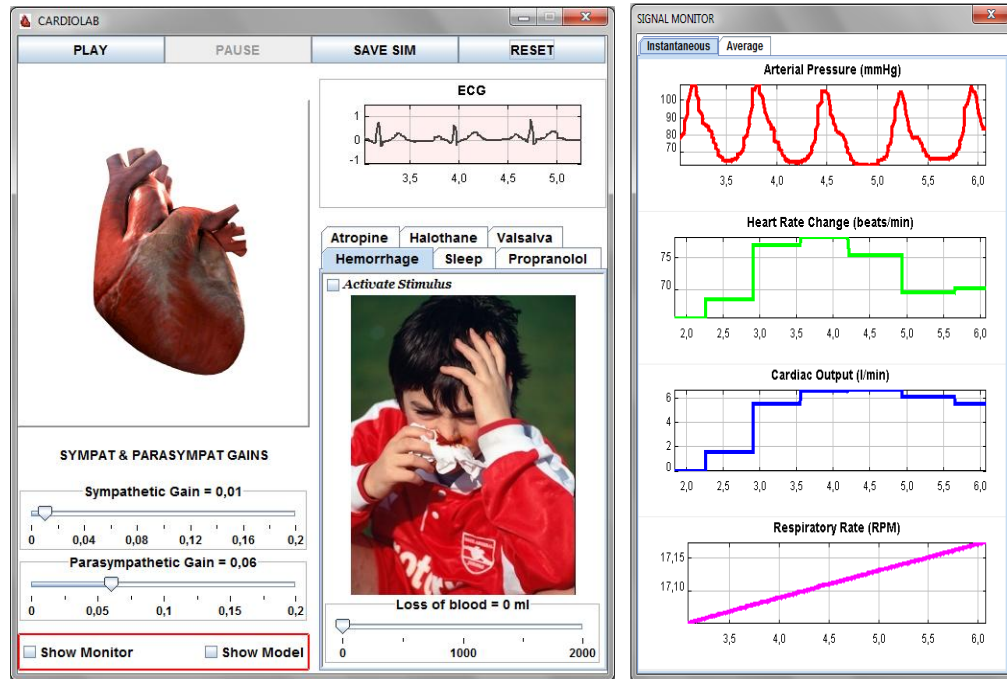


# CardioLab Guide

Computational tool for learning the cardiovascular system

Mayo 2011



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# Session 1      Introduction of Cardiovascular System

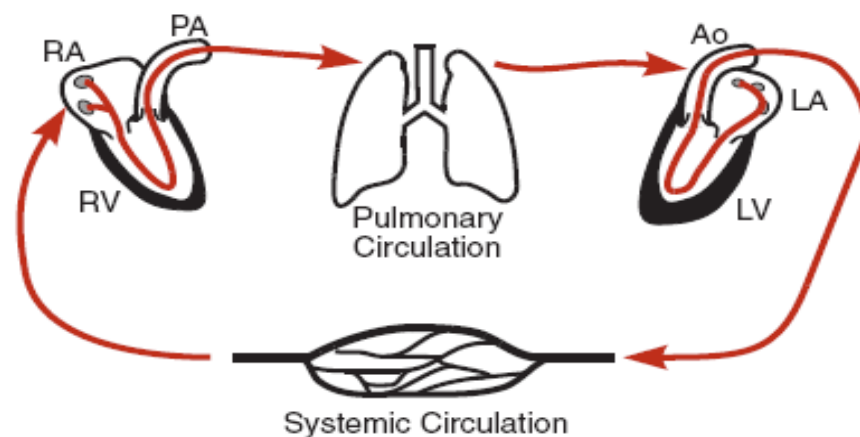
## 1.1. *Description*

All eukaryotic cells require metabolic substrates (e.g., oxygen, amino-acids, glucose) and a mechanism by which they can remove the metabolism products (e.g., carbon dioxide, lactic acid). Single-cell organisms exchange these substances directly with their environment through diffusion and cellular transport systems. In contrast, most cells of large organisms have limited or no exchange capacity with their environment because their cells are not in contact with the outside environment. Nevertheless, exchange with the outside environment must occur in order to guarantee the cellspreservation. To accomplish this necessary exchange, high-level organisms have a sophisticated system of blood vessels that transports metabolic substrates between cells and blood, and between blood and environment. The smallest of these blood vessels, capillaries, are in close proximity to all cells in the body, thereby permitting exchange to occur. For example, each cell in skeletal muscle is surrounded by two or more capillaries. This arrangement of capillaries around cells ensures that exchange can occur between blood and surrounding cells. Cells require a proper balance of water and electrolytes (e.g., sodium, potassium, and calcium) to function. The circulation transports ingested water and electrolytes from the intestine to cells throughout the body, including those of the kidneys, where excessive mounts of water and electrolytes can be eliminated in the urine [1].

