set appeared to produce reasonable estimations based on the blood pressure and clinical picture, while others did not. It was determined that the best periods for cardiac output calculation were periods with high levels of stability, such as during the plateau of rebreathing and the period just prior to rebreathing. When there was great uniformity in the signal, a distinguishable plateau was created in the end-tidal component. Periods where this occurred were partially attributed to stable CvCO2 and
partially to stable breath size, respiratory rate, and otherwise stable breathing patterns, as observed in the recorded data.

2.4.3.3 Discussion. The large percent of rebreathing was found to be much more appropriate than the small percent of rebreathing for producing clinically useful measurements in spontaneously breathing subjects. The changes in both CO₂ and V̇CO₂ signals initiated by the large percent of rebreathing were greater than those initiated by the small percent of rebreathing, and the change was enough to result in cardiac output estimates with a lower standard deviation than in the small percent rebreathing tests. The period of the data collected when the subjects were standing contained the most inconsistency and error. Because this portion of the data had to be eliminated, it was decided to pursue data collection in the supine position in all subsequent studies.

As the data were examined, it was determined that the signal processing program and data rejection algorithm needed to be altered. As the program was initially written, there was no indication of time within each cycle, and there was no relation of the data points to each other. Periods of rebreathing were not distinguished from periods of nonrebreathing. The number of points evaluated within each measurement period was set, and it was impossible to weight some points more heavily than others. An example of the original presentation of the large percent rebreathing data is shown in Figure 2.4. Processes to improve the data processing and presentation were begun, and it was decided that the implemented changes would be based on the data collected from the clinical study. These processes are described in detail in chapter four.

The larger and more frequently varying tidal volumes of most spontaneously breathing people necessitated this larger rebreathing volume in order to achieve a measurable change in the end-tidal CO₂ and V̇CO₂ signals. More of the cardiac output estimates made from large rebreathing volumes were reasonable values for people at rest with stable blood pressure, although this could not be confirmed with a reference method. Based on the results of this study and the newly developed data processing algorithms, the large amount of rebreathing was
preliminarily chosen for the clinical ICU studies. It was hoped that this configuration would provide clinical data that would be useful during replay for further algorithm refinement. A set of experiments for volunteers with total rebreathing was also developed in the event that the data from total rebreathing was markedly better for cardiac output estimations than large percent rebreathing data.

2.4.4 Total Rebreathing

2.4.4.1 Materials and methods. Following IRB approval and informed subject consent, three healthy volunteers were requested to breathe through the previously selected face mask and NICO2 assembly during automated rebreathing maneuvers. A reusable pulse oximeter was affixed to the index finger. Cycles lasted three minutes and were repeated sequentially, with 50 seconds of total rebreathing in each cycle. Each study lasted approximately 30 minutes. The data were collected automatically and saved for later analysis.

2.4.4.2 Results. The change in the end-tidal CO2 signal was larger during total rebreathing than during partial rebreathing (average change 9.05 mmHg, standard deviation 1.56 mmHg). The standard deviation of the baseline signal was 0.95 mmHg. As in partial rebreathing, some cycles displayed a plateau in the PETCO2 values, while other cycles were highly irregular in shape. During the 50 seconds of total rebreathing, the oxygen levels, as monitored by the pulse oximeter, regularly dropped on average from 98% to 93%. During the recovery period after rebreathing, the strong respiratory drive response caused hyperventilation and an associated tendency to reduce the PETCO2 to lower than normal levels, resulting in an unstable baseline respiratory signal. In most cases, the periodic shape of the signal, which was caused by the cyclical alterations in ventilation, ceased before the next rebreathing maneuver began. The SpO2 level returned to normal levels between rebreathing maneuvers. The subjects uniformly commented that total rebreathing was uncomfortable after 20-35 seconds.

2.4.4.3 Discussion. No reference standard was used in this study, so cardiac output estimation performance could not be directly evaluated. Total rebreathing was found to provide
the best signal to noise ratio with the unaltered algorithm. The changes initiated in end-tidal CO$_2$ and VCO$_2$ in response to rebreathing were significant in comparison to the noise generated by spontaneous ventilation. However, total rebreathing was more of a disturbance to the subjects’ ventilation and comfort level, and it initiated a stronger respiratory drive response in spontaneously breathing subjects than the partial rebreathing measurements did. The response of respiratory drive initiated by total rebreathing caused more extreme variation in the signal, which negatively impacted the repeatability of the measurements. Subsequent studies were designed to determine whether the strong signal and clear PETCO$_2$ plateau produced during total rebreathing could be used in conjunction with a shorter rebreathing period.

It was concluded that 50 seconds of total rebreathing was too long for the comfort and safety of most spontaneously breathing subjects. The hemoglobin saturation drop observed in healthy, spontaneously breathing subjects indicated that this total rebreathing setup was not safe for sick patients who potentially could not efficiently perform gas exchange. Because of the oxygen saturation drop during rebreathing, studies were also planned for oxygen delivery during measurement periods.

### 2.5 Length of Rebreathing Time

#### 2.5.1 Introduction

These tests were developed to test whether a total rebreathing maneuver could be used in conjunction with a shorter rebreathing period to create large enough changes in end-tidal CO$_2$ and VCO$_2$ to make good estimates of cardiac output while minimizing the respiratory drive response.

#### 2.5.2 Variable Length of Total Rebreathing (1200 mL deadspace)

**2.5.2.1 Materials and methods.** Following IRB review and informed subject consent, five healthy volunteers at rest in a supine position were asked to breathe through the previously
selected face mask and the NICO₂ rebreathing assembly. Rebreathing was set in increments of five from 10 to 40 seconds within a three-minute measurement period. A reusable pulse oximeter was affixed to the index finger. The data collection process lasted approximately 25 minutes for each subject. SpO₂, PETCO₂, and VCO₂ were monitored and recorded automatically for later analysis and data playback.

2.5.2.2 Results. Total rebreathing periods between 20-30 seconds provided the best data for cardiac output calculation, but with total rebreathing periods, SpO₂ dropped significantly in most subjects, from an average of 98% to 93% saturation. The end-tidal CO₂ measurements reached the maximum level, or plateau (change in PETCO₂ signal between subsequent breaths less than approximately 0.5 mmHg), during rebreathing when the rebreathing was at least 20 seconds or longer. An example graph of a 25 second rebreathing period that displayed the desired plateau of the CO₂ signal is shown in Figure 2.5. In some files, the end-tidal CO₂ reached a plateau during rebreathing, but then was reduced to a lower level after 30 seconds of rebreathing due to the ventilatory drive response initiated by long total rebreathing periods. Periods of rebreathing shorter than 20 seconds did not produce a meaningful signal for cardiac output calculation (resultant C.O. estimates ± >100%). An example plot of the end-tidal CO₂ for a 15 second period of rebreathing is shown in Figure 2.6. Subjects reported that rebreathing periods shorter than 25-30 seconds were not uncomfortable.

2.5.3 Variable Length of Partial (60-80%) Rebreathing

2.5.3.1 Materials and methods. Following IRB review and informed subject consent, volunteers were asked to breathe through the previously selected face mask and the NICO₂ rebreathing assembly. Partial rebreathing (60-80% of the average tidal volumes) was set in increments of five from 20 to 40 seconds within a three-minute measurement period. A reusable pulse oximeter was affixed to the index finger. The data collection process lasted approximately 25 minutes for each subject. SpO₂, PETCO₂, and VCO₂ were monitored and recorded automatically for later analysis and data playback.
2.5.3.2 Results. The SpO₂ did not drop significantly in the subjects tested (average drop from 98 to 97 percent). Partial rebreathing periods of 35 seconds with this setup were long enough for the end-tidal CO₂ signal to reach a plateau (change in signal between subsequent breaths less than approximately 0.5 mmHg) for a cardiac output calculation. A strong ventilatory response to the rebreathing was not evident in the resultant respiratory signal. The average change of PETCO₂ within one measurement cycle was 4.5 ± 0.9 mmHg, while the average change in V̇CO₂ was 162 ± 25 mL/min.

2.5.4 Discussion

In contrast to the original NICO₂ 50 second rebreathing method, shorter periods of partial and total rebreathing were found to be sufficient to create significant changes in end-tidal CO₂ and V̇CO₂. Since the patient comfort was much greater during partial rebreathing than during total rebreathing, and because the signal quality did not increase substantially in total rebreathing, partial rebreathing was selected for the subsequent patient studies. To balance the needs of patient comfort and signal quality, partial rebreathing periods of 35 seconds were selected for the subsequent clinical data collection study.

Another disadvantage of the total rebreathing was that it generally caused a reduction in the oxygenation levels of the blood. The reduction of oxygenation levels from 98 to 97 percent during rebreathing periods did not pose a threat to healthy volunteers, but the saturation levels of sick patients may have decreased further if they were subjected to the total rebreathing maneuvers. Therefore, the safety feature of an oxygen delivery system was considered for development for the clinical trials. This was considered a relevant precaution for clinical testing of shorter partial rebreathing maneuvers on spontaneously breathing subjects.
2.6 Oxygen Delivery Mask with the METI

Human Patient Simulator

2.6.1 Introduction

Because healthy volunteers experienced a slight drop in the oxygenation levels of the blood during preliminary testing, oxygen delivery was determined to be a prudent precaution for the clinical testing phase of the modified NICO2 system. It was not known whether the delivery of oxygen during respiratory measurements would affect the mainstream capnometer, flow sensors, or cardiac output estimates. The following tests allowed for the development of an oxygen delivery system that did not hamper any of the components of mainstream signal acquisition. Two types of mask were chosen for these experiments: an adult oxygen delivery mask (Hudson Oxygen Therapy Sales Co., Temecula, CA) and an anesthesiology mask (Sims, Smiths Industries, Fort Myers, FL), as described above.

These tests were initially performed on a patient simulator (METI, Sarasota, FL) because the mixing chamber of the METI lungs is sidestream sampled and analyzed with an HP oxygen sensor (Hewlett Packard M1025B, Palo Alto, CA). This allows one to sample the gas concentrations in the alveoli and gain a better understanding of what gas is being delivered to the mask. Once these tests were completed, the best setups were verified on human subjects.

The purpose of the first set of studies was to determine whether an O2 delivery mask provided a sufficient means of simultaneous mainstream signal acquisition and oxygen delivery.

2.6.2 Basic Setup

2.6.2.1 Materials and methods. Measurements were made with a human patient simulator as the subject. The patient simulator’s internal oxygen sensor allowed for the measurement of alveolar oxygen levels. As when monitoring a patient, one can also measure PETCO2 and FETO2 expired from the mannequin’s mouth and nose with mainstream or sidestream
gas analyzers. Respiratory rate was set to 11 breaths/min, while tidal volume was 690 mL/breath to represent ventilation of a standard man.

