On-line computer analysis and breath-by-breath graphical display of exercise function tests

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METHODS

Subjects were studied under exercise stress on a cycle ergometer (Lanooy, Instrumentation Associates). The breathing apparatus consisted of an Otis-McKerrow two-way valve (W. E. Collins, Cambridge, Mass.), with a pneumotachograph (Fleisch model 3, Instrumentation Associates) in the expiration arm connected to a differential pressure transducer (Statham, model PM 97). This pneumotachograph system is linear through flows of 600 liters/min at normal exercise respiratory frequencies. Small lumen sampling lines (PE-90) connected to the mouthpiece lead to a fast responding oxygen analyzer (Westinghouse, model 211) and a carbon dioxide analyzer (Beckman, model LB-1) connected through standard input couplers of a laboratory oscillographic recorder (Beckman type RM Dynograph). Heart rate is obtained from a cardiogonimeter in the same recorder. The input to the computer is connected to the analog output channels of the recorder through a multiplexed analog-to-digital converter. The computed results can be recorded on digital magnetic tape, and at the same time played back to the oscillographic recorder through digital-to-analog output channels. After the study, selected records on the magnetic tape can be played back simultaneously on eight channels of the laboratory recorder. Figure 1 is a functional diagram of the hardware.

Processing is controlled through a push-button console on which labeled switches enable the user to call various programs as needed by his protocol. These programs include the entry of parameters and constants describing the study, calibration of the input sensors and analog output channels, all necessary manipulation of the digital tape, including file creation and deletion, and control of the data processing program itself. A message screen is provided to convey error messages and status reports from the computer programs to the user.

The computer is a Varian 620/1 with 12-thousand 16-bit words of core memory. This machine is time shared simultaneously with a program which is used to compute studies on-line from an adjacent respiratory function laboratory (P. H. Griffith, W. L. Beaver, and K. Wasserman, to be published). The programs described in this paper can be contained in 8-thousand words of core memory. The computer has 16 analog input channels, although only 4 are used by the on-line data analysis program: CO2 and O2 concentrations, expired airflow, and heart rate. The data are processed in each sample interval and are retained in memory only long enough to compensate for time delays of some of the signals.

The gas concentration signals have rise times of the order of 0.2 sec and are essentially free from frequencies above 10 Hz. The signal from the pneumotachograph pressure transducer contains high-frequency artifacts and is filtered in the recorder input coupler before introduction into the computer. The heart-rate signal is generated in the recorder and does not need filtering. The analog signals are sampled and digitized at a rate of 50 times/
Signals which contain frequency components above 25 Hz would have to be filtered before digitization to prevent the introduction of aliasing distortion and frequency components above 10 Hz will not be accurately represented because of quantization and interpolation errors (3). The time to digitize all four channels is less than 100 μsec at the beginning of each sampling cycle; the remainder of the 20 msec interval between sampling times is used for computation. The digitized data are digitally filtered using a five-point least-squares smoothing filter (6), which has a zero response (cut-off) at 10.7 Hz. (This may be calculated by the method given in ref 2, p. 314.) This filter has been generally satisfactory but can produce artifactual responses to very abrupt changes in signal level.

In the breathing apparatus, the inspired and expired air are separated by the subject breathing through the two-way valve; expired air flow only is measured. (See APPENDIX for discussion of moisture and heat artifacts.) Figure 2 shows the flow signal, together with carbon dioxide and oxygen partial pressures, which are sampled at the mouthpiece during both the inspiratory and expiratory phases. We define a breath to extend from the beginning of inspiration to the end of expiration. The end-expiratory point is sensed by determining when the flow signal passes below a threshold which is located a small increment above the zero-flow baseline. Expired volume is derived by trapezoidal rule digital integration. Flow and gas concentration baseline levels are sensed during the inspiratory period of each breath and corrections are made for baseline drift breath-by-breath.

The gas partial pressure input signals occur delayed in time with respect to the flow signal by the time required to transport the sampled air from the mouthpiece to the sensors (Fig. 2). During the calibration procedure, this delay is determined and introduced into the program, thus compensating for it so that the gas concentrations and the flow are appropriately in phase and can be multiplied and integrated at each sample interval to give oxygen uptake (\(V_{EO2}\)) and carbon dioxide production (\(V_{ECO2}\)) for each breath. Correction factors for the respiratory exchange ratio (R), water vapor, and breathing valve dead space are applied by the computer breath-by-breath to the \(V_{EO2}\) and \(V_{ECO2}\) calculations (see APPENDIX).

A switch can be used to signal the time of an event, such as the start of exercise. The times of these events are recorded by the computer and are displayed as pulse signals on the laboratory recorder to enable correlation of the measurements with events.

