MOXUS CARDIAC OUTPUT MODULE Option
CARBON DIOXIDE REBREATHING METHOD

CO2 REBREATHING METHOD

Cardiac output has traditionally been measured by the Fick technique which relates the oxygen uptake to the arterial to mixed venous O*2* content in the following equation
Qt = VO2 CaO2 – CvO2
Where: Qt = Cardiac Output VO2 = Oxygen Uptake CaO2 = Arterial blood oxygen content CvO2 = Mixed venous blood oxygen content
As the collection of arterial and mixed venous blood samples requires the invasive placement of catheters, this technique has not enjoyed widespread use in exercise physiology measurements.
An indirect Fick method has been developed which substitutes the use of CO2 measurements in the equation as follows:
Qt = VCO2 CaCO2 – CvCO2
Where: VCO2 = Carbon dioxide production CaCO2 = Arterial blood carbon dioxide content CvCO2 = Mixed venous blood carbon dioxide content
Arterial blood CO2 content is non-invasively estimated by measuring the expired CO2 at the mouth with a rapid CO2 analyzer and examining the observed waveform for it's peak. This measurement is commonly referred to as "end-tidal CO2 or PetCO2" and is measured in mmHg [torr]. This measurement closely approximates PaCO2 (the partial pressure of CO2 in arterial blood) in subjects with normal lungs. CaCO2 is then calculated with the following formula:
CaCO2 (ml) = antilog [(loge PaCO2 x 0.296) + 2.38]
For subjects with underlying pulmonary disease, the software allows entry of arterial blood PCO2 in place of end-tidal PCO2 measurements in order to more accurately estimate cardiac output.
Measurement of VCO2, of course, is non-invasive and is routinely measured during exercise testing. The measurement of mixed-venous CO2 content can also be approximated non-invasively. It is known that, if a normal subject rebreathes from a bag filled with CO2 roughly approximating that of the mixed CO2 in the blood, a rapid equilibration occurs between the lungs, the alveolar capillary blood and the rebreathing bag.
To be accurate, the equilibration needs to be completed with 10 seconds; otherwise, recirculation of the blood from the lungs through the system and back to the lungs is likely to occur. Thereafter, the result will then be a constant increase of CO2 in the rebreathing bag, nullifying the measurement. This is easily corrected in subsequent measurements by either adjusting the rebreating bag target CO2 either up or down. The screens below show acceptable and suboptimal CO2 rebreathing curves.

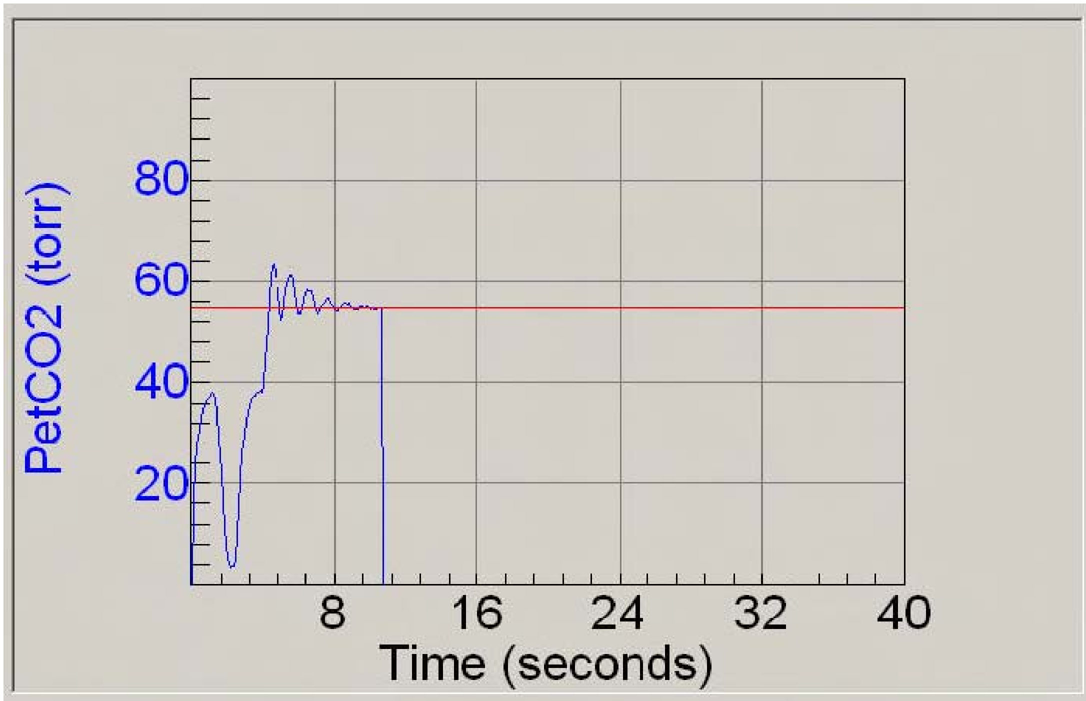
The following equations are used in the program to calculate cardiac output

CaCO2 ml = antilog [($\log_e$ PaCO2 x 0.396) + 2.38]
Note: If entered into the program, arterial CO2 substitutes for PetCO2.

