A BREATH-BY-BREATH RESPIRATORY MEASUREMENT SYSTEM

AND IMPLEMENTATION OF A FUNCTIONAL RESIDUAL

CAPACITY ALGORITHM

by

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LIST OF SYMBOLS

BTPS   body temperature and pressure conditions of a saturated gas.

CO_2 molecular carbon dioxide.

$e(V_{CO2})$ the error in the volume of carbon dioxide produced in one breath.

$e(\dot{V}_{CO2})$ the error in carbon dioxide production calculations.

$e(\dot{V}_{CO2})_A$ the error in carbon dioxide production calculations with the functional residual capacity algorithm implemented (A specifies calculations relating to the alveolar space).

$e(\dot{V}_{CO2})_M$ the error in carbon dioxide production calculations without the functional residual capacity algorithm implemented (M specifies calculations at the mouth).

$e(V_E)$ the error in the measurement of expiratory volume.

$e(\dot{V}_E)$ the error in the measurement of expiratory ventilation.

$e(V_I)$ the error in the measurement of inspiratory volume.

$e(\dot{V}_I)$ the error in the measurement of inspiratory ventilation.

$e(V_{O2})$ the error in the volume of oxygen consumed.

$e(\dot{V}_{O2})$ the error in oxygen consumption calculations.

$e(\dot{V}_{O2})_A$ the error in oxygen consumption calculations with the functional residual capacity algorithm implemented (A specifies calculations relating to the alveolar space).

$e(\dot{V}_{O2})_M$ the error in oxygen consumption calculations without the functional residual capacity algorithm implemented (M specifies calculations

	at the mouth).
F	test statistic used to determine whether the between sample variability is large when compared to the within sample variability.
F_{ACO2}	fractional concentration of carbon dioxide in the alveolar space estimated with end-tidal fractional concentrations.
F_{AN2}	fractional concentration of nitrogen in the alveolar space estimated with end-tidal fractional concentrations.
F_{AO2}	fractional concentration of oxygen in the alveolar space estimated with end-tidal fractional concentrations.
$F_{\bar{E}CO2}$	fractional concentration of carbon dioxide in the mixed-expired gas.
$F_{\bar{E}N2}$	fractional concentration of nitrogen in the mixed-expired gas.
$F_{\bar{E}O2}$	fractional concentration of oxygen in the mixed-expired gas.
F_{ECO2}	fractional concentration of carbon dioxide in the expired gas as a function of time.
F_{EN2}	fractional concentration of nitrogen in the expired gas as a function of time.
F_{EO2}	fractional concentration of oxygen in the expired gas as a function of time.
F_{ICO2}	fractional concentration of carbon dioxide in the inspired gas.
F_{IN2}	fractional concentration of nitrogen in the inspired gas.
F_{IO2}	fractional concentration of oxygen in the inspired gas.
FRC	functional residual capacity.
O_2	molecular oxygen.

p	level of significance of a statistical test which is the probability of observing a an outcome more contradictory than the null hypothesis.
R	respiratory exchange ratio defined as the ratio of carbon dioxide production to oxygen consumption.
S	error sensitivity.
STPD	standard temperature and pressure conditions of a dry gas.
T	the period of a breath.
$\hat{V}(t)$	general ventilation term (can be either inspiratory or expiratory ventilation).
V_{CO2}	volume of carbon dioxide produced.
$\dot{V}_{CO2}$	minute carbon dioxide production.
$(\dot{V}_{CO2})_A$	minute carbon dioxide production calculated with the functional residual capacity algorithm implemented. This is an estimate of the gas exchange across the alveolar-capillary membrane.
$(\dot{V}_{CO2})_M$	minute carbon dioxide production calculated without the functional residual capacity algorithm implemented.
V_E	expiratory volume.
$\dot{V}_E$	minute expiratory ventilation.
V_I	inspiratory volume.
$\dot{V}_I$	minute inspiratory ventilation.
V_L	end-tidal lung volume estimated with the subject's functional residual capacity.
ΔV_L	the change in end-tidal lung volume from one breath to the next breath.
ΔV_{LN2}	the change in the volume of nitrogen in the lung from one breath to the next breath.

ΔV_{LO2} the change in the volume of oxygen in the lung from one breath to the next breath.

ΔV_{LX} the change in the volume of any gas (designated gas X) in the lung from one breath to the next breath.

$\dot{V}_{N2}$ minute nitrogen exchange.

$\dot{V}_{O2}$ minute oxygen consumption.

$(V_{O2})_A$ the volume of oxygen exchanged across the alveolar-capillary membrane, calculated with the functional residual capacity algorithm implemented. This is an estimate of the gas exchange across the alveolar-capillary membrane.

$(V_{O2})_M$ the volume of oxygen consumed at the mouth, calculated without the functional residual capacity algorithm implemented.

$(\dot{V}_{O2})_A$ minute oxygen consumption calculated with the functional residual capacity algorithm implemented. This is an estimate of the gas exchange across the alveolar-capillary membrane.

$(\dot{V}_{O2})_M$ minute oxygen consumption calculated without the functional residual capacity algorithm implemented.

$(V_X)_A$ the volume of gas X exchanged across the alveolar-capillary membrane.

$(V_X)_M$ the volume of gas X exchanged at the mouth.

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IV. ACKNOWLEDGEMENTS

I would like to thank my committee members Dr. Marion Roger Fedde and Dr. Stephen Dyer for their help and suggestions throughout this project. I wish to extend a special thanks to my major professor, Dr. Richard Gallagher, for his guidance and support.

I would also like to thank Gary Noyes for the countless hours he spent helping with data collection and for volunteering to be a subject. Thanks also goes to the other subjects, James Stafford, Brad Badke, and Steven Noyes, who freely volunteered their time and endured discomfort for the sake of the project. Finally, I wish to thank Dr. Sally McNulty and Dr. Ruth Dyer for their help with the statistical analyses and the experimental protocol.

I dedicate this work to my parents who have supported me throughout my life. Without their support I would not have been able to complete this project.

Part I. THE VALIDATION OF A BREATH-BY-BREATH

INSTRUMENTATION SYSTEM

A computerized breath-by-breath respiratory measurement system was tested to validate the accuracy of its results in the steady state. The breath-by-breath measurement system consisted of a mass spectrometer for measuring fractional concentrations of O_2 and CO_2, a pneumotachograph for measuring inspiratory and expiratory flows, and a rapidly responding thermocouple for measuring the temperature of the flow stream. These were connected to a microcomputer via a custom-built, data-acquisition module. Correction routines were implemented in software to correct for errors introduced by the misalignment of the flow and fractional concentration signals and errors caused by the sensitivity of the pneumotachograph to changes in temperature and gas concentration.

No evidence of a statistically significant difference was found between the steady-state results of the breath-by-breath measurement system and those of the mixed-expired gas-collection technique for inspiratory ventilation, expiratory ventilation, oxygen consumption, carbon dioxide production and respiratory exchange ratio. This evidence suggests that the breath-by-breath measurement system accurately measures these variables.

V.B. Introduction and Objectives

During the last twenty years breath-by-breath respiratory measurement systems have been developed and refined (2,3,8,11,13,15,17,21). The primary advantage in both clinical and research uses for these systems relates to the possibilities of obtaining calculated respiratory quantities associated with resting and exercise protocols. These systems are computer-based systems which utilize rapidly responding transducers to measure fundamental respiratory variables, such as gas concentrations, flow, and temperature. Using these signals, other respiratory variables of interest, such as tidal volumes, ventilation, oxygen consumption, carbon dioxide production, and respiratory quotient, may be calculated for each breath. Hence the descriptor breath-by-breath.

The traditional method used to obtain the respiratory variables mentioned above has involved the collection of mixed-expired gas and the subsequent determination of its volume and component gas concentrations. Breath-by-breath measurement systems offer two distinct advantages over this traditional method. First, since breath-by-breath measurement systems calculate respiratory quantities for each breath, transient changes in respiratory function can be studied. The traditional method yields only an average

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value of a respiratory quantity over the number of breaths collected, limiting the usefulness of this technique in the study of respiratory transients. Second, since breath-by-breath measurement systems are automated systems, data collection and analysis is typically faster and easier. These advantages have made the breath-by-breath measurement system a valuable and increasingly common research and clinical tool.

Breath-by-breath measurement systems do however, have a number of inherent technical problems. These include flow measurement errors and the misalignment of gas concentration and flow signals. Hardware and software compensations must be made before accurate results can be obtained. This research evaluates the accuracy of a computerized breath-by-breath measurement system in which these problems have been addressed. Comparisons of results obtained with the breath-by-breath measurement system and the standard bag-collection technique under steady-state conditions are presented.

V.C.   Methods

V.C.1.   System Description.

The Computer-Based Respiratory Measurement System (CBRMS) used in this study was developed by Creel(5) and

Riblett(15) and further modified by Masters(12). A block
diagram of the system hardware is shown in Figure 1. A
pneumotachograph (Hans Rudolph model 3813) was mounted on a
face mask (Hans Rudolph #7900-M) and was connected to a
differential pressure transducer (Godart pneumotachograph
type 17212) to measure inspiratory and expiratory flow. A
sampling capillary (2.59 m), inserted into the
pneumotachograph fittings between the face mask and the
pneumotachograph, was connected to a mass spectrometer
(Perkin-Elmer MGA 1100) to measure fractional
concentrations of O_2 and CO_2. A rapidly responding
thermocouple (Omega Type E Cromel-Constatin) was inserted
into the flow stream on the side of the pneumotachograph
open to room air to measure the temperature of the inspired
and expired gas. Outputs from the differential pressure
transducer, the mass spectrometer O_2 and CO_2 channels, and
the thermocouple were interfaced with a microcomputer
(Hewlett-Packard 9826) via a custom-built, data-acquisition
system(6). Subjects exercised on a bicycle ergometer
(Monarch model 868), and heart rate was monitored with an
Amerec 150 telemetric heart rate monitor.

