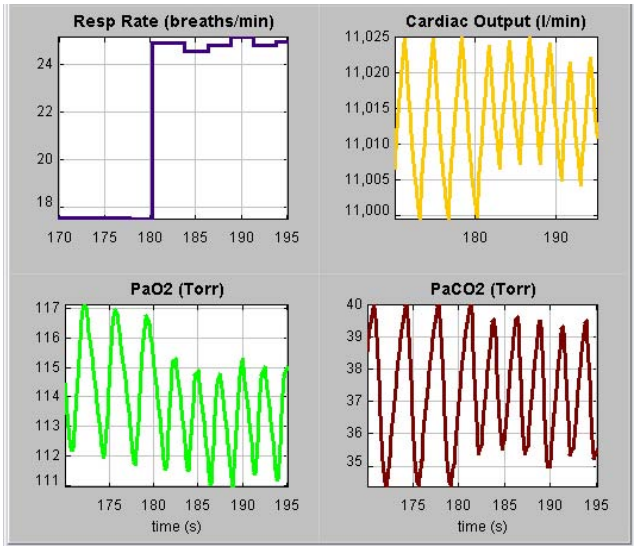
LABORATORY GUIDE

Virtual Laboratory for Analysis of Human Respiratory System

May 2006



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This guide to be used with a Virtual Laboratory for the analysis of human respiratory system is divided in three sessions. The first one is an introduction to the main concepts of the respiratory physiology and mathematical models. It corresponds to a virtual session where the students have to prepare it and work by themselves with the provided teaching material and bibliography. The second session explains different experiments in order to study the response of normal respiratory system when it is stimulated. The third one goes deeper in the study of the mechanical part of the respiratory system and it shows the effect in ventilation when mechanical parameters change related with pulmonary diseases.

This guide has to be used with the "RESPILAB User Manual" where how to use the Virtual Laboratory is described in detail.

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Session 1:

Introduction of

Respiratory System

1.1 Description

The respiratory system is composed by two lungs, conducting airways, pulmonary vasculature, respiratory muscles, and surrounding tissues and structures (Figure 1.1). Each plays an important role in influencing respiratory responses.

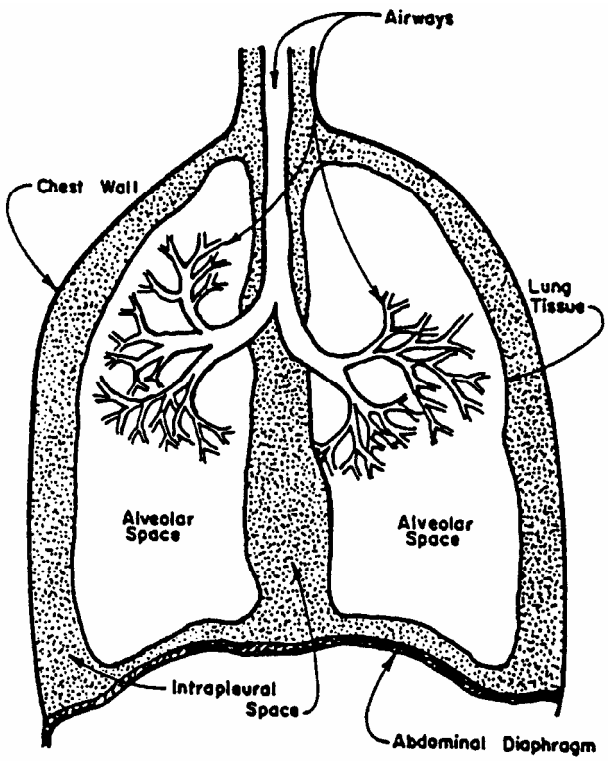

Figure 1.1: Schematic representation of the respiratory system. Reproduced from Biomedical Engineering Handbook.

There are two lungs in the human chest; Lung tissue is spongy because of the very small (200 to 300×10^{-6}m diameter in normal lungs at rest) gas-filled cavities called alveoli, which are the ultimate structures for gas exchange.