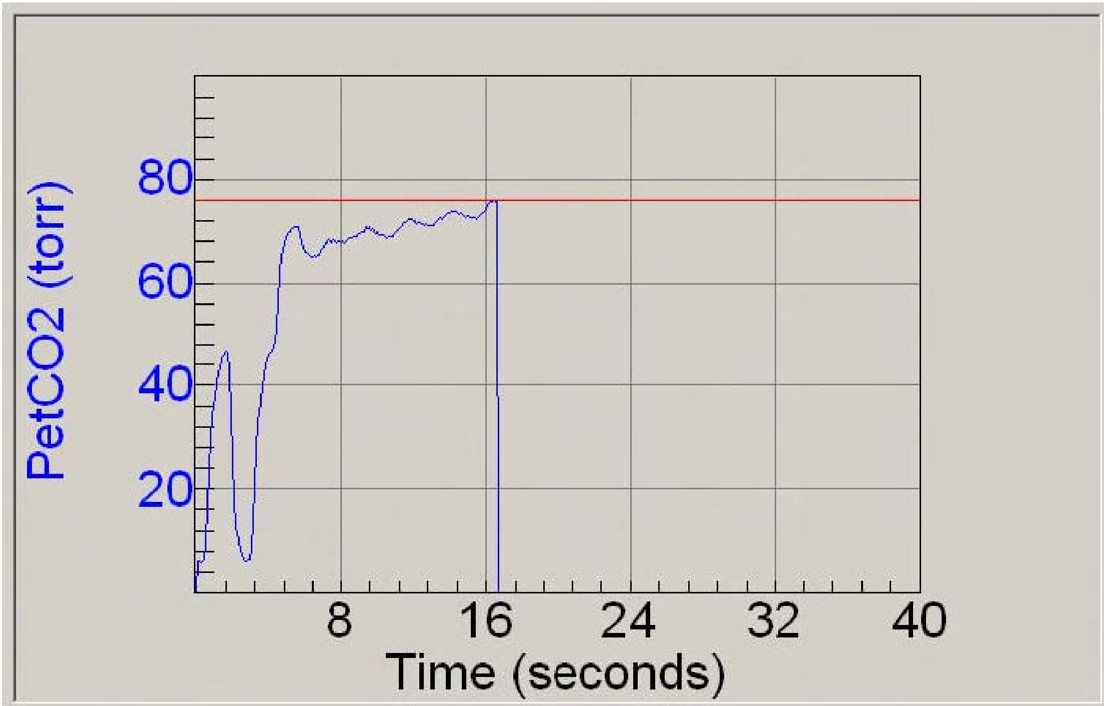
$CvCO2$ ml = antilog [($\log_e PvCO2 \times 0.396$) + 2.38]

Cardiac Output (Q) ml/min = $VCO2 / ((CvCO2 - CaCO2) \times 1000)$

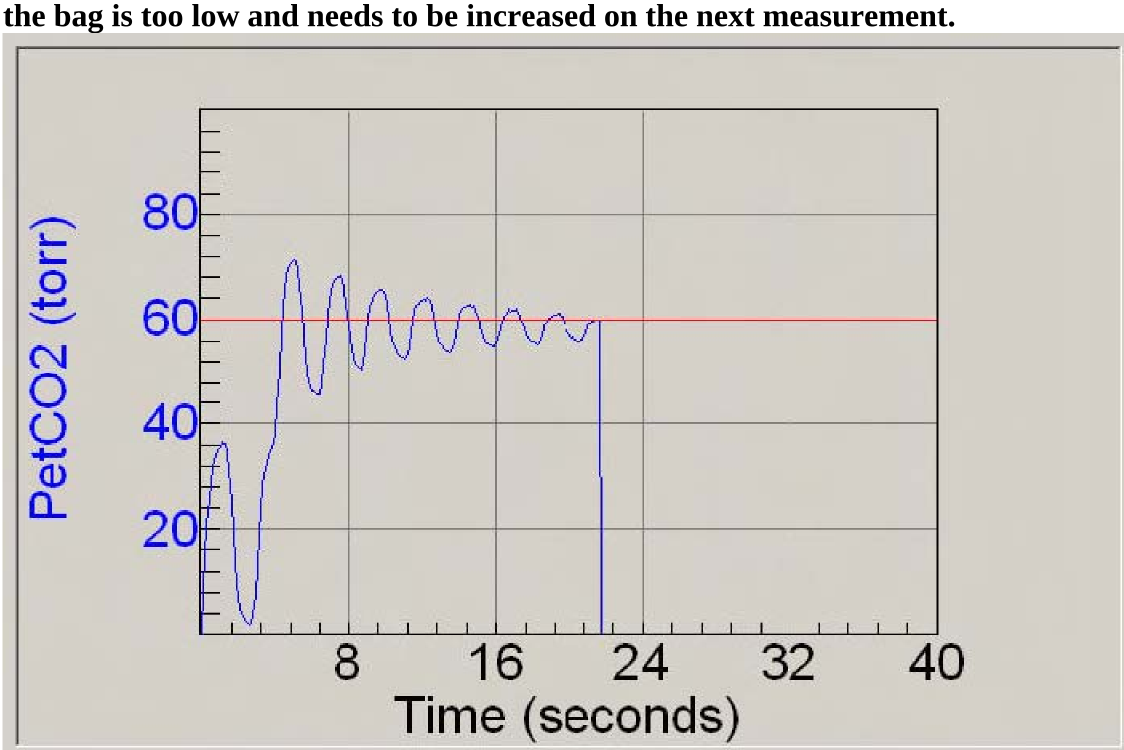
NOTE: To filter the effect of aberrant breaths on the data, the program averages 20 PetCO2 values and 10 VCO2 values prior to each measurement. Ven PCO2 is measured by moving the line to the equilibration point on the graph.



Acceptable CO2 curve showing equilibration at the placement of the blue line



CO2 concentration does not equilibrate and continues to rise. CO2 concentration in the bag is too low and needs to be increased on the next measurement.