V.C.1.a. Calibration.

System calibration was performed prior to data
collection. This allowed voltage values that were stored
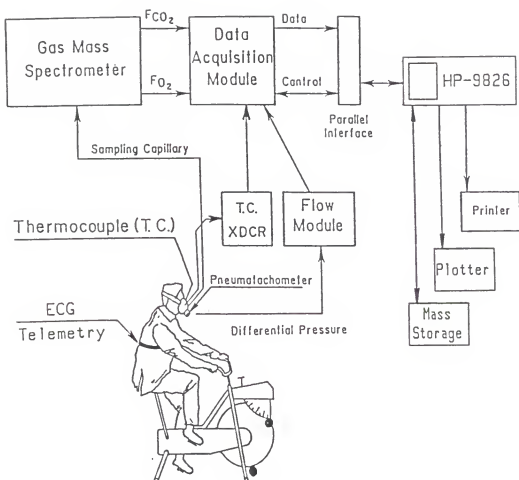
Figure 1. Block diagram of the breath-by-breath instrumentation system (11).

in the computer to be accurately related to the quantities being transduced. For flow calibration, the pneumotachograph was connected to a 3-liter syringe. With the plunger completely forward to prevent any airflow, a voltage for zero flow was read by the computer. Next, the syringe was used to pump a 3-liter volume through the pneumotachograph to simulate inspiration and expiration. This was repeated until twelve inspiratory and twelve expiratory cycles were completed. The flow signal was sampled at 50 Hz and was digitally integrated to give a computer-measured volume for each stroke of the syringe. An average computer-measured volume was then computed for inspiration and expiration by averaging the twelve inspiratory and twelve expiratory volumes respectively. This gave an average computer-measured volume for inspiration and expiration which could be related to the known three liter input. This was repeated at eight different pumping rates, and a third degree polynomial was used to relate the computer-measured volume to the three liter input at each pumping rate. This repetition was necessary because Noyes(14) had shown that the response of the pneumotachograph was not linear over the range of flows found in the exercising human.

The O_2 and CO_2 channels of the mass spectrometer were calibrated by sampling two known mixtures of gases; room

air and a 7% CO_2 and 13% O_2 (balance N_2) mixture. After each gas mixture was sampled with the mass spectrometer and the output read by the computer, the known concentrations of O_2 and CO_2 were entered into the computer and used to determine a linear calibration relationship between the voltage output of the mass spectrometer read by the computer and the gas concentrations of O_2 and CO_2.

The thermocouple used to measure the temperature of the inspired and expired gas was calibrated by measuring the temperature of four water baths with temperatures of approximately room temperature, 30 °C, 35 °C, and 40 °C simultaneously with a standard mercury thermometer. Four measurements were made at each temperature and a least squares fit to a third degree polynomial was used to relate the thermocouple output to the temperature measured with the standard mercury thermometer. The thermocouple was not calibrated unless measurement of a known temperature indicated that the previous calibration curve no longer accurately described the response of the device.

V.C.1.b. Data Collection.

To measure respiratory function with the breath-by-breath measurement system, a subject was instrumented with the respiratory face mask and attached transducers described above. After entering the sampling frequency (50

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Hz) and the total number of data points to be collected into the Hewlwtt-Packard computer, the computer operator began data collection with a single keystroke. The data-acquisition module sampled the four input signals (the O_2 and CO_2 fractional concentration signals from the mass spectrometer, the flow signal from the pneumotachograph, and the temperature signal from the thermocouple) simultaneously at the specified sampling frequency (50 Hz), digitized them with an A/D converter, and stored them in computer memory until data collection was complete, at which time they were stored on floppy (Hewlett-Packard 9895A) or hard disk (Hewlett-Packard 9134A) for analysis.

V.C.1.c. Data Analysis.

Program ANALYSIS retrieved the four signals stored in data collection and calculated several quantities of physiological significance. These included tidal volume, ventilation, oxygen consumption, carbon dioxide production, respiratory exchange ratio, and respiratory frequency.

Two correction routines were used to compensate for two inherent technical problems in the system; the effects of temperature and viscosity changes on the pneumotachograph and the misalignment of the flow and fractional concentration signals.

Several investigators have noted that the output of

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the pneumotachograph is very sensitive to changes in temperature and gas viscosity (7,19,20). This is a source of error in a system that uses a single pneumotachograph to measure both inspiratory and expiratory flows since both gas composition and gas temperature change significantly from inspiration to expiration. To minimize this problem, Masters implemented a correction routine based upon Wilke's equation(22) that calculated the relative viscosity of each gas species (O_2, CO_2, N_2, and H_2O) based upon the temperature of the gas and the fractional concentration of each gas component, and used this calculated viscosity and the gas temperature to correct the flow signal(12).

A second problem inherent in the system was the time delay between the flow signal from the pneumotachograph and the simultaneously sampled fractional concentration signals from the mass spectrometer. This delay was caused by two factors: the transport time of the gas through the sampling capillary, and the response time of the mass spectrometer. Since accurate volume calculations of O_2 and CO_2 require these signals to be time aligned, Creel(5) used the algorithm of Sue(17) to calculate the time delay on a breath-by-breath basis and then shift the fractional concentration signals forward in time so that they were properly aligned with the flow signal before the oxygen consumption and carbon dioxide production calculations were

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made.

Analysis was begun by identifying the first complete inspiration by noting the point at which the flow first decreased below the zero flow value obtained in calibration. Each subsequent inspiration or expiration was identified by the flow being greater than (expiration) or less than (inspiration) the zero flow threshold.

Inspiratory or expiratory tidal volume was calculated using the general formula

$$V_T \;=\; \int \dot{V}(t)\,dt \tag{1}$$

All integrations were evaluated numerically using the Trapezoidal Rule. Oxygen consumption was calculated by taking the difference between the inspired oxygen and expired oxygen volumes as

$$V_{O2} \;=\; \int_{insp} F_{IO2}\cdot\dot{V}_I\,dt \;-\; \int_{exp} F_{EO2}\cdot\dot{V}_E\,dt \tag{2}$$

and was converted to standard temperature and pressure under dry conditions (STPD). Carbon dioxide production was calculated similarly with the appropriate change of sign. The respiratory exchange ratio for a breath was calculated by dividing the carbon dioxide produced by the oxygen consumed. The respiratory frequency was determined by inverting the time duration of each breath.

Finally, the algorithm developed by Beaver(2) to correct for changes in the end-tidal lung volumes from breath-to-breath and to reduce the sensitivity of oxygen consumption calculations to flow errors was implemented. Further discussion of this correction is found in Part II of this work.

V.C.1.d. Data Display.

The analyzed data was displayed in tabular or graphical form. The tabular output consisted of a breath-by-breath display of all derived quantities printed in table format. If desired, the average of specified time intervals or the average of a specified number of breaths were printed also. The graphical output consisted of plots of all derived quantities versus time (12).

V.C.2. Validation of the System.

To test the accuracy of the breath-by-breath measurement system, steady-state results obtained from the system for four different exercise workloads were compared to results obtained from the collection of mixed-expired gases for identical workloads. Values for inspiratory ventilation, expiratory ventilation, oxygen consumption, carbon dioxide production, and respiratory exchange ratio were compared.

V.C.2.a. Subjects.

Four normal healthy untrained male subjects (ages 20
to 25) volunteered for this validation study. They ranged
in weight from 66 to 86 kilograms. Each underwent a
physical examination to screen for any abnormalities which
might adversely affect the subject or the experimental
results under test conditions. Approval was obtained from
Kansas State University's Research Involving Human Subjects
Committee for all subjects and procedures. None of the
subjects were involved in any physical conditioning program
at the time.

V.C.2.b. Experimental Protocol.

Measurements from four subjects were taken at rest and
at three exercise workloads, 80 watts, 150 watts, and 200
watts, using the breath-by-breath measurement system and
the collection of mixed-expired gases. Measurements were
repeated three times on each subject for each method at
each workload. Thus the subject performed each workload six
times, and an average value was obtained for inspiratory
ventilation, expiratory ventilation, oxygen consumption,
carbon dioxide production, and respiratory exchange ratio
from the three trials at each workload. Each subject
performed one trial at the same time each day, Monday
through Friday. The order of the workloads was randomly

selected, but once one trial of a workload was performed, all six trials for that workload were completed before moving to another workload. On a given day the method of measurement was randomly selected.

The protocol for all exercise tests consisted of forty seconds of rest, six minutes of exercise, followed by another two minutes and twenty seconds of rest. In order to compare steady-state results from the two methods, it was necessary to compare results from the same steady-state time intervals for each method. These time intervals were chosen to give the subject sufficient time to reach a steady-state condition and to prevent the volume of the collected expired gas from exceeding 120 liters, the maximum volume held by the spirometer. Table 1 shows the time intervals during which steady-state measurements were made at each workload.

Table 1. Steady-state measurement time intervals.

Workload (Watts)	Begin Collection (Min)	End Collection (Min)	Total Time (Min)
0	1	6	5
80	4	6	2
150	5	6	1
200	5.16	6	.83

V.C.2.c. Measurements.