The oxygen delivery mask, with attached NICO₂ mainstream CO₂ and flow sensor, was strapped to the simulator’s head. The O₂ delivery mask is manufactured with twelve 0.3 cm diameter safety holes distributed across the surface, which are intended to prevent patient suffocation in the event of oxygen delivery failure. The extra holes also aid in inspiration and expiration if the mask forms an airtight seal with the face. An O₂ delivery port and a six inch long, 24 mm diameter tube were attached distal to the NICO₂ sensor and face mask. The setup is depicted in Figure 2.7. The 24 mm tube acted as a collecting reservoir for the oxygen in between breaths, thus aiding the delivery of higher oxygen concentration during inspiration. Oxygen was administered through the O₂ port at flow rates of 0, 1.5, 2, 3, and 4 L/min. The sidestream gas analyzer inlet tube from a Datex anesthesia monitoring system, the Capnomac Ultima (Division of Instrumentarium Corp., Helsinki, Finland), was inserted into the deadspace between the mask and the simulator’s mouth. Internal alveolar gas concentrations, PETO₂, and PETCO₂ were manually recorded after stabilization at each level of O₂ delivery.

2.6.2.2 Results. Increasing O₂ flow raised alveolar oxygen from a baseline of 14% (109 mmHg) to a peak level of 36%, (277 mmHg) but caused measured PETCO₂ to drop from 37 to 25 mmHg during the same period. Alveolar CO₂ remained at 40 ±1 mmHg throughout the study. The results are depicted in Figure 2.8. The mask-face seal was too poor to maintain clinically useful mainstream PETCO₂ numbers at the same time as increased oxygenation in the alveoli, although oxygen was delivered effectively during inspiration. Upon expiration, gas was observed to preferentially flow through the lower resistance areas of the mask-face seal and the safety holes in the mask before reaching the comparatively high resistance area of the mainstream sensor.
2.6.3 Airflow Prevented During Inspiration

2.6.3.1 Materials and methods. The basic setup (section 2.6.2.1) was altered such that the holes in the mask were covered externally with plastic tabs that prevented airflow during inspiration, but allowed some passage of air during expiration, albeit at a higher initial resistance. This setup was intended to force more airflow past the mainstream sensor than the basic setup in order to produce a better mainstream PETCO$_2$ signal.

2.6.3.2 Results. This setup yielded poor mainstream PETCO$_2$ readings during periods of elevated oxygen delivery. Alveolar oxygen levels increased from 14% (103 mmHg) to 32% (245 mmHg), but measured PETCO$_2$ dropped from 37 to 20 mmHg during the same period (Figure 2.9). Both oxygenation and PETCO$_2$ levels were worse with this setup than the basic setup.

2.6.4 Airflow Prevented During Inspiration, No O$_2$ Reservoir

2.6.4.1 Materials and methods. The previous setup (section 2.6.3.1) was altered such that the six inch oxygen reservoir tube was detached. The NICO$_2$ assembly was replaced with a simple Capnostat® and flow sensor window. This setup was intended to reduce the resistance to flow past the mainstream sensor of the previous setups and thereby obtain a better PETCO$_2$ signal concurrent with oxygenation. Oxygen was administered through the delivery port at flow rates of 0, 1.5, and 2 L/min.

2.6.4.2 Results. Mainstream PETCO$_2$ measurements fell from 45 to 12 mmHg with only 2 L/min O$_2$ flow. The face seal was extremely poor, allowing much of the expired gas to escape before reaching the mainstream sensor. Gas was observed to preferentially flow through the safety holes of the mask.

2.6.5 Airflow Prevented During Inspiration and Expiration

2.6.5.1 Materials and methods. The holes in the O$_2$ delivery mask of the basic setup (2.6.2.1) were sealed closed during both inspiration and expiration for this study. All other
components of the basic setup were maintained the same. This setup was intended to force more expired air past the mainstream sensor.

2.6.5.2 Results. Again, poor mainstream PETCO₂ readings were observed during periods of elevated oxygen delivery. Upon exhalation, gas was observed to preferentially flow past the poor face seal, thereby reducing the mainstream PETCO₂ signal. Alveolar oxygen levels increased from 14% (107 mmHg) to 29% (226 mmHg), but measured PETCO₂ dropped from baseline 37 to 23 mmHg (Figure 2.10). In this experiment, oxygenation was worse than in previous experiments, and measured PETCO₂ numbers remained clinically unacceptable.

2.6.6 Discussion

The oxygen delivery mask was found to be unacceptable for simultaneous oxygen delivery and mainstream PETCO₂ signal acquisition on the patient simulator. An excessive volume of the exhaled gas flowed past the mask-face seal and through the safety holes, thereby preventing accurate mainstream PETCO₂ readings. Respiration could still be detected via the diminished PETCO₂ signal, but for the purpose of CO₂ production and cardiac output calculations, these setups were inadequate.

2.7 Anesthesia Face Mask Oxygen Delivery

with the METI Patient Simulator

2.7.1 Introduction

The purpose of this set of studies was to determine whether the face mask chosen in section 2.3 as tested in differing conformations would provide a better face seal and thereby maintain a mainstream PETCO₂ signal concurrent with oxygen delivery. These tests were performed on the METI human patient simulator.
2.7.2 Basic Setup

2.7.2.1 Materials and methods. For the basic setup, the anesthesiology face mask was connected to the NICO₂ mainstream CO₂ and flow sensor. As described in the previous section, an oxygen inlet port was connected on the distal end of the NICO₂ sensor, and a six inch, 24 mm diameter oxygen reservoir tube was connected distal to the mask, sensor, and oxygen inlet port (Figure 2.11). O₂ was delivered through the inlet port at flow rates of 0, 1.5, 2, 3, 4, 5, 6, 7, 8, and 9 L/min while the patient simulator continued spontaneous ventilation. The NICO₂ mainstream sensor was used to monitor P\text{\text{ETCO}}₂. A Datex sidestream monitoring inlet tube was inserted between the mask and the simulator’s mouth to monitor P\text{\text{ETCO}}₂ and inspired CO₂. Internal alveolar oxygen concentrations were monitored with the METI HP gas analyzer. All gas measurements were recorded after stabilization at each level of O₂ delivery.

2.7.2.2 Results. The good face seal ensured both good oxygenation and good mainstream P\text{\text{ETCO}}₂ numbers, even with flow rates of 1.5 - 9 Liters O₂/min (Figure 2.12). The alveolar oxygen level increased from 14% (160 mmHg) to 48% (368 mmHg), while the mainstream P\text{\text{ETCO}}₂ was measured to be 30-31 mmHg throughout the study (confirmed by the Datex sidestream monitor).

2.7.3 Safety Holes Added, No O₂ Reservoir

2.7.3.1 Materials and methods. This setup was tested as a possible means of combining the benefits of both the anesthesiology and O₂ delivery masks. Holes in the mask similar to those in the O₂ delivery mask were created on the surface of the mask with a good face seal (inflatable balloon). The basic setup (2.7.2.1) was altered such that nine 0.4 cm holes similar to those found in the oxygen delivery mask were created on the surface of the face mask. The oxygen reservoir tube was also detached from the distal end of the assembly. Oxygen was administered at the inlet port at flow rates of 0, 2, 4, and 6 L/min. Internal alveolar oxygen concentrations were monitored with the METI gas analyzer. The Datex sidestream gas analyzer was inserted between the mask and the mouth to monitor P\text{\text{ETCO}}₂.
2.7.3.2 Results. Mainstream PEtCO₂ measurements was reduced from 44 to 23 mmHg, compared to Datex PEtCO₂, which fell from 46 to 44 mmHg as O₂ flow rates were increased from 0 to 6 L/min. Alveolar oxygenation increased linearly, from 13% to 28%, as O₂ flow was increased (Figure 2.13).

2.7.4 Capnostat® Sensor Window and Safety Holes, No O₂ Reservoir

2.7.4.1 Materials and methods. The setup from the previous section (2.7.3.1) was altered such that the NICO₂ assembly was replaced with a simple Capnostat® and flow sensor window. This was done to test whether the turbulent flow through the NICO₂ assembly itself caused the poor mainstream PEtCO₂ readings. Oxygen delivery flow rates were set to 0, 2, 4, and 6 L/min.

2.7.4.2 Results. Mainstream PEtCO₂ measurements fell from 39 to 26 mmHg with increased O₂ flow rates, but did not fall as sharply at 2 L/min as it did in the previous setup. However, the Datex sidestream PEtCO₂ levels remained at about 45 mmHg throughout the study. Alveolar oxygenation increased almost linearly, from 13% to 27% as O₂ delivery flow was increased (Figure 2.14).

2.7.5 Capnostat® Sensor Window and Safety Holes with O₂ Reservoir

2.7.5.1 Materials and methods. The anesthesiology mask setup from section 2.7.4.1 was altered such that a six inch long, 24 mm diameter tube was attached proximal to the sensor window. Oxygen collected in this tube during the end-expiratory pause, thus aiding the delivery of higher oxygen concentration during inspiration. As in the previous setup, O₂ was administered at 0, 2, 4, and 6 L/min.

2.7.5.2 Results. Mainstream PEtCO₂ measurements fell from 40 mmHg to 20 mmHg with increased O₂ flow rates. Internal alveolar oxygenation increased almost linearly, from 13% to 35%, which was higher than previous setups with holes in the anesthesiology face mask (Figure 2.15).
2.7.6 Discussion

In the studies with the patient simulator and oxygen mask, the benefits of increased levels of oxygenation were often offset by the inability of the mainstream sensor to measure $\text{PETCO}_2$ because the expired gas flowed preferentially past the face seal or through the safety holes. This problem was corrected in these tests with an anesthesiology face mask. The best setup for concurrent oxygen delivery and accurate $\text{PETCO}_2$ monitoring on the simulator was found to be an anesthesiology face mask with no holes, the NICO$_2$ assembly sensor, and an additional proximal oxygen reservoir (Section 2.7.2.1, Figure 2.11). In this best setup, alveolar oxygenation levels were raised in a linear fashion from 14% to 48%, while the measured $\text{PETCO}_2$ signal remained constant at about 31 mmHg. Another valuable feature of this setup was that the oxygen delivery flow rates could be raised up to 9 L/min without any deleterious effects on the $\text{PETCO}_2$ signal.

It should be noted that although this mask yields the best respiratory signals and oxygen delivery because of the face seal, the setup is not intended for unobserved monitoring of the patient. Clinical and laboratory testing with this setup on people should occur during subject supervision to assure uninhibited ventilation.

2.8 Oxygen Delivery to Human Subjects

2.8.1 Introduction

Once the preferred oxygen delivery system had been developed on the patient simulator, the efficacy needed to be tested on people. The effects of oxygen delivery on the physiologic response, the respiratory measurements, and the cardiac output algorithm were examined to confirm that the oxygen delivery system did not introduce a systematic bias to the $\text{CO}_2$ respiratory signal or cardiac output estimations. All tests in this section were performed on human volunteers.
2.8.2 Effect of Oxygen Delivery on Mainstream Respiratory Measurements

The objective of this study was to test whether the mode of oxygen delivery originally developed with a patient simulator would hamper the mainstream $\text{PETCO}_2$ measurements when tested on humans.