CO2 concentration does not equilibrate and continues to oscillate after 10 seconds. CO2 concentration in the bag is too high and needs to be decreased on the next measurement.

SOURCES OF ERROR AND LIMITATIONS WITH THE FICK REBREATHING TECHNIQUE

The Fick method of measures cardiac output by an indirect method. As with any indirect measurement, the accuracy of the measurement is subject to certain conditions.

The "Fick" method of measuring cardiac output is based on the assumption that the cardiac output of an individual is the result of dividing the CO_2 production of that individual by the difference between the arterial CO_2 (coming out of the lungs) and the mixed venous CO_2 (going into the lungs). To do this measurement accurately, we must, first, measure the mixed expired CO_2 and the end-tidal CO_2, immediately before rebreathing. This is a valid assumption if the subject is at a constant level of activity during these measurements.

Another assumption is that, if a subject rebreathes his or her exhaled gas, under certain circumstances, that an equilibration point will be reached which is equal to the CO_2 concentration of mixed venous blood. This may be valid when the test subject has healthy lungs, and when the tidal volume of the subject is large enough to flush out his or her dead space (bronchi, pharynx, etc.). In subjects with impaired breathing, and significant intrapulmonary mixing, or in subjects with very low tidal volumes (less than 2x dead-space), the "Fick" method determines the mixed venous value inaccurately.

Another basic assumption, is that the end-tidal CO_2 partial pressure, represents a similar value to the alveolar CO_2 partial pressure. This also is only true for subjects with healthy, homogeneous, lungs, and it is not true for those with lung disease, or those who breathe with very low tidal volumes (insufficient to wash out their dead space).

Another assumption, that must be made, is that the additional CO_2 that is generated in the rebreathing process will not return to the lungs before equilibration is reached. It is generally assumed that if equilibration occurs within 10 seconds of the onset of rebreathing, that this will not be a factor. In order to ensure rapid equilibration the CO_2 content and the volume added to the rebreathing bag is critical to hasten equilibration.

The analysis of the gas in the rebreathing bag is, also, not without its problems. Background levels of oxygen, within the bag, affect the measurement of CO_2 by non-dispersive infrared analyzers. To be assured that the test subject does not become hypoxic, while rebreathing, the bag must be filled with a higher concentration of oxygen than room air (typically 40%), which is reduced as the subject consumes oxygen during rebreathing. The changing level of oxygen during rebreathing has an effect on the measurement of the CO_2 concentration; however, it has minimal error [$<2\%$].

Higher levels of CO_2 are a stimulant to respiration. Because of this, the "Fick" rebreathing procedure is very uncomfortable at higher levels of exercise. This test is much more tolerable at lower levels of exercise, or at rest.

SETTING UP OF THE SYSTEM

Select Menu: Tools > Hardware Dx

Check the Cardiac Output checkbox.

Choose Properties/Setup/Cardiac Output.

Set the Low CO_2-Low O_2 and High CO_2-High O_2 values of the gas cylinders. The Low O_2 (regardless of its label) should be the O_2 level in the Low CO_2 cylinder. The High O_2 should be the O_2 level in the High CO_2 cylinder.

Set the target $ETCO_2$ level as the torr level above the end-tidal CO_2 during re-breathing. For instance, if the end-tidal CO_2 is 40 and a rebreathing CO_2 of 46 is desired, set the target rebreathing CO_2 level at 6 torr above the end-tidal CO_2.

Set the Volume Fill for the rebreathing bag as a multiple of the tidal volume. For instance, if the tidal volume is 1.0 liters and you wish to have the bag filled to 1.5 liters, enter a setting of 1.5. This setting will yield a bag volume of 3 liters if the patient's tidal volume is 2 liters. A setting of 1.5 is initially recommended. Initial studies have shown it to be the minimal volume achievable without complete collapsing of the bag as rebreathing of CO_2 progressively triggers an increase in tidal volume throughout the cardiac output test.

Max Bag Fill Volume is set by default to 5000 ml. This setting is used primarily for safety to prevent overfilling the rebreathing bag. For a standard 5 liter rebreathing bag, we recommend leaving it set at the default value.

Breaths ignored after CO is set to 10 by default. The purpose of this entry is to allow the subject's ventilation to reestablish to normal levels following carbon dioxide rebreathing with resulting tachypnea. This, in conjunction with normal analyzer delays and dead space volume settings, accounts for the delay seen in the resumption of data plots following cardiac output studies.

Press Save and OK to exit the window.

