CZECH TECHNICAL UNIVERSITY IN PRAGUE

Faculty of Electrical Engineering

Department of Cybernetics

Study Programme: Biomedical Engineering and Informatics

Branch of Study: Biomedical Engineering

Master Thesis

Design of a Model for ECMO Demonstration and Teaching

Thesis supervisor: Ing. Filip Ježek

Author: Bc. Anna Doležalová

January 2014

České vysoké učení technické v Praze
Fakulta elektrotechnická

Katedra kybernetiky

ZADÁNÍ DIPLOMOVÉ PRÁCE

Student: Bc. Anna D o l e ž a l o v á

Studijní program: Biomedicínské inženýrství a informatika (magisterský)

Obor: Biomedicínské inženýrství

Název tématu: Návrh modelu pro výuku ECMO

Pokyny pro vypracování:

- Prozkoumejte současné pomůcky pro výuku ECMO, s důrazem na simulátory.
- Vyberte vhodný model cirkulace a přenosu krevních plynů.
- Implementujte model cirkulace tak, aby používal principy knihovny Modelica.Fluid.
- Rozšiřte o model jednoduchého dýchacího přístroje pro nácvik.
- Zahrňte do modelu ECMO nastavení dle reálného přístroje, včetně průtoku, teploty apod.
- Ke všem modelům doplňte odpovídající dokumentaci.
- Navrhněte výukovou aplikaci, včetně doprovodného textu. Samotná implementace není vyžadována.

Seznam odborné literatury: Dodá vedoucí práce.

Vedoucí diplomové práce: Ing. Filip Ježek

Platnost zadání: do konce zimního semestru 2014/2015

ČESKÉ VYSOKÉ UČENÍ TECHNICKÉ V PRAZE Fakulta elektrotechnická L.S.

Kybic

doc. Dr. Ing. Jan Kybic
vedoucí katedry

prof. Ing. Pavel Ripka, CSc.
děkan

V Praze dne 12. 8. 2013

Czech Technical University in Prague
Faculty of Electrical Engineering

Department of Cybernetics

DIPLOMA THESIS ASSIGNMENT

Student: Bc. Anna D o l e ž a l o v á

Study programme: Biomedical Engineering and Informatics

Specialisation: Biomedical Engineering

Title of Diploma Thesis: Design of a Model for ECMO Demonstration and Teaching

Guidelines:

- Present an overview about tools for ECMO training with emphasize on model-based simulators.
- Choose appropriate model of human blood circulation and blood gases transport.
- Implement the circulation model in Modelica language and based on Modelica.Fluid library principles.
- Add a simple model of artificial ventilator and ECMO, including basic settings possibilities, such as flow, temperature etc.
- All models must be documented correspondingly.
- Prepare a design of the training application, including the explicatory text. The implementation itself is not required.

Bibliography/Sources: Will be provided by the supervisor.

Diploma Thesis Supervisor: Ing. Filip Ježek

Valid until: the end of the winter semester of academic year 2014/2015

L.S.

doc. Dr. Ing. Jan Kybic
Head of Department

prof. Ing. Pavel Ripka, CSc.
Dean

Prague, August 12, 2013

PROHLÁŠENÍ AUTORA PRÁCE

Prohlašuji, že jsem předloženou práci vypracovala samostatně a že jsem uvedla veškeré použité informační zdroje v souladu s Metodickým pokynem o dodržování etických principů při přípravě vysokoškolských závěrečných prací.

V Praze dne 2. 1. 2014

Podpis autora práce

AUTHOR'S STATEMENT

I hereby declare that I made this master thesis by myself and that I listed all the used information resources in accordance with Methodological guideline about adherence to ethical principles during the preparation of university final theses.

In Prague on 2. 1. 2014

Author's signature

AUTHOR'S NOTE

I would like to note that during my ERASMUS study period in Denmark I worked on a similar topic as is now my master thesis. In Denmark, students are supposed to write a large semester project in the 3rd semester of their master's studies, that is one semester before writing their master thesis. I wrote this project in the second semester of my stay as the beginning of my thesis in the Czech Republic. The project was called *Mathematical Model for Optimizing ECMO Settings in Case of Respiratory Failure*.

The model has the same basis and structure as the model that I developed during the last semester in Denmark. Nevertheless, the components are distinctly upgraded, improved and the code is clearer.

My former project is listed in the bibliography and it is mentioned in certain places after the parts of the text which were taken from the project.

Moreover, the project in Denmark had a very different purpose. The aim was to find an appropriate ECMO settings in order to achieve sufficient oxygenation and carbon dioxide removal in different cases of pulmonary function. The goal of my master thesis is to upgrade the model in order to create a design of a computer application for educational purposes.

ACKNOWLEDGMENTS

I would like to thank to everyone who helped me create this master thesis and who supported me through that time.

I wish to thank especially my supervisor Ing. Filip Ježek who helped me greatly with the project that I worked on during my stay in Denmark and who also led me during the work on my master thesis. It would not have been possible to create the model, which is the most important part of this project, without his support and help.

ABSTRAKT

ABSTRAKT

Venovenózní mimotělní membránové oxygenace (VV ECMO) je modifikovaná forma mimotělního oběhu, kde je krev čerpána ze žilního systému pacienta, okysličena v části ECMO zvané oxygenátor a vracena zpět do žilího řečiště [Betit, 2009]. VV ECMO je využíváno v případě, kdy je srdeční výdej dostatečný a je potřeba kompletní či částečná podpora plicní funkce [Lindstrom et al., 2009]. Cílem této diplomové práce bylo vylepšení a rozšíření počítačového modelu oběhového systému člověka, plic s nedokonalou funkcí, tkání a VV ECMO, na kterém jsem pracovala v mém dřívějším projektu [Doležalová, 2013]. Druhým úkolem bylo na základě tohoto modelu vytvořit návrh počítačové aplikace pro výukové účely. Model byl vytvářen v programovacím (modelovacím) jazyku Modelica. S cílem zjistit, zda se model chová v mezích očekávání, byla vytvořena série simulačních experimentů a model byl testován. Výsledky ukázaly, že model se chová uspokojivě a lze ho považovat za dobrý základ pro počítačovou aplikaci pro výukové účely. Model a počítačová aplikace by měly pomoci studentům medicíny, biomedicínského inženýrství a dalšímu zdravotnickému personálu k hlubšímu pochopení funkce ECMO.