2.8.2.1 Materials and methods. Following IRB approval and informed subject consent, three healthy volunteers at rest in a sitting position were asked to rebreathe for 50 seconds within automated, repeated three-minute cycles. The volunteers wore anesthesiology face masks, which were held in place with head straps. The NICO$_2$ assembly, with rebreathing tube fully extended, oxygen delivery port, and six inch oxygen reservoir were attached distal to the face mask. A Datex sidestream respiratory monitor inlet tube was inserted between the mask and the mouth. Oxygen was delivered through the inlet port at 0, then 5, then 2.5 L/min. A reusable pulse oximeter (Novametrix Medical Systems, Wallingford, CT) was affixed to the index finger. Respiratory values ($\text{FiO}_2$, $\text{FETO}_2$, and $\text{PETCO}_2$) and $\text{SpO}_2$ were recorded manually during both rebreathing and nonrebreathing periods. Each experiment lasted approximately 30 minutes.

2.8.2.2 Results. End-tidal $\text{O}_2$ rose and fell in response to the oxygen delivery flow rate, with 2.5 L/min being sufficient to raise $\text{FETO}_2$ to more than double the normal level (a change from 13% to 40%). $\text{SpO}_2$ was raised to an average of 98.5% with 2.5 L/min of oxygen delivered ($\text{FiO}_2$ of 42%) and to 99% with 5 L $\text{O}_2$/min ($\text{FiO}_2$ of 55%). Mainstream $\text{PETCO}_2$ measurements remained unchanged during all levels of oxygen delivery used in the study (Figure 2.16 and Table 2.4).

2.8.3 Effect of Differing Peak Inspiratory Flow on Oxygenation Levels

The objective was to test whether differing PIFs would change the amount of oxygen delivered and the level oxygenation, as measured by $\text{FiO}_2$ and $\text{FETO}_2$. 
2.8.3.1 Materials and methods. Following IRB approval and informed subject consent, one healthy volunteer at rest in a supine position was asked to breathe through the NICO2 assembly and anesthesiology face mask. Distal to the NICO2 assembly was an oxygen delivery port, where oxygen flow rates were set to 4, 7, and 10 L/min. No oxygen reservoir was connected distal to the NICO2 assembly in this study. A Datex sidestream respiratory monitor inlet tube was inserted between the mask and the mouth as described above. The volunteer altered the peak inspiratory flow according to verbal instructions so that a full range of peak inspiratory flows (PIFs) from 19 to 70 L/min was investigated.

2.8.3.2 Results. Oxygenation levels were increased for all oxygen delivery flow rates tested when compared to room air. As expected, PIFs less than or equal to 30 L/min (the normal level, when no verbal instructions were given) showed the best increases in oxygenation, as measured by both FIO2 and FETO2. At an O2 flow rate of 4 L/min, a PIF of 20 L/min resulted in an FIO2 of 54% and an FETO2 of 34%; at 10 L/min, the same PIF resulted in an FIO2 of 90% and an FETO2 of 61%. The results for all combinations of PIFs and O2 delivery rates can be seen in Figure 2.17.

2.8.4 Effect of Differing O2 Flow Rates on Oxygenation Levels and Mainstream Respiratory Monitoring in Human Subjects and with Rebreathing

The objective was to test whether this setup with various O2 flow rates and absence of oxygen reservoir could concurrently increase FETO2 and allow for a useful mainstream PETCO2 signal for cardiac output determination in human subjects. This setup would be safer in the event of oxygen delivery failure because it would minimize deadspace during the nonrebreathing portion of the measurement. Respiratory rate was also monitored for possible changes induced by the changes in gas concentrations.

2.8.4.1 Materials and methods. After IRB approval and informed subject consent, one volunteer was asked to breathe through an anesthesiology face mask with head strap and the NICO2 assembly, with the standard rebreathing loop fully extended (approximately 450 mL
deadspace). Distal to the NICO\textsubscript{2} assembly was an oxygen delivery port, where oxygen gas flow rates were set to 0, 4, 6, 8, 10, and then 0 L/min. Partial rebreathing was actuated by NICO for 30 seconds every three minutes.

**2.8.4.2 Results.** The results are shown in Figure 2.18. Mainstream end-tidal CO\textsubscript{2} measurements and respiratory rate remained constant throughout the study, while $F_{ETO2}$ increased linearly from 16\% to 52\% with flow rates of 0, 4, 6, 8, and 10 L/min. Delivered oxygen ($FiO2$) was also increased linearly, from 22\% to 62\%. This setup for oxygen delivery without the extra reservoir was thereby verified to function satisfactorily for concurrent oxygen delivery and mainstream $PETCO2$ measurements on human subjects and was selected for the subsequent clinical patient studies.

**2.8.5 Modified Oxygen Delivery Mask**

The objective was to test for a better face seal and resultant respiratory measurements than what was observed during the tests on the patient simulator. This would determine whether simultaneous oxygen delivery and mainstream monitoring could be accomplished with the oxygen delivery mask instead of the anesthesiology mask on humans. The oxygen delivery mask would have the advantage of not requiring direct supervision during the measurements.

**2.8.5.1 Materials and methods.** A simple flow and CO\textsubscript{2} sensor window was attached to an oxygen delivery mask. The O\textsubscript{2} delivery mask holes were lightly covered externally with a plastic tab that sealed the holes during inspiration, but moved to allow airflow during expiration. Distal to the sensor window, an oxygen inlet port was connected, where O\textsubscript{2} was dispensed at flow rates of 0 to 10 L/min in increments of 2 L/min. After IRB approval and informed consent, one healthy volunteer was asked to breathe through the assembly for approximately 30 minutes. A Datex sidestream monitor inlet tube was inserted between the mask deadspace and the mouth for comparison measurements.

**2.8.5.2 Results.** Mainstream $PETCO2$ measurements of 40 mmHg during no oxygen flow were reduced to 36 mmHg at high O\textsubscript{2} flow rates of 8 and 10 L/min. The Datex monitor
registered a similar change in $P_{ETCO_2}$ measurements (36 to 31 mmHg), signifying that the changes observed were due to true changes rather than problems associated with simultaneous $O_2$ delivery and mainstream monitoring. Datex sidestream $F_{ETO_2}$ measurements increased from 16% to 60% with oxygen gas flow rates of 0 to 10 L/min during the same period. The results are shown in Figure 2.19. This performance was much better than the performance observed with the human simulator, and was attributed to the better face seal obtained with real skin instead of plastic. However, the reduction in $P_{ETCO_2}$ was greater than with the anesthesiology mask setup.

2.8.6 Discussion

A modified version of the best oxygen delivery system as tested on the simulator was confirmed to perform the best for human subjects, as well. Section 2.8.4 describes the best system for concurrent oxygen delivery and signal acquisition on humans. The oxygen delivery mask worked well for oxygen delivery on people and moderately well for end-tidal CO$_2$ signal collection, but the anesthesiology mask and sensor combination was found to be best for concurrent signal acquisition and oxygen delivery. The configuration with the safety feature of oxygen delivery was selected for the human clinical studies, contingent upon good results from the study described in Section 2.9.

2.9 Feasibility Tests: Measurement During $O_2$ Delivery to Human Subjects

2.9.1 Introduction

Previous studies had shown that a large percent of rebreathing during a long period (50 seconds every three minutes) caused a greater change in $P_{ETCO_2}$ and $\dot{V}CO_2$ (thus producing the best signal to noise ratio) than a small percent of rebreathing. Other studies had shown shorter rebreathing periods to be sufficient for cardiac output calculation with a very large percent of rebreathing. Still other tests had suggested that oxygen delivery provided additional safety
during measurements with a face mask while allowing for concurrent mainstream CO₂ measurements. This study was performed to evaluate whether the individual findings held true when they were combined during cardiac output monitoring. This study design was the pilot study for the upcoming clinical trial, and as such, the rebreathing volume was set to three sizes to simulate a clinician adjusting the deadspace according to the instructions on the monitor screen for optimal measurements. Varying the deadspace during measurements on each person would also verify that cardiac output estimates were not directly related to rebreathing volume. The estimated cardiac output value, the pulmonary capillary blood flow estimates (PCBF), the PETCO₂ and the SpO₂ were monitored in spontaneously breathing subjects.

### 2.9.2 Materials and Methods

After informed subject consent and IRB approval, four healthy volunteers were requested to breathe through the anesthesiology face mask and NICO₂ rebreathing assembly for 30 second rebreathing periods within repeated, three minute cycles, for approximately 35 minutes. Oxygen was delivered at 4 L/min through the oxygen delivery port and reservoir. The rebreathing volume was set to three different levels, small, medium, and large. The small volume was approximately 150 mL, the medium volume was approximately 300 mL, and the largest volume was approximately 450 mL of rebreathing deadspace. A reusable pulse oximeter was affixed to the index finger. During the thirty-minute tests, the SpO₂, cardiac output estimates, pulmonary capillary blood flow estimates, and mainstream PETCO₂ levels were monitored to observe whether they were altered by the various percentages of partial rebreathing during spontaneous respiration.

The original algorithms (designed for mechanical and mixed ventilation) were used for the calculation of cardiac output and PCBF. The rebreathing volume was set to three different sizes (small, medium, and large).
2.9.3 Results

There were no observed differences in the SpO₂, the cardiac output estimates, the pulmonary capillary blood flow estimates, or mainstream \( P_{ETCO_2} \) measurements related to the changing volume of rebreathing deadspace. The results for each of the subjects can be seen in Figures 2.20-2.23.

2.9.4 Discussion

Since there were no observed differences in any of the monitored critical values associated with altering the rebreathing volume during spontaneous respiration, it was decided that the setup was ready for data collection in human clinical studies.

2.10 Discussion

The experiments described in this chapter suggested that the best patient interface configuration for the subsequent clinical studies would be an anesthesiology face mask with head strap, the \( \text{NICO}_2 \) rebreathing assembly (with standard loop appropriately extended to deliver a large percent of rebreathing), and an oxygen delivery port as a safety measure. Considerations for this finding included patient comfort, \( \text{NICO}_2 \) performance, patient safety, and optimal signal acquisition. For clinical data collection, oxygen could be administered at rates from 2-10 L/min without affecting the quality of the respiratory signal or the cardiac output estimations. The oxygen reservoir was optional, since the oxygenation level achieved without it was found to be acceptable.

Large percent rebreathing was loosely defined such that patients with large tidal volumes (approximately 650-900 mL/breath) would require large rebreathing volumes (roughly 450 mL), and patients with small tidal volumes (400-600 mL/breath) would require small rebreathing volumes (about 200 mL). That is, the goal was defined to be approximately 60%-80% rebreathing to achieve a large enough change in respiratory signals for good C.O.
estimations. In the clinical study, patients would be monitored with 35 seconds of partial rebreathing actuated within a three-minute, repeated measurement cycle.

The tests described were performed on simulators and healthy subjects, so the performance of the system with this setup on sick ICU patients would have to be tested in the clinical patient study. It remained to be seen in the clinical trials whether the device was easy to set up and comfortable for sick subjects.
Figure 2.1. The measurement of physiologic deadspace in a single exhalation period. Physiologic deadspace is measured as the point on the exhaled volume axis at which the vertical line creates equal areas, “p” and “q”.

FECO₂

Exhaled Volume

|<-----------------| Exhaled Tidal Volume |-----------------|

|<-----------------| Airway Deadspace |-----------------|
Figure 2.2. The anesthesiology face mask with inflation valve and hook ring chosen for clinical studies.
Table 2.1

Volume of expired air measured for various attachments.