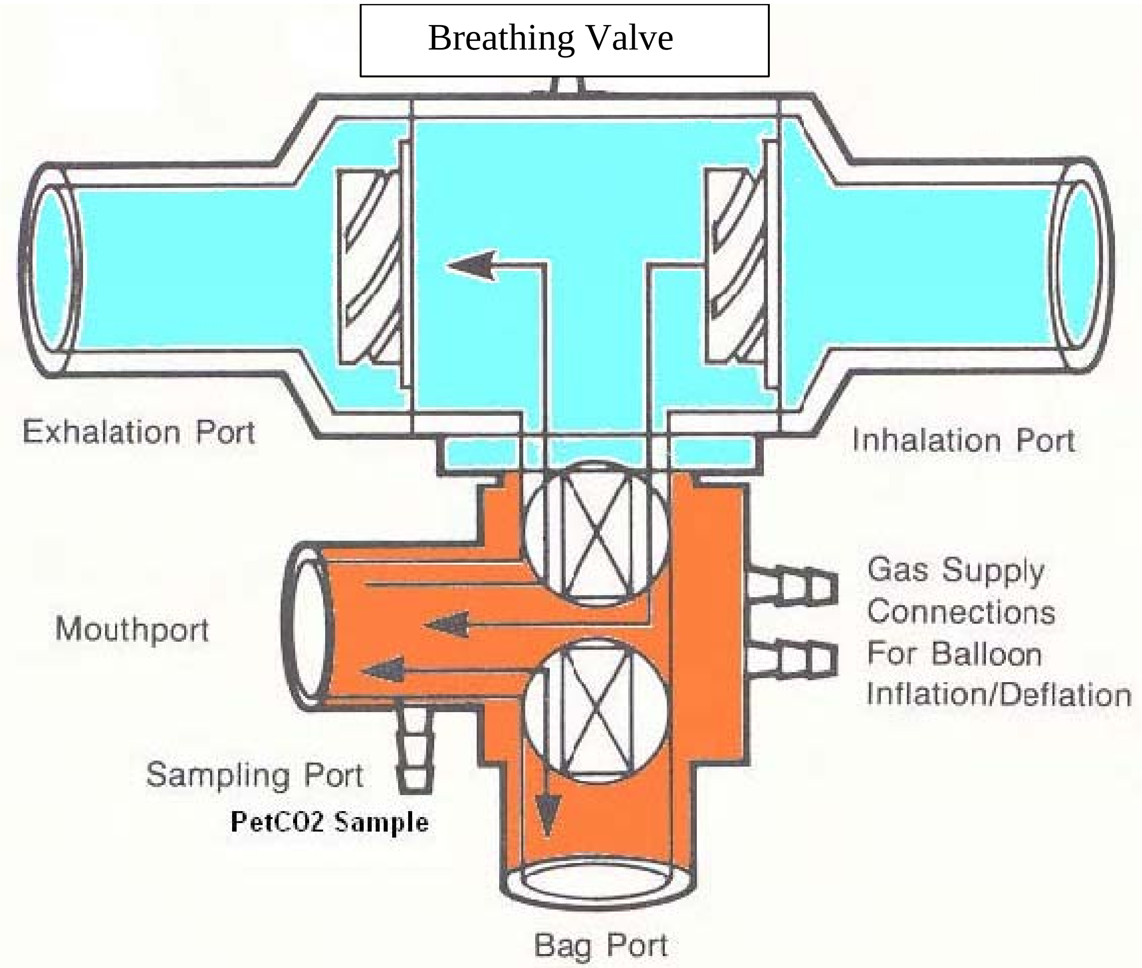
<u>Electrical connections</u>

Connect the 9 pin DB ribbon cable between the Cardiac Output module and Cardiac Output connection on the Interface Box [or MAX-II].
Connect the Cardiac Output module to power.
Connect BNC 'T' connector common to the $etCO_2$ connector on the Interface Box.
Disconnect the BNC cable from the CO_2 input on the Interface box [cable from the CD-3A analyzer] and connect to one end of the BNC 'T' connector. Connect the supplied BNC cable from the other end of the BNC 'T' connector to the CO_2 input on the Interface box.

<u>Tubing connections and valve assembly</u>

Connect the 15%CO_2/40%O_2 and 6%CO_2/40%O_2 cylinders the cardiac output module Hi and Low Fill Tank fittings with 1/8 inch ID tubing, respectively. The outlet pressure on both regulators should be set to approximately 20 psig and resulting in the flow to the bag of about 100 ml./sec.

Connect the compressed air cylinder to the system with the white plastic quick connect hose to the Pressure Tank connector. The outlet pressure on this regulator should be set to 55 psig.
Remove the mouth port from the standard Hans Rudolph 2700 valve and attach the Hans Rudolph cardiac output valve in it's place as shown below:



Breathing Valve is shown in blue. Cardiac output valve is shown in orange.

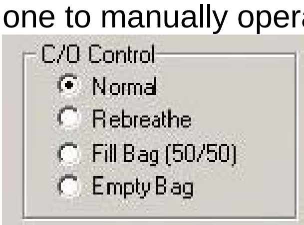
The cardiac output valve and bag assembly is supplied with tubing connected at one end. Connect the other end to the rear of the Cardiac Output module as follows:
Connect small 1/16 inch ID tubing to the Mouth Port fitting .
Connect large 1/4 inch ID tubing to the Empty Bag fitting.
Connect 1/8 inch ID tubing with Black tape to the Top Balloon fitting.
Connect 1/8 inch ID tubing with Blue tape to the Bottom Balloon fitting .
Connect 1 of the 2 remaining 1/8 inch ID tubing to the Fill Bag fitting.
Connect the remaining 1/8 inch ID tubing to the Sensing fitting.
Disconnect the Nafion tube from the Interface Box and connect to the Dryer port on the Cardiac Output Module using 1/16 inch ID tubing. Keep the tube as short as possible.

Connect from the Dryer top barb on the Interface Box to the Cal Valve port on the Cardiac Output Module using 1/16 inch ID tubing. Keep the tube as short as possible.