In summary, the ultimate purpose for the cardiovascular system is to facilitate exchange of gases, fluid, electrolytes, large molecules and heat between cells and the outside environment. The heart and vasculature ensure that adequate blood flow is delivered to organs so that this exchange can take place.

The cardiovascular system has two primary components: the heart and blood vessels. A third component, the lymphatic system, does not contain blood, but nonetheless serves an important exchange function in conjunction with blood vessels. The heart can be viewed functionally as two pumps with the pulmonary and systemic circulations situated between the two pumps (see *Figure 1*). The *pulmonary circulation* consists of the blood flow within the lungs that is involved in the exchange of gases between the blood and alveoli. The *systemic circulation* is comprised of all the blood vessels within and outside of organs excluding the lungs. The right side of the heart

comprises the right atrium and the right ventricle. The *right atrium* receives venous blood from the systemic circulation and the *right ventricle* pumps it into the pulmonary circulation where oxygen and carbon dioxide are exchanged between the blood and alveolar gases. The left side of the heart comprises the left atrium and the left ventricle. The blood leaving the lungs enters the *left atrium* by way of the pulmonary veins. Blood then flows from the left atrium into the left ventricle. The *left ventricle* ejects the blood into the *aorta*, which then distributes the blood to all the organs via the arterial system. Within the organs, the vasculature branches into smaller and smaller vessels, eventually forming capillaries, which are the primary site of exchange. Blood flow from the capillaries enters venules and the veins, which return blood flow to the right atrium via large systemic veins (the superior and inferior cava vein).



**Figure 1.** Overview of the cardiovascular system. The right side of the heart, pulmonary circulation, left side of the heart, and systemic circulation are arranged in series. RA, right atrium; RV, right ventricle; PA, pulmonary artery; Ao, aorta; LA, left atrium; LV, left ventricle [2].

As blood flows through organs, some of the fluid, along with electrolytes and small amounts of protein, leaves the circulation and enters the tissue interstitium (a process termed fluid filtration). The *lymphatic vessels*, which are closely associated with small blood vessels within the tissue, collect the excess fluid that filters from the vasculature and transport it back into the venous circulation by way of lymphatic ducts that empty into large veins (subclavian veins) above the right atrium. It is important to understand that organ blood flow is not driven by the output of the heart per se, but rather by the

pressure generated within the arterial system as the heart pumps blood into the vasculature, which serves as a resistance network. Organ blood flow is determined by the arterial pressure minus the venous pressure, divided by the vascular resistance of the organ. Pressures in the cardiovascular system are expressed in millimeters of mercury (mmHg) above atmospheric pressure. Vascular resistance is determined by the size of blood vessels, the arrangement of the vascular network, and the viscosity of the blood flowing within the vasculature [3].

The right atrium receives systemic venous blood (venous return) at very low pressures (near 0 mmHg). Right ventricular contraction ejects blood from the right ventricle into the pulmonary artery. This generates a maximal pressure (systolic pressure) that ranges from 20 to 30 mmHg within the pulmonary artery. As the blood passes through the pulmonary circulation, the blood pressure falls to about 10 mmHg. The left atrium receives the pulmonary venous blood, which then flows passively into the left ventricle; atrial contraction provides a small amount of additional filling of the left ventricle. As the left ventricle contracts and ejects blood into the systemic arterial system, a relatively high pressure is generated (100–140 mmHg maximal or systolic pressure). Therefore, the left ventricle is a high-pressure pump, in contrast to the right ventricle, which is a low-pressure pump.