Conducting Airways transports the air from the atmosphere to the alveoli. Conduction of air begins at the larynx, at the entrance to the trachea, which is a fibromuscular tube 10 to 12 cm in length and 1.4 to 2.0 cm in diameter. At a location called the carina, the trachea terminates and divides into the left and right bronchi. The bronchi subdivide into subbronchi, which further subdivide into bronchioli, which further subdivide, and so on, until finally reaching the alveolar level. In the adult human there are considered to be 23 such branchings, or generations, beginning at the trachea and ending in the alveoli.

Movement of gases in the respiratory airways occurs mainly by bulk flow (convection) throughout the region from the mouth to the nose to the fifteenth generation. Beyond the fifteenth generation, gas diffusion is relatively more important.

Viewing the lungs as an entire unit, one can consider the lungs to be elastic sacs within an air-tight barrel — the thorax — which is bounded by the ribs and the diaphragm. Any movement of these two boundaries alters the volume of the lungs. The normal breathing cycle in humans is accomplished by the active contraction of the inspiratory muscles, which enlarges the thorax. This enlargement lowers intrathoracic and interpleural pressure even further, pulls on the lungs, and enlarges the alveoli, alveolar ducts, and bronchioli, expanding the alveolar gas and decreasing its pressure below atmospheric. As a result, air at atmospheric pressure flows easily into the nose, mouth, and trachea.

Tidal volume (V_T) is normally considered to be the volume of air entering the nose and mouth with each breath. Alveolar ventilation volume, the volume of fresh air that enters the alveoli during each breath, is always less than tidal volume (the difference is called dead space volume). The extent of this difference in volume depends primarily on the anatomic dead space, the 150- to 160-ml internal volume of the conducting airway passages.

The primary purpose of the respiratory system is gas exchange. In the gas-exchange process, gas must diffuse through the alveolar space, across tissue, and through plasma into the red blood cell, where it finally chemically joins to hemoglobin. A similar process occurs for carbon dioxide elimination.

All individual gases in a mixture are considered to fill the total volume and have the same temperature but reduced pressures. The pressure exerted by each individual gas is called the partial pressure of the gas. Dalton's law states that the total pressure is the sum of the partial pressures of the constituents of a mixture.

Control of respiration occurs in many different cerebral structures and regulates many things. Respiration must be controlled to produce the respiratory rhythm, ensure adequate gas exchange, protect against inhalation of poisonous substances, assist in maintenance of body pH, remove irritations, and minimize energy cost. Respiratory control is more complex than cardiac control for at least three reasons:

- Airways airflow occurs in both directions.
- The respiratory system interfaces directly with the environment outside the body.

- Parts of the respiratory system are used for other functions, such as swallowing and speaking.

As a result, respiratory muscular action must be exquisitely coordinated; it must be prepared to protect itself against environmental onslaught, and breathing must be temporarily suspended on demand.

All control systems require sensors, controllers, and effectors. Figure 1.2 presents the general scheme for respiratory control. There are mechanoreceptors throughout the respiratory system. For example, nasal receptors are important in sneezing, apnea (cessation of breathing), bronchodilation, bronchoconstriction, and the secretion of mucus. Laryngeal receptors are important in coughing, apnea, swallowing, bronchoconstriction, airway mucus secretion, and laryngeal constriction. Tracheobronchial receptors are important in coughing, pulmonary hypertension, bronchoconstriction, laryngeal constriction, and mucus production. Other mechanoreceptors are important in the generation of the respiratory pattern and are involved with respiratory sensation.