KLÍČOVÁ SLOVA

ECMO, modelování, počítačová aplikace, Modelica

ABSTRACT

ABSTRACT

Venovenous extracorporeal membrane oxygenation (VV ECMO) is a modified form of a cardiopulmonary bypass in which blood is drained from the venous system of the patient, pumped through the oxygenator where oxygenation takes place and re-infused to the venous bloodstream [Betit, 2009]. VV ECMO is used when the cardiac output is sufficient and complete or partial lung support is needed [Lindstrom et al., 2009]. The aim of the project was to improve and upgrade the computer model of blood circulation, lungs, tissues and VV ECMO that I worked on in my former project [Doležalová, 2013]. The second goal was to create a design of a computer application for educational purposes based on the functions of the model. The model was created in the programming (modeling) language called Modelica. In order to test the function of the model, a set of simulation experiments were designed. The results have shown that the model has satisfactory behavior and it can be considered as a basis for a computer application for educational purposes. The model and the computer application will help the students of medicine and biomedical engineering and other medical staff develop a deeper understanding of the function of ECMO.

KEY WORDS

ECMO, modeling, computer application, Modelica

TABLE OF CONTENTS

[1] This section is taken from my former project [Doležalová, 2013]

CHAPTER 1

MOTIVATION

The purpose of using venovenous extracorporeal oxygenation (VV ECMO) is to take the place of lung function providing time for the lungs to recover from a disease, injury or surgery [Lindstrom et al., 2009, Rodriguez-Cruz, 2011]. The most important functions of the lungs are oxygenation and carbon dioxide removal. The gas exchange takes place in alveoli where oxygen passes to blood and carbon dioxide passes to the air by diffusion. The air is afterwards breathed out. An adequate gas exchange maintains the balance of important parameters providing an acid-base homeostasis of the blood [Silbernagl and Despopoulos, 2009]. If lungs do not work sufficiently, ECMO has the responsibility to manage the gas exchange and therefore maintain the acid-base homeostasis.

The main problems in introducing and leading ECMO are both anatomical and physiological and include issues such as bleeding usually caused by anticoagulation, insufficient perfusion of some parts of the patient's body and the introduction of drainage. Furthermore, there are some technical aspects which are necessary to adjust in order to achieve a successful use of ECMO. These are mainly ECMO flow (blood flow), gas flow and oxygen level, which are dependent on the level of patient's lung and heart function. The values have to be modified according to the function present in the patient's body [Schmidt et al., 2012]. A model of VV ECMO, blood circulation, lungs with insufficient function and tissues may help with adjusting the values of ECMO settings in order to achieve proper oxygenation and carbon dioxide removal. Since a computer model is not a threat for the patient, it might be helpful for educational purposes to implement a model with explanatory or predictive functions. After implementing the model, a design of a visual computer application might be valuable. It might be especially useful in the training of new medical staff and for teaching students of medicine and biomedical engineering. Trainees might learn the basic functions and features of the device and understand the way it works. More experience and a better understanding of the technology can possibly improve the outcomes of using this device and result in the saving of lives [Doležalová, 2013].

1.1 Aim

The aim of this master thesis is to improve and upgrade the computer model of blood circulation, lungs, tissues and VV ECMO that I worked on during my stay at a university in Denmark. My second goal is to create a design of a training application including the explicatory text.

1.2 Expected process

The master thesis consists of several goals which are necessary to achieve. Mainly, it is required to build a model which has particular functions. It should represent human blood circulation

through the lungs, tissues and additionally a VV ECMO device. The model of the lungs should contain mechanical ventilation which supports the insufficient pulmonary function together with ECMO. Lung insufficiency should be represented by a pulmonary shunt. Two important processes of gas exchange should be described in the lungs and ECMO - carbon dioxide removal and transfer of oxygen into the bloodstream. The model of the tissues should describe opposite processes than lungs and ECMO - oxygen uptake and carbon dioxide production. In order to demonstrate the changes in oxygen saturation, oxygen and carbon dioxide concentrations and partial pressures during the passage throughout the circulation, the model should describe the basic acid-base chemistry of the blood [Doležalová, 2013].

The model should demonstrate the behavior of the human body within physiological standards. After the modeling part, it is therefore necessary to design a set of experiments which will show if the model behaves satisfactorily. In order to find out what satisfactorily means, it is important to understand the physiology of particular parts of the human body especially human circulation, acid-base chemistry of blood, respiratory system and pathology of the lungs. Part of the model should be a VV ECMO machine and therefore it is necessary to describe and state the basic information about this device.

The second goal of this master thesis is to design a computer application which will be possibly used for an ECMO training. Therefore, it is worthwhile to do research about available training options.

Creating a model is a highly complex process which includes a lot of programming. The programming language which will be used is not a very common tool, so it is relevant to describe the approach and explain the most important features of this programming language, its advantages and disadvantages in comparison to a common approach.

CHAPTER 2

INTRODUCTION

ECMO is a device which is connected with the patient's circulatory system and supports pulmonary and/or cardiac functions. For an understanding of the ECMO function it is necessary to have basic knowledge of blood, acid-base chemistry of blood, and of the human circulatory and respiratory systems.