<table>
<thead>
<tr>
<th></th>
<th>Big Mask</th>
<th>Small Mask</th>
<th>Mouth piece</th>
<th>No Accessory</th>
<th>Big Mask +NC</th>
<th>Small Mask +NC</th>
<th>MP +NC</th>
<th>NC Only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Actual Deadspace (mL)</strong></td>
<td>150</td>
<td>125</td>
<td>7</td>
<td>0</td>
<td>150</td>
<td>125</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Meas. Deadspace (mL)</strong></td>
<td>242.4</td>
<td>203.6</td>
<td>194</td>
<td>164</td>
<td>176</td>
<td>138.5</td>
<td>165.3</td>
<td>129.6</td>
</tr>
<tr>
<td><strong>Diff. (meas -actual) (mL)</strong></td>
<td>92.4</td>
<td>78.6</td>
<td>187</td>
<td>164</td>
<td>26</td>
<td>13.5</td>
<td>158.3</td>
<td>129.6</td>
</tr>
<tr>
<td><strong>Standard Deviation(mL)</strong></td>
<td>15.8</td>
<td>7.2</td>
<td>7.7</td>
<td>9.1</td>
<td>7.9</td>
<td>7.9</td>
<td>8.8</td>
<td>10.5</td>
</tr>
</tbody>
</table>
Table 2.2

Measurements of systolic and diastolic cuff blood pressure, noninvasive cardiac output, and noninvasive blood oxygen saturation for four subjects in two positions, standing and supine.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Supine Systolic BP (mmHg)</th>
<th>Supine Diastolic BP (mmHg)</th>
<th>Supine C.O. (L/min)</th>
<th>Supine SpO₂ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ave</td>
<td>StDev</td>
<td>Ave</td>
<td>StDev</td>
</tr>
<tr>
<td>1</td>
<td>114.0</td>
<td>2.9</td>
<td>57.9</td>
<td>3.5</td>
</tr>
<tr>
<td>2</td>
<td>130.9</td>
<td>2.6</td>
<td>83.8</td>
<td>4.2</td>
</tr>
<tr>
<td>3</td>
<td>129.8</td>
<td>5.9</td>
<td>62.3</td>
<td>6.4</td>
</tr>
<tr>
<td>4</td>
<td>126.7</td>
<td>6.4</td>
<td>73.5</td>
<td>3.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th>Standing Syst. BP (mmHg)</th>
<th>Standing Diast. BP (mmHg)</th>
<th>Standing C.O. (L/min)</th>
<th>Standing SpO₂ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ave</td>
<td>StDev</td>
<td>Ave</td>
<td>StDev</td>
</tr>
<tr>
<td>1</td>
<td>116.1</td>
<td>9.5</td>
<td>65.4</td>
<td>3.5</td>
</tr>
<tr>
<td>2</td>
<td>129.9</td>
<td>1.6</td>
<td>80.0</td>
<td>1.9</td>
</tr>
<tr>
<td>3</td>
<td>132.5</td>
<td>5.7</td>
<td>76.5</td>
<td>6.6</td>
</tr>
<tr>
<td>4</td>
<td>133.6</td>
<td>7.9</td>
<td>78.2</td>
<td>9.4</td>
</tr>
</tbody>
</table>
Figure 2.3. Example $\dot{V}CO_2$ vs. $C_{c}'CO_2$ plot of a fifty second period of a small percent of rebreathing for one measurement cycle. Measurements were made with an anesthesiology face mask attachment during spontaneous ventilation.
Table 2.3
Results for seven subjects during large percent rebreathing, as measured with noninvasive means.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
<th>Cardiac Output (L/min)</th>
<th>SpO₂ (% saturation)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ave</td>
<td>StDev</td>
<td>Ave</td>
<td>StDev</td>
</tr>
<tr>
<td>1</td>
<td>132.8</td>
<td>7.8</td>
<td>77.2</td>
<td>5.1</td>
</tr>
<tr>
<td>2</td>
<td>101.6</td>
<td>6.3</td>
<td>68.6</td>
<td>3.2</td>
</tr>
<tr>
<td>3</td>
<td>115.9</td>
<td>6.7</td>
<td>72.6</td>
<td>4.5</td>
</tr>
<tr>
<td>4</td>
<td>100.6</td>
<td>2.9</td>
<td>73.4</td>
<td>2.2</td>
</tr>
<tr>
<td>5</td>
<td>124.8</td>
<td>3.3</td>
<td>72.0</td>
<td>3.0</td>
</tr>
<tr>
<td>6</td>
<td>116.6</td>
<td>6.9</td>
<td>71.4</td>
<td>4.5</td>
</tr>
<tr>
<td>7</td>
<td>111.4</td>
<td>5.5</td>
<td>64.4</td>
<td>3.0</td>
</tr>
</tbody>
</table>
Figure 2.4. Example $\dot{V}CO_2$ vs. $Cc'CO_2$ plot of a fifty second period of a large percent of rebreathing for one measurement cycle. Measurements were made with an anesthesiology face mask attachment during spontaneous ventilation.
Figure 2.5. Example of data collected during twenty-five seconds of total rebreathing. Note that the rebreathing period is easily distinguished from the baseline period and that a plateau is formed in the PETCO2 signal at the end of the rebreathing period.
Figure 2.6. Example of data collected during fifteen seconds of total rebreathing. Note that the rebreathing period is more difficult to separate from the baseline period than it was in the longer period of rebreathing. Note that the plateau in the PETCO$_2$ signal during rebreathing was not met before the rebreathing period was over.
Figure 2.7. The basic setup for oxygen delivery.
Figure 2.8. Test on human patient simulator with O₂ delivery mask with holes and oxygen reservoir.
Figure 2.9. O₂ delivery mask with reservoir and no holes on simulator.
Figure 2.10. O₂ delivery mask on simulator with holes completely covered.
Figure 2.12. Anesthesiology face mask with oxygen delivery and human simulator.
Figure 2.13. Combining the benefits of the anesthesiology and O₂ delivery masks by adding holes to the anesthesiology mask.
Figure 2.14. Replacing the setup from 2.7.3 with a Capnostat CO₂ sensor window.
Figure 2.15. Adding a reservoir to the setup from the setup of the previous section.
Figure 2.11. Optimal setup for oxygen delivery on patient simulator.
Figure 2.16. Concurrent O₂ administration and mainstream CO₂ monitoring on a human subject.
Figure 2.17. Resultant FETO₂ for differing peak inspiratory flows.
Figure 2.18. Response in PETCO₂, FETO₂, and RR to differing O₂ administration flow rates.
Figure 2.19. O2 Delivery mask on a human volunteer had a better face seal than on the simulator, but did not work as well for concurrent mainstream respiratory measurements and oxygen delivery. Sidestream Datex (DPETCO2) and mainstream NICO (NPETCO2) measurements were compared.
Figure 2.20. Response of SpO₂, P\textsubscript{ETCO₂}, C.O., and PCBF during monitoring of first volunteer with rebreathing volumes of various sizes.
Figure 2.21. Response of SpO$_2$, PETCO$_2$, C.O., and PCBF during monitoring of second volunteer with rebreathing volumes of various sizes.
Figure 2.22. Response of SpO$_2$, P$_{ET}$CO$_2$, C.O., and PCBF during monitoring of third volunteer with rebreathing volumes of various sizes.
Figure 2.23. Response of SpO₂, PETCO₂, C.O., and PCBF during monitoring of fourth volunteer with rebreathing volumes of various sizes.
Table 2.4
Subject oxygenation and mainstream end-tidal CO₂ measurements in response to oxygen delivery at various flow rates.

<table>
<thead>
<tr>
<th></th>
<th>0.0 Liters/minute O₂</th>
<th>2.5 Liters/minute O₂</th>
<th>5 Liters/minute O₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average SpO₂ (%)</td>
<td>96</td>
<td>97.4</td>
<td>98</td>
</tr>
<tr>
<td>Standard Dev. SpO₂ (%)</td>
<td>0</td>
<td>0.23</td>
<td>0</td>
</tr>
<tr>
<td>Ave. Mainstream PETCO₂ (mmHg)</td>
<td>45.5</td>
<td>40.4</td>
<td>46.5</td>
</tr>
<tr>
<td>Standard Dev. PETCO₂ (mmHg)</td>
<td>0.25</td>
<td>0.82</td>
<td>0.63</td>
</tr>
<tr>
<td>Average FiO₂ (%)</td>
<td>20.1</td>
<td>20</td>
<td>39.7</td>
</tr>
<tr>
<td>Standard Dev. FiO₂ (%)</td>
<td>0.5</td>
<td>0</td>
<td>2.1</td>
</tr>
<tr>
<td>Average FETO₂ (%)</td>
<td>12.5</td>
<td>14</td>
<td>29.7</td>
</tr>
<tr>
<td>Standard Dev. FETO₂ (%)</td>
<td>0.5</td>
<td>0</td>
<td>0.4</td>
</tr>
</tbody>
</table>
CHAPTER 3

EVALUATION OF THE MODIFIED NICO₂ CARDIAC OUTPUT
MEASUREMENTS IN NONINTUBATED PATIENTS

3.1 Introduction

This chapter describes a performance evaluation of the partial rebreathing system described in chapter two when used on clinical patients. This study was the first to compare the modified system with a reference method (conventional thermodilution cardiac output) in recently extubated, spontaneously breathing patients. Because the system had not previously been studied with spontaneously breathing subjects, a second objective of this study was to identify challenges associated with monitoring cardiac output in this patient population. Third, input was sought from the clinicians regarding the usefulness of and clinical need for a noninvasive cardiac output monitor that could be used to assess the cardiac health of patients who were spontaneously breathing.

3.2 Materials and Methods

Following IRB approval, each of 28 intensive care patients was monitored in the ICU post cardiac surgery for up to sixty minutes with the modified mask-based version of the noninvasive partial rebreathing cardiac output monitor (NICO₂, Novametrix Medical Systems, Wallingford, CT). Patients were included in the study if they had a pulmonary artery catheter in place and they had been extubated. Patients with severe pulmonary disease were not monitored.
The anesthesiology mask selected in chapter two was secured with a headstrap to provide a good seal with the face, thereby facilitating useful respiratory measurements. The partial rebreathing volume was set to be 60-80% of the average tidal volume for each patient. A reusable pulse oximeter (Novametrix Medical Systems, Wallingford, CT) was affixed to a finger. Patients were in a prone position, with the head of the bed raised approximately 45 degrees. Oxygen was administered per clinician discretion at 2 to 10 L/min through the oxygen delivery port. Relevant details about each case, such as actions by the patient or medical attention given, were also noted.

Bolus thermodilution measurements (room temperature saline, 10 mL) were made manually in triplicate every 20 to 30 minutes and were randomized over all parts of the respiratory cycle. All heart rate, SpO₂, and respiratory data were automatically saved using the computer system during this period. The data were later analyzed and replayed to compare rebreathing cardiac output to corresponding average thermodilution cardiac output values, when available.

Data were eliminated from all or part of the cycle if the patient was coughing, vomiting, talking or snoring, if the patient’s tidal volume was consistently less than 400 mL, or if the face seal was broken. These conditions prohibited reliable end-tidal CO₂ and ŶCO₂ measurements. As described in chapter four, very small tidal volumes did not flush out the deadspace volume of the face mask, which led to erroneous measurements of P\textsubscript{ETCO₂} and hypoventilation, even during baseline periods.