To measure steady-state values for comparison with

data obtained from the breath-by-breath measurement system, the subjects were instrumented with a mouthpiece attached to a non-rebreathing valve (Hans Rudolph model 2700). The total dead space of the mouthpiece and valve was 130 milliliters. The inspiratory port of the non-rebreathing valve was connected to a 120 liter spirometer (W.E. Collins) with one meter of plastic hose (3 cm in diameter) via a three way ball valve to measure inspiratory volume. The expired gas was collected in a neoprene weather balloon which was attached to a three-way ball valve. This valve, in turn, was connected to the expiratory port of the non-rebreathing valve with eighteen centimeters of plastic hose (3.5 cm in diameter). Expiratory volume was determined by transferring the expired gas into the spirometer. Mixed concentrations of oxygen and carbon dioxide were measured with a mass spectrometer (Perkin-Elmer MGA 1100) as the gas was transferred to the spirometer. These measurements allowed the calculation of inspiratory and expiratory ventilation, oxygen consumption, carbon dioxide production, and respiratory exchange ratio for comparison with the results from the breath-by-breath measurement system. The ECG was monitored with the Amerec 150 heart rate monitor. Body temperature was measured before and after exercise with a mercury thermometer placed under the tongue to allow conversion of quantities to BTPS conditions. Barometric

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pressure and the temperature of the inspired and expired
air were measured to allow the conversion of quantities to
STPD conditions.

Breath-by-breath measurements were taken as previously
described, and the breath-by-breath results were averaged
over the appropriate time interval to obtain steady-state
values which could be compared with the results from the
collection of mixed-expired gases.

V.C.2.d. Data Analysis.

An analysis of variance for a split plot design was
used to determine if a significant difference ($p < 0.05$)
existed between the means of the five measured variables
from the breath-by-breath measurement system and from the
mixed-expired gas-collection technique. Subject-by-
workload mean sum-of-squares was used to test for
differences in workload, the whole plot factor. The mean
square-error was used to test for differences in method,
the subplot factor. A log transformation of the data was
used to accommodate the increasing variance found with
increasing population means.

V.D. Results

Examples of the output of the breath-by-breath
measurement system are shown in Figures 2, 3A, 3B, and 3C.
Figure 2 shows the computer reproduction of the four
measured signals for five breaths during a 150-watt
exercise test which were sampled at 50 Hz. These are
digital signals which appear continuous because sampled
points are connected by the plotting routine. The time
delay between the flow signal and the gas concentration
signals can be seen here.

Figures 3A, 3B, and 3C show the graphical output of
the analyzed data for six calculated variables of a 150-
watt exercise test which consisted of forty seconds of
rest, six minutes of 150-watt exercise, and another two
minutes and twenty seconds of rest. Changes occur with the
onset and termination of exercise in each variable. The
measurement and subsequent analysis of these transients are
two of the most important advantages of the breath-by-
breath measurement system. A comparison of steady-state
values from the breath-by-breath measurement system with
values from the mixed-expired gas-collection technique
showed good agreement between the two methods. Figure 4
shows V_E, V_{O2}, V_{CO2}, and R calculated with the breath-by-
breath measurement system plotted against the results from

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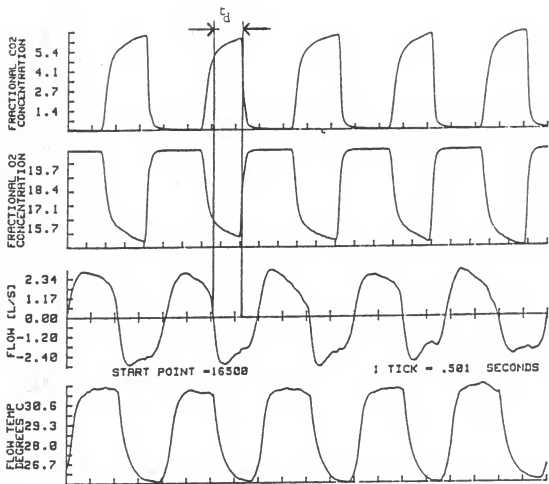
Figure 2. A computer reproduction of the four analog signals collected and stored by the breath-by-breath measurement system. The time delay (t_d) between the fractional concentration signals and the flow signal is shown.
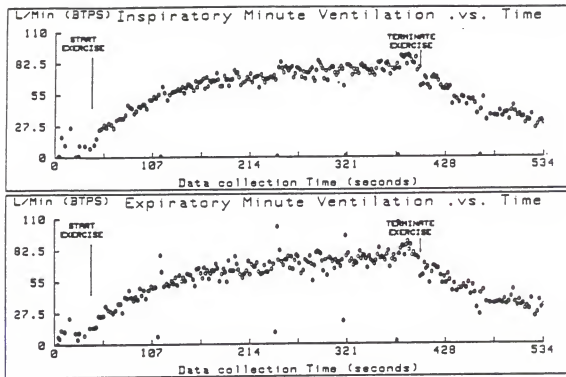
Figure 3.(A). Graphical output from the breath-by-breath measurement system for a 150-watt exercise test showing inspiratory (top) and expiratory (bottom) ventilation. Each point represents one breath.
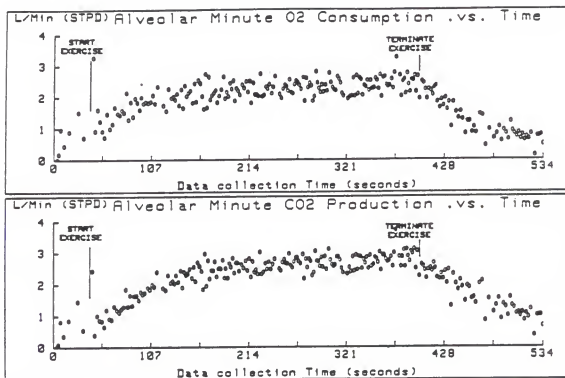
Figure 3.(B). Graphical output from the breath-by-breath measurement system for a 150-watt exercise test showing oxygen consumption (top) and carbon dioxide production production (bottom) versus time. Each point represents one breath.
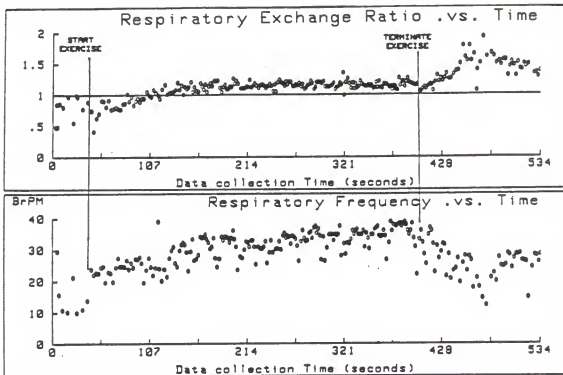
Figure 3.(C). Graphical output from the breath-by-breath measurement system for a 150-watt exercise test showing respiratory exchange ratio (top) and respiratory frequency (bottom) versus time. Each point represents one breath.
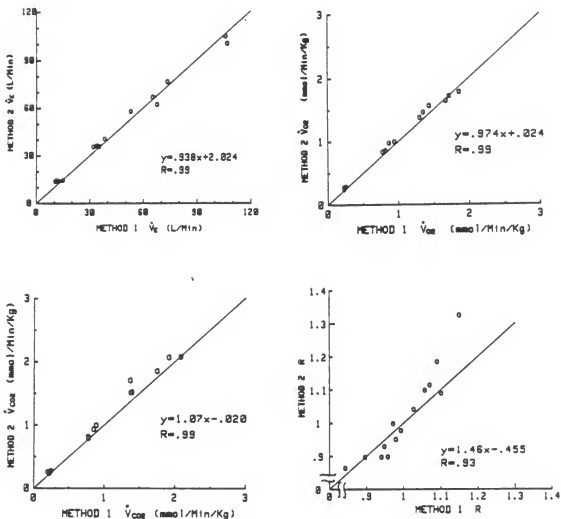
Figure 4. The steady-state results of the breath-by-breath measurement system (ordinate) as compared to the mixed-expired gas-collection technique (abscissa) for $\dot{V}_E$, $\dot{V}_{O2}$, $\dot{V}_{CO2}$, and R. The unity line is plotted for comparison. The regression line is not plotted, but the equation is shown on each graph. Method 1 = Mixed-expired gas collection technique. Method 2 = Breath-by-breath measurement system.

the collection of mixed-expired gases. There is close agreement between the two methods for all four variables.

No evidence of a statistical difference between the steady-state results of the breath-by-breath measurement system and the results of the mixed-expired gas-collection technique was found in the analysis of variance. A summary of this analysis is shown in Table 2. All F values for a difference in method are small indicating that there is no difference in the results of the two methods.

Table 2. Analysis of variance summary.

		$\dot{V}_E$	$\dot{V}_I$	$\dot{V}_{O2}$	$\dot{V}_{CO2}$	R
Work	F-value	1598.79*	1284.79*	588.77*	664.75*	57.07*
	p value	0.0001	0.0001	0.0001	0.0001	0.0001
Method	F-value	0.01	1.31	0.05	0.52	0.22
	p value	0.9202	0.2793	0.8344	0.4858	0.6509
Work by	F-value	0.48	0.57	2.19	2.30	5.81*
Method	p value	0.7031	0.6474	0.1527	0.1389	0.0145

p value < .05 indicates significant difference
 * denotes significance
critical F value is 5.59

V.D. Discussion

The CBRMS evaluated in this study was developed to provide a flexible and accurate system for making calculations of respiratory function in clinical and research settings. The system is flexible such that many

different flow and gas concentration transducers found in a typical pulmonary function laboratory are compatible with it. This makes the system easily adaptable to different research activities involving measurements on both human and nonhuman subjects. Further, the system is easy to use. Data collection and analysis are completely automated and are performed with the aid of one computer operator with minimal training. The system calibration is not fully automated, but can be performed by one or two persons in about thirty minutes.