2.1 Human circulatory system

The main function of the human circulatory system is a transport of blood throughout the entire body. It consists of a system of tubes - blood-vessels in which blood circulates towards the blood pump - the heart. The heart is composed of two pumps in series which lead the blood to the two circuits - systemic also called large loop, and pulmonary also called small loop. The description of both circuits is seen in figure 2.1. Both pumps consist of an atrium (auxiliary pump) and a ventricle (main pump). The right ventricle has a much thiner wall and it conducts deoxygenated blood to the low pressure pulmonary circuit. The left ventricle has much more developed muscles and it conducts the oxygenated blood to the high pressure systemic circuit and therefore to the whole body [Langmeier et al., 2009].

The heart is a hollow muscular organ and it provides the circulation throughout the entire body of vertebrate animals, including humans. The circulation is provided by periodical contractions of the heart muscle. The heart is the only muscle which works constantly. The heart muscle has a similar structure as the skeletal muscles, but we are not able to control it by our own will as normal skeletal muscles. The heart is situated in the chest between the lungs, sternum and diaphragm. Its wall is formed by a special type of muscle called myocardium. From the inside the heart is lined with endocardium which is strongly connected with myocardium. The surface of the heart is covered with a membrane called pericardium. The heart is divided into four cavities - right atrium and ventricle and left atrium and ventricle, detailed description of the heart structure is seen in picture 2.2. Atriums are divided from the ventricles by valves which let blood go just in one direction. Blood is accumulated in the atriums and the ventricles pump the blood out from the heart. The functioning of the heart is provided by a rhythmic changing of relaxation (diastole) and contraction (systole) of the heart muscle. During diastole, the ventricles are filled with blood and during systole, the blood is pumped out from the heart to the big arteries such as aorta and pulmonary artery. The heart is connected by a complex system of blood-vessels. The blood-vessels which lead the blood to the heart are called veins and those which lead the blood from the heart to the entire body are called arteries. The arteries have more flexible and stronger walls than veins because they have to handle high pressure caused by blood pumping from the heart. Very important arteries are coronary arteries which are responsible for the blood supply to the heart muscle [Langmeier et al., 2009, Elišková and Naňka, 2006].

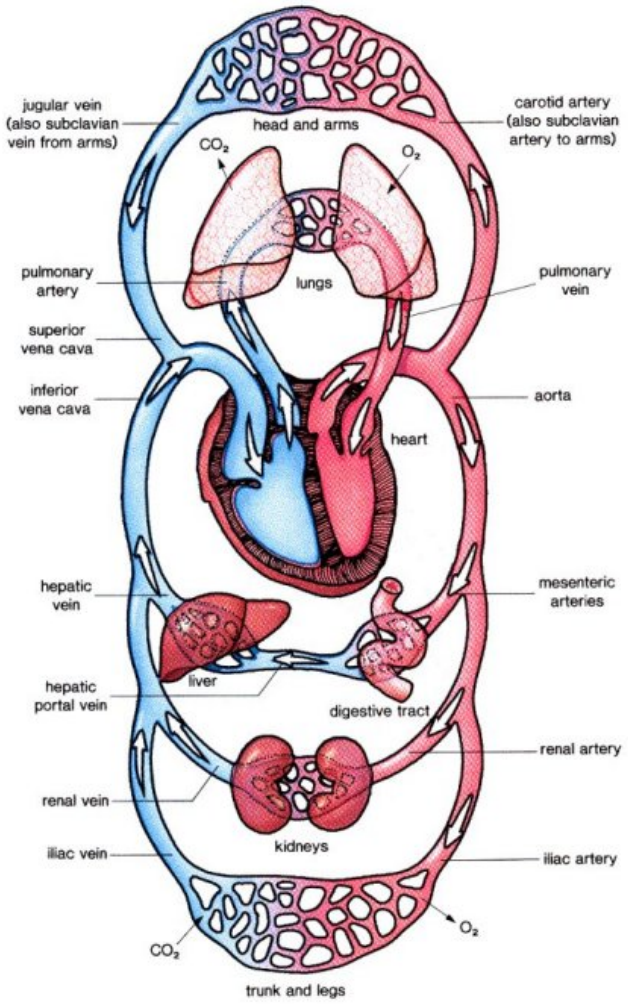


Figure 2.1: Description of pulmonary and systemic circulation [Darling, 1999]

The blood flow is secured by contraction (systole) and relaxation (diastole) of the heart muscle. Deoxygenated blood flows to the right atrium by the superior and inferior vena cava. Then it is transferred through the tricuspid valve into the right ventricle. After that, the blood is during systole pumped through the pulmonary valve to the right and left pulmonary artery and led to the lungs. The blood is oxygenated in the lungs and it travels to the left atrium through the pulmonary veins. This circuit is called a small or pulmonary circuit.

The large or systemic circuit begins when the oxygenated blood enters the left atrium. From the left atrium, blood goes through the mitral valve to the left ventricle. Afterwards, it is pumped through the aortic valve to the aorta and to the whole body. Both circuits are described in picture 2.1.

Human circulatory system is a very complex system which provides the supply of oxygen to the whole body and ensures that carbon dioxide leaves the body. It is a difficult task and it is affected by a lot of factors.