Testing Equipment Operation

We recommend checking all equipment operation prior to the beginning of the test. The Properties window under Tools displays a Cardiac Output tab that allows alteration

of settings before and during the test. It also displays a Control tab that allows one to manually operate the equipment, before a test, as shown below:

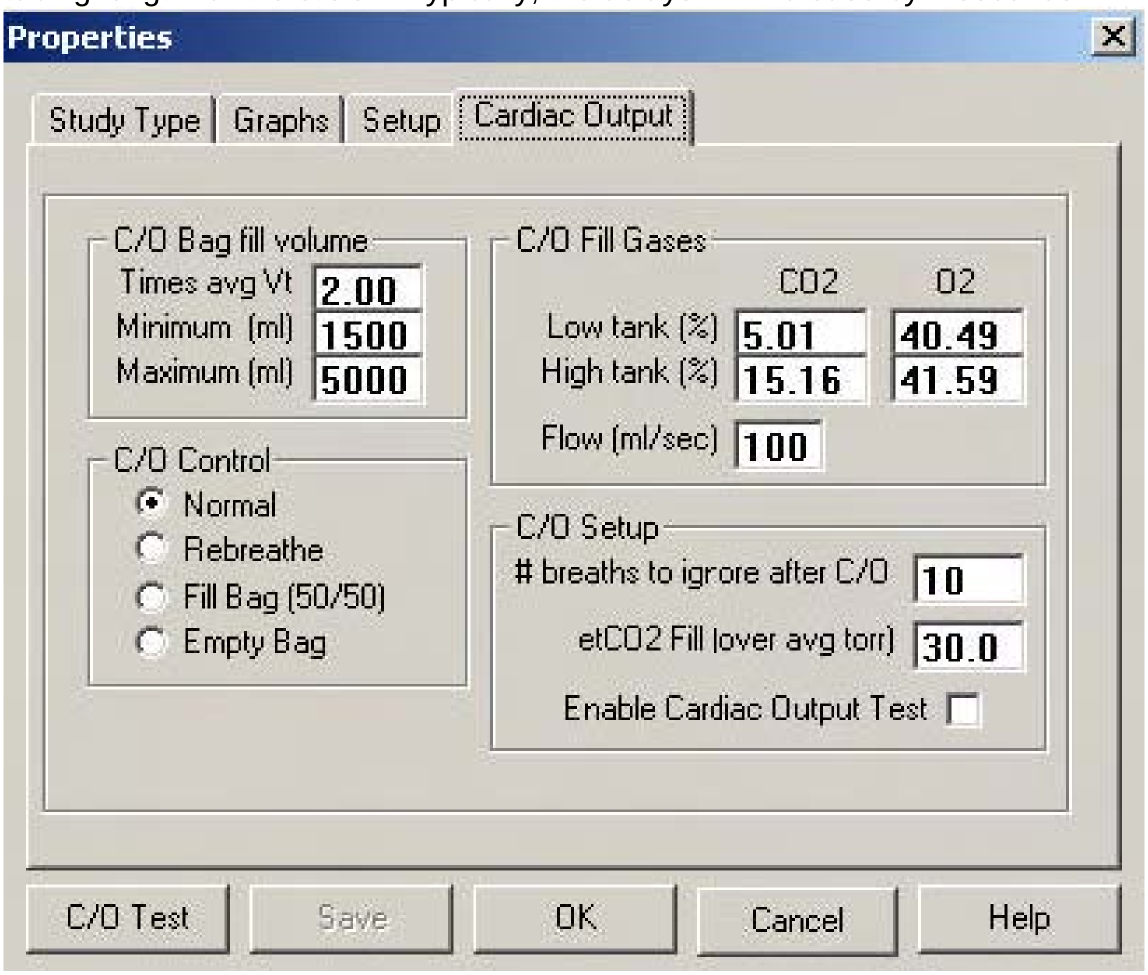


When "Normal" is selected, the lower balloon (the balloon nearest the rebreathing bag) inflates and the upper balloon deflates. The lower balloon should be examined to make sure that it remains fully inflated and does not slowly deflate.

When "Rebreathe" is selected, the lower balloon deflates and the upper balloon inflates. The upper balloon should be examined to make sure that it remains fully inflated and does not slowly deflate. If either balloon appears to be "sucked-in", simply remove and replace the tubing to that balloon, and switch to the other mode (either "normal" or "rebreathe"), to allow air to be sucked into the balloon pump with the disconnected tubing..

When "Fill Bag" is selected, the lower balloon inflates and the rebreathing bag fills, using a 50/50 mixture, to the minimum volume, as indicated by both Hi Fill and Lo Fill lights on the Cardiac Output module illuminating. If the bag does not fill, check all tubing connections, the lower balloon inflation and the pressure setting on the regulators and the cylinder contents.
When "Empty Bag" is selected, the Cardiac Output bag evacuation pump activates, and remains "on" until the bag is deflated completely. The pump turns off once the bag is fully deflated. If the pump does not turn off, check the tubing between the vacuum / pressure switch, check the bag for leaks and check the inflation of the lower balloon.

All other routine configuration settings are made in the properties window:
<u>Setup tab</u>
The O2 and CO2 delays will need to be increased to account for the increased tubing length for the etCO2. Typically, the delays will increase by 2 seconds.



<u>Cardiac Output tab</u>
The filling of the rebreathing bag with respect to volume and CO2 concentration is automated and changes to meet the patient's condition. Twenty tidal volumes prior to a CO2 rebreathing trial are observed and averaged. This tidal volume average determines the volume to which the bag will be filled and is influenced by the

settings in the "C/O Bag fill volume". As shown above, the bag will be filled to 3 liters (2 x the average tidal volume) if the subject's tidal volume is 1.5 liters. Regardless, the bag volume will never be less than 1500 ml nor larger than 5000 ml regardless of the tidal volume as a safety measure. As the filling of the bag is based on time, the software needs to know the filling flow rate of the gas mixture. Typically, this will be about 100 ml/sec if the gas regulators on the cylinders are set to 20 PSIG.

The target bag CO2 concentration is achieved by proportionally mixing gases from both cylinders. The software requires the entry of gas concentrations from both cylinders in order to determine how much of each gas is needed to achieve the proper CO2 target value.