To show that the results obtained in this study are reasonable, the calculated mean oxygen consumption as a function of workload is compared to data of other investigators in Figure 5. Oxygen consumption was selected for comparison because it was the most universally comparable variable measured. Even though there were slight differences in subject ages and in the time interval in which measurements were taken during the exercise bouts, good agreement is seen with these data. In order to insure the accuracy of the results of the system, several problems typically associated with breath-by-breath measurement systems have been corrected or their adverse effects reduced. In addition to the time alignment and temperature corrections mentioned previously, the direct measurement of temperature in the flow stream with a rapidly responding
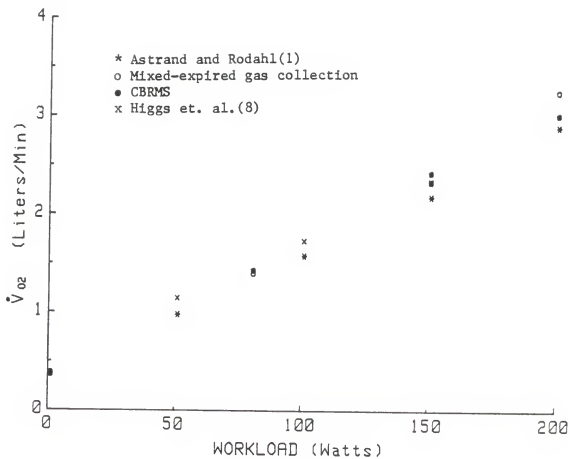
Figure 5. A comparison of mean oxygen consumption
calculations with those of other investigators.

thermocouple allows the direct determination of water vapor pressure in the expired air. This eliminates errors associated with the estimation of temperature or water vapor content of the expired air.

Secondly, the placement of a single pneumotachograph at the mouth for flow measurement has eliminated the need for a non-rebreathing valve to separate inspired and expired flows. This reduces the system dead space and resistance, and eliminates the need for a correction of the breathing valve dead space(17).

Other investigators have suggested that the pneumotachograph configuration used in these studies is subject to flow measurement errors due to the turbulence produced by the irregular flow pathways near the pneumotachograph(4,7,18). This study did not address the problem of flow measurement errors directly. However, significant flow errors would be expected to produce significantly different volume measurements and subsequently significantly different oxygen consumption and carbon dioxide production calculations between the breath-by-breath measurement system and the standard used for comparison, the mixed-expired gas-collection technique. No evidence of a statistical difference in method was found in the analysis of variance of the results from the breath-by-breath measurement system as compared to the mixed-expired

gas-collection technique. Thus, it is concluded that the breath-by-breath measurement system measures these respiratory quantities in the steady-state as accurately as the mixed-expired gas-collection technique. This indirectly suggests that there are no significant flow measurement errors present as a result of the pneumotachograph configuration.

Showing that a breath-by-breath measurement system accurately measures respiratory quantities is difficult because there exists no universally accepted standard with which to compare breath-by-breath results. In this research, steady-state results derived from the breath-by-breath data were compared to the results of a universally accepted standard steady-state measurement technique, the mixed-expired gas-collection technique. Statistical methods were used to show that there was no difference in method. This is not a completely adequate comparison.

First, the transient results of the system are not evaluated in such a comparison. Since the transient results are usually of primary importance in a breath-by-breath measurement system, this is a shortfall of the validation. Second, from a theoretical standpoint, classical statistical methods cannot be used to prove that one system is better than the other. Each method used in this comparison has a certain amount of inherent

variability, so that the results given by each method are the sum of a set of true responses plus some error. Given this, the best validation which can be achieved is to show that the results of one system lie within the variability of the other. This is taken as evidence that one system measures as well as the other. No stronger conclusion can be drawn from a statistical analysis of variance.

These results demonstrate that the breath-by-breath measurement system measures expiratory ventilation, inspiratory ventilation, oxygen consumption, carbon dioxide production, and respiratory quotient accurately. The microcomputer-based system is simple and flexible as compared to earlier systems and has the potential to be used for a variety of respiratory measurements ranging from pulmonary function tests to exercise tests on animal subjects. The simplicity and accuracy of such systems will continue to make them valuable clinical and research tools.

V.E. References

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PART II.   IMPLEMENTATION OF A FUNCTIONAL RESIDUAL

CAPACITY ALGORITHM INTO A BREATH-BY-BREATH

RESPIRATORY MEASUREMENT SYSTEM

VI.A Abstract

A software routine, which estimates changes in lung gas stores on a breath-by-breath basis and then corrects gas exchange calculations at the mouth, was implemented into a computer-based breath-by-breath respiratory measurement system.

Implementation of the software routine significantly improved the respiratory exchange ratio calculations of the breath-by-breath measurement system as compared to the standard mixed-expired gas-collection technique. The software routine reduced the sensitivity of oxygen consumption calculations to errors in inspiratory and expiratory ventilation and provided a means to test the results of the breath-by-breath measurement system for flow errors. Implementation of a functional residual capacity algorithm is necessary to obtain accurate results with a breath-by-breath system in which flow errors are present.

VI.B Introduction and Objectives

The net gas exchange at the mouth for any gas can be determined by subtracting the volume of the gas expired from the volume inspired. Thus, net exchange for oxygen is

$$\dot{V}_{O2} \;=\; F_{IO2} \cdot \dot{V}_I \;-\; F_{EO2} \cdot \dot{V}_E \tag{1}$$

Likewise, the net exchange for nitrogen is

$$\dot{V}_{N2} \;=\; F_{IN2} \cdot \dot{V}_I \;-\; F_{EN2} \cdot \dot{V}_E \tag{2}$$

But since nitrogen is neither given off nor taken up in the lung in the steady state, Equation 2 becomes

$$F_{IN2} \cdot \dot{V}_I \;=\; F_{EN2} \cdot \dot{V}_E \tag{3}$$

and inspiratory ventilation can be calculated by measuring expiratory ventilation and inspired and expired nitrogen concentrations. This is the open circuit assumption which bases all gas exchange calculations on the measurement of expiratory ventilation and which is valid only under steady-state conditions. For two reasons early breath-by-breath measurement systems (3,7) used this assumption in their design. First, it eliminated the need to measure inspiratory ventilation, thus reducing the system instrumentation. Second, and more important, independent measurement of inspiratory and expiratory ventilation

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resulted in a high percentage error in oxygen consumption calculations when only small errors were present in the measurement of flow. This was caused by the fact that a large expired volume of oxygen was subtracted from a large inspired volume of oxygen to obtain a small difference(2).

Since the open circuit assumption is valid only in the steady state, it cannot be used when transient results are being measured. Therefore both inspiratory and expiratory ventilation must be measured which leads to a high percentage error in oxygen consumption calculations when flow errors are present. Even when both inspiratory and expiratory ventilation are measured, it is possible for significant changes in lung gas stores to distort gas exchange calculations made at the mouth(1,2,12). For this reason, several algorithms have been developed which estimate the changes in lung gas stores on a breath-by-breath basis and then correct the oxygen consumption and carbon dioxide production calculations for these changes(2,6,10,11). These same algorithms also decrease the sensitivity of gas exchange calculations to flow errors.

This study analyzes the problems associated with changes in lung gas stores and problems with the high sensitivity of oxygen consumption calculations to flow errors, and evaluates the effects of an algorithm developed

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by Beaver(2) on the results of the breath-by-breath
measurement system developed by Creel(4), Riblett(9), and
Masters(8). A summary of Beaver's development is given in
Appendix B.

VI.C. Methods

VI.C.1. Implementation of the Algorithm.

The functional residual capacity correction algorithm
developed by Beaver(2) was implemented in the software of
the breath-by-breath respiratory measurement system
developed by Creel(3), Riblett(7), and Masters(6). This
system consisted of a pneumotachograph (Hans Rudolph model
3813) mounted on a face mask (Hans Rudolph #7900-M) and
connected to a differential pressure transducer (Godart
pneumotachograph type 17212) to measure inspiratory and
expiratory flow. A sampling capillary (2.59 m), inserted
into the pneumotachograph fittings between the face mask
and the pneumotachograph, was connected to a mass
spectrometer (Perkin-Elmer MGA 1100) to measure fractional
concentrations of O_2 and CO_2. A rapidly responding
thermocouple (Omega Type E Cromel-Constatin) was inserted
into the flow stream on the side of the pneumotachograph
open to room air to measure the temperature of the inspired
and expired gas. Outputs from the differential pressure

transducer, the mass spectrometer O_2 and CO_2 channels, and the thermocouple were interfaced with a microcomputer (Hewlett-Packard 9826) via a custom-built, data-acquisition system. Subjects exercised on a bicycle ergometer (Monarch model 868), and heart rate was monitored with an Amerec 150 telemetric heart rate monitor.

The functional residual capacity algorithm was implemented as a subroutine in the analysis software in this system. The BASIC code of the subroutine is presented in Appendix A.

VI.C.2. Testing the Algorithm.

To determine what effect the implementation of the correction routine had on the calculated oxygen consumption, carbon dioxide production, and respiratory exchange ratio from the breath-by-breath measurement system, these data were compared to the data obtained from the collection of mixed-expired gases for identical workloads.

VI.C.2.a. Subjects.

Four normal healthy untrained male subjects (ages 20 to 25) volunteered for this study. They ranged in weight from 66 to 86 kilograms. Each underwent a physical examination to screen for any abnormalities which might

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adversely affect the subject or the experimental results under test conditions. Approval was obtained from Kansas State University's Research Involving Human Subjects Committee for all subjects and procedures. None of the subjects were involved in any physical conditioning program at the time.

VI.C.2.b. Measurement of Functional Residual Capacity.

The functional residual capacity algorithm developed by Beaver(2) required an estimate of end-tidal lung volume to calculate changes in lung gas stores. The subject's functional residual capacity was used as an estimate of this volume. Each subject's functional residual capacity was measured twice using the nitrogen washout method(10) and the mean of the two measurements was used as the estimate for end-tidal lung volume. The estimates for each subject are shown in Table 1.

VI.C.2.c. Experimental Protocol.