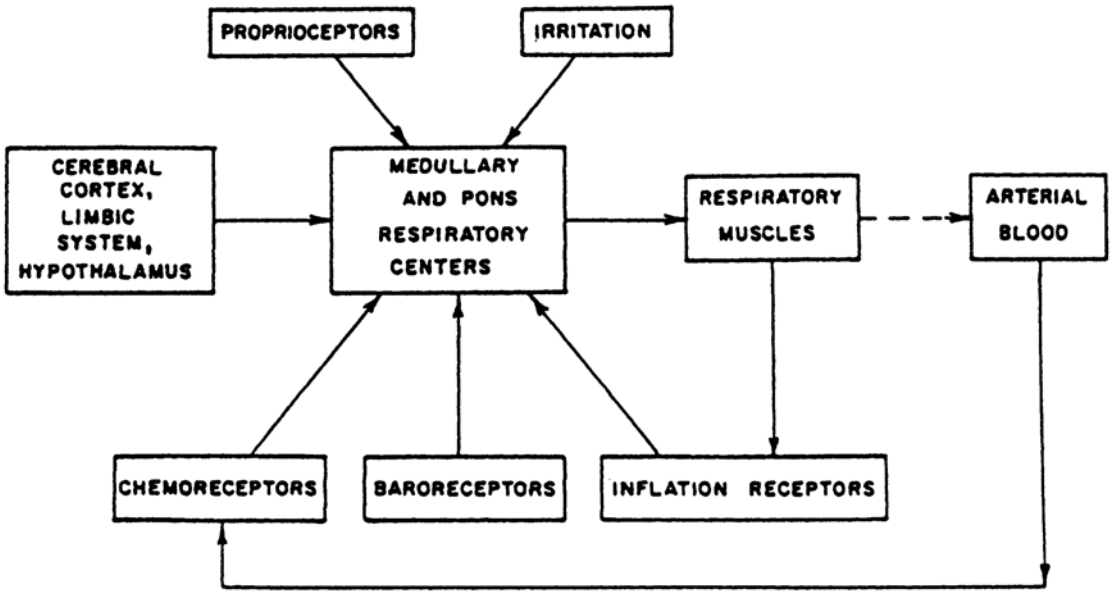

Figure 1.2: General scheme of respiratory control system.

Respiratory chemoreceptors are sensitive to partial pressures of CO_2 and O_2 and to blood pH. The respiratory controller is located in several places in the brain. Each location appears to have its own function. Unlike the heart, the basic respiratory rhythm is not generated within the lungs but rather in the brain and is transmitted to the respiratory muscles by the phrenic nerve.

Effector organs are mainly the respiratory muscles, as described previously. Other effectors are muscles located in the airways and tissues for mucus secretion. Control of respiration appears to be based on two criteria:

(1) Removal of excess CO_2 and

(2) Minimization of energy expenditure.

It is not the lack of oxygen that stimulates respiration but increased CO_2 partial pressure that acts as a powerful respiratory stimulus. Because of the buffering action of blood bicarbonate, blood pH usually falls as more CO_2 is produced in the working muscles (associated with a higher consumption of O_2. Lower blood pH also stimulates respiration.

1.2 Objectives

After this Session, students will know:

- The basics of breathing mechanisms: why it is produced and how it is regulated
- The different parts of the body or components involved in the respiration and their role
- The most important respiratory variables and stimuli in order to be evaluated in the following sessions

1.3 Documentation

The following material is available at the Intranet (http://dossiers.ub.edu/dos.php?d=10556) and Internet:

- John B. West *"Respiratory Physiology. The essentials". "Chapter 8: Control of Ventilation. How gas exchange is regulated"* pp.103-115, Lippincott Williams & Wilkins, 1999.
- Ian White "Breathing", pp. 1-7, 2005
- http://www.biologymad.com/GaseousExchange/GaseousExchange.htm

1.4 Questionnaire

Please, after a carefully reading of the previous references, answer the following questions:

(1) How gas exchange is regulated?

(2) Which muscles are implicated in the breathing process and which is their function?

(3) What is the activity of diaphragm during active expiration.

(4) Where is located respiratory control center anatomically?

(5) Which volumes are described in the documentation and what are the relationships between them?

(6) Why does total ventilation increase during exercise?

(7) Which are normal values of P_aCO_2, P_aO_2, breathing frequency and tidal volume at rest?

Students have to deliver the short answers via Intranet before starting next Lab Session.

Session 2:

Respiratory System Response under Ventilatory Stimuli

2.1 Introduction

There are three main stimuli in order to understand the operation of respiratory system:

Exercise

It is one of the most common and important stimulus of the respiratory system, being its ventilatory response the most used stimulus for the model validation and for understanding changes in respiratory variables. During exercise, the cellular metabolism increase, that is O_2 consumption ($\dot{V}O_2$) and CO_2 production ($\dot{V}CO_2$) rise a lot to counterbalance the metabolic increased demand. A value of $\dot{V}CO_2 = 0.2$ l/min is considered at rest, and increases with exercise.