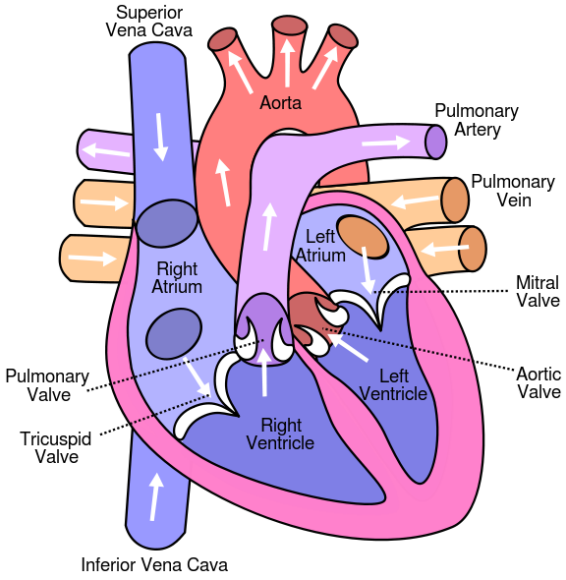


Figure 2.2: Detailed description of the heart [Wikimedia.Commons, 2013a]

2.2 Blood

Blood is a red fluid which contains blood plasma and blood cells (red, white, platelets). The functions of blood include the transport of gases (oxygen and carbon dioxide), nutrients, hormones, vitamins, catabolites and ions. Another important function is the maintenance of body temperature and the internal environment (homeostasis). Blood volume of an adult is usually around 8% of his or her body mass. The average amount of blood is between 4 and 4.5 l in women and between 4.5 and 5 l in men. The volume ratio of red blood cells to the total blood volume is called hematocrit. Hematocrit is usually between 33 and 47% in women and between 39 and 57% in men. Plasma is the fluid portion of the blood with dissolved electrolytes, nutrients, metabolites, vitamins, hormones, gases and proteins. Plasma proteins are involved in humoral immune defense and maintain oncotic pressure, which helps to keep the blood volume constant. Many plasma proteins are involved in blood clotting. Red blood cells transport oxygen and play an important role in pH regulation. White blood cells are responsible especially for nonspecific and specific immune defense. Platelets, also called thrombocytes are needed for hemostasis. The hemostatic system stops bleeding. Thrombocytes and other factors interact to seal leaks in blood vessels by a platelet plug. Some important data about blood are displayed in table 2.1 [Silbernagl and Despopoulos, 2009, Langmeier et al., 2009].

Blood segment	Unit	Value in women	Value in men
Red blood cells (Erythrocytes)	10^{12} per liter of blood	4.2 - 5.4	4.6 - 5.9
White blood cells (Leukocytes)	10^{9} per liter of blood	3 - 11	3 - 11
Platelets	10^{9} per liter of blood	180 - 400	170 - 360
Hemoglobin	g per liter of blood	120 - 160	140 - 180
Plasma proteins	g per liter of serum	66 - 85	66 - 85

Table 2.1: Blood features [Silbernagl and Despopoulos, 2009]

The length of the life of blood cells is different for each type. Dying blood cells have to be constantly restored. The formation of blood cells (hematopoiesis) occurs in the red bone mar-

row of flat bone in adults and in the spleen and liver of the fetus. Red blood cells and platelets usually live 110 - 120 and 9 - 12 days, respectively. The life span of leukocytes differs with the type of white blood cells; some of them live a few hours, some of them days and some of them weeks. The most important component of red blood cells is hemoglobin - red blood pigment. It consists of four units and is able to bind oxygen [Silbernagl and Despopoulos, 2009, Langmeier et al., 2009].

2.2.1 Acid-base chemistry of blood

Acid production is a result of normal metabolism. An acid is a proton or hydrogen ion (H^+) donor. On the contrary, a base is a proton or hydrogen ion acceptor. There are a lot of potential hydrogen ions in the human body. Most of them are not in free form, they are usually buffered. The normal concentration of free H^+ is very small, around 40 nmEq/l (nmEq/l is equivalent to one millionth of a mEq/l). The term pH represents the negative logarithm of free H^+ concentration. The relationship between pH and concentration of free H^+ is inversely proportional. Free H^+ concentration increases when pH decreases, and vice versa. A normal arterial pH of 7.4 corresponds with a free H^+ concentration of 40 nmEq/l [Curley and Moloney-Harmon, 2001].

In normal metabolism, hydrogen is produced in two forms - as a volatile or fixed acid. Acids must be buffered or excreted, in order to maintain pH within its normal narrow range between 7.35 and 7.45. Buffer is a substance that reduces free H^+ concentration change in a solution when an acid or base is added. In other words, buffer increases the amount of acid or base that has to be added in order to change the pH in the solution [Curley and Moloney-Harmon, 2001]. There are many of types of buffers and they are responsible for maintaining a constant pH. The most important buffer for blood and other body fluids is the bicarbonate/carbon dioxide buffer system (HCO_3^-/CO_2) (equation 2.1). The main function of this system in blood is to buffer H^+ ions. The second most important buffer in blood is hemoglobin, a non-bicarbonate buffer (equation 2.2) [Silbernagl and Despopoulos, 2009].

$$CO_2 + H_2O \longleftrightarrow H^+ + HCO_3^- \tag{2.1}$$

$$HbH \longleftrightarrow Hb^- + H^+ \tag{2.2}$$

The acid-base balance maintains the pH in the extracellular fluid around 7.4 by excreting carbon dioxide in the lungs and non-carbonic acid or base in the kidneys. Good functioning of lungs and kidneys results in a normal blood status - for instance, a normal pH, a normal carbon dioxide partial pressure etc. [Siggaard-Andersen, 2005]. Normal ranges for parameters relevant to acid-base homeostasis, as measured in arterial and venous blood are listed in tables 2.2 and 2.3. Acid base homeostasis exists when certain balances are maintained. Firstly, it is the balance between H^+ production and addition, HCO_3^- production and addition and H^+ plus HCO_3^- excretion. The balance is expressed by the equation 2.3 [Silbernagl and Despopoulos, 2009].

$$\begin{aligned}(H^+ addition + production) - (HCO_3^- addition + production) = \\ (H^+ excretion) - (HCO_3^- excretion) \approx 60 mmol/day (diet - dependent)\end{aligned} \tag{2.3}$$

Secondly, it is necessary to maintain the balance between CO_2 production and excretion. The balance is expressed by the equation 2.4.

$$(CO_2 production) = (CO_2 excretion) \approx 15000 - 20000 mmol/day \tag{2.4}$$

H^+ production and excretion are the main factors influencing the first balance. If the function of lungs or kidneys is impaired, acid-base disturbances may occur. There are two acid-base disturbances - alkalosis and acidosis. Alkalosis occurs when the pH of blood increases above the normal range (7.45). On the contrary, acidosis occurs when pH of the blood is below the normal range (7.35). There are two causes of acid-base disturbances; these are respiratory or metabolic impairments. Respiratory disturbances are caused by primary changes in the carbon dioxide partial pressure. Metabolic disturbances occur due to primary changes in the bicarbonate concentration [Silbernagl and Despopoulos, 2009].