Steady-state exercise measurements of oxygen consumption, carbon dioxide production, and respiratory quotient from these four subjects were taken at rest and at three exercise workloads, 80 watts, 150 watts, and 200 watts, using the breath-by-breath measurement system and the collection of mixed-expired gases. Measurements were

Table 1. Functional residual capacity measurements.				
Subject	Height (cm)	Weight (Kg)	Age (yr)	Functional Residual Capacity (L) BTPS
B	180	86	25	4.0
S	178	77	23	3.8
N	178	70	20	3.6
G	173	61	22	3.2

repeated three times on each subject for each method at each workload. Thus the subject performed each workload six times, and an average value was obtained for oxygen consumption, carbon dioxide production, and respiratory exchange ratio from the three trials at each workload. Each subject performed one trial at the same time each day, Monday through Friday. The order of the workloads was randomly selected, but once one trial of a workload was performed, all six trials for that workload were completed before moving to another workload. On a given day the method of measurement was randomly selected. The protocol for all exercise tests consisted of forty seconds of rest, six minutes of exercise, followed by another two minutes and twenty seconds of rest. To compare steady-state results from the two methods, it was necessary to compare results from the same steady-state time intervals for each method. These time intervals were chosen to give the subject sufficient time to reach a steady-state oxygen consumption and to prevent the volume of the collected

expired gas from exceeding 120 liters, the maximum volume held by the spirometer. Table 2 shows the time intervals during which steady-state measurements were made at each workload.

Table 2. Steady-state measurement time intervals.

Workload (watts)	Begin Collection (Min of exercise)	End Collection (Min of exercise)	Total Time
0	1	6	5
80	4	6	2
150	5	6	1
200	5.16	6	.83

VI.C.2.d. Data Collection.

VI.C.2.d.1. The Breath-by-Breath Measurement System.

To collect respiratory function data with the breath-by-breath measurement system, a subject was instrumented with the respiratory face mask and attached transducers described above. After entering the sampling frequency (50 Hz) and the total number of data points to be collected into the Hewlwtt-Packard computer, the computer operator began data collection with a single keystroke. The data acquisition module sampled the four input signals (the O_2 and CO_2 fractional concentration signals from the mass spectrometer, the flow signal from the pneumotachograph, and the temperature signal from the thermocouple)

simultaneously at the specified sampling frequency (50 Hz), digitized them with an A/D converter, and stored them in computer memory until data collection was complete, at which time they were stored on floppy (Hewlett-Packard 9895A) or hard disk (Hewlett-Packard 9134A) for analysis.

Program ANALYSIS retrieved the four signals stored in data collection and calculated several quantities of physiological significance. These included tidal volume, ventilation, oxygen consumption, carbon dioxide production, respiratory exchange ratio, and respiratory frequency. For this study the data collected were analyzed twice; once without the functional residual capacity correction algorithm implemented in the ANALYSIS software, and once with the algorithm implemented.

VI.C.2.d.2. The Mixed-Expired Gas-Collection Technique.

To measure steady-state values for comparison with data obtained from the breath-by-breath measurement system, the subjects were instrumented with a mouthpiece attached to a non-rebreathing valve (Hans Rudolph model 2700). The total dead space of the mouthpiece and valve was 130 milliliters. The inspiratory port of the non-rebreathing valve was connected to a 120 liter spirometer (W.E. Collins) with one meter of plastic hose (3 cm in diameter) via a three-way ball valve to measure inspiratory volume.

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The expired gas was collected in a neoprene weather balloon which was attached to a three-way ball valve. This valve, in turn, was connected to the expiratory port of the non-rebreathing valve with eighteen centimeters of plastic hose (3.5 cm in diameter). Expiratory volume was determined by transferring the expired gas into the spirometer. Mixed-expired concentrations of oxygen and carbon dioxide were measured with a mass spectrometer (Perkin-Elmer MGA 1100) as the gas was transferred to the spirometer. These measurements allowed the calculation of inspiratory and expiratory ventilation, oxygen consumption, carbon dioxide production, and respiratory exchange ratio for comparison with the results from the breath-by-breath measurement system. The ECG was monitored with the Amerec 150 heart rate monitor. Body temperature was measured before and after exercise with a mercury thermometer placed under the tongue to allow conversion of quantities to BTPS conditions. Barometric pressure and the temperature of the inspired and expired air were measured to allow the conversion of quantities to STPD conditions.

Breath-by-breath measurements were taken as previously described, and the breath-by-breath results were averaged over the appropriate time interval to obtain steady-state values which could be compared with the results from the collection of mixed-expired gases.

VI.C.2.e. Data Analysis.

Analysis of variance was performed to determine if any difference could be found between the results of the mixed-expired gas-collection technique and the corrected and uncorrected results obtained from the breath-by-breath measurement system.

Two separate statistical analyses were performed in this study. One compared the uncorrected oxygen consumption, carbon dioxide production, and respiratory exchange ratio results from the breath-by-breath measurement system to those of the mixed-expired gas-collection technique. The second analysis compared the corrected oxygen consumption, carbon dioxide production, and respiratory exchange ratio results to the results of the mixed-expired gas-collection technique. Both analyses were analyses of variance for a split plot design to determine if a significant difference (p<.05) existed between the measured results of each method. Subject-by-workload mean sum-of-squares was used to test for differences in workload, the whole plot factor. The mean square-error was used to test for differences in method, the subplot factor.

In addition, a sensitivity analysis based upon the published work of Beaver(2) was performed to determine the extent of flow error sensitivity reduction brought about by

the functional residual capacity corrections. Finally the system flow errors as determined by the functional residual capacity algorithm were examined.

VI.D. Results

VI.D.1. Error Sensitivity.

The error sensitivity of a quantity is the factor by which the error in the measured quantity is greater than or less than the error in the derived quantity(2). For example,

$$\frac{e(\dot{V}_{02})}{\dot{V}_{02}} = S \cdot \frac{e(\dot{V}_{I})}{\dot{V}_{I}} \tag{4}$$

where S is the error sensitivity, $e(\dot{V}_{I})$ is the error in $\dot{V}_{I}$, the measured quantity and $e(\dot{V}_{02})$ is the error in $\dot{V}_{02}$, the derived quantity.

This idea of error sensitivity is not commonly used and deserves further discussion. Considering Equation 4 again, the term $e(\dot{V}_{I})/\dot{V}_{I}$ is the fractional error in the measurement of inspiratory ventilation. Since $e(\dot{V}_{I})$ and $\dot{V}_{I}$ have the same units, their ratio is a dimensionless quantity. Likewise, $e(\dot{V}_{02})/\dot{V}_{02}$ is the fractional error in the calculated oxygen consumption and is also a dimensionless quantity.

From the equations in Appendix B, it is obvious that

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that the calculated oxygen consumption is dependent upon
the measured ventilation. Likewise, errors in the oxygen
consumption calculations are dependent upon the errors in
the measurement of ventilation. The magnitude of these
errors in the oxygen consumption calculations will depend
not only on the magnitude of the error in measured
ventilation but also upon S, the error sensitivity. For
example, if S=1, a 1% error in the measured ventilation
will cause a 1% error in the oxygen consumption
calculations. An error sensitivity greater or less than
one will result in proportionately greater or less error in
the oxygen consumption calculation. The value of S, the
error sensitivity, is dependent upon the form of the
mathematical expressions and the measured signals used to
make the oxygen consumption calculations.

Beaver(2) has derived the equations which describe the
sensitivity of oxygen consumption and carbon dioxide
production calculations to inspiratory and expiratory flow
errors in a breath-by-breath measurement system with no
functional residual capacity corrections implemented.
These are shown in Equations 5 and 6. Application of the
functional residual capacity correction algorithm changes
these sensitivity expressions to those illustrated in

$$\frac{e(\dot{V}_{O2})}{\dot{V}_{O2}}_M = \frac{F_{IO2}}{(F_{IO2} - F_{\bar{E}O2})} \cdot \frac{e(\dot{V}_I)}{\dot{V}_I} - \frac{F_{\bar{E}O2}}{(F_{IO2} - F_{\bar{E}O2})} \cdot \frac{e(\dot{V}_E)}{\dot{V}_E} \qquad (5)$$

$$\frac{e(\dot{V}_{CO2})_M}{\dot{V}_{CO2}} = \frac{e(\dot{V}_E)}{\dot{V}_E} \tag{6}$$

Equations 7 and 8.

$$\frac{e(\dot{V}_{O2})_A}{\dot{V}_{O2}} = \frac{(F_{IO2} - F_{AO2})}{(F_{IO2} - F_{EO2})} \cdot \frac{e(\dot{V}_I)}{\dot{V}_I} - \frac{(F_{EO2} - F_{AO2})}{(F_{IO2} - F_{EO2})} \cdot \frac{e(\dot{V}_E)}{\dot{V}_E} \tag{7}$$

$$\frac{e(\dot{V}_{CO2})}{\dot{V}_{CO2}} = \frac{(F_{ACO2} - F_{ICO2})}{(F_{ECO2} - F_{ICO2})} \cdot \frac{e(\dot{V}_I)}{\dot{V}_I} - \frac{(F_{ACO2} - F_{ECO2})}{(F_{ECO2} - F_{ICO2})} \cdot \frac{e(\dot{V}_E)}{\dot{V}_E} \tag{8}$$

Table 3 contains measured and calculated steady-state quantities from three different exercise workloads that are required to calculate the sensitivity of oxygen consumption and carbon dioxide production calculations to errors in inspiratory and expiratory ventilation. Substitution of these values into Equations 5 and 6 yields the sensitivities of the oxygen consumption and carbon

Table 3. Steady-state quantities needed to determine the error sensitivities to flow errors.			
Workload	80 Watt	150 Watt	200 Watt
F_{IO2}	.210	.210	.210
F_{EO2}	.162	.167	.172
F_{AO2}	.150	.159	.165
F_{ICO2}	.006	.005	.006
F_{ECO2}	.477	.456	.437
F_{ACO2}	.597	.570	.533
$\dot{V}_E$ (L/Min)	37.09	72.29	104.70
$\dot{V}_I$ (L/Min)	36.67	71.60	104.90

dioxide production calculations to flow errors without the functional residual capacity algorithm implemented. These sensitivities are shown in Table 4. Substitution of the values in Table 3 into Equations 7 and 8 yields the sensitivities of the system to flow errors with the functional residual capacity algorithm implemented. These sensitivities are shown in Table 5. The sensitivities of

Table 4. Sensitivities of O_2 consumption and CO_2 production calculations to errors in inspiratory and expiratory ventilation with no functional residual capacity corrections.