Exercise is conveniently studied on a treadmill or static bicycle. As work rate (or power) is increased, $\dot{V}O_2$ and $\dot{V}CO_2$ increase linearly. However, above certain work rate, $\dot{V}O_2$ becomes constant; this is known as the $\dot{V}O_2$ max. An increase in work rate above this level can occur only through anaerobic glycolysis.

The arterial PCO_2 does not increase during exercise; indeed during severe exercise it typically falls slightly. The arterial PO_2 usually increases slightly, although it may fall at very high work levels.

Cardiac output increases approximately linearly with work level as a result of increases in both heart rate and stroke volume. However, the change in cardiac output is only about a quarter of the increase in ventilation (in l/min). This makes sense because it is much easier to move air than to move blood. The increase in cardiac output is associated with elevations of both the pulmonary artery and pulmonary venous pressures, which account for the recruitment and distension of pulmonary capillaries. Pulmonary vascular resistance falls.

Hypoxia

The barometric pressure decreases with distance above the earth's surface in an approximately exponential manner. The pressure at 5800 m is only one-half the normal 760 torr, so the PO_2 of most inspired gas is $(380-47)\times 0.2093 = 70$ torr (47 torr is the partial pressure of water vapor at body temperature). At the summit of Mount Everest (altitude 8848 m), the inspired PO_2 (P_IO_2) is only 43 torr. At 19200 m, the barometric pressure is 47 torr so that P_IO_2 is zero. In general hypoxia is the result of a reduction in P_IO_2 and also occurs because disturbances of respiration.

The most important feature of hypoxia is hyperventilation that is the result of hypoxic stimulation of the peripheral chemoreceptors. The consequence of hyperventilation is low P_aCO_2 (alkalosis) that tend to inhibit this increase in ventilation, but after a day or two of acclimatization, the cerebrospinal fluid (CSF) pH is brought partly back by movement of bicarbonate out of the CSF, and after 2 or 3 days, the pH of the arterial blood is returned to near normal by renal excretion of bicarbonate. These brakes on ventilation are then reduced, and it increases further. In addition, there is now evidence that the sensitivity of the carotid bodies to hypoxia decreases during acclimatization. Interestingly, people who are born at high altitude have a diminished ventilatory response to hypoxia that is only slowly corrected by subsequent residence at sea level. Conversely, those born at sea level who move to high altitudes retain their hypoxic response intact for a long time. Apparently, therefore, this ventilatory response is determined very early in life.

In order to simulate hypoxia, an input variable, P_IO_2, is considered with values lower than 159 torr (21% of atmospheric pressure) corresponding to normal conditions at sea level.

Hypercapnia

Hypercapnia corresponds to a presence of CO_2 in the inhaled gas or CO_2 retention. It is the most frequent and main stimulus in the hypoventilation imbalance during Acute Respiratory Failure; arterial blood O_2 level decreases and CO_2 level increases, particularly in patients with Chronic Obstructive Pulmonary Disease (COPD).

In the course of daily activity with periods of rest and exercise, the arterial PCO_2 is probable held to within 3 torr. During sleep it may rise a little more.

The ventilatory response to CO_2 is normally measured by having the subject inhale CO_2 mixtures or rebreathe from a bag that is prefilled with a known mixture of CO_2 and O_2.

Hypercapnia is present in different pathologies and it's the more widely used stimulus to study the respiratory control system.

In order to simulate hypercapnia, the input variable P_ICO_2 is considered whit a normal value of 0 torr (0% of atmospheric pressure) and increases with the hypercapnic stimulus.

Use the panel of ventilatory situations to do the experiments proposed in this Session.