The major output quantities and their mathematical equivalents are listed below:

**Quantities Calculated by the Computer and Their Mathematical Equivalents**

1) Tidal volume, \(V_T\) (ATP) = \(\int V_E\, dt\) (liters)
2) Breathing frequency, \(f = \frac{1}{t_2 - t_1}\) (min⁻¹)
3) Maximum expiratory flow = \(\frac{\Delta V_{EO2}}{\Delta t}\) (liters/min)
4) Minute ventilation (ATPS), \(V_E = V_T \times f\) (liters/min)
5) End-tidal $P_{CO_2}$, $PET_{CO_2} = P_{CO_2}$ (highest expired value) (mm Hg)

6) End-tidal $P_{O_2}$ difference, $\Delta PET_{O_2}$
   $= P_{O_2}$ (lowest expired value) - $P_{O_2}$ (inspired) (mm Hg)

7) Average heart rate, $HR$ (beats/min)

8) $\dot{V}CO_2$, CO$_2$ production rate,
   $\dot{V}CO_2 = \left[ \int_{t_1}^{t_2} \left( V_E \left( \frac{P_{CO_2}}{P_B} \right) \right) dt \right] \times f$ (liters/min)

9) $\dot{V}O_2$, $O_2$ consumption rate,
   $\dot{V}O_2 = \left[ \int_{t_1}^{t_2} \left( V_E \left( \frac{P_{O_2}}{P_B} \right) \right) dt \right] \times f$ (liters/min)

10) Respiratory gas exchange ratio (R), $R = \frac{\dot{V}CO_2}{\dot{V}O_2}$

11) $O_2$ uptake/heart beat = $\dot{V}O_2$/HR (liters/beat)

12) $P_{CO_2}$ min = inspired $P_{CO_2}$ (mm Hg)

13) $P_{O_2}$ max = inspired $P_{O_2}$ (mm Hg)

14) Minute ventilation (BTPS and corrected for breathing valve dead space) (liters/min)

15) Event signal

where $t_1$ = time of beginning of the breath; $t_2$ = time of end expiration of the breath; $V_E$ = inspiratory flow rate; $P_{CO_2}$ = instantaneous CO$_2$ partial pressure; $P_{O_2}$ = instantaneous $O_2$ partial pressure; and $P_B$ = barometric pressure. These calculations are completed at the end of each breath and can be output to tape as well as displayed on-line on the oscillographic recorder. Up to eight of the calculated quantities may be selected and plotted from the digital tape simultaneously after the study. The plot-back speed is limited by the response time of the recorder pens and can be made any multiple of the original data acquisition speed. Scaling factors for the plots can be changed at the discretion of the investigator, permitting normalization or optimum use of the width of the chart.

**Calibration**

The computer program calculates calibration factors based on data input during a computerized calibration procedure. Calibration consists of three phases.

1) The gas concentration and heart rate channels of the recorder are calibrated by introducing known gases or standard signals. By offsetting the pens predetermined amounts, two different voltages are then generated at the output of each recorder channel corresponding to values determined by the calibration. These quantities are then entered through the numeric input keyboard on the console. Using these voltages and input quantities, the computer automatically calculates the conversion factors for these channels.

2) The flow channel is calibrated by passing a known volume of air through the pneumotachygraph using a standard syringe. The computer calculates a value for the volume which is then compared with the actual volume. This permits the correct conversion factor to be derived in order to get the computer output to exactly equal the calibration volume.

3) The gas transport delay times are found by connecting the gas sampling tubes to the output port of an electrically driven valve, which switches between two inputs connected to two different gas mixtures. This generates a square wave of gas concentration and an electrical signal, the latter indicated on the recorder at the time of switching. The delay is measured on the chart from the switching signal to the point where the gas concentration tracing begins shifting to the new concentration. These delay times are entered into the computer through the numeric keyboard, and are used by the program to synchronize the gas concentrations with the flow signal.

**RESULTS**

Figure 3 shows the played-back record of an exercise study involving heavy work on the cycle ergometer for a period of 10 min. Starting at the top, minute ventilation, CO$_2$ production, $O_2$ consumption, gas exchange ratio, end-tidal CO$_2$ partial pressure, and heart rate breath-by-breath were selected for this particular playback. The value associated with each breath is plotted for the duration of that breath, giving a histogram-like appearance to the tracings.

In a typical recording of measurements during exercise (Fig. 3), transient phenomena are readily observed. Many physiologically interesting features are seen in these curves. For example, sudden changes can be seen in $V_E$ at the start and cessation of exercise. a
subject of some current interest in the study of the control of ventilation (1). The lack of stable values for $V_e$, $V_{O_2}$, heart rate, and $P_{ETCO_2}$ demonstrate that the subject was in a state of partial anerobiosis throughout the exercise. The respiratory gas exchange ratio, $R$, exhibits complex transient behavior after the beginning and after the end of exercise, showing the relative differences in carbon dioxide and oxygen transfer. The transient periods of end-tidal carbon dioxide are also complex, reflecting the interplay between ventilation, cardiac output and mixed venous $CO_2$. Detailed study of the transient behavior of these quantities have been found to be very useful in the study of exercise physiology.