Blood vessels constrict and dilate to regulate arterial blood pressure, alter blood flow within organs, regulate capillary blood pressure, and distribute blood volume within the body. Changes in vascular diameters are brought about by activation of vascular smooth muscle within the vascular wall by autonomic nerves, metabolic and biochemical signals from outside of the blood vessel, and vasoactive substances released by cells that line the blood vessels. *The baroreceptors*, through their afferent neural connections to the brain, provide the central nervous system with information regarding the status of blood pressure in the body. A decrease in arterial pressure from its normal operating point elicits a rapid baroreceptor reflex that stimulates the heart to increase cardiac output and constricts blood vessels to restore arterial pressure (a *negative feedback* control mechanism). These cardiovascular adjustments occur through rapid changes in *autonomic nerve activity* (particularly through sympathetic nerves) to the heart and vasculature. In addition to altering autonomic nerve activity, a fall in arterial pressure stimulates the release of *hormones* that help to restore arterial pressure by acting on the heart and blood vessels; they also increase arterial pressure by increasing blood volume through their actions on renal function. In contrast to the rapidly acting

autonomic mechanisms, hormonal mechanisms acting on the kidneys require hours or days to achieve their full effect on blood volume [4].

The primary function of the heart is to impart energy to blood to generate and sustain an enough arterial blood pressure to adequately perfuse organs. The heart achieves this objective by contracting its muscular walls around a closed chamber to generate the enough amount of pressure to propel blood from the left ventricle, through the aortic valve, and into the aorta. Each time the left ventricle contracts, a volume of blood is ejected into the aorta. This stroke volume (SV), multiplied by the number of beats per minute (heart rate, HR), equals the cardiac output (CO):

$$CO = SV * HR$$

Cardiac Output is a clinically used index that quantifies the efficiency of cardiovascular pump. The units for cardiac output are expressed as either mL/min or liters/min. The units for stroke volume are milliliters/beat (mL/beat), and the units for heart rate are beats/min. In a resting adult, cardiac output typically ranges from 5–6 L/min [5, 6].

Although cardiac output is determined by both heart rate and stroke volume, changes in heart rate are generally more important quantitatively in producing changes in cardiac output. These changes in heart rate are brought about primarily by changes in sympathetic and parasympathetic nerve activity at the sinoatrial node. Changes in heart rate alone inversely affect stroke volume.

## 1.2. *Objectives*

After this Session, students will know:

- The basics of cardiovascular system behavior: How it works and how it is regulated
- The different parts of the body or components involved in the cardiovascular system
- The most important cardiovascular variables

### 1.3. *Documentation*

- [1] HERNÁNDEZ, A.M. Et al. RespiLab: A Virtual Laboratory for the analysis of Human Respiratory Control System. ACE'06 7th IFAC Symposium on Advances in Control Education. Madrid, 2006.
- [2] BARRET, Kim. Et al. Ganong's Review of Medical Physiology: Cardiovascular physiology. Edición Veintitresava. EEUU: Editorial Mc Graw Will Medical, 2010. Sección VI: Capítulo 31, p. 494 – 562.
- [3] GUYTON, Arthur. HALL, John. Textbook of medical physiology. Edición onceava. Mississippi, EEUU: Editorial Elsevier Saunders, 2006.
- [4] KLABUNDE, Richard. Cardiovascular Physiology Concepts: Introduction to the Cardiovascular System. EEUU: Editorial Lippicott Williams & Wilkins, 2005. Capítulo 1, p. 3.

### 1.4. *Questionnaire*

- a. How the peripheral vascular resistance affects the arterial blood pressure?
- b. How is defined and which factors influence the heart rate?
- c. What information could be inferred from the electrocardiogram?
- d. Which is the function of the cardiovascular system?
- e. Which is the importance of the autonomous nervous system in the regulation of the function of the cardiovascular system?
- f. Which is the function of the sympathetic system in the regulation of the cardiovascular system?
- g. Which is the function of the parasympathetic system in the regulation of the cardiovascular system?
- h. Describe the effects of anesthetic agents on the cardiovascular system?