2.2 Objectives

After this Session, students will know:

- To use the virtual laboratory (Respilab) in different ways and they will get little expertise simulating respiratory stimuli: rest, hypercapnia hypoxia and exercise.
- To analyze and obtain conclusions from the results of simulations by means of experimental data and by means of knowledge learnt from reading suggested documentation in the previous Session.
- To understand the complexity of respiratory system and its interaction with cardiovascular system.
- To identify the sensitivity of respiratory system to environment characteristics

2.3 Resting conditions

The situation of rest is shown by a man seated in a bench. This situation is active by default in Respilab just clicking <play> button. Remind that variables will need a few seconds to reach a steady state with a specific respiratory pattern and then the system is ready to be modified by another stimulus.

- Click <play> button to start the simulation and click <pause> when you think the variables have reached the steady state (when they practically do not change). For this purpose, display the <Signal Monitor> in the average mode could be more appropriate. Write down the value of the following variables in the first column of report table 2.1 (report document): tidal volume (V_T), ventilation (V_E), respiratory frequency (f), cardiac output (Q), arterial O_2 *and* CO_2 pressures (PaO_2 and $PaCO_2$).
- Respilab uses the most common expression (Otis' equation) by default. Repeat the process with the other two equations that have been proposed in the literature to calculate the respiratory frequency (see Respilab User Manual). Reset the application and simulate rest with Mead and Widdicombe's equations (Fill in the table 2.1).
- Compare and comment the results obtained with different equations.

2.4 Exercise

Reset the application and simulate resting conditions until the stabilization of the system using the Otis' equation. Afterwards, <pause> the simulation and click on tab <Exercise>. A normal value of $\dot{V}CO_2$ at rest is 0.2 l/min and it increases with exercise.

- Increase the $\dot{V}CO_2$ value until 0.8 l/min (moderate exercise) and wait for the stabilization of variables. Write down their values in the second column of table 2.2.
- Compare the results obtained during resting conditions and explain briefly their changes (or not) related with the physiological basics learnt in the previous Session.

2.5 High Altitude

Reset the application and click on tab <Exercise at High Altitude>. Increases of altitude represent decreases in barometric pressure, so the PO_2 on inspired air at high altitude is smaller than few meters near sea level.

- Increase the altitude to 2500 m (140 million people live higher than this elevation) and simulate rest (do not change the $\dot{V}CO_2$ = 0.2 l/min). Write values of variables in the third column of table 2.2.
- Keep the altitude at 2500 m and increase $\dot{V}CO_2$ until 0.8 l/min in order to simulate exercise at high altitude. Fill in the fourth column of table 2.2.
- Analyze the results obtained in this section and explain briefly their changes (or not) related with the physiological basics learnt in the previous Session.

2.6 Hypercapnia

Reset the application and simulate resting conditions until the stabilization of the system using the Otis' equation. Then pause the simulation and click on tab <Hypercapnia>. In the Introduction, this guide has explained that hypercapnia corresponds to a presence of CO_2 in the inhaled gas or CO_2 retention.

- Simulate continuously during the same session (without clicking <reset>) the following levels of hypercapnia[1] corresponding to different values of P_ICO_2: 0, 15, 30, 45 and 60 torr.

  Each one of these stimulus levels must be applied after stabilization of the previous one. During the simulation, fill in the table 2.3.
- Analyze the results obtained and explain briefly their changes (or not) related with the physiological basics learnt in the previous Session.
- Repeat the simulation detecting only the respiratory frequency (f), tidal volume (V_T) and ventilation (V_E) for Mead and Widdicombe's equations. Fill in table 2.4.

[1] Whit the basal level (0 torr) it would be five levels

Then, results of simulation will be compared with experimental data from a normal subject with five different levels of CO_2 inhaled. This will be carried out with Matlab.

- Download from the Intranet the file "exp_hyperc.mat" that contains experimental data of one health subject stimulated with hypercapnia, and load it to Matlab. Three vectors with five elements will be loaded to the Workspace: respiratory frequency (resfreq), tidal volume (vol) and ventilation (vent). Each element in the three vectors corresponds to the same hypercapnic stimulus.
- Create the same previous vectors for the simulation data in each respiratory frequency equation (from table 2.3 and table 2.4).
- For a visual comparison, plot four different traces (respiratory frequency vs. ventilation) in a same figure: experimental data, Otis, Mead and Widdicombe's equation. Repeat the same plot but tidal volume vs. ventilation in another figure. Decide if RESPILAB simulates the respiratory pattern under hypercapnic stimulus and which equation is the best one for the simulation.