It is important that cylinder content values be precisely entered. Therefore, whenever a cylinder is changed, the technologist must examine the cylinder label to ascertain it's true gas mixture. The target bag CO2 value is determined similarly to the target tidal volume. The software averages 10 CO2 measurements prior to the cardiac output trial. This average is then compared to the value entered under "etCO2 Fill (over average Torr). Therefore, if an average end-tidal CO2 is measured at 40 torr, the software will fill the bag to a concentration of 70 torr (40 torr end-tidal CO2 + setting of 30 torr).

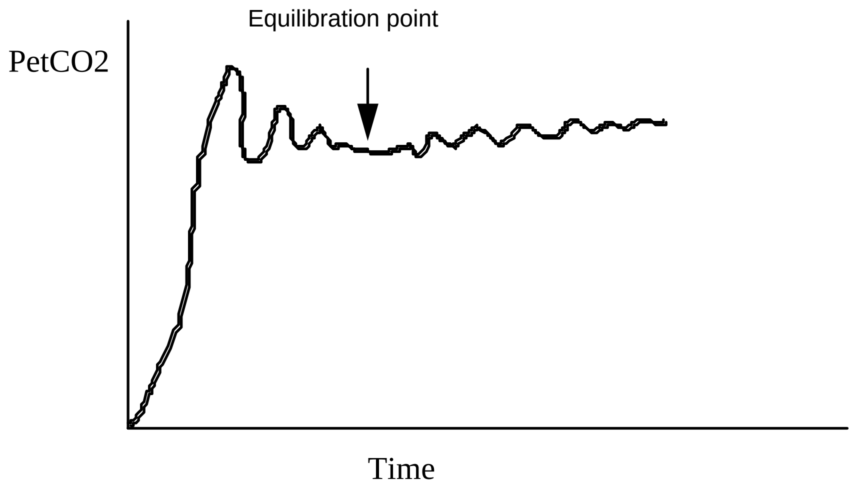
Normal oxygen uptake and carbon dioxide production measurements are interrupted while a CO2 rebreathing trial is underway. Upon completion of a cardiac output trial, the extra CO2 that has accumulated in the blood during the rebreathing trial must be washed out of the lungs prior to resumption of VCO2 measurements. Otherwise, spuriously high VCO2 and RER data will result. It is for this reason that there is a setting in the C/O setup window for "# breaths to ignore after CO".

Once all configuration settings are made, click on OK.

All settings can be changed during an exercise test to allow modifications for bag filling volumes and target CO2.

EtCO2 CALIBRATION

Enter the Cal High and Cal Low values for the etCO2 channel on the Calibration screen. These values should be identical to the values for the CO2 channel. Then select both the CO2 and etCO2 channels for calibration. Perform both Hi and Lo software calibration. Save the result.


Equilibration point
PetCO2
Time

RUNNING A CARDIAC OUTPUT TEST

Prior to running a test flow volume and all analyzers must be calibrated. See the Calibration section for further instructions.

Once the study has begun and after a 10 breath waiting period the Cardiac Output button appears. Pressing this button will enable the Cardiac Output process.

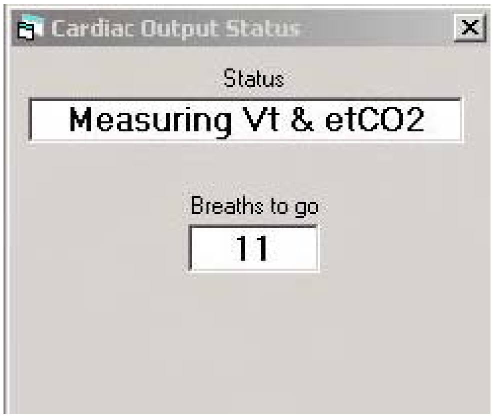
A Cardiac Output status box will appear. The rebreathing bag will initially empty at the start of the program to begin preparing it for the next cardiac output trial.

The next status box shows Measuring CO_2. During this time, the system is measuring the averaged VCO_2 used in cardiac output calculations. The system is performing the standard metabolic measurements until the Fill Bag button is pressed. The screen shows the CO_2 overfill – The amount of CO_2 in torr to add to the measured end-tidal CO_2 to determine the target value (see above). This can be changed before each CO measurement.

NOTE: as workloads are changed the subject should be allowed to stabilize at the workload prior to starting a cardiac output measurement. It is advised to note the CO2 and Volume reading just before the initiation of cardiac output. Following the CO measurement, the subject should be allowed to reestablish these measurements prior to calling additional measurements in order to assure that all rebreathed CO2 has been cleared from the subject and normal VCO2 is achieved.