## Session 2      Cardiovascular system response to stimuli

### 2.1. *Introduction*

The cardiovascular system responds to different stimuli through the autonomic nervous system modulation where the pharmacological or mechanical stimuli are sensed by receptors who send the information to the sympathetic and parasympathetic systems who finally modify heart rate, heart contractility, vasoconstriction and other cardiovascular effectors. In CardioLab are included some common stimuli like:

- *Valsalva maneuver*

The function of the receptors can also be tested by monitoring the changes in pulse and blood pressure that occur in response to brief periods of straining (forced expiration against a closed glottis: the Valsalva maneuver).

Valsalva maneuvers occur regularly during coughing, defecation, and heavy lifting. The blood pressure rises at the onset of straining because the increase in intrathoracic pressure is added to the pressure of the blood in the aorta. It then falls because the high intrathoracic pressure compresses the veins, decreasing venous return and cardiac output. The decreases in arterial pressure and pulse pressure inhibit the baroreceptors, causing tachycardia and a rise in peripheral resistance. When the glottis is opened and the intrathoracic pressure returns to normal, cardiac output is restored but the peripheral vessels are constricted. The blood pressure therefore rises above normal, and this stimulates the baroreceptors, causing bradycardia and a drop in pressure to normal levels.

- *Sleep*

The dream defines as the unconsciousness state del that can be waked up a person by means of sensitive stimuli of another type. During the dream, any person crosses phases of two types of dream that alternate to each other:



- Dream of slow waves, because in this class the cerebral waves are very powerful and their VLF.
- Dream of fast ocular movements (dream REM, by its English denomination in rapid eye movement), because in this stage the eyes undergo fast movements although the person still is slept.

During the dream is given rise are some physiological changes, such as:

- The muscular tone of all the body is gotten depressed enormously, which indicates a powerful inhibition of the muscular control areas in the marrow.
- The frequencies cardiac and respiratory normally become irregular.
- In spite of the extreme inhibition of peripheral muscles, irregular muscular movements exist. They take place aside from the fast movements of the eyes.
- The brain is in the dream REM very active and the global cerebral metabolism can increase until a 20%.

It is common that the dream state is not continuous, because the subject experiments to wake up of short duration during the time in which it is slept. These micro-to wake up diminish the effect of the parasympathetic system and sometimes they diminish the level of rest reached in comparison with a dream without micro-waking up

## 2.2. *Objectives*

After this Session, students will know:

- To use the virtual laboratory (CardioLab) in different ways and they will get little expertise simulating cardiovascular stimuli: Valsalva maneuver and Sleep.
- Which cardiovascular variables are affected by the Valsalva maneuver and the Sleep.
- To analyze the correlation between cardiovascular signals and applied stimuli.

### 2.3. *Valsalva maneuver*

The Valsalva maneuver stimulus is applied to a healthy person. After double clicking on CardioLab.jar you indicate the value "Start" and "Duration" and later you must press <play> button to start connection with Matlab. Click <pause> when you think the variables have reached the steady state (when they practically do not change in a range of 5%). For this purpose, activating the signal monitor <Show Monitor> in the average mode could be more appropriate.

The parameters with which it will recreate the Valsalva maneuver are *start time* and *duration time*. The *start time* must be less than the simulation time has been run at the moment before applying the stimulus. The *duration time* must be less than 30 seconds.

#### ***Exercise***

- a. Choose the tab "Valsalva". Given the above conditions, choose a value for "Start" and apply 5 s for "Duration" and press "Play". Select the "Activate stimulus" in order to simulate the Valsalva maneuver.
- b. When the variables in the average view had reached the steady state (less than 5% of variation) "Pause" the simulation and "Save" the obtained results.
- c. Apply with the same procedure Valsalva maneuvers of 10 s, 15 s and 20 s.
- d. Close CardioLab and using Matlab compares the response to different Valsalva maneuver duration times.
- e. Evaluates the cross correlation between the ECG signal and respiratory frequency during rest conditions and during Valsalva maneuver.

## 2.4. *Sleep*

The Sleep stimulus is applied to a healthy person. After to pressing reset the application you must press <play> button to start connection with Matlab. Click <pause> when you think the variables have reached the steady state (when they practically do not change in a range of 5%). For this purpose, activating the signal monitor <Show Monitor> in the average mode could be more appropriate.