The data were examined to determine the ideal basis of the algorithm for spontaneously ventilated patients. Initially, the data were processed with original NICO₂ algorithms. Similar and dissimilar cardiac output estimations were noted and the data examined. Next, the signals were manually processed with spreadsheets, charts, and inspection for trends. The data were split into two periods, rebreathing and non-rebreathing. The rebreathing periods were divided into sections and analyzed both separately and together to create consistent outputs. As the main parameters were selected and trends isolated, another member of the team began to
automate the manual data processing techniques. A more detailed description of the data analysis methods created in response to the information gleaned from the clinical study can be found in chapter four. To the extent possible, comparison results reported here were processed with the modified NICO₂ algorithms as described in the following chapter.

3.3 Results

Patients generally reported being comfortable during monitoring. However, one patient did begin to hyperventilate when the mask with the large deadspace was in place. This file was eliminated from analysis.

The face mask seal performed satisfactorily in all patients monitored. Oxygenation was maintained at an acceptable level during the monitoring phase for each patient, as determined by the clinician present during the study. Clinicians uniformly commented that the prototype device looked too large and bulky for routine clinical use.

Linear correlation of the paired cardiac output measurements (n=59) showed a correlation coefficient of 0.408 and a slope of 0.875 (Figure 3.1).

Bland-Altman tests on the paired cardiac output measurements (n=59) from twenty-seven patients (Figure 3.2) (mean TD = 5.21 L/min) revealed a standard deviation of the difference (rebreathing-thermodilution) of 1.21 L/min (±46%), limits of agreement of -2.76 and 2.08, and a bias of -0.34 L/min.

3.4 Discussion

This study revealed that some of the anticipated challenges of monitoring spontaneously ventilated patients were met successfully, while others were only partially met. Numerous areas for improvement and future modifications were also identified during the clinical study, and those areas provided the foundation of the work to improve the rebreathing method for future clinical trials.
The patient population in this study was found to be a difficult one. Some subjects had been extubated within one hour of being monitored; for these patients stable breathing was difficult. Some of the breaths were smaller than about 400 mL, which was found to be too small to get a good signal with the face mask. Further studies were planned to ascertain the reason for the signal deterioration and the smallest tidal volume acceptable for monitoring. Because of the tendency for very recently extubated, post-surgery patients to ventilate with quite small breaths, it was determined that it would have been preferable to wait two to three more hours after extubation to begin monitoring for this preliminary study. The mask worked well for PETCO₂ readings in cases with a tidal volume greater than 400 mL. This observation was further addressed, as described in the following chapter.

The oxygen delivery system described in chapter two worked well for these sick patients; oxygen saturation was maintained at safe levels, even during rebreathing periods, for each of the patients studied. In most cases, this was accomplished with oxygen flow rates between 2 and 4 liters/min.

The thirty-five second rebreathing period was long enough to initiate a meaningful change in the CO₂ and VCO₂ signals in many cases. Insufficient signal clarity was often caused by other factors, such as sporadic respiration, and interfered with the readings at baseline or rebreathing levels. It was observed that in many cases where signal clarity was diminished, the preceding or following cycle would often estimate a value close to the thermodilution value.

Because the algorithm and rebreathing method used in this study were largely developed for mechanically ventilated patients, the preliminary performance of the modified rebreathing system was viewed as somewhat favorable, although not yet ready for clinical use. One should keep in mind the proper perspective on the performance of this first attempt to noninvasively monitor spontaneously ventilated patients. Even when two similar methods, continuous cardiac output (CCO) and thermodilution (TDCO), share the same catheter and therefore the same placement and mixing conditions, the standard deviation is approximately 0.8 L/min. It should also be remembered that typical thermodilution measurements are
only accurate within ±10 to 20%. Therefore, precision of 1.21 L/min (±46%) in the first trial indicates that the method warrants further development.

During this study, several potential software and hardware improvements were identified which should lead to a noninvasive cardiac output monitor for spontaneously breathing patients with improved bias and precision performance. Substantial algorithm development and data filtering were found to be necessary since some cycles during spontaneous ventilation were still too irregular for cardiac output determination. Many small breaths were detected during the data collection from ICU patients; the artifact rejection filter would likely eliminate these breaths in future algorithm developments. Hardware and software that would perform well in the presence of small tidal volumes and irregular breathing patterns would be a useful modification for the ICU setting.

As mentioned earlier, some of the challenges encountered were due to the timing of the study period for some subjects. For the purpose of device refinement, future studies with the rebreathing monitor will no longer target use immediately following extubation, but rather two to three hours after extubation and beyond. The first two hours following extubation denote a period when respiration is too irregular for initial data collection and algorithm development. There is a clinical need for a monitor that can be used throughout the course of medical treatment, so the goal would be to refine the monitor first on typical data from spontaneous breaths, and later on unstable respiration. A possible solution for periods of unstable breathing or clinical need that would not require continuous monitoring for many hours would be a spot check monitor. Such a monitor could conceivably be used to monitor the patient for ten minutes and then produce a measurement. Short setup times for this device would make a spot check mode of operation practical.

Some patients were uncomfortable after 20 to 30 minutes of data collection, so it would be desirable if the measurement period required for meaningful estimations could be shortened. It is hoped that the rebreathing maneuver can be made less intrusive to patient comfort and ventilation. Efforts for the future development aimed at this goal are detailed in chapter four.
Figure 3.1. Linear regression of partial rebreathing cardiac output (NICO₂) and Thermodilution (TD) for twenty-seven recently extubated post cardiac surgery patients. Correlation coefficient = 0.41, slope = 0.875.
Figure 3.2. Bland-Altman comparison for partial rebreathing cardiac output (NICO₂) and Thermodilution (TD) for twenty-seven recently extubated post cardiac surgery patients. Results for the paired measurements (n=59) from twenty-seven patients (mean TD = 5.21 L/min) revealed a standard deviation of 1.21 L/min (±46%), limits of agreement of -2.76 and 2.08, and a bias of -0.34 L/min.
CHAPTER 4

ISSUES IDENTIFIED BY THE CLINICAL STUDY

4.1 Redesign of the Patient Interface

The clinical studies revealed that the patient interface selected for spontaneously breathing subjects was incompatible with the small tidal volumes typical of some sick patients. Because the target setting of the cardiac output monitor for spontaneously ventilated patients includes the ICU environment, the patient interface needed to be re-designed to accommodate tidal volumes of all sizes. This section describes the confirmation of and hardware solution for the problem of tidal volumes smaller than 400 mL.

4.1.1 Single Breath CO₂ Measurements

4.1.1.1 Introduction. When a large deadspace volume is placed between the patient and the capnometer, a small tidal volume will cause the PETCO₂ measurements to appear smaller than they should. The reduced reliability of the measurements means that the monitor functions more like an apnea monitor, since the gas measurements are incorrect. This is because the first part of the expired breath mixes with the air in the deadspace, thereby diluting the concentration of the gas being measured. The choice of the face mask for the clinical study described in chapter three was based on good performance in healthy volunteers and the assumption that the 150 mL deadspace would be flushed out during expiration and allow a reliable respiratory signal, even with small tidal volumes. It became evident during the clinical study that tidal volumes smaller than 400 mL were not sufficient to provide dependable respiratory signals.
This study was designed to determine the reasons for this observation and to identify the point at which respiratory measurements from a large face mask were reliable.

4.1.1.2 Materials and methods. A disposable medium adult anesthesiology face mask with inflation valve and hook rings and approximately 150 mL of deadspace volume (Smiths Industries, Fort Myers, FL) and a mouthpiece with approximately 7 mL of deadspace, were each used to monitor the end-tidal CO\(_2\) of spontaneously breathing human volunteers. The mouthpiece was used in conjunction with a nose clip. All respiratory measurements were made with a NICO\(_2\) monitor (Novametrix Medical Systems, Wallingford, CT). The F\(_{ECO2}\) vs. volume plots were examined for each set of breaths with each attachment. The volume of expired air required for a true P\(_{ETCO2}\) measurement with each attachment was recorded.

4.1.1.3 Results. For the face mask with 150 mL of deadspace, approximately 500 mL of expired air were required to flush out enough dead space to obtain a reliable end-tidal CO\(_2\) measurement (Figure 4.1). This is indicated as the point in the F\(_{ECO2}\) vs. volume plot where the curve begins to flatten out and plateau at a high level. The slope of the plateau is called the phase 3 slope. Approximately 270 mL of expired air were required to obtain a reliable measurement from the mouthpiece (Figure 4.2). A comparison of the phase 3 slopes for a face mask and for a mouthpiece can be seen in Figure 4.3.

4.1.1.4 Discussion. Results from this study verified the necessity to eliminate breaths smaller than 400 mL for analysis of the clinical data. In fact, it would have been justified to remove breaths as large as 500 mL for the analysis. The deadspace within the mask of 150 mL mixed with the expired breath via turbulent flow; therefore an expired volume two to three times as large as the deadspace was required to flush out the air from the previous breath and record a reliable measurement. This indicated that the face mask selected for the clinical study was not appropriate for the small tidal volumes of some sick patients. The mouthpiece did not add significant deadspace during nonrebreathing periods and allowed reliable P\(_{ETCO2}\) measurements for breaths as small as 300 mL. Efforts to design a modified mask with a small
deadspace that combines the benefits of a mouthpiece and a standard mask are described in Section 4.1.2.

### 4.1.2 Minimized Deadspace Volume Mask

#### 4.1.2.1 Introduction.
The mouthpiece has a very small deadspace volume of 7 mL, which provides reliable and consistent respiratory data, but is difficult to wear for extended periods. Proper use of the mouthpiece requires concurrent use of a nose clip to prevent expired air from escaping without being measured by the gas monitor. Patient discomfort, mainly related to the inability to swallow and the effort required to hold the mouthpiece in place, is the most important disadvantage of the attachment.

In contrast to the mouthpiece, a standard face mask is comfortable and can maintain a good seal with the face even without patient interaction. Swallowing is comfortable, and expired air can be measured if it exits through the mouth or the nose. The main disadvantage of the commercially available face masks is that those which provide a good seal with the face have a very large deadspace volume. It was observed (Section 4.1.1) that small tidal volumes prohibit meaningful respiratory measurements when a face mask with a large deadspace volume is chosen as the patient interface. This section describes the development of a comfortable mask with a small deadspace volume that would allow respiratory measurements equivalent to those obtained from a mouthpiece. The performance of the modified mask was determined by comparing the CO₂ vs. volume curves of single breaths with the same curves for a mouthpiece.

#### 4.1.2.2 Materials and methods.
A disposable medium adult anesthesiology face mask with inflation valve and hook rings and approximately 150 mL of deadspace volume (Smiths Industries, Fort Myers, FL) was modified to minimize the deadspace around the patient’s face. This was done by filling the deadspace with tape and foam padding, such that approximately 15 mL of deadspace remained. A mouthpiece with approximately 7 mL of deadspace was also tested in conjunction with a nose clip. Each of the attachments was used to
monitor the end-tidal CO₂ of spontaneously breathing human volunteers. All respiratory measurements were made with a NICO₂ monitor (Novametrix Medical Systems, Wallingford, CT). The CO₂ vs. volume plots and the phase 3 slopes were examined for each set of breaths with each attachment. The volume of expired air required for a true PETCO₂ measurement with each attachment was recorded.