Variable	Normal value	Unit	Description
ph_p	7.35 - 7.45	-	Potential of hydrogen in plasma
ph_e	7.19	-	Potential of hydrogen in erythrocytes
pO_2	74.3 - 108 10 - 13	mmHg kPa	Partial pressure of oxygen
pCO_2	35 - 45 4.67 - 6	mmHg kPa	Partial pressure of carbon dioxide
HCO_3^-	22 - 26	mmol/l	Concentration of bicarbonate buffer base in plasma
$CO_{2,p}$	1.23	mmol/l	Concentration of physically dissolved carbon dioxide in plasma
$NBB(A)$	17.2	mmol/l	Concentration of non-bicarbonate buffer base in plasma
BB	41.7	mmol/l	Concentration of buffer base in plasma
$HNBB(HA)$	6.3	mmol/l	Concentration of non-bicarbonate buffer acid in plasma
$tNBB(tA)$	23.5	mmol/l	Concentration of non-bicarbonate buffer in plasma
$pKHCO_3$	6.1	-	Dissociation constant for bicarbonate in plasma
$pKNBB$	6.96	-	Dissociation constant for non-bicarbonate buffers in plasma
DPG	5	mmol/l	Concentration of 2,3-diphosphoglycerate in blood
Hb	135 - 180 7.4 - 10.9	g/l mmol/l	Amount of hemoglobin in the blood
α_{CO_2}	0.00023	mmol/l.Pa	Solubility coefficient of carbon dioxide in plasma
α_{O_2}	0.00001	mmol/l.Pa	Solubility coefficient of oxygen in plasma
FiO_2	21	%	Fraction of oxygen in the air
sO_2	95 - 99	%	Percent of blood cells filled with oxygen
tO_2	7.1 - 9.9 200	mmol/l ml/l	Total concentration of oxygen in blood
tCO_2	25.7	mmol/l	Total concentration of carbon dioxide in plasma

Table 2.2: Normal range of blood variables in arterial blood [Rees and Andreassen, 2005, Martin, 1999, Siggaard-Andersen et al., 1987]

Variable	Normal value	Unit	Description
ph_p	7.371	-	Potential of hydrogen in plasma
ph_e	7.169	-	Potential of hydrogen in erythrocytes
$HCO^-_{3,p}$	26.2	mmol/l	Concentration of bicarbonate buffer base in plasma
$CO_{2,p}$	1.403	mmol/l	Concentration of physically dissolved carbon dioxide in plasma
$NBB(H)$	16.9	mmol/l	Concentration of non-bicarbonate buffer base in plasma
BB_p	43.1	mmol/l	Concentration of buffer base in plasma
BB_e	70.7	mmol/l	Concentration of buffer base in erythrocytes
BB	55.3	mmol/l	Concentration of buffer base in blood
$HNBB(HA)$	6.6	mmol/l	Concentration of non-bicarbonate buffer acid in plasma
$tNBB(tA)$	23.5	mmol/l	Concentration of non-bicarbonate buffer in plasma
$pKHCO_3$	6.1	-	Dissociation constant for bicarbonate in plasma
$pKNBB$	6.96	-	Dissociation constant for non-bicarbonate buffers in plasma
DPG	5	mmol/l	Concentration of 2,3-diphosphoglycerate in blood
Hb	135 - 180 7.4 - 10.9	g/l mmol/l	Amount of hemoglobin in the blood
$tCO_{2,p}$	27.6	mmol/l	Total concentration of carbon dioxide in plasma

Table 2.3: Normal range of blood variables in venous blood [Rees and Andreassen, 2005]

One of the most important indicators of acid-base balance is the carbon dioxide tension - carbon dioxide partial pressure (pCO_2). When pCO_2 increases, the concentration of free dissolved carbon dioxide increases as well as the concentration of carbonic acid. Therefore, the concentration of hydrogen ions also rises (equation 2.1) [Siggaard-Andersen, 2005]. As mentioned previously, the relationship between pH and concentration of hydrogen ions is inversely proportional. Thus, when pCO_2 increases, pH decreases.

Another important relationship which describes the acid-base balance is the relationship between oxygen saturation and oxygen partial pressure (pO_2). This relationship is called oxyhemoglobin dissociation curve and it is shown in figure 2.3 together with the explanation what the shifts of the curve mean. The oxyhemoglobin dissociation curve expresses how the blood carries and releases oxygen. As pO_2 rises, hemoglobin bind more molecules of oxygen until the maximum is reached. When blood is fully saturated, no other molecules can be bound [Varjavand et al., 2000].