Validation

To validate the computed values of $V_e$, $V_{O_2}$, $V_{CO_2}$, and $R$, exercise studies were made at various work rates. The expired air was collected in a container for 1 or 2 min at steady state for each work rate and analyzed by the methods previously used in the exercise laboratory (7, 8). For comparison, the gas transfer was calculated by the computer and averaged for the same time interval as the collection.

These simultaneous determinations of $V_e$, $V_{O_2}$, $V_{CO_2}$, and $R$ for several subjects during a wide range of exercise metabolic rates are shown in Fig. 4, where the line of identity is also plotted. There is no significant difference between the regression line for the experimentally determined points and the line of identity.

The computer system described here is an intimate part of the laboratory apparatus. It provides the ability to observe dynamics of gas exchange and has contributed to our understanding of cardiorespiratory physiology in a way that would not have been possible by the alternative, traditional technique of collecting an average sample for later analysis. The advantage of being able to see the derived data on-line during a study, as well as being able to see unaveraged continuous breath-by-breath measurements of gas exchange to study cardiopulmonary phenomena in health and disease has proven to be of great value.

APPENDIX

In the following, the actual computation algorithms for $V_{O_2}$, $V_{CO_2}$, $V_e$, and $R$ are derived.

$O_2$ Consumption

Gas passing through the Fleisch pneumotachygraph is assumed to be raised to screen temperature in the flow channels. Thus the same mass of air gives approximately the same indication regardless of its original temperature. Calibration is ordinarily carried out using air at ambient temperature. Therefore, the measured flow always refers to the flow at ambient temperature.

During expiration, the temperature of the column of air between the mouthpiece and the screen cools and water vapor condenses. Thus the same mass of air gives approximately the same indication regardless of its original temperature. Calibration is ordinarily carried out using air at ambient temperature. Therefore, the measured flow always refers to the flow at ambient temperature.

During expiration, the temperature of the column of air between the mouthpiece and the screen cools and water vapor condenses. Thus the same mass of air gives approximately the same indication regardless of its original temperature. Calibration is ordinarily carried out using air at ambient temperature. Therefore, the measured flow always refers to the flow at ambient temperature.

The oxygen consumption is calculated from the integral of the $O_2$ consumption in the breath is calculated from this quantity by applying a number of correction factors which are derived using the expression for net $O_2$ transport in a breath:

$$V_{O_2} = \int_{t_1}^{t_2} (F_{O_2} - F_{ETO_2})V_e dt$$

With the breathing apparatus used, $V_{I02}$ is composed of two components, since at the beginning of inspiration the dead space in the breathing apparatus (the chamber between the valves and the gas sampling outlets in the mouthpiece) contains expired air that has been measured as expired and is then inspired again. This component of inspired air is not room air but is end-tidal expired air from the previous breath. Thus,

$$V_{I02} = F_{I02}V_t + F_{ETO2}V_{NB} - F_{O2}V_t - (F_{I02} - F_{ETO2})V_{NB}$$

Using equation 4 in equation 3 and collecting terms in a way that will be useful in the derivation,

$$V_{O2} = \int_{t_1}^{t_2} (F_{O2} - F_{ETO2})V_e dt + F_{I02}(V_t - V_i)$$

$$+ (F_{I02} - F_{ETO2})V_t - (F_{I02} - F_{ETO2})V_{NB}$$

The quantity $V_t$ can be derived by accounting for all fractional components in both the inspired and the expired air as follows:

$$V_t - V_r = V_{I02} - V_{ETO2} + V_{IN2} - V_{TN2}$$

$$\mid V_{I02} \mid V_{ETO2} \mid V_{IN2} \mid V_{TN2}$$

Some simplification occurs if the dry equivalent of the inspired room
air is used, in which case
\[ \text{V}_{\text{th}0} = 0 \]
and
\[ \text{V}_{\text{i}0} = 0.209 \times \text{V}_{\text{i}} \]
also,
\[ \text{V}_{\text{o}2} = \text{V}_{\text{i}2} - \text{V}_{\text{T}02} \]
\[ \text{V}_{\text{co}2} = \text{V}_{\text{T}02} - \text{V}_{\text{i}02} \]
The inspired and expired Nz are assumed to be equal, so that finally
\[ \text{V}_{\text{i}} - \text{V}_{\text{T}} = \text{V}_{\text{o}2} - \text{V}_{\text{co}2} - \text{V}_{\text{i}02} \quad (7) \]
In addition, the quantity \((\text{F}_{\text{o}2} - \text{F}_{\text{i}0}2)\) is the difference between dry and ambient Oz concentration due to water vapor dilution. It can be shown that
\[
\text{F}_{\text{i}0}2 \cdot \text{F}_{\text{i}0}2 = \text{F}_{\text{i}0}2 \text{F}_{\text{i}0}2\]
Using equations 5-8, we have
\[
\text{V}_{\text{o}2} = \left( \frac{\int_{\text{t}1}^{\text{t}2} (\text{F}_{\text{e}0}2 - \text{F}_{\text{i}0}2) \text{V}_{\text{e}} \text{d}t - \text{F}_{\text{i}0}2 \text{V}_{\text{co}2}}{\text{F}_{\text{i}0}2 - \text{F}_{\text{o}2}} \right) \quad (9)
\]
Equation 9 contains the equivalent of the gas exchange ratio (R) correction for oxygen consumption (7), as well as corrections for water vapor and breathing valve dead space. \(\text{V}_{\text{o}2}\) is obtained by dividing \(\text{V}_{\text{o}2}\) of equation 9 by the breath interval in minutes.

**CO\textsubscript{2} Production**

The CO\textsubscript{2} production calculation is symmetrical with equation 9; the positive direction of flow is normally out of, rather than into, the lung, so that using
\[ \text{V}_{\text{co}2} = \text{V}_{\text{Tco}2} - \text{V}_{\text{i}02} \]
Analogous with equation 9 we have
\[
\text{V}_{\text{co}2} = \left( \frac{\int_{\text{t}1}^{\text{t}2} (\text{F}_{\text{e}co}2 - \text{F}_{\text{i}co}2) \text{V}_{\text{e}} \text{d}t - \text{F}_{\text{i}co}2 \text{V}_{\text{co}2} + (\text{F}_{\text{i}e}2 - \text{F}_{\text{i}co}2) \text{V}_{\text{e}} \text{d}t}{\text{F}_{\text{i}co}2} \right) \quad (10)
\]
Equation 10 reduces to the following when inspired CO\textsubscript{2} is zero. This expression is used in the computer program. \(\text{V}_{\text{co}2}\) is obtained by dividing \(\text{V}_{\text{co}2}\) of equation 10 by the breath interval in minutes.
\[
\text{V}_{\text{co}2} = \left( \frac{\int_{\text{t}1}^{\text{t}2} \text{F}_{\text{e}co}2 \text{V}_{\text{e}} \text{d}t - \text{F}_{\text{e}co}2 \text{V}_{\text{e}} \text{d}t}{\text{t}2 - \text{t}1} \right) \quad (11)
\]

**Temperature Correction**

\(\text{V}_{\text{o}3}\) and \(\text{V}_{\text{co}2}\) in equations 9 and 11 are ATPD because the pneumotachygraph is calibrated at ambient temperature. To reduce \(\text{V}_{\text{co}2}\) and \(\text{V}_{\text{o}3}\) to standard conditions, STPD, the quantities in equations 9 and 11 are multiplied by the quantity
\[
\left( \frac{273}{T + 273} \right) \quad \text{where } T = \text{temperature, } ^{\circ}\text{C.} \quad (12)
\]

**Gas Exchange Ratio**

The gas exchange ratio, R, of the breath is computed from the expression
\[
\text{R} = \frac{\text{V}_{\text{co}2}}{\text{V}_{\text{o}3}} \quad (15)
\]

**Definition of Symbols**

The standard symbols for respiratory physiology (5) are used, with the following special symbols and interpretations:

\(\text{F}_{\text{i}0}2\), \(\text{F}_{\text{i}co}2\), \(\text{F}_{\text{e}2}\) = instantaneous expired fractional concentration for the gas indicated

\(\text{F}_{\text{i}0}2\) = equivalent dry inspired Oz fractional concentration = 0.209

\(\text{F}_{\text{e}2}\) = ambient (reference) Oz fractional concentration

\(\text{F}_{\text{e}co}2\) = end-tidal Oz fractional concentration

\(\text{F}_{\text{e}co}2\) = end-tidal CO\textsubscript{2} fractional concentration

\(\text{F}_{\text{e}co}2\) = inspired CO\textsubscript{2} fractional concentration

\(\text{V}_{\text{e}}\) = expired gas flow rate (instantaneous)

\(\text{V}_{\text{T}}\) = the expired tidal volume

\(\text{V}_{\text{i}}\) = total inspired volume

\(\text{V}_{\text{o}3}\), \(\text{V}_{\text{co}2}\), \(\text{V}_{\text{i}02}\), \(\text{V}_{\text{i}co2}\) = the expired volume of the respective gases

\(\text{t}1\) and \(\text{t}2\) = the times of beginning and ending of the given breath

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