4.1.2.3 Results. There was no significant difference between the improved mask and the mouthpiece in the PETCO₂ measurements recorded, and the FECO₂ vs. volume curves for both attachments displayed a steep phase 3 slope and a plateau (onset of phase 3 slope) within 280 mL of expired tidal volume. See Figure 4.4 for the FECO₂ vs. volume curve from a modified mask. A graph showing equivalent performance of the mouthpiece and the modified mask as demonstrated by the phase 3 slopes can be seen in Figure 4.5.

4.1.2.4 Discussion. The modified mask performed as well as the mouthpiece for producing reliable PETCO₂ measurements at small tidal volumes. Thus, future experiments for spontaneously breathing patients were planned with the modified mask in place of the original mask.

4.2 Further Algorithm Development

4.2.1 Introduction

The comparison studies in the clinical setting revealed a number of areas for improvement of the cardiac output estimation algorithm. 35% of the cycles remained too irregular for proper analysis, and some study participants commented it would have been preferable to have shorter data collection periods. As the signal processing program was initially written, there was no indication of time within each cycle, and there was no relation of the data points to each other. Periods of rebreathing were not distinguished from periods of nonrebreathing. The number of points evaluated within each period was set, and it was impossible to weight some points more heavily than others.
Several methods of data processing and analysis were developed to detect the important information within the irregular cycles. The most important of these processes are outlined in this section. They include identifying and eliminating useless information, changing the algorithm to weight the most important data the most heavily, data filtering, and developing methods of calculation that were not corrupted by extraneous points. Specific parts of the recorded data were analyzed independently and together in many combinations to develop algorithms for calculation and data rejection. A new, abbreviated method for measurement, which was based on the important components of these observations, was developed for future studies.

4.2.2 Identifying Important Signal Components

4.2.2.1 Introduction. The irregular nature of the respiratory signals acquired during spontaneous ventilation necessitated more robust data processing capabilities for reliable cardiac output estimations than the signals generated during mechanical ventilation did. This section details the work to understand why the signal was irregular and to develop an understanding of how the data were affected by the rebreathing and nonrebreathing periods.

4.2.2.2 Materials and methods. Respiratory data on file from the previous patient, animal, and volunteer studies were analyzed. In order to determine why the signal was irregular and to develop an understanding of how the data were related to the rebreathing period, the data were presented in a way that expressed the relationship among the various points and time. The relationship among the points and events was later used to select the most important data for consistent measurements. Since the most important data for the conventional method of rebreathing cardiac output was the data during the plateaus in the signals, plateaus were also sought. The data before, during, and after rebreathing were analyzed both together and separately to identify consistent cardiac output estimation. Differing lengths of time of the measurement cycle (e.g., 10 to 180 seconds) were selected to determine the best consistency of
cardiac output calculation. A second criterion for evaluating the reliability of estimations was the regression value of the slope of the $\dot{\text{VCO}}_2$ vs. $\text{Cc'CO}_2$ data, with lower values being less reliable. The data from the files were repeatedly replayed and examined for evident trends.

4.2.2.3 Results. An example of a single cycle of a $\dot{\text{VCO}}_2$ vs. $\text{Cc'CO}_2$ plot that relates the sequential points with each other is shown in Figure 4.6. Plotting the two signals this way made it evident that even during irregular spontaneous respiration, there was a general pattern of the signals forming a loop about the ideal line described by the Fick equation (Chapter 1). It was observed that, while a majority of the data points occurred at either the nonrebreathing or the partial rebreathing position on the line, there were many data points in the vicinity of the line during the transition to and from the rebreathing periods.

An example plot from several sequential measurement cycles is shown in Figure 4.7. The data are separated into rebreathing and nonrebreathing components. With repeated estimations using the $\dot{\text{VCO}}_2$ vs. $\text{Cc'CO}_2$ regression approach and with knowledge of the proportion of the data in each period, it became apparent that too many data points were collected during the nonrebreathing period. It was theorized that it was not necessary to record all these data for a reliable cardiac output measurement, since many of them appeared at the same general location on the regression plot. Cardiac output calculations that only took small portions of the data into account were made with the regression approach.

The most consistent calculation of cardiac output was achieved with a small portion of the data (20-30 data points) that incorporated information from before, during and after rebreathing, as well as the transitions to and from rebreathing periods. Evaluating only the points closest to the rebreathing periods (e.g., within 10 to 15 seconds) enhanced the consistency of the measurements and the reliability as measured by the correlation coefficient. The standard deviation for measurements derived from all data per measurement cycle in six volunteers was 2.37 L/min, while the SD for measurements for data from the 25 data points closest to rebreathing periods was 1.32 L/min. The correlation coefficient fell from an average of 0.51 to 0.26 when all nonrebreathing data were included in the cardiac output estimation.
4.2.2.4 Discussion. The results of this analysis were somewhat unexpected. It was previously assumed that a long baseline period contributed to the reliability of the measurement, since there was less frequent perturbation of the system with long baseline periods. In fact, rebreathing cardiac output estimations are mostly dependent on the information gathered during rebreathing and the transition to and from rebreathing periods. The data collected during the long baseline period of no rebreathing contain mostly redundant information. Eliminating a portion of the baseline data for cardiac output estimation enhanced consistency.

The observation that the most important data were found near the rebreathing periods, especially the transitions to and from rebreathing, meant that some of the baseline period of no rebreathing was wasted time in between measurements. For a monitor that is based on continuous measurements over a period of hours, three minutes per measurement may be an adequate rate. However, one of the target uses of a monitor for spontaneously ventilated patients is a spot check monitor that has a pre-set beginning and ending point for the measurement process. Such a monitor would preferably produce the first estimate sooner than three minutes. Cutting the baseline period to last only as long as required for the measurement would mean that a measurement period could be much shorter.

The original theory of rebreathing relied on the fact that one could make a baseline and a rebreathing measurement and from those two points, calculate the cardiac output. The irregular nature of the data from the spontaneously ventilated patients led to the idea that perhaps multiple breaths before and during rebreathing would need to be averaged together at each level in order to obtain reliable data for cardiac output calculation. Upon examination of this theory, however, it became clear that this could not work because the data in the transition between the two states was also important. Because of the spontaneous nature of the breaths, the signal during the transition was rather irregular, but removing it from the calculation meant that only two to four data points at the plateau level were used for the measurement. Thus, for spontaneous ventilation, it was considered best to use the transitional data.
Another observation related to the transition period was that the $\dot{V}\text{CO}_2$ signal appeared more irregular than the $\text{PETCO}_2$ signal. Shifting the $\dot{V}\text{CO}_2$ signal by one to two breaths with respect to the $\text{PETCO}_2$ signal resulted in slightly different outputs, but did not make a clear difference in the calculated estimates. It was observed that the $\text{PETCO}_2$ signal was slower to change in response to the ventilation change than the $\dot{V}\text{CO}_2$ signal was. This observation led to the developments described in Section 4.2.3.

4.2.3 Algorithm Modification

4.2.3.1 Introduction. Information important to the measurement is generated throughout the partial rebreathing process. It was also observed that the $\dot{V}\text{CO}_2$ signal appeared more irregular than the $\text{PETCO}_2$ signal during rebreathing and that this was a large contributor to the inconsistency of the cardiac output estimates. Shifting the $\dot{V}\text{CO}_2$ signal forward or backward two breaths relative to the $\text{PETCO}_2$ signal did not solve this problem, but it led to other developments.

The detection of the signal change created during rebreathing is different for the two signals. The $\dot{V}\text{CO}_2$ signal appears to change immediately in response to the ventilation change because at the onset of rebreathing, the inspired CO$_2$ is subtracted from the expired CO$_2$. In contrast, the onset of rebreathing in the $\text{PETCO}_2$ signal is not immediately evident. This is because the change in the $\text{PETCO}_2$ signal is a result of physiologic changes occurring at the alveolar level, while $\dot{V}\text{CO}_2$ is measured at the mouth and includes a component of the CO$_2$ stores of the body. The $\text{PETCO}_2$ signal is slow to change because the concentration change of CO$_2$ in the alveolar gas is not immediate. The CO$_2$ buffering capacity of the lung tissue acts as a low pass filter.

Another member of the team recognized that this difference in the signals could be resolved by applying a low pass filter to the $\dot{V}\text{CO}_2$ signal measured at the mouth,

$$\dot{V}_{\text{CO}_2\text{LP}}(n) = \alpha \dot{V}_{\text{CO}_2\text{LP}}(n-1) + (1-\alpha)\dot{V}\text{CO}_2(n),$$  \hspace{1cm} (4.1)

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where alpha with a value between 0 and 1 is a parameter that affects the amount of low pass filtering that takes place and $\dot{V}_{CO2LP}$ is the CO2 production after the low pass filter has been applied.

When this filter has been applied, some of the hysteresis and irregularity observed in the $\dot{V}_{CO2LP}$ signal at the onset of rebreathing is minimized, and the two signals appear to be inversely related to each other (Figures 4.8 and 4.9). The work in this section dealt with choosing the appropriate values for the filter that would work for all patients and with all measurement cycles.

A second component of the work of this section had to do with identifying which measurement cycles were more reliable than others. As the data was replayed and the estimates compared with the reference method values, decisions were made as to which data were outliers and should therefore be eliminated before cardiac output calculation.

4.2.3.2 Materials and methods. As the data were replayed and examined, multiple values for the alpha variable in the low pass filter were tested for the best reliability of cardiac output calculation when applied to the $\dot{V}CO2$ signal. A method was sought to automatically and reliably remove the respiratory data that were usually recognizable by a person manually processing the data as being outliers. This method of removing the unimportant data and weighting the important data more heavily was mainly done after the low pass filter had been applied to the $\dot{V}CO2$ signal.

4.2.3.3 Results. The ideal alpha variable required for the low pass filter was found to change with each measurement cycle for each patient (as determined by the largest correlation coefficient obtained for each measurement cycle). First, the correlation coefficient of the regression of the two signals ($\dot{V}CO2$ and $P_{ETCO2}$) was calculated. Then, the low pass filter was iteratively adapted until the correlation coefficient was maximized for each cycle. An example of the application of the low pass filter to the $\dot{V}CO2$ signal during one measurement cycle is shown in Figures 4.10 and 4.11. The data used to calculate the correlation coefficient were defined to be the ones closest to each other; the user could define the distance between the
accepted points. The method of using the points closest to each other was chosen because often the outliers were very far away from the reliable data.

4.2.3.4 Discussion. The implementation of the adaptive low pass filter led to the theory that thirty-five seconds of rebreathing was longer than necessary. It was decided this shorter period of rebreathing could possibly be combined with a shorter period of nonrebreathing to make a faster measurement cycle. A shorter cycle could be repeated more frequently so that the data from three rebreathing periods could be collected in the same time originally required for one measurement.