### *Exercise*

- a. Choose the tab “Sleep”. Given the above conditions, choose “Wakefulness” equal to zero. Select the "Activate stimulus" in order to simulate the Sleep and simulate for 300 s.
- b. When it has simulated 300 s “Pause” the simulation and apply with the same procedure “Wakefulness” of 0.3 and 0.5.
- c. Save the simulation when variables have reached the steady state after last wakefulness.
- d. Close CardioLab and using Matlab compares the response to different Wakefulness. It calculates the sensitivity of the variables of the system to the variations of “Wakefulness”.
- e. Evaluates the cross correlation between the ECG signal and respiratory frequency during rest conditions and during Sleep.

## Session 3    Cardiovascular    system    response    to pharmacological agents

### 1.1. *Introduction*

The cardiovascular system responds to different stimuli through the autonomic nervous system modulation where the pharmacological or mechanical stimuli are sensed by receptors who send the information to the sympathetic and parasympathetic systems who finally modify heart rate, heart contractility, vasoconstriction and other cardiovascular effectors. In CardioLab are included some common stimuli like:

- *Halothane*

Halothane (2-chloro-2-bromo-1,1,1-trifluoroethane) is a potent inhalational anesthetic agent, inhalation is irritating to the airways and makes it acceptable odor for induction of anesthesia with facial mask. This agent causes a reduction in driving, causing sinus bradycardia and also produce QT interval prolongation.

- *Propranolol*

Propranolol is lipid soluble, and therefore depends on the liver for clearance. Drugs cleared by the liver usually have a short half-life, and several doses a day of propranolol might be needed for it to be effective.

This drug was the first  $\beta$ -blocker to be introduced into therapy in 1965. Thirty years later, about 20 different congeners were marketed in different countries. As a rule, this basic structure is linked to an aromatic nucleus by a methylene and oxygen bridge. The side chain C-atom bearing the hydroxyl group forms the chiral center. With some exceptions (e. g., timolol, penbutolol), all  $\beta$ -sympatholytics exist as racemates.

### 1.2. *Objectives*

After this Session, students will know:

- To use the virtual laboratory (CardioLab) in different ways and they will get little expertise simulating cardiovascular some anesthetic agents and some drugs: Halothane and Propranolol.
- Which cardiovascular variables are affected by Halothane and Propranolol.
- To analyze the correlation between cardiovascular signals and applied stimuli.

### 1.3. *Halothane*

The Halothane stimulus is applied to a healthy person. After double clicking on CardioLab.jar you must press <play> button to start connection with Matlab. Click <pause> when you think the variables have reached the steady state (when they practically do not change in a range of 5%). For this purpose, activating the signal monitor <Show Monitor> in the average mode could be more appropriate.

#### *Exercise*

- a. Choose the tab “Halothane”. Given the above conditions, choose the minimal alveolar concentration (MAC) of 0.5 %. Select the "Activate stimulus" in order to simulate the Halothane.
- b. When the variables in the average view had reached the steady state (less than 5% of variation) “Pause” the simulation and apply with the same procedure a MAC of 1.0 %, 2.0 % and 3.0 %.
- c. Save the simulation when variables have reached the steady state after last MAC.
- d. Close CardioLab and using Matlab compares the response to different dose of Halothane.
- e. Evaluates the cross correlation between the ECG signal and respiratory frequency during rest conditions and during Sleep.

## 1.4. *Propranolol*

The Propranolol stimulus is applied to a healthy person. After to pressing reset the application you must press <play> button to start connection with Matlab. Click <pause> when you think the variables have reached the steady state (when they practically do not change in a range of 5%). For this purpose, activating the signal monitor <Show Monitor> in the average mode could be more appropriate.

### *Exercise*

- a. Choose the tab “Propranolol”. Given the above conditions, choose the dose of Propranolol of 45 mg. Select the "Activate stimulus" in order to simulate the Propranolol.
- b. When the variables in the average view had reached the steady state (less than 5% of variation) “Pause” the simulation and apply with the same procedure dose of Propranolol of 80 mg, 100 mg and 120mg.
- c. Save the simulation when variables have reached the steady state after last dose of Propranolol.
- d. Close CardioLab and using Matlab compares the response to different dose of Propranolol.
- e. Evaluates the cross correlation between the ECG signal and respiratory frequency during rest conditions and during Sleep.