Henderson-Hasselbalch equation 2.5 is often used for describing the acid-base balance. It is derived from the law of mass action and describes the relationship between pH, concentration of HCO^-_3, free dissolved carbon dioxide and pK which is a dissociation constant for bicarbonate [Siggaard-Andersen, 2005]. It describes the distribution of bicarbonate buffers in plasma [Rees and Andreassen, 2005].

$$pH = pKHCO_3 + log_{10}\frac{HCO_3^-}{CO_2} \tag{2.5}$$

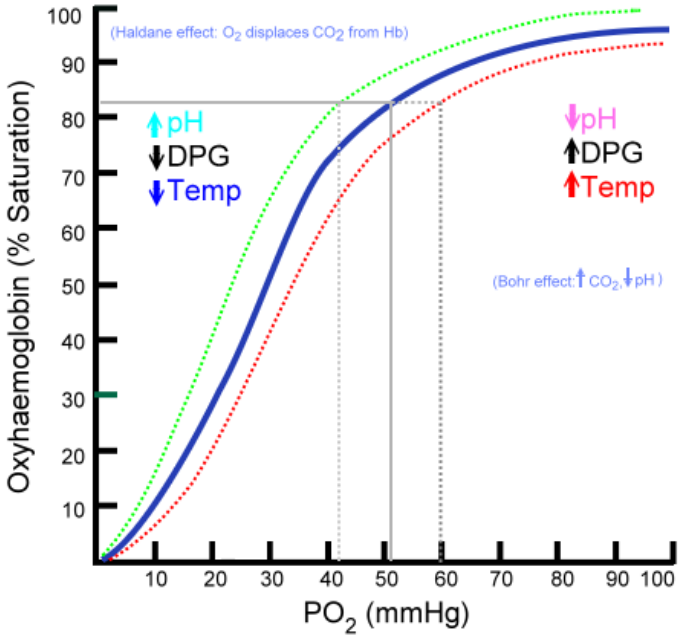


Figure 2.3: Oxyhemoglobin dissociation curve [Wikimedia.Commons, 2013b]

There are a lot of factors which affect the acid-base homeostasis. It is a fragile system and human life depends on it. Three independent systems are responsible for the maintaining of the homeostasis - respiratory, buffering and renal. All three systems have to work well otherwise the homeostasis is not achieved.

2.3 Human respiratory system

The human body needs energy for its correct functioning. It is obtained from the fission of nutrients such as carbohydrates, fats and amino acids. During the fission, the body uses oxygen and creates carbon dioxide [Langmeier et al., 2009].

The gas exchange between the air and the lungs is provided by pulmonary ventilation. The gas exchange between alveoli and blood is ensured by diffusion. The blood then transports the gases to the tissues and lungs. Specifically, the oxygen is transported to the tissues where it diffuses to the cells and afterwards to the mitochondria. Carbon dioxide, which is produced by mitochondria, is transported back to the lungs [Langmeier et al., 2009, Silbernagl and Despopoulos, 2009]. Gas transport throughout the body is displayed in figure 2.4.

The respiratory system has other functions such as adjusting the temperature, cleaning of the inspired air and humidification. The integrity and good function of the respiratory system also play a role in defense against infections [Langmeier et al., 2009].

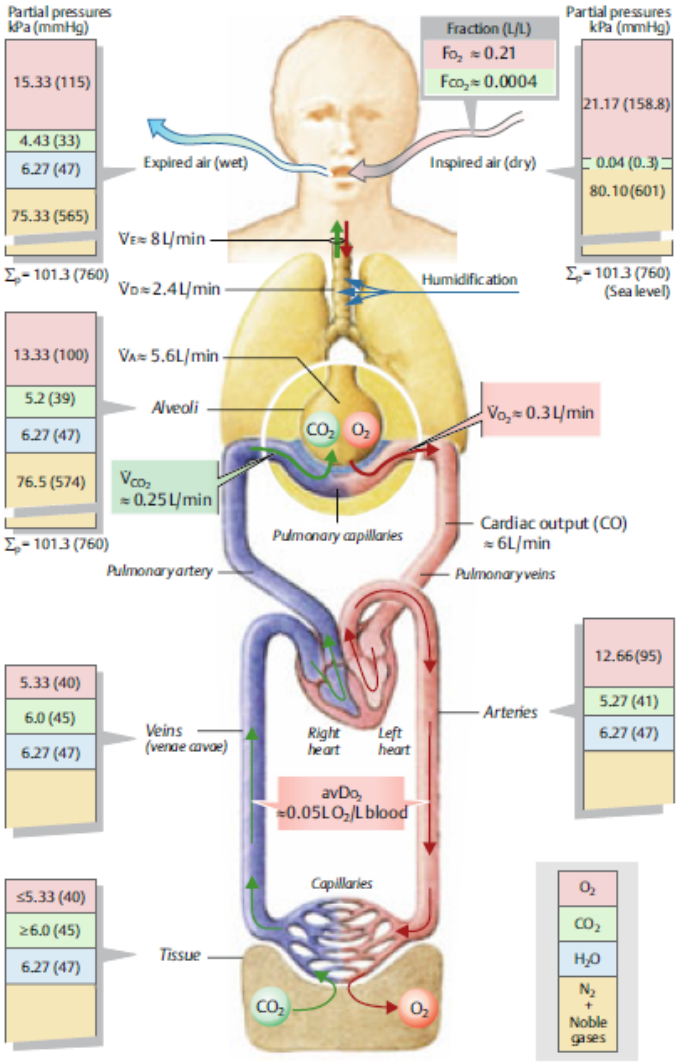


Figure 2.4: Gas transport throughout the body [Silbernagl and Despopoulos, 2009]

Atmospheric air consists of a combination of gases with different concentrations. The composition of the air is displayed in table 2.4. The sum of the partial pressures of the gases is equal to the atmospheric (barometric) pressure. The partial pressure changes due to air humidity and altitude. The reference point for the measuring of the barometric pressure is the sea level where the value is around 101.325kPa. With higher altitudes, the barometric pressure decreases and therefore the partial pressures decrease as well.