4.2.4 Discussion

As result of the clinical study, both the hardware and the algorithms were altered significantly. With the new changes in place, it was apparent that both the baseline and rebreathing periods in the first clinical study may have been longer than necessary for consistent measurements. Originally, it was hoped that the data from the clinical study could be used for all algorithm development and testing. However, the changes proposed in this chapter were significant enough to require new animal and clinical trials. A new study was planned to test the performance of the new algorithm approach when used on mechanically ventilated dogs. The new measurement cycle, composed of 30 seconds of rebreathing and 30 seconds of nonrebreathing, would be tested. Stated another way, one complete measurement would be composed of a 15 second baseline period, a thirty second partial rebreathing period, and a 15 second recovery period of no rebreathing.
Figure 4.1. F\textsubscript{ETCO}_2 vs. volume plot of a face mask with 150 mL of deadspace. Note that approximately 500 mL of expired volume were required to flush out enough deadspace to obtain a reliable P\textsubscript{ETCO}_2 measurement.
Figure 4.2. FETCO₂ vs. volume plot with a mouthpiece containing 7 mL of deadspace. Note that approximately 270 mL of expired volume were required to flush out enough deadspace to obtain a reliable PETCO₂ measurement.
Figure 4.3. Phase three slope of the $F_{ECO_2}$ vs. expired volume curve while breathing first with a nose clip and mouthpiece, then with the unmodified mask.
Figure 4.4. $F_{ECO_2}$ vs. volume plot with a modified face mask containing 15 mL of deadspace. Note that approximately 280 mL of expired volume were required to flush out enough deadspace to obtain a reliable $P_{ETCO_2}$ measurement.
Figure 4.5. Phase three slope of the $\text{FeCO}_2$ vs. expired volume curve while breathing first with a nose clip and mouthpiece, then with the unmodified mask, and finally with a modified face mask.
Figure 4.6. Example of regression plot relating the points to each other.
Figure 4.7. Data from several measurement cycles, separated into two groups, rebreathing (dark circles) and nonrebreathing (light diamonds).
Figure 4.8. Respiratory signals of one cycle from spontaneous ventilation without low pass filtering.
Figure 4.9. Respiratory signals of one cycle with spontaneous respiration (same cycle as Figure 4.8) after low pass filtering.
Figure 4.10. Before application of linear regression-determined low pass filter application (same cycle as Figures 4.8 and 4.9).
Low Pass Filtered Regression Approach for C.O. Estimation

\[ y = -9.0063x + 3708.2 \]
\[ R^2 = 0.9503 \]

Figure 4.11. After application of linear regression-determined low pass filter application (Same measurement cycle as Figures 4.8-4.10).
5.1 Feasibility Testing in an Animal Model of a Partial CO₂ Rebreathing System with a Shorter Measurement Cycle

After testing and development of the system as described in chapters two, three and four, the modified system was readied for feasibility testing. The new system was not known to pose any threats to the safety of subjects; however, safety precautions called for the first tests to be performed in an animal model with mechanical ventilation. After successful testing in an animal model, the system was used to monitor spontaneously breathing volunteers. No reference method for cardiac output determination was used on the volunteer subjects, as this would have been considered too risky for healthy subjects. Upon satisfactory performance of the new system in volunteers, further testing would be planned for spontaneously ventilated subjects who had a reference method in place.

5.1.1 Introduction

The NICO₂ noninvasive cardiac output monitor presently available for purchase uses 50 seconds of partial rebreathing within a three-minute measurement cycle to calculate cardiac output. Based on the findings described in chapters three and four, it would be desirable to shorten both the rebreathing period and the measurement cycle. A shortened cycle could be repeated more frequently, thereby improving the reliability of the measurements and providing better support for clinical decisions. It also provides more data so that averaging can be applied. For this preliminary study, the NICO₂ monitor was altered so that the rebreathing
period lasted only 30 seconds within a repeated one minute measurement cycle. Three cycles were analyzed together for one cardiac output estimation. Corresponding cardiac output estimations from modified NICO₂ and thermodilution cardiac output (TDCO) were compared in five mechanically ventilated dogs.

5.1.2 Materials and Methods

Using an IACUC approved protocol, five mongrel dogs (25.75kg - 42.4 kg) were induced with tiletamine and zolazepam, then intubated and mechanically ventilated. Anesthesia was maintained with halothane and isoflurane. A DualTherm (B. Braun, Bethlehem, PA) pulmonary artery catheter was placed for thermodilution cardiac output and central pressure measurements.

The sensor for the NICO₂ noninvasive cardiac output monitor was attached between the endo-tracheal tube and the breathing circuit wye piece. Respiratory data from the NICO₂ monitor were automatically recorded to a disk for subsequent analysis. Rebreathing and nonrebreathing periods were set to be 30 seconds each.

Cardiac output changes (TD ranging from 0.64 to 10.88 L/min) were initiated with dobutamine, halothane, and xylazine. Thermodilution cardiac output measurements (iced saline, 10 ml) were made in triplicate every 10 minutes at random times during the respiratory cycle.

5.1.3 Results

The correlation coefficient for the linear regression (Figure 5.1) between NICO₂ and thermodilution cardiac output measurements was $r^2 = 0.966$ (n = 96). Bland-Altman comparisons for mean TDCO of 4.88 L/min (Figure 5.2) showed a bias of -0.059 L/min, standard deviation of 0.58 L/min ($±24\%$) and limits of agreement of (-1.19 and 1.08L/min).
5.1.4 Discussion

Cardiac output estimations based on a shorter rebreathing period correlated well with thermodilution in this animal study. The performance of the modified device in this study was improved from the observed performance of the original NICO device (bias = -1.1 L/min, s.d. = 0.62 L/min) \(^{41}\). Although the rebreathing period of the modified device was shorter, it still provided sufficient data for cardiac output estimates because the transition data were incorporated into the calculation. Previously, the transition data were eliminated so that only the information recorded during steady state was considered. The shorter nonrebreathing period allowed the rebreathing period to be repeated more frequently, which provided more data for averaging. Because more data were collected, occasional spurious breaths could be better identified and eliminated. With further algorithm refinements and clinical testing in patients, the precision may be increased and it may be possible to reduce the measurement period from three minutes to one minute. The increase in frequency of cardiac output measurements using the NICO\(_2\) could help make earlier clinical decisions during episodes of hemodynamic instability. A faster measurement cycle of one minute would also be of great help to clinicians when performing fluid challenges.

Safety of the new device did not differ from the original device. The ratio of rebreathing time to nonrebreathing time was increased compared to the original device (i.e., from 1:2.6 to 1:1). This small reduction in ventilation was not considered unsafe, since oxygen levels remained high throughout the studies. Because the signal to noise ratio was quite high, it may also be possible to reduce the rebreathing volume and still obtain reliable estimates. It would be useful to observe how the change in ventilation affects the oxygen and carbon dioxide levels in spontaneously breathing subjects after surgery, as the changes may be smaller with spontaneous ventilation.

The more robust nature of the modified algorithm may be adequate for noninvasively monitoring cardiac output of spontaneously breathing patients. The study described in the
following section tested whether the modified device was able to report consistent estimates for healthy, spontaneously breathing human volunteers.

5.2 Feasibility Testing of the Modified System in Human Volunteers

5.2.1 Introduction

The modified NICO₂ system (Chapter four) was designed to have improved performance and patient comfort when monitoring the cardiac output of spontaneously ventilated human subjects. Following acceptable safety and performance of the modified system in an animal model, tests were developed to demonstrate feasibility of use in spontaneously ventilated human volunteers.

5.2.2 Materials and Methods

After IRB approval and subject consent, five healthy human volunteers were asked to breathe spontaneously (without instruction regarding respiratory pattern) through a mouthpiece version of a new prototype NICO₂ monitor (described in Chapter 4) while wearing a nose clip. A pulse oximeter was attached to the finger to monitor blood oxygen saturation. Partial rebreathing maneuvers were actuated automatically every thirty seconds. Subjects were monitored for fifteen minutes each, and all data were automatically saved with the computer system for further analysis. Data from three subsequent rebreathing periods of thirty seconds each and the corresponding nonrebreathing periods (total of three minutes of data) were analyzed together for each C.O. estimation. Cardiac output values and the quality of the recorded signals were reviewed. Because the number of subjects and sets of readings are small in this study, bias and precision statistics were not applied to determine the significance of variability present.
5.2.3 Results

The cardiac output estimations for each subject are shown in Table 5.1. The average standard deviation of the mean cardiac output (15.33 L/min) was 1.95 L/min (± 12.7%). SpO$_2$ remained between 96% and 99% for each volunteer monitored. An example of the appearance of the respiratory signals, plotted as $\dot{\text{VCO}}_2$ vs. $\text{Ce'}\text{CO}_2$, (after converting from P$_{\text{ETCO}}_2$) is shown in Figure 5.3.

5.2.4 Discussion

The cardiac output calculated by this modified system seems to be higher than expected for resting individuals; it is clinically accepted that an adult at rest has a cardiac output of 5 L/min and that during exercise, the cardiac output may increase up to 35-45 L/min. The volunteers in this test were healthy and young (20-30 yrs), and they had not received any drugs that would lower CO. Because of the risk associated with inserting catheters, no reference method was used for these volunteer feasibility tests. It can therefore not be said how accurate the rebreathing cardiac output values were, but the variability within each subject was improved when compared to that of the original partial rebreathing device. The average standard deviation for the original system with spontaneously breathing subjects was 5.5 L/min. With the modified system, the performance was somewhat improved to have a standard deviation of 1.95 L/min.

Given the acceptable performance in the mechanically ventilated dogs and the appearance of lower standard deviation in this study on humans, further testing is planned to improve the standard deviation and to test the bias and precision. Future tests of the modified system should be performed on spontaneously ventilated human subjects who already have a reference method such as a thermodilution catheter in place.
Comparison of Modified NICO$_2$ and TD in an Animal Model

![Graph showing linear regression plot](image)

Figure 5.1. A linear regression plot for data from five mongrel dogs (25.75kg - 42.4 kg) monitored during mechanical ventilation. The correlation coefficient was found to be 0.966, and the slope was 0.866.
Measurements from Modified NICO₂ and TD in an Animal Model

Figure 5.2. Bland-Altman for measurements from five mechanically ventilated mongrel dogs (25.75kg - 42.4 kg). Average (TD) C.O. was 4.88 L/min. Bias was -0.059 L/min, standard deviation (SD) was 0.58 L/min (±24%) and limits of agreement were (-1.19 and 1.08L/min).
<table>
<thead>
<tr>
<th></th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Subject 4</th>
<th>Subject 5</th>
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<tbody>
<tr>
<td>Cycle 1</td>
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<td>14.1</td>
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<td>13.6</td>
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<td>17.0</td>
</tr>
<tr>
<td>Mean</td>
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<td>17.13</td>
<td>11.83</td>
<td>15.80</td>
<td>16.50</td>
</tr>
<tr>
<td>S.D.</td>
<td>0.55</td>
<td>2.91</td>
<td>1.70</td>
<td>2.11</td>
<td>2.49</td>
</tr>
</tbody>
</table>
Figure 5.3. Example of respiratory data measured during spontaneous ventilation of a human subject, as monitored with the modified NICO₂ system and mouthpiece attachment. The signals are plotted in the regression style for analysis.
CHAPTER 6

CONCLUSION

The advancements made to the partial rebreathing technique during the course of this research led to a new means of signal acquisition and processing for cardiac output estimation. The new method no longer requires patient sedation, mechanical ventilation, or long periods of measurement for estimation of cardiac output. Hardware modifications provided a new patient interface for nonintubated subjects. Together, the algorithm and hardware changes expand the utility of the noninvasive device to ICUs and outpatient clinics where patients are spontaneously breathing. Furthermore, the new method allows for more frequent updates (every minute rather than every three minutes), shorter rebreathing periods, shorter time required for reliable measurements, and more comfort for the subject because of reduced ventilatory drive in response to CO₂ rebreathing. Preliminary studies indicate the new method is safe, may be more accurate, and may have a faster response time than the original monitor.