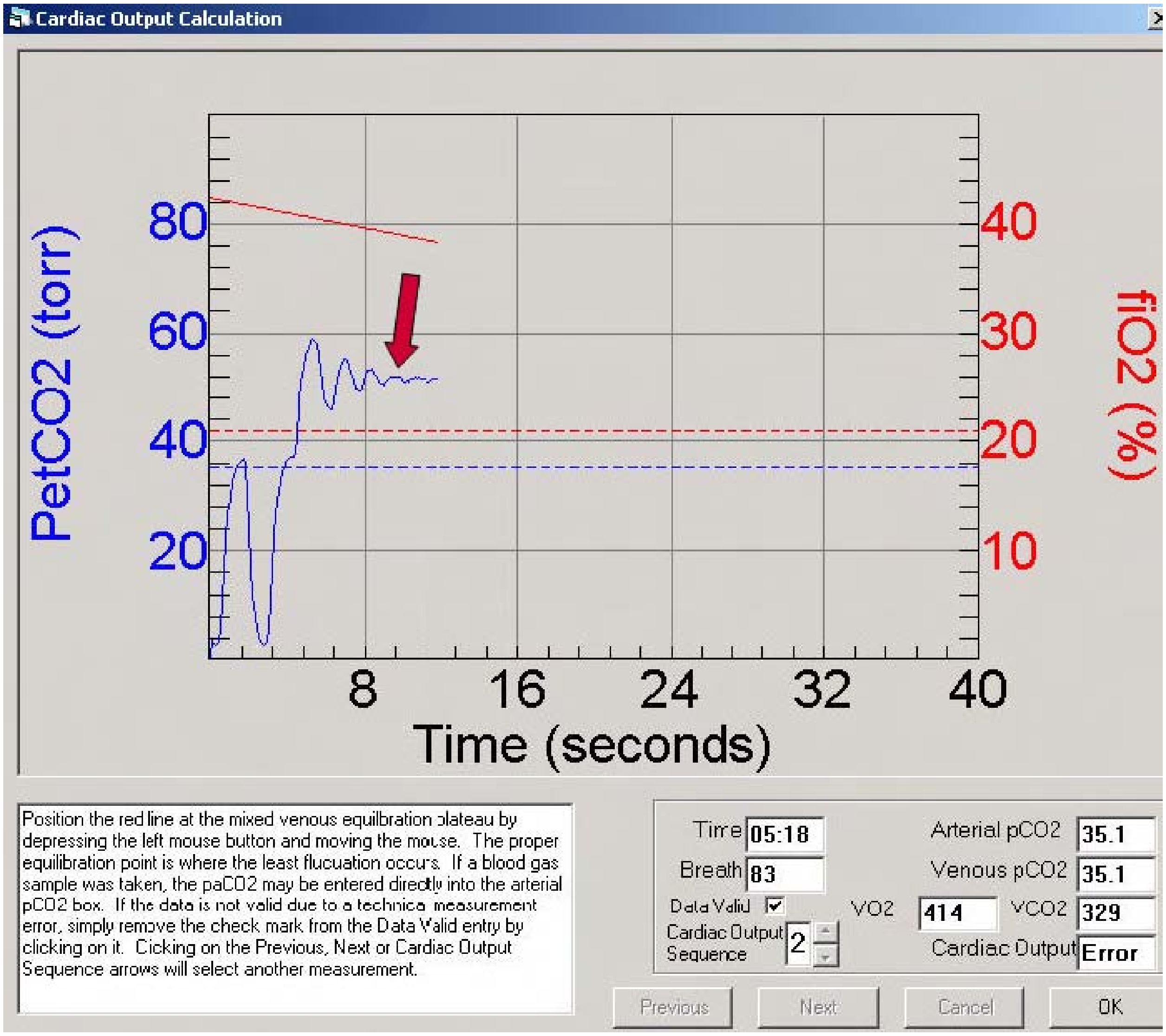
Cardiac output testing is begun by clicking on “Fill Bag” button. The rebreathing bag is filled (Fills bag to the target CO2 concentration and volume. Note that the minimum and maximum volume are always as set in the CO Setup window under Properties. Therefore, if the minimum volume was set at 1500 ml, then the bag will be filled to 1500, even if the Vt multiplier results in a volume less than this minimum volume. The same rule applies to maximum volume.)

The system will now wait for 20 processed breaths to occur to determine the averaged tidal volume and VCO_2.



NOTE: *It is important to remember that the subject is rebreathing CO2 and will experience dizziness, shortness of breath and tachycardia if the test is prolonged more than necessary. The test should be terminated as soon as equilibration is achieved (shown by the arrow), ideally within a 10 second window and, more importantly, before recirculation begins.*
NOTE: *For safety reasons, the test will automatically end and the subject will be switched back to normal metabolic measurement if the test is prolonged up to 30 seconds.*

This is immediately followed by the re-breathing process. The picture shows the cardiac output rebreathing display. Allow the patient to rebreathe from the bag until an equilibration is achieved. Click DONE when the subject has reached equilibration or you have determined that equilibration will not be achieved at this time. The Cardiac Output test will terminate and the normal testing sequence will continue. However, this screen will remain open to allow setting the equilibration point manually via the mouse.
Click OK to close this screen and display the Cardiac Output value.



Following a cardiac output test, the status box will sequence through Emptying Bag and
Ignoring Breaths (To allow washout of the extra CO2 loaded to the patient during the rebreathing trial.)

NORE: The tabular metabolic data should be observed for restabilization of the target volume and CO2 before another cardiac output trial is measured. This assures that all rebreathed CO2 is cleared from the subject and that the RER is stabilized.

Additional trials can be measured simply by clicking on the "Fill Bag" button.

After the last trial, it is recommended that the tabular metabolic data be allowed to restabilize before stopping the test and removing the subject from the mouthpiece. This will allow the phase delays from normal metabolic measurements prior to the cardiac output trial to be processed and the CO data to be properly tagged in time.