Atmospheric air	**Percent in the air**	**Partial pressure [kPa (mmHg)]**
Nitrogen and rare gases	78.06	78.06 (600)
Oxygen	20.98	20.98 (160)
Carbon dioxide	0.04	0.04 (0.3)
Atmospheric pressure		101.325 (763.3)

Table 2.4: The composition of the atmospheric air and partial pressures of the components [Langmeier et al., 2009]

As mentioned previously, pulmonary ventilation provides the gas exchange between the at-

mosphere and alveoli. The air travels to or from the lungs in the direction of the pressure gradients. The air travels to the lungs when the pressure in the lungs is lower than the atmospheric pressure. And it travels to the atmosphere when the pressure in the lungs is higher than the atmospheric pressure [Langmeier et al., 2009].

2.3.1 Mechanics of breathing

During inspiration, the air flows through the airways to the lungs in the direction of the pressure gradient. The contraction of the inspiratory muscles (diaphragm, scalene muscles and external intercostal muscles) causes the diaphragm to lower (flatten) and an expansion of the chest. Due to a high adhesion of visceral and parietal pleura, the lungs follow the movement of the chest and expand. Therefore, the pressure in the lungs decreases. The high adhesion of the pleuras is caused by a small amount of fluid between them and by a higher atmospheric pressure. The inspiration is dependent on the respiratory muscles and therefore it is an active process [Langmeier et al., 2009, Silbernagl and Despopoulos, 2009].

When the activity of the respiratory muscles stops, the volume of the chest and lungs decrease. The pressure in the lungs increases above the atmospheric pressure and the air flows through the airways to the atmosphere until the pressures are equal. The expiration is a passive process at rest, but it can be active during deep breathing [Langmeier et al., 2009].

2.3.2 Lung volumes

The tidal volume (V_t) is a volume of the air moved in and out during one respiratory cycle. It is usually around 0.5l during normal quiet respiration. There are typically between 12 and 16 respiratory cycles in one minute. The inspiration can be increased by another 3l during forced inspiration. This volume is called the inspiratory reserve volume (IRV). The expiratory reserve volume (ERV) is about 1.7l. Residual volume (RV) is around 1.3l and it is the volume of air which remains in the lungs after a forced expiration. The maximal amount of air that can be moved in and out during a single breath is called vital capacity (VC). VC is the sum of IRV, ERV and V_t. The average human (20-year-old male, 1.8m tall) has a VC of about 5.3l. Total lung capacity is the sum of VC and RV - normally 6 - 7l [Silbernagl and Despopoulos, 2009].

2.3.3 Respiratory failure

In order to explain the reasons for using ECMO as a treatment for lung insufficiency, the definition of respiratory failure will be provided in this section. ECMO is usually used in patients with severe conditions who do not respond to conventional management such as mechanical ventilation [Oshima et al., 2010]. Respiratory failure is defined as a syndrome of inadequate gas exchange - insufficient oxygen supply and/or carbon dioxide removal. It can be caused by a dysfunction of essential components of the respiratory system such as chest wall (including pleura and diaphragm), airways, alveolar-capillary units, pulmonary circulation, nerves or central nervous system and brain stem. Causes of these dysfunctions can be lung diseases such as chronic obstructive pulmonary disease, pneumonia, pulmonary embolism and cystic fibrosis. It can also be spinal cord injuries, muscular dystrophy and stroke which can affect nerves and muscles that control breathing. Any injury of the chest, ribs and tissue around the lungs may possibly cause pulmonary failure as well as drug or alcohol overdose. Another cause might be injuries from inhaling smoke or harmful fumes. The classification of pulmonary failure depends on the cause and whether it is hypoxemic (failure of oxygen exchange) or hypercapnic (failure of carbon dioxide removal). The treatment of respiratory failure also depends on the cause and whether it is acute (short-term) or chronic (ongoing) [Katyal and Gajic, 2013].

Adult respiratory distress syndrome (ARDS) is a complex physiological and clinical syndrome which is characterized by a severe respiratory failure [Churg et al., 2005]. The main features of ARDS are severe dyspnea, hypoxemia and diffuse pulmonary infiltrations [Petty and Newman, 1978]. Dyspnea is described as difficult or labored breathing. Hypoxemia is an abnormally low level of oxygen in the blood and in the case of ARDS is caused by intrapulmonary shunting [Silbernagl and Despopoulos, 2009, Simmons et al., 1979]. There are a lot of disorders which are related to the ARDS such as infection, trauma, aspiration, drugs, inhaled toxins and hematologic, metabolic and miscellaneous disorders [Simmons et al., 1979].

Respiratory failure is a very severe condition which is commonly treated by mechanical ventilation. If the patient is refractory to conventional management, ECMO is the last choice.

2.4 ECMO [1]

ECMO is a modified form of cardiopulmonary bypass in which blood is drained from the venous system of the patient, pumped through the oxygenator where the oxygenation takes place and is re-infused to the patient [Betit, 2009]. There are some differences between ECMO and cardiopulmonary bypass. ECMO is often introduced by cervical cannulation, which can be provided under local anesthesia. Conversely, the transthoracic cannulation, which has to be instituted under general anesthesia, is usually used for cardiopulmonary bypass. ECMO is frequently used for long-term support measured in days (3-10), but cardiopulmonary bypass can be used just for a short period measured in hours. There is also a difference in the purpose of use. Cardiopulmonary bypass is usually used for the heart and lung support during various types of cardio surgical procedures. ECMO can provide complete or partial support of the heart and/or lung function and give the time for recovery after disease, surgery, injury or respiratory or cardiac failure [Rodriguez-Cruz, 2011, Lindstrom et al., 2009]. ECMO is a final option for the patients whose condition is refractory to other management, for instance mechanical ventilation [Lindstrom et al., 2009, Oshima et al., 2010]. The most important parts of the basic ECMO circuit are vascular cannulae to drain and return blood, circuit tubing, a pump, artificial organ - oxygenator and a heater or heater-cooler that sustain the blood temperature (figure 2.5) [Lindstrom et al., 2009].