The irregular nature of spontaneous ventilation was a significant challenge to the development of a reliable monitor. The work outlined in this thesis includes the critical observation that the information recorded during the transition to and from the rebreathing state is important for reliable cardiac output measurements in spontaneously ventilated patients. The original Fick-based theories of rebreathing focused on deriving the cardiac output from two steady states: rebreathing and baseline. Now it is evident that the information during the transition should be included in the analysis, especially in the case of spontaneous ventilation, because the data are irregular and the short rebreathing periods do not allow for substantial data collection during the rebreathing period. Without the data obtained during the transition,
irregular breaths within a short measurement cycle can corrupt the measurements, and the resulting cardiac output estimation can be unreliable. By filtering and analyzing the respiratory data obtained during transitional periods rather than waiting for a steady state period after perturbation of the system, the difference in timing of the respiratory signals due to the inability of the sensors to directly measure the gas within the alveoli is resolved.

With older rebreathing techniques, one had to wait 3 minutes or longer before another estimate could be made. In addition, the total rebreathing techniques made subjects feel very uncomfortable, such that immediate or continuous repetition of the measurement was difficult. This modified partial rebreathing setup has the advantages of a short rebreathing period (30 seconds) and the option to administer oxygen to assure that sick patients can be adequately oxygenated.

### 6.1 Monitor Performance

A comparison study between thermodilution and NICO₂ was performed in the ICU with twenty-seven post cardiac surgery patients who were spontaneously breathing. Linear correlation of the paired measurements (n=59) showed an $r^2$ of 0.408 and a slope of 0.875. Bland-Altman tests on the paired measurements (n=59) (TD mean = 5.21 L/min) showed a standard deviation of the difference (rebreathing-thermodilution) of 1.21 L/min (±46%) and a bias of -0.34 L/min.

Following the ICU study, additional modifications were made, and the new system was tested on five mechanically ventilated mongrel dogs. The correlation coefficient for the linear regression between the new NICO₂ and thermodilution cardiac output measurements was $r^2 = 0.966$ (n = 96). Bland-Altman comparisons (mean TD of 4.88 L/min) revealed a bias of -0.059 L/min and a standard deviation of 0.58 L/min (±24%). Compared to the performance of the original device on mechanically ventilated animals (bias = -1.1 L/min, S.D. = 0.62 L/min, ±30%), the cardiac output estimates of the modified system were improved.
The new system was then preliminarily tested on five spontaneously breathing volunteers. Estimates were not compared with those of an invasive method for safety reasons. The device was safe with regard to oxygenation levels of the blood (as measured with a pulse oximeter). The standard deviation of the modified system in spontaneously breathing humans was 1.95 L/min, compared to the s.d. of the original device of 5.5 L/min.

The performance of the modified NICO₂ monitor in these studies demonstrated that the modified monitor performs at least as well as other commercially available techniques. When the measurements from the original NICO₂ monitor (three minute measurement cycle) were compared to conventional TDCO in three clinical studies⁶⁶-⁶⁸, they had a bias between 0.07 and 0.46 L/min and precision of 0.81 to 0.95 (±30%) L/min. When bioimpedance measurements were compared to transit time flow probe measurements, bias was reported to be 0.15 L/min, and the limits of agreement (mean difference ±1.96 × SD) were -2.53 to 2.82 L/min³⁷. When compared to thermodilution, bioimpedance had limits of agreement⁴⁰ of ±37%. Doppler has been shown to have a bias of -0.01 L/min and limits of agreement of 1.12 L/min (±65%) when compared to conventional thermodilution³⁸,⁴⁰. Because clinical cardiac output techniques have an inherent lack of precision, limits of agreement between the new and the reference technique of up to ±30% are currently regarded as clinically acceptable⁴⁰.

Partial rebreathing may fulfill a need for clinicians who want a noninvasive option for monitoring cardiac health, especially when other monitors are too expensive, unavailable, or too risky. It seems likely that a device can be developed for both spot checks and long-term monitoring of the hemodynamic function.

A limitation of these studies was that the spontaneously ventilated patients, in whom a reference method was in place, had recently undergone cardiac surgery. Thus, the cardiac output values were not distributed over a wide range. Many patients were experiencing a significant amount of pain and therefore tended to have smaller tidal volumes than healthy people. It would have been preferable to test a larger group of patients. Another limitation was
that the volunteer tests were all performed on healthy people. Sick or very old volunteers may have reacted to the monitoring differently.

The reference method (TD) chosen for this study is only accurate within 10%. Also, in an analysis of data from fourteen comparison studies, Stetz found that there is a 22% error for single measurements of TD, but that the error could be reduced to 13% if triplicate measurements were averaged. Therefore, the performance of the new system is difficult to evaluate in some cases. Future trials with other standards, such as the Fick method or an electromagnetic flow meter may yield additional useful information about the performance of the system.

6.2 Monitor Utility

Intubation is not required for the modified device. This allows for use in more settings and on more types of patients. The noninvasive monitor is ideal for patients for whom the other methods of monitoring are too dangerous, invasive, or expensive. For example, patients who have undergone surgery or have questionable cardiac health may benefit from being monitored noninvasively. Often, these patients are well enough to be spontaneously breathing and are not in critical care environments. They may be receiving health care in emergency rooms, family clinics, rest homes, or at home.

Use of the monitor does not require excessive training or special skills, so a wide variety of clinicians could easily set it up and begin monitoring. Some other methods require specialized training for setup and monitoring; invasive methods often require long setup periods. Setup time for this monitor is less than three minutes, so it could be beneficial in emergency cases.

The device is not intended for patients with severe lung disease or patients who cannot tolerate higher levels of CO₂. The method also has the disadvantage of not providing the clinician with wedge pressure measurements as a PA catheter would. The wedge pressure is
usually used to assess the volume status of the patient; volume status could alternatively be inferred from the change in cardiac output in response to a fluid challenge to the patient.

Measurements from this new method of cardiac output estimation are always made at the same time within the respiratory cycle. Other methods such as thermodilution can be subject to changes in cardiac output caused by the increased intra-thoracic pressure that occurs when the lungs are filled. This is especially of concern when the patient is hypovolemic and respiration adds significant variation in the preload of the heart. It can be difficult for clinicians to determine whether their treatments have been effective if the respiratory cycle alters the cardiac output within each breath. The respiratory data obtained during rebreathing measurements all originate from the time just before exhalation, so all measurements are based on this point in time relative to the respiratory cycle. This can be an advantage to clinicians watching for small changes in response to medical treatments they may have administered.

The one minute measurement cycle makes the monitor as fast as or faster than many other currently available methods for cardiac output determination. Minute by minute information about the cardiac function could form the basis for clinical decisions in times of hemodynamic instability. For example, clinicians could use the monitor to gauge the response of the cardiac output to various treatments. Understanding how the heart responds to medical treatment would allow physicians to quickly diagnose and treat patients rather than trying multiple approaches to treatment over a longer period.

### 6.3 Future Enhancements

Further testing is required to determine the performance of the modified monitor in spontaneously ventilated human subjects. In addition, it is likely that the modified algorithm will provide improvement to the performance of the monitor in mechanically ventilated and mixed ventilation cases. These studies should also be undertaken. Following the comparison studies, additional algorithm enhancement and data filtering should be done during data
playback. It would also be clinically relevant to examine the relationship between arterial CO₂ content and the new rebreathing method.

It may be possible for the partial rebreathing system to estimate the patient’s venous CO₂ levels. Future implications could be that one could noninvasively estimate this blood gas level and possibly use it for clinical procedures or monitoring. Future tests on the feasibility of this process should also be undertaken.

With additional hardware modification, a cardiac stress test C.O. monitor using this technology could be developed. Currently, the resistance to airflow prohibits the copious volumes of airflow required for exercise. If this limitation could be eliminated, it may be possible to determine whether the cardiovascular health of patients scheduled for catheter lab treatment really warranted catheterization. It may be valuable to do such a study as the technology development allows.

Future device development could include a hand-held monitor. A monitor designed for use on spontaneously ventilated patients in clinics and outpatient settings would be the most convenient if it were a small, hand-held unit that produced results in 10-15 minutes. To this end, several design suggestions for a hand-held unit were put forth. The ideal properties of a hand-held unit include a handle, a simple patient interface, and a lightweight, minimal size. The best two choices for the patient interface were considered to be a mouthpiece or a modified mask. Several design prototypes were built that adhered to these specifications.

With further testing and development, the new partial rebreathing system has the potential to become more clinically accepted in the OR and to begin to be used in new areas, such as emergency rooms, intensive care units, and outpatient clinics. Compared to current modes of monitoring, the new device holds promise of support for targeted medical treatment, reduced costs in healthcare, and reduced patient morbidity.
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>C.O.</td>
<td>Cardiac output (L/min)</td>
</tr>
<tr>
<td>$C_A\text{CO}_2$</td>
<td>Carbon dioxide content of alveolar blood (mL CO$_2$/liter blood)</td>
</tr>
<tr>
<td>$C_A\text{CO}_2$</td>
<td>Carbon dioxide content of arterial blood (mL CO$_2$/liter blood)</td>
</tr>
<tr>
<td>$Cc'\text{CO}_2$</td>
<td>Pulmonary end-capillary concentration of carbon dioxide (mL CO$_2$/liter blood)</td>
</tr>
<tr>
<td>$C_V\text{CO}_2$</td>
<td>Carbon dioxide content of mixed venous blood (mL CO$_2$/liter blood)</td>
</tr>
<tr>
<td>$F_{\text{IO}_2}$</td>
<td>O$_2$ concentration of the inspired gas (fraction)</td>
</tr>
<tr>
<td>$F_{\text{ECO}_2}$</td>
<td>CO$_2$ concentration of the expired gas (fraction)</td>
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<td>$F_{\text{ETO}_2}$</td>
<td>O$_2$ concentration of the end-tidal gas (fraction)</td>
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<td>Partial pressure of end-tidal CO$_2$ (mmHg)</td>
</tr>
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<td>$\dot{Q}_t$</td>
<td>Cardiac output, total (L/min)</td>
</tr>
<tr>
<td>$\dot{Q}_{\text{PCBF}}$</td>
<td>Pulmonary capillary blood flow (L/min)</td>
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<td>$\dot{Q}_s$</td>
<td>Intrapulmonary shunt blood flow (L/min)</td>
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<tr>
<td>$\dot{V}\text{CO}_2$</td>
<td>Volume of CO$_2$ excreted per minute, as measured at the mouth (mL/min)</td>
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