Sensitivity of	to Errors in	80 Watt	Workload 150 Watt	200 Watt
$\dot{V}_{O2}$	$\dot{V}_E$	4.38	4.98	5.52
$\dot{V}_{O2}$	$\dot{V}_I$	3.38	3.98	4.53
$\dot{V}_{CO2}$	$\dot{V}_E$	1.81	3.39	1.52
$\dot{V}_{CO2}$	$\dot{V}_I$	0	0	0

Table 5. Sensitivities of O_2 consumption and CO_2 production calculations to errors in inspiratory and expiratory ventilation with the functional residual capacity algorithm implemented.

Sensitivity of	to Errors in	80 W	Workload 150 W	200 W
$\dot{V}_{O2}$	$\dot{V}_E$	1.25	1.19	1.18
$\dot{V}_{O2}$	$\dot{V}_I$	0.25	0.19	0.18
$\dot{V}_{CO2}$	$\dot{V}_E$	0.25	0.25	0.22
$\dot{V}_{CO2}$	$\dot{V}_I$	1.25	1.25	1.22

oxygen consumption calculation to errors in inspiratory and expiratory ventilation with the functional residual capacity corrections implemented (shown in Table 5) are much lower for all workloads than those in Table 4 without the correction routine implemented thereby illustrating the reduction in error sensitivity brought about by implementation of the correction routine.

VI.D.2. Analysis of Variance.

Analysis of variance was used to compare the mean steady-state oxygen consumption, carbon dioxide production, and respiratory exchange ratio calculations of the breath-by-breath measurement system to those calculated from measurements made with a standard technique, the mixed-expired gas-collection technique. Two analyses were performed. The first analysis compared the corrected results (with the functional residual capacity correction algorithm implemented) from the breath-by-breath measurement system with those of the mixed-expired gas-collection technique. There was no statistically significant difference in method for any variable with the functional residual capacity correction algorithm implemented as shown in Table 6. The F values for method are all small and all associated p values are greater than .05 indicating no difference in method.

The second analysis compared the oxygen consumption, carbon dioxide production, and respiratory exchange ratio calculations from the breath-by-breath measurement system

Table 6. Analysis of variance summary for the corrected data.

		$\dot{V}_{O2}$	$\dot{V}_{CO2}$	R
Work	F-value	588.77*	664.75*	57.07*
	p value	0.0001	0.0001	0.0001
Method	F-value	0.05	0.52	0.22
	p value	0.8344	0.485	0.6509
Work by Method	F-value	2.19	2.30	5.81*
	p value	0.1527	0.1389	0.0145

p value < .05 indicates significant difference
* denotes significance
critical F value is 5.59

without the functional residual capacity calculations to those from the mixed-expired gas-collection technique. This analysis, shown in Table 7, showed that there is a significant difference between methods (p=.0241) in the calculation of respiratory exchange ratio, but in no other variable. These results suggest that implementation of the functional residual capacity correction routine significantly improved the calculation of respiratory exchange ratio by the breath-by-breath measurement system. No significant improvement was seen for oxygen consumption or carbon dioxide production calculations.

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		$\dot{V}_{O_2}$	$\dot{V}_{CO_2}$	R
	Table 7.	Analysis of variance summary for the uncorrected data.		

		$\dot{V}_{O_2}$	$\dot{V}_{CO_2}$	R
Work	F-value	593.24*	725.85*	11.47*
	p value	0.0001	0.0001	0.0043
Method	F-value	3.27	2.11	7.04*
	p value	0.1005	0.1770	0.0241
Work*method	F-value	2.34	1.53	2.42
	p value	0.1354	0.2673	0.1264

p value < .05 indicates significant difference
* denotes significance
critical F value is 5.59

VI.E. Discussion

Implementation of the functional residual capacity algorithm developed by Beaver(2) improved the breath-by-breath measurement system in three ways.

VI.E.1. Gas Exchange in the Transient State.

The functional residual capacity correction routine provided results which more accurately described the gas exchange in the transient state. Gas exchange measurements made at the mouth were distant from the actual site of gas exchange in the lung, so these measurements were affected by what happened to the gas in the non-exchange regions of the respiratory system. Equation 1 provides a good

illustration of this. If $\dot{V}_I$ was large and $\dot{V}_E$ was small it would be possible to obtain a negative value for oxygen consumption during that breath, meaning that oxygen was somehow produced. This is evident in Table 8. It shows ventilation and gas exchange values calculated for the first five breaths of a 150-watt exercise step test. The negative oxygen consumption values for breaths 2 and 4, caused by the inequality of the inspiratory and expiratory tidal volumes for these breaths for the uncorrected data, are inaccurate calculations. These negative values were

Table 8. Breath-by-breath transient results with and without the functional residual capacity correction algorithm.

Breath	Uncorrected $\dot{V}_{O_2}$ (L/Min)	$\dot{V}_{CO_2}$ (L/Min)	Corrected $\dot{V}_{O_2}$ (L/Min)	$\dot{V}_{CO_2}$ (L/Min)	Insp Tidal Volume (L)	Exp Tidal Volume (L)
1	.324	.423	.437	.436	.75	.78
2	-.653	.873	.492	.498	.66	1.02
3	.088	.849	1.045	.926	.68	.81
4	-.051	.770	.192	.251	.59	.72
5	.566	.702	.921	.747	.63	.66

not present in the corrected data which provided a more reasonable description of gas exchange for these breaths.

These negative oxygen consumption calculations were not a true representation of gas exchange for these breaths. A more likely scenario was that oxygen still

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passed across the alveolar-capillary membrane into the blood such that oxygen consumption was near normal. The apparent negative oxygen consumption was instead caused by the fact that the inequality of inspiratory and expiratory volumes for the breath decreased the volume of oxygen stored in the lung. This oxygen stored in the lung volume was expired during the breath which greatly increased the magnitude of the volume of the oxygen in the expirate and lead to the calculation of a negative oxygen consumption.

Over the course of several breaths and in the absence of flow errors, the mean oxygen consumption at the mouth provides an accurate representation of gas exchange in the lung because, over time, the change in lung gas stores tends toward zero. However, if the first few breaths following the onset of exercise are of interest, the discrepancies between the true alveolar gas exchange and the gas exchange measured at the mouth can be significant(12).

The functional residual capacity algorithm addressed this problem by calculating nitrogen exchange at the mouth as in Equation 2. By assuming a value for the fractional concentration of alveolar gas based upon end-tidal fractional concentrations, the total volume change of the lung gas stores was calculated as well as the change in volume of each gas component. The change in lung gas

stores was added to the gas exchange measured at the mouth to obtain an estimate of the true gas exchange for the breath. Again referring to Table 8, the functional residual capacity algorithm corrected all negative oxygen consumption values. This provided a more reasonable description of the gas exchange.

VI.E.2. Reduction in Error Sensitivity.

The functional residual capacity correction algorithm reduced the sensitivity of oxygen consumption and carbon dioxide production calculations to errors in the measurement of inspiratory and expiratory ventilation. The results of Tables 4 and 5 demonstrate this well.

VI.E.2.a. Oxygen Consumption Calculations.

The sensitivity of oxygen consumption calculations to errors in inspired ventilation without the functional residual capacity corrections applied ranged from 4.3 to 5.5 (Table 4). The functional residual capacity corrections reduced these sensitivities to the range of 1.2 to 1.3 (Table 5), a reduction in sensitivity by a factor of 3.4 to 4.6. Likewise, the sensitivity of oxygen consumption calculations to errors in expiratory ventilation ranged from 3.4 to 4.6 (Table 4) without the functional residual capacity corrections and from .18 to

.25 (Table 5) with the functional residual capacity corrections, a reduction by a factor of 14 to 25.

As can be seen from Equations 5-8, the sensitivities to inspiratory and expiratory flow errors can either be complementary or antagonistic depending on the signs of the error terms. If both error terms have the same sign, the total sensitivity may approach 10 for the uncorrected results. This agrees very well with Beaver's published results(2). Application of the functional residual capacity corrections reduced this total sensitivity to 1.5 in the worst case.

These reductions in error sensitivity yielded very different oxygen consumption values in the steady state when the functional residual capacity corrections were applied. Figure 1 shows a plot of fitted oxygen consumption curves versus time for a 150-watt exercise run. The corrected and uncorrected data are presented to graphically illustrate the difference that the correction routine can make in the oxygen consumption calculations of a breath-by-breath measurement system. In Figure 1, application of the functional residual capacity corrections reduced the steady-state oxygen consumption for this 150-watt exercise bout by 26 per cent. By evaluating Equations 5 and 7 with data from this run (shown in Table 9) and calculating the error in the measurement of ventilation
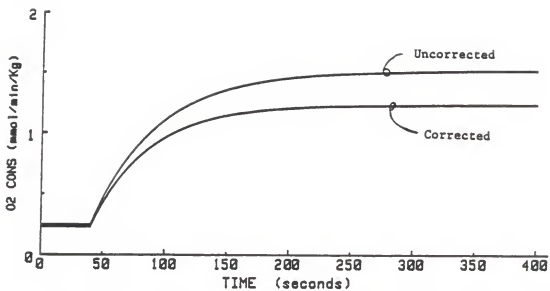
Figure 1. Corrected and uncorrected oxygen consumption curves versus time for a 150 watt workload.

Table 9. Measured and calculated quantities needed to calculate the error in oxygen consumption in the steady state illustrated graphically in Figure 1.