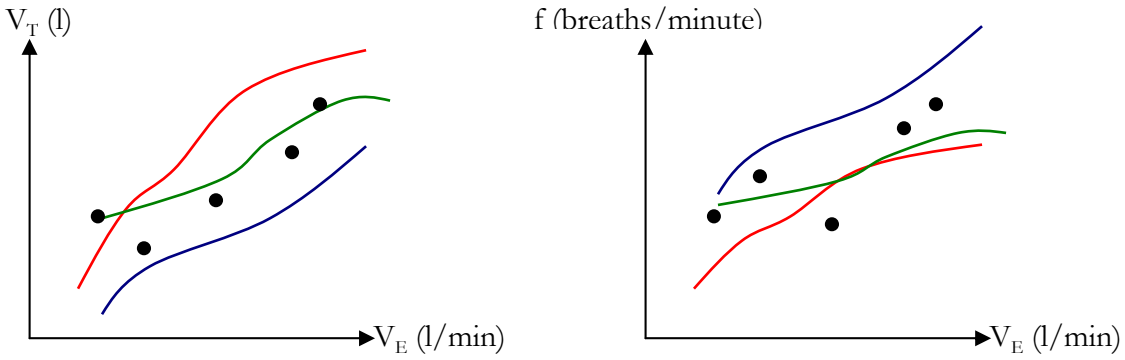

Figure 2.1:Plot examples (f vs. V_E and V_T vs. V_E) in order to compare simulation with experimental data (traces are invented)

- The prediction error of tidal volume (V_T) and respiratory frequency (f) for Otis, Mead and Widdicombe's equation will be calculated as follows

$$P_{Error}(\%) = \frac{1}{n}\sum_{i=1}^{n}\left|\frac{Xi_{real} - Xi_{sim}}{Xi_{real}}\right| * 100 \qquad (2.1)$$

being Xi_{real} and Xi_{sim} the value of f or V_T with a specific value of V_E in study (experimental or simulated respectively) and n is the number of stimulus levels. As the points (V_T,V_E) and (f, V_E) obtained in simulation do not correspond with the same five experimental values V_E, an interpolation with the command *spline* is suggested.

- Create new interpolated vectors for each trace by means of the command *spline* and using ten equidistant values of V_E between 8 to 24 l/min.

- Calculate the prediction error with the equation (2.1) being n=10 and fill in the table 2.5. Comment the results.

Students have to deliver all the results (Tables, Plots and Comments) via Intranet before starting next Lab Session.

Session 3:

Respiratory Diseases based on Mechanical Loads

3.1 Introduction

The respiratory system exhibits properties of resistance, compliance, and inertance analogous to the electrical properties of resistance, capacitance, and inductance. Of these, inertance is generally considered to be of less importance than the other two properties.

The traditional approach to model respiratory mechanics places one ideal resistive element and a compliant element in series configuration where *Pmus* corresponds to the total pressure performed by the muscles (see Figure 3.1).

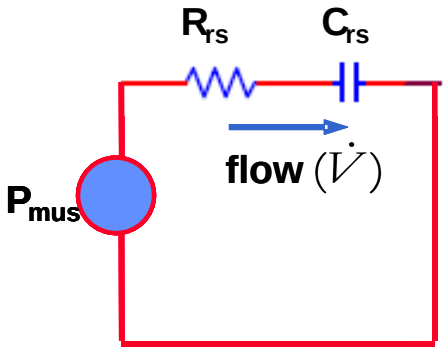

Figure 3.1: Traditional model of mechanical breathing system.

Resistance is the ratio of pressure to flow:

$$R = P/\dot{V} \qquad (0.1)$$

Resistance can be found in the conducting airways, in the lung tissue, and in the tissues of the chest wall. Airways exhalation resistance is usually higher than airways inhalation resistance because the surrounding lung tissue pulls the smaller, more distensible airways open when the lung is being inflated. Thus airways inhalation resistance is somewhat dependent on lung volume, and airways exhalation resistance can be very lung volume–dependent.