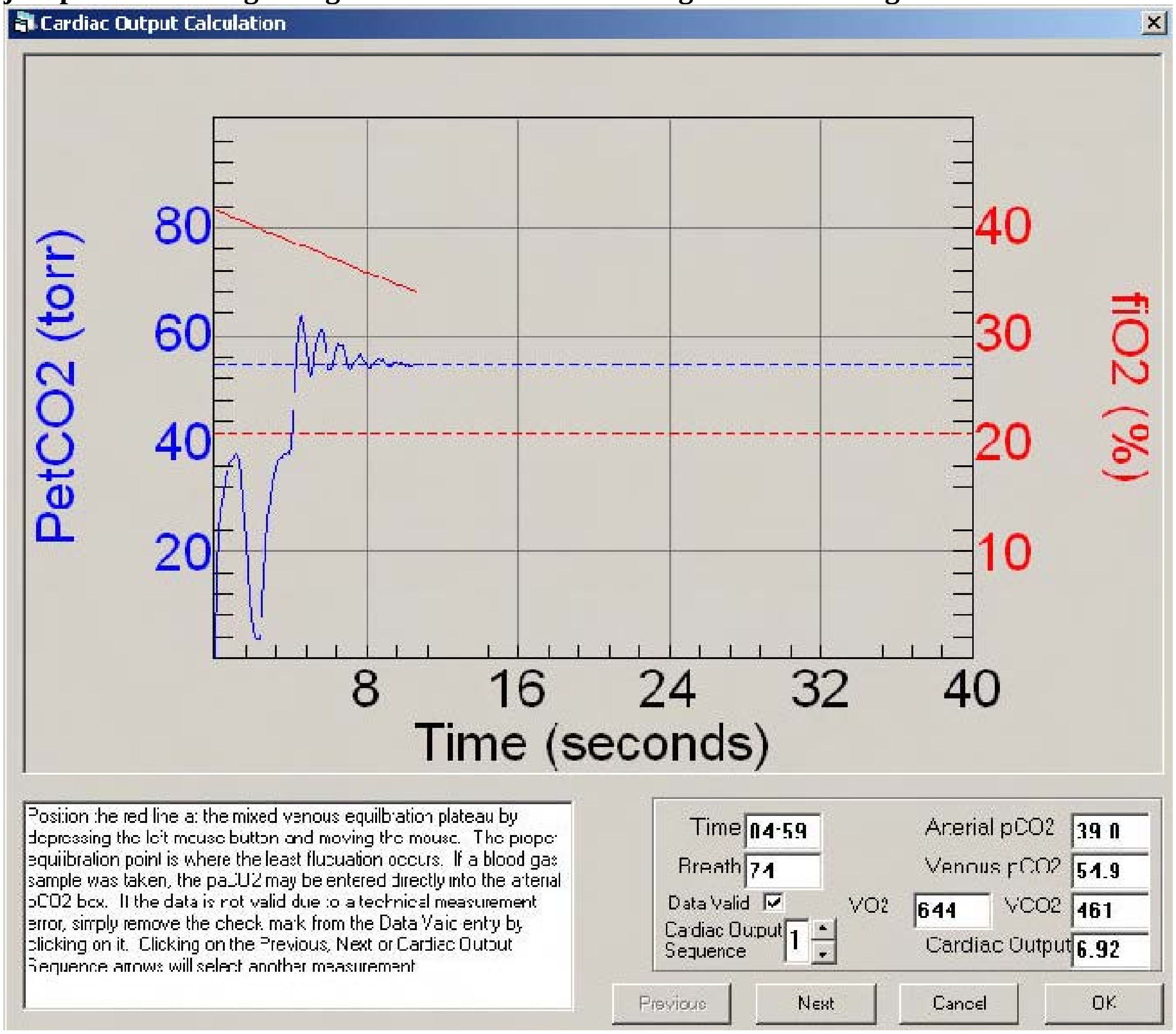
Following completion of the metabolic study, the cardiac output trials must be reviewed and processed for the data to appear on the report.

PROCESSING CARDIAC OUTPUT DATA

First press the Preview CO button. Processing of data consists of examining the equilibration curve from each of the trials, deciding whether or not the equilibration is valid, rejecting those that are deemed invalid, identifying the equilibration point, adjusting the equilibration marker as needed, and manually entering $PaCO_2$ when it is directly measured from arterial blood.

A typical processing screen for CO_2 equilibration is displayed on the next page: Detailed instructions are provided in the window located in the lower left hand corner. The red downward sloping straight line displayed on the graph represents an estimate of the FiO_2 in the rebreathing bag based on the oxygen consumption

just prior to the beginning of the trial and the starting FiO2 in the bag.



Time, Breath number and Cardiac Output Sequence (trial number) are displayed to assist the operator in determining the timing of the measurement relative to the entire exercise test.

Upon viewing a graph, the technologist should first determine whether or not the curve is valid for measurement. There should be a discernable equilibration point where there is minimal to no oscillation of the CO2 tracing and it must occur within ten seconds from the onset of rebreathing (the time at which the CO2 tracing rises from the baseline to start the equilibration process). If no discernable equilibration is present, the trial should be deemed invalid, and the checkmark should be removed from the "Data Valid" checkbox.

Next, the technologist should determine whether or not he/she agrees with the computer's determination of the equilibration point. If not, the equilibration line is easily moved using the left button mouse drag function. Both the Venous pCO2 and Cardiac Output readings will instantly change as the line is dragged to the desired placement point.

Normally, the "Arterial pCO2" value, which is displayed, represents the averaged end-tidal CO2 measured just before the trial. If desired, a measured arterial blood PCO2 result may be manually entered in substitution. The Cardiac Output reading will be updated once the mouse is clicked outside of this box.
Additional trials may be evaluated by either clicking the Next button or clicking on the Up arrow next to the Cardiac Output Sequence window. At any point, you may view earlier trials by clicking on the Down arrow next to the Cardiac Output Sequence window or clicking on the Previous button.
The Cancel button exits from the measurement and disregards all changes.
Once all graphs have been processed, click on the OK button to store the data.

VIEWING GRAPHS AND PRINTING REPORTS

Once the data is processed and selected, cardiac output (CO) and Venous PCO2 data is automatically display in the screen and printed tabular data listing. Cardiac output and mixed venous PCO2 data is also available for graphing against time or any other test parameter.