F_{IO2}		.210	$\dot{V}_E$(true) (L/Min)	72.29
$F_{\bar{E}O2}$		.167	$\dot{V}_I$(true) (L/Min)	71.60
F_{AO2}		.159	$e(\dot{V}_E)$ (L/Min)	4.97
$\dot{V}_E$(measured)	(L/Min)	75.87	$e(\dot{V}_I)$ (L/Min)	9.73
$\dot{V}_I$(measured)	(L/Min)	78.57		

using the ventilation values from the mixed-expired gas-collection technique as the true ventilation values (also shown in Table 9), the calculated oxygen consumption is 28 percent lower for the corrected results. This corresponded well with the observed change in Figure 1. This example demonstrates how the change in sensitivity to flow errors can account for the differences in the corrected and uncorrected results.

VI.E.2.b. Carbon Dioxide Production Calculations.

Since CO_2 production calculations were not as sensitive as oxygen consumption calculations to flow errors, the improvement in error sensitivity for carbon dioxide production calculations was small. Without the functional residual capacity corrections implemented, the sensitivity of carbon dioxide production calculations to errors in inspiratory ventilation was approximately zero

because of the very low fractional concentration of carbon dioxide in inspired air. Application of the functional residual capacity corrections actually increased the sensitivity of CO_2 calculations to errors in inspiratory ventilation because this error sensitivity was no longer dependent only on the fractional concentration of the inspired CO_2, but also on the fractional concentration of CO_2 in the lung. However, this increase was offset by a decrease in the sensitivity to errors in expiratory ventilation as illustrated in Table 4 and 5. The worst case sensitivity of carbon dioxide production calculations to flow errors was 3.39 without the functional residual capacity corrections and 1.50 with the functional residual capacity corrections implemented.

VI.E.3. Analysis of Variance.

This reduction in error sensitivity significantly improved the accuracy of the steady-state results of the breath-by-breath measurement system as compared to the mixed-expired gas-collection technique. No evidence of a statistical difference was found between the results of the mixed-expired gas-collection technique and those of the breath-by-breath measurement system with the functional residual capacity corrections implemented as shown in Table 7.

However, the analysis of variance performed on the uncorrected data (Table 6) showed that the measurement of respiratory exchange ratio was significantly different for the two methods (p=.02). Further, the oxygen consumption and carbon dioxide production measurements, while not significantly different, had much larger F ratios than the corrected results (3.27 vs. 0.05 and 2.11 vs. 0.52).

VI.E.4. Quantification of Flow Measurement Errors.

The functional residual capacity algorithm provided a means to quickly test results for systematic flow errors(2). In the absence of flow errors, changes in lung gas stores in the steady state over time should have been zero. Any systematic change in lung gas stores over time was then indicative of flow errors in the system.

Using this as a criteria for identifying flow errors in the system, Table 10 displays the change in lung gas stores in the steady state as a percentage of expiratory ventilation.

The flow errors presented in Table 10 once again point out the problem of the high sensitivity of oxygen consumption calculations to flow errors in breath-by-breath measurement systems. The average error in Table 10 is 3.0% which is reasonable accuracy for a pneumotachograph. However, when this 3.0% error is multiplied by a

Table 10. Flow errors (the average difference in inspira-
tory and expiratory ventilation as a function of
expiratory ventilation) calculated with the
functional residual capacity algorithm of Beaver.

Workload (watts)	Subject	Flow Errors (%)
000	N	+1.17
000	N	+2.40
000	N	+0.33
000	B	+1.41
000	B	+0.50
000	B	+0.98
000	S	-2.14
000	S	-0.08
000	S	-1.73
000	G	+0.12
000	G	+1.24
000	G	+1.81
080	N	+2.30
080	N	+3.17
080	B	-0.95
080	B	+1.26
080	B	+1.66
080	S	-6.70
080	S	+3.18
080	S	-8.31
080	G	+0.29
080	G	+3.81
080	G	+1.47
150	N	+6.61
150	N	+2.83
150	N	+3.66
150	B	+3.39
150	B	+3.35
150	B	+4.38
150	S	+2.08
150	S	+2.18
150	S	+4.34
150	G	+6.06
150	G	+8.18
150	G	+5.26
200	B	+1.52
200	B	+5.72
200	B	+3.57
200	S	-2.11
200	S	+1.02
200	S	+1.68

sensitivity of three to five, the resulting error in the oxygen consumption calculation is 9 to 15 percent. In order to obtain acceptable accuracy in oxygen consumption calculations in a breath-by-breath measurement system that measures both inspiratory and expiratory ventilation, it is necessary to reduce the sensitivity to flow errors to approximately one or to reduce flow errors to approximately one percent or less. Implementation of the functional residual capacity corrections accomplishes the former.

VI.E.5. The Effect of the Flow Errors on the Analysis of
        Variance.

     The flow errors in Table 10 were reflected in the results of the analyses of variance presented in Tables 6 and 7.

VI.E.5.a. Oxygen Consumption Calculations.

     First, the differences between the corrected and uncorrected oxygen consumption calculations from the breath-by-breath measurement system as compared to the mixed-expired gas-collection technique were considered. The average values of the natural logarithm of the mean oxygen consumption calculations for all four subjects are shown in Table 11. There was a significant difference between methods for the uncorrected data at the 150-watt

workload which was associated with the highest flow errors
in Table 10. When these flow errors were multiplied by the
error sensitivity values in Table 4, a statistically
significant difference was found between the breath-by-
breath measurement system and the mixed-expired gas-
collection technique at this workload. At the other
workloads, flow errors still existed, but they did not

Table 11. The natural logarithms of the calculated oxygen
           consumption values for Method 1 and Method 2.
           Workload 1 = Rest   Workload 2 = 80 watts
           Workload 3 = 150 watts   Workload 4 = 200 watts

           Method 1 = Mixed-expired gas collection.
           Method 2 = Breath-by-breath measurement system.

		Uncorrected Results Workload				Corrected Results Workload		
		1	2	3	4	1	2	3	4
Method 1		-1.59	-.199	.346*	.551	-1.59	-.199	.346	.551
	2	-1.61	-.171	.537	.549	-1.62	-.173	.371	.491

* Methods 1 and 2 differ, p<.05
Units are Natural logarithm (mmol/Min/Kg)

cause statistically significant differences. In contrast,
there was no significant difference in method at any
workload for oxygen consumption measurements when comparing
the functional-residual-capacity-corrected results with
those of the mixed-expired gas-collection technique. The
flow errors in Table 10 were still present, but the
sensitivity of the oxygen consumption calculations to these

errors was reduced (Table 5) such that no significant difference in method remained. This reduction in error sensitivity at all workloads also accounted for the lower F ratios for a difference in method (Table 4 as compared to Table 5).

VI.E.5.b. Carbon Dioxide Production Calculations.

Since the CO_2 calculations of the breath-by-breath measurement system had a low sensitivity to flow errors, the flow errors in Table 10 did not cause a significant difference at any workload between the CO_2 production calculations of Method 2 and those of Method 1 regardless of whether the functional residual capacity corrections were implemented. There was however, a slight reduction in the F ratio for a difference in method with the corrected data because of the slight reduction in the error sensitivity of carbon dioxide production calculations to flow errors.

VI.E.5.c. Respiratory Exchange Ratio Calculations.

A significant difference was found (p=.02) between the uncorrected respiratory exchange ratio measured by the breath-by-breath measurement system and that measured by the mixed-expired gas-collection technique. Table 12 shows the natural logarithm of the mean respiratory exchange

ratio for the four subjects at each workload. The
respiratory exchange ratio from the breath-by-breath
measurement system was lower at all workloads and was
significantly lower at the 150-watt workload. This
followed from the fact that the uncorrected carbon dioxide
values from the breath-by-breath measurement system were
lower at all workloads and that the oxygen consumption
calculations at the 150-watt workload were significantly

Table 12. The natural logarithm of the calculated
           respiratory exchange ratio for Method 1 and
           Method 2.
           Workload 1 = Rest   Workload 2 = 80 watts
           Workload 3 = 150 watts   Workload 4 = 200 watts

           Method 1 = Mixed-expired gas collection.
           Method 2 = Breath-by-breath measurement system.

		Uncorrected Results Workload				Corrected Results Workload		
		1	2	3	4	1	2	3	4
Method 1		-.103	-.034	.056*	.123	-.103	-.033	.056	.123
	2	-.168	-.050	-.161	.124	-.134	-.052	.067	.232

---

* = Method 1 and 2 differ, p<.05
R is a dimensionless quantity.

higher than those of the mixed-expired gas-collection
technique. Application of the functional residual capacity
correction algorithm eliminated any significant difference
between methods.

     In general, implementation of Beaver's functional
residual capacity correction algorithm improved the

accuracy of the results of the breath-by-breath measurement system without a large cost in software or hardware. It accomplished this through estimation of breath-by-breath changes in lung gas stores and through the reduction in error sensitivity of oxygen consumption calculations and carbon dioxide production calculations to flow errors. The algorithm provided a quantitative estimate of flow errors present in the system during a run and thereby provided a means by which to check the validity of the results. These improvements made the algorithm a necessary addition to the system software to meet the demand of accurate breath-by-breath respiratory measurements.

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The BASIC Code for the Functional Residual Capacity Algorithm.