Compliance is the ratio of lung volume to lung pressure:

$$C = V/P \qquad (0.2)$$

The inverse of compliance -Elastance (E)- is usually used more often.

As the lung is stretched, it acts as an expanded balloon that tends to push air out and return to its normal size. The static pressure-volume relationship is nonlinear, exhibiting decreased static compliance at the extremes of lung volume.

There are two main types of lung diseases, obstructive and restrictive, which are related to changes in the following respiratory parameters: R_{rs} and E_{rs}. Both mechanical parameters are included in respiratory frequency equations used in the model. Restrictive lung diseases are caused either by an alteration in lung tissue or by disease of the chest wall, or neuromuscular apparatus. There is a decrease in the lungs ability to expand, or a decrease in the lung ability to transfer O_2 to the blood (or CO_2 out of the blood). In these conditions, the total lung volume and the transfer of oxygen from air to blood may be reduced. Restrictive disorders include sarcoidosis, interstitial pneumonitis, pulmonary fibrosis and pneumonia.

In obstructive lung conditions, airways are narrowed, usually causing an increase in the time it takes to empty the lungs. Obstructive lung disease can be caused by conditions such as emphysema, bronchitis, infection (which produces inflammation) and asthma, and includes the common chronic obstructive pulmonary disease (COPD).

3.2 Objectives

After this Session, students will know:

- To simulate respiratory pathologies by means of Respilab.
- To analyze and obtain conclusions from the results of simulations by means of experimental data and knowledge acquired from reading of suggested documentation.
- The effect of an increase in respiratory resistance or elastance in the ventilatory pattern.

3.3 Changes of mechanical parameters on respiratory system

Reset Respilab and simulate rest until the stabilization of the system using the Otis equation and values of R and E by default corresponding to a normal subject (2.6 l/cmH_2O/s and 10 l/cmH_2O). Pause and fill in the first column of table 3.1. Afterwards, increase the airway resistance until 3.6 l/cmH_2O/s and simulate this new situation until the stabilization of the system. Fill in the second column of table 3.1.

- Repeat the last steps, but in this case at high altitude (2500 m). Fill in the third and fourth columns of table 3.1 in the report.

- Reset Respilab and simulate rest until the stabilization of the system again, using the Otis equation and values of R and E by default. Fill in the first column of table 3.2. Increase the Elastance until 20 l/cmH_2O and simulate this new situation until the stabilization of the system. Fill in the second column of table 3.2. Then, repeat the steps at high altitude. Fill in the third and fourth columns of the table 3.2.

Obtain conclusions from the results of tables 3.1 and 3.2 in order to answer the questionnaire at the end of the session.

3.4 Restrictive Disease during Exercise

Restrictive disease is characterized by an increase in respiratory elastance (or compliance reduction). In order to simulate this kind of illness, to rise the respiratory system elastance (E) from its normal value (10 cmH_2O/l) is enough.

Observation: In the following simulations use the equation to calculate respiratory frequency that provided the lowest prediction error during simulation of hypercapnia in the previous Lab Session.

Reset the application and simulate resting conditions until the stabilization of the system using the mechanical parameters by default (normal subject). Then pause the simulation and click on tab <Exercise>.

- Simulate continuously during the same session (without clicking <reset>) the following levels of exercise[2] corresponding to different values of $\dot{V}CO_2$: 0.2, 0.4, 0.6, 0.8 and 1 l/min.

  Each one of these stimulus levels must be applied after stabilization of the previous one. During the simulation, fill in the table 3.3.

- Repeat the simulation for E=20 cmH_2O/l and E=30 cmH_2O/l. Fill in table 3.4 and table 3.5.

- Analyze the results obtained in these three tables in order to answer the Questionnaire at the end of this Session.

Then, the settling time of the respiratory system during a step increase of the level of exercise will be calculated.

- Reset the application and simulate resting conditions until the stabilization of the system using E=30 cmH_2O/l.

[2] Whit the basal level (0.2 l/min) it would be five levels

- Increase dramatically the level of exercise until $\dot{V}CO_2$ = 0.8 l/min (moderate exercise) and wait for the stabilization of the system.
- Save the simulation <Save-Sim> to analyze the result.
- Calculate stabilization time of PaO_2 by means of Matlab. Stabilization time or settling time is the instant when the variable reaches the 95% of its final value.

Then, results of simulation from table 3.3 to table 3.5 will be compared with experimental data from a restrictive patient during exercise with different levels of $\dot{V}CO_2$. This will be carried out with Matlab.

- Download from the Intranet the file "exp_restrictive_exer.mat" that contains experimental data of one restrictive patient stimulated with exercise, and load it to Matlab. Three vectors will be loaded to the Workspace: respiratory frequency (resfreq), tidal volume (vol) and ventilation (vent). Each element in the three vectors corresponds to the same exercise level.
- Create the same previous vectors (respiratory frequency (resfreq), tidal volume (vol) and ventilation (vent)) for the simulation data in each elastance value (table 3.3 to table 3.5).
- For a visual comparison, plot four different traces (respiratory frequency vs. ventilation) in a same figure: experimental data, E=10 cmH_2O/l, E=20 cmH_2O/l, E= 30 cmH_2O/l). Repeat the same plot but tidal volume vs. ventilation in another figure. Decide if RESPILAB simulates the respiratory pattern during exercise stimulus and which is the best value of elastance in order to simulate this patient.

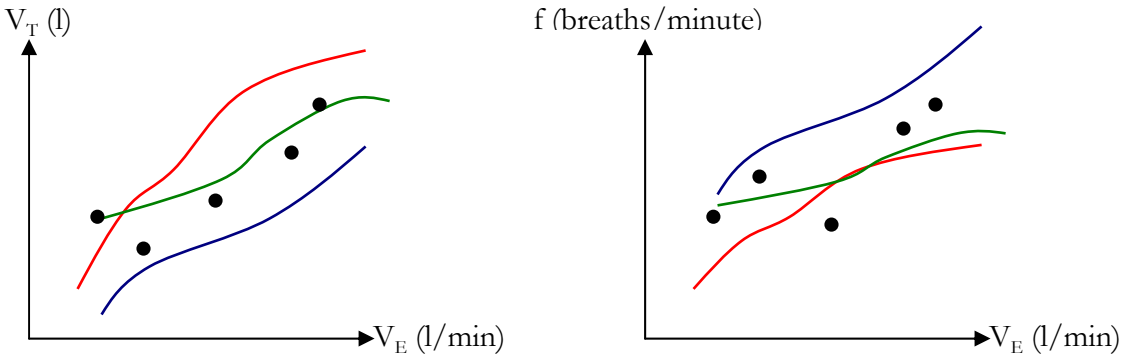

Figure 3.2:Plot examples (f vs. V_E and V_T vs. V_E) in order to compare simulation with experimental data (traces are invented)

- Calculate the prediction error in tidal volume (V_T) and respiratory frequency (f) with the equation (2.1). Follow the same steps explained in the previous Session. Consider also ten values of total ventilation (V_E) into the range 8 to 24 l/min (n=10) and fill in the table 3.6. Comment the results.

3.5 Questionnaire

Please, answer the following questions from the results obtained in this Lab Session:

(1) Obtain conclusions from the data in table 3.1. How does an increase of airway resistance effect in the respiratory pattern?

(2) Obtain conclusions from the data in table 3.1. How does an increase of respiratory elastance effect in the respiratory pattern?

(3) Which is the effect of hypoxia in patients with higher respiratory elastance?

(4) Which is the effect of exercise in patients with higher respiratory elastance?

(5) Obtain conclusions from Figure 3.1 and table 3.1. Experimental data from a restrictive patient could be predicted by RespiLab using higher values of elastance? Which elastance value obtains the best prediction of respiratory system response during exercise for the selected restrictive patient with?

(6) Are the graphs of V_T *vs* V_E and F *vs* V_E coherent with the prediction error you found?

Students have to deliver all the results (Tables and Plots) and answers via Intranet by next week.