The FRC correction algorithm of Beaver was implemented into the ANALYSIS software as a subroutine called Frc_calc. The BASIC code of this subroutine is shown below and definitions of the variables used by the subroutine are given.

```
Frc_calc: !
Frac_co2_1=(Line1(Max_index)-Co2_dc_offset)*Co2cal
Frac_o2_1=(Line2(Max_index)-O2_dc_offset)*O2cal+O1
Frac_n2_1=1-Frac_co2_1-Frac_o2_1-0.005
!
If Num_breaths>1 THEN
    Chng_fo2=Frac_o2_1-Frac_o2_2
    Chng_fco2=Frac_co2_1-Frac_co2_2
    Chng_fn2=Frac_n2_1-Frac_n2_2
!
!       Compute change in lung volume.
    Chng_lung_vol=(N2store-V1*Chng_fn2)/Frac_n2_1
    Tot_lung_chng=Tot_lung_chng+Chng_lung_vol
!
!        Correct O2 consumption and CO2 production
        calculations.
    Frc_o2cons=O2cons+(Chng_lung_vol*Frac_o2_1+Chng_fo2*V1)

Frc_co2prod=Co2prod+(Chng_lung_vol*Frac_co2_1+Chng_fco2*V1)
    Lung_vol=Lung_vol+Chng_lung_vol
ELSE
    Frc_o2cons=O2cons
    Frc_co2prod=Co2prod
END IF
Frac_o2_2=Frac_o2_1
Frac_co2_2=Frac_co2_1
Frac_n2_2=Frac_n2_1
RETURN
```

<u>Definition of variables</u>

Chng_fco2   REAL variable equal to the change in end-
                 tidal fraction concentration of carbon
                 dioxide from the previous breath to the
                 current breath.

Chng_fn2   REAL variable equal to the change in end-
                 tidal fractional concentration of nitrogen
                 from the previous breath to the current
                 breath.

Chng_fo2   REAL variable equal to the change in end-
                 tidal fractional concentration of oxygen
                 from the previous breath to the current
                 breath.

Chng_lung_vol   REAL variable equal to the change in end-
                 tidal lung volume from the previous breath
                 to the current breath.

Co2prod   REAL variable equal to the carbon dioxide
                 production calculated at the mouth (the
                 uncorrected carbon dioxide production).

Frac_co2_1   REAL variable containing end-tidal
                 fractional concentration of carbon dioxide
                 for the current breath.

Frac_n2_1   REAL variable containing end-tidal
                 fractional concentration of nitrogen for the
                 current breath.

Frac_o2_1   REAL variable containing end-tidal
                 fractional concentration of oxygen for the
                 current breath.

Frac_co2_2   REAL variable containing end-tidal
                 fractional concentration of carbon dioxide
                 for the previous breath.

Frac_n2_2   REAL variable containing end-tidal
                 fractional concentration of nitrogen for the
                 previous breath.

Frac_o2_2   REAL variable containing end-tidal
                 fractional concentration of oxygen for the
                 previous breath.

Frc_co2prod   REAL variable equal to the corrected carbon dioxide production in liters per minute.

Frc_o2cons   REAL variable equal to the corrected oxygen consumption in liters per minute.

Lung_vol   REAL variable equal to the end-tidal lung volume after the current.

N2store   REAL variable equal to the change in the end-tidal volume of nitrogen in the lung from the previous breath to the current breath.

O2_cons   REAL variable equal to the oxygen consumption calculated at the mouth (the uncorrected oxygen consumption).

Tot_lung_vol   REAL variable equal to the change in end-tidal lung volume from the first breath analyzed to the current breath.

Vl   REAL variable equal to the end tidal lung volume which is assumed to remain constant at the subject's function residual capacity.

A Summary of the Development of the Functional Residual
Capacity Algorithm.

It is very helpful for the reader to see the
theoretical development of the equations used by Beaver (2)
in the functional residual capacity correction routine.
This development is summarized here to assist the reader in
understanding the ideas presented in this study.

The idealized model of the lung on which the following
development is based is shown in Figure B.1. The lung is
divided into a single homogenous compartment. Oxygen,
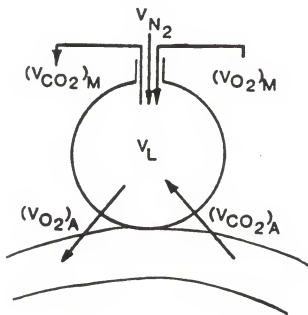carbon dioxide, and nitrogen are exchanged at the mouth,

Figure B.1. The simplified theoretical model of the
lung on which the functional residual capacity algorithm is
based (2).

but only oxygen and carbon dioxide are exchanged across the alveolar-capillary membrane. The volume of gas exchanged at the mouth is given by the following equations

$$V_{O2} = \int_{insp} \dot{V}_I \cdot F_{O2} \; dt \;\; - \int_{exp} \dot{V}_E \cdot F_{O2} \; dt \qquad (1)$$

$$V_{CO2} = \int_{exp} \dot{V}_I \cdot F_{CO2} \; dt \;\; - \int_{insp} \dot{V}_E \cdot F_{CO2} \; dt \qquad (2)$$

$$V_{N2} = \int_{insp} \dot{V}_I \cdot F_{N2} \; dt \;\; - \int_{exp} \dot{V}_E \cdot F_{N2} \; dt \qquad (3)$$

Gas exchange in the exchange region of the lung differs from that at the mouth by the change in gas stored in the lung, V_L (actually the end-tidal lung volume when considered on a per breath basis). For any gas

$$(V_X)_M \;\; = \;\; (V_X)_A \;\; + \;\; \Delta V_{LX} \qquad (4)$$

where $(V_X)_M$ is the volume of the gas exchanged at the mouth, $(V_X)_A$ is the volume of gas exchanged across the alveolar-capillary membrane, and ΔV_{LX} is the change in the volume of the gas stored in the lung during one breath. The breath-by-breath measurement system calculates gas exchange at the mouth for oxygen, carbon dioxide, and nitrogen as previously described. In order to determine the gas exchange in the exchange region of the lung an estimate of the change in lung gas stores (ΔV_{LX}) is

needed.

The amount of a particular gas stored in the lung can be changed in two ways. Either the total volume of gas in the lung can change during the breath so that the change in the volume of any particular gas, oxygen for example would be

$$\Delta V_{LO2} = \Delta V_L \cdot F_{AO2} \qquad (5)$$

or the fractional concentration of the gas can change with the total volume remaining constant

$$\Delta V_{LO2} = V_L \cdot \Delta F_{AO2} \qquad (6)$$

The total changes in lung gas stores for oxygen during one breath is then

$$\Delta V_{LO2} = \Delta F_{AO2} \cdot V_L + \Delta V_L \cdot F_{AO2} \qquad (7)$$

An analogous expression can be developed for carbon dioxide.

To estimate the change in lung gas stores necessary to calculate the gas exchange in the exchange region of the lung for a breath, Equations 4 and 7 can be combined

$$(V_{O2})_A = (V_{O2})_M - \Delta V_L \cdot F_{AO2} - \Delta F_{AO2} \cdot V_L \qquad (8)$$

B.3

$(V_{O2})_M$ is calculated by the breath-by-breath respiratory measurement system, and V_L, end-tidal lung volume, is estimated by the subject's functional residual capacity. F_{AO2} and ΔF_{AO2} are estimated with end-tidal fractional concentrations. ΔV_L is determined by assuming no nitrogen exchange across the alveolar-capillary membrane, the change in the lung nitrogen stores must be equal to the nitrogen exchange calculated at the mouth

$$V_{N2} = \Delta V_{LN2} = \Delta F_{AN2} \cdot V_L + \Delta V_L \cdot F_{AN2} \qquad (9)$$

Since V_{N2} is calculated by the breath-by-breath measurement system, ΔV_L can be estimated by rearranging Equation 9 as

$$\Delta V_L = \frac{V_{N2} - V_L \cdot \Delta F_{AN2}}{F_{AN2}} \qquad (10)$$

Now all terms on the right side of Equation 8 have been estimated or calculated and $(V_{O2})_A$ can be calculated. $(V_{CO2})_A$ is calculated in the same manner.

Four assumptions were made to make these calculations: (1) the lung was modelled as a two compartment organ, (2) FRC was assumed to be end-tidal volume during rest and exercise (3) end-tidal concentrations were assumed to be equal to alveolar concentrations, and (4) no nitrogen exchange was assumed across the alveolar-capillary

membrane. The accuracy of the corrections depend upon these assumptions being valid.

A BREATH-BY-BREATH RESPIRATORY MEASUREMENT SYSTEM
AND IMPLEMENTATION OF A FUNCTIONAL RESIDUAL
CAPACITY ALGORITHM

by

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A computerized breath-by-breath respiratory measurement system was tested to validate the accuracy of its results in the steady-state. The breath-by-breath measurement system consisted of a mass spectrometer for measuring fractional concentrations of O_2 and CO_2, a pneumotachograph for measuring inspiratory and expiratory flows, and a rapidly responding thermocouple for measuring the temperature of the flow stream. These were connected to a microcomputer via a custom built data acquisition module. Correction routines were implemented in software to correct for errors introduced by the misalignment of the flow and fractional concentration signals and errors caused by the sensitivity of the pneumotachograph to changes in temperature and gas concentration.

In addition, the functional residual capacity algorithm developed by Beaver et. al. was implemented into the system software and tested to determine if it had any effect on the oxygen consumption, carbon dioxide production, and respiratory exchange ratio calculations of the breath-by-breath system.

No evidence of a statistically significant difference was found between the steady-state results of the breath-by-breath measurement system with the functional residual capacity correction algorithm implemented and those of the mixed-expired gas collection technique for inspiratory ventilation, expiratory ventilation, oxygen consumption,

carbon dioxide production and respiratory exchange ratio. This evidence suggests that the breath-by-breath measurement system accurately measures these variables.

Implementation of the functional residual capacity software routine significantly improved the respiratory exchange ratio calculations of the breath-by-breath measurement system as compared to the standard mixed-expired gas collection technique. The software routine reduced the sensitivity of oxygen consumption calculations to errors in inspiratory and expiratory ventilation and provided a means to test the results of the breath-by-breath measurement system for flow errors. Implementation of a functional residual capacity algorithm is necessary to obtain accurate results with a breath-by-breath system in which flow errors are present.