[1] This section is taken from my former project [Doležalová, 2013]

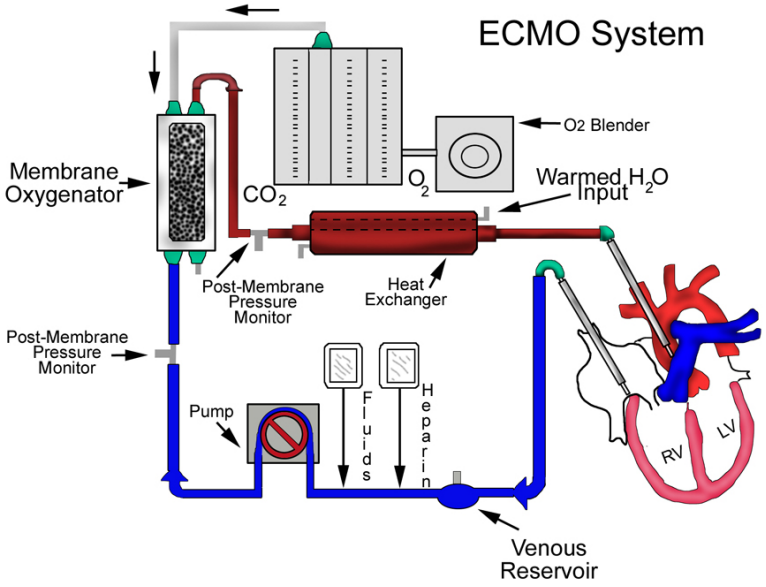


Figure 2.5: Description of ECMO system [Rodriguez-Cruz, 2011]

There are two possible methods or modalities of ECMO (figure 2.6) - venovenous (VV) and venoarterial (VA). VV is used to support mainly pulmonary function and VA supports both cardiac and pulmonary function [Betit, 2009].

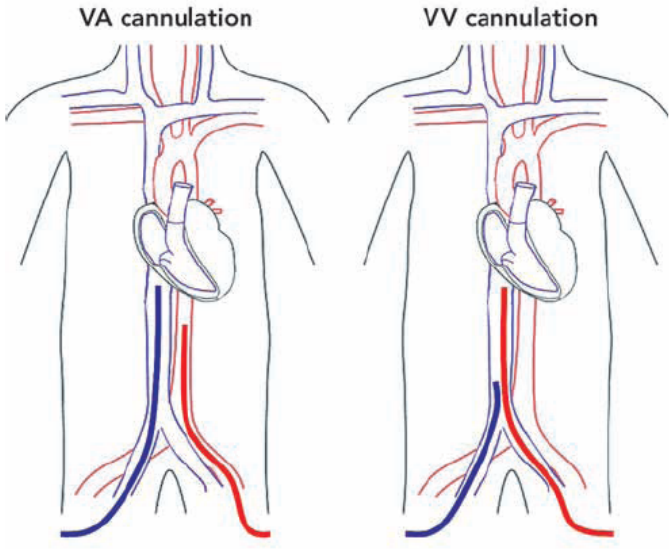


Figure 2.6: Examples of cannulation for venovenous (VV) and venoarterial (VA) extracorporeal membrane oxygenation (ECMO); blue cannulae represents deoxygenated blood and red cannulae represents oxygenated blood [Lindstrom et al., 2009]

In case of VV ECMO, the blood is drained from venous bloodstream and re-infused back to the venous system. This modality is used when the cardiac output is sufficient and complete or partial lung support is needed [Lindstrom et al., 2009]. The exact placement of the cannulation depends on the size of the patient. In older children and adults, the deoxygenated blood is drained from one or both femoral vessels and the oxygenated blood is returned through the

right-internal jugular vein. After the return to the venous system, oxygenated blood passes through the pulmonary system and therefore the gas exchange is sufficient. The optimal ECMO flow is assured by optimization of venous drainage [Betit, 2009]. VV ECMO can also be introduced by a single double-lumen cannula, which allows drainage and return through the right internal jugular vein [Betit, 2009, Lindstrom et al., 2009]. The cannula consists of the two channels; one is used for draining the deoxygenated blood from the vena cava and the second is placed into the right atrium where the oxygenated blood is sent. When the placement is proper, the suitable gas exchange is achieved and just one vessel is affected. The insertion of double-lumen cannula is easier and the complications associated with femoral cannulation are eliminated. However, the flow limitations may occur [Betit, 2009].

In VA ECMO deoxygenated blood is drawn from venous system and oxygenated blood is re-infused into the arterial circulation, which provides gas exchange and cardiac support [Betit, 2009, Lindstrom et al., 2009]. There are two possible ways of cannulation - peripheral and central. With central cannulation, blood is drained from the right atrium and re-infused to the proximal thoracic aorta. With peripheral cannulation, blood is drawn from femoral or jugular vein and re-infused to the aorta via carotid, axillary or femoral artery. The femoral cannulation is useful, because the compressible site can help in haemorrhage control, but these vessels are usually too small in neonates, so it is most commonly used in adults. When high ECMO flow is required, it is possible to use twin drainage cannulae - jugular and femoral [Lindstrom et al., 2009]. VA ECMO, in general, is more commonly used in neonates, especially when both heart and lung function is threatened. In neonates collateral circulation develops, so cannulation and ligation of the carotid artery is tolerated and therefore cardiac and also pulmonary support is achieved [Betit, 2009].

2.4.1 History of ECMO

Since 1953 when Gibbon used first extracorporeal oxygentation during open heart surgery, ECMO and other extracorporeal technology have continued to develop [Lindstrom et al., 2009]. Recently, ECMO is most commonly used for patient with acute respiratory distress syndrome (ARDS). Patients with the most severe forms of this disease usually have a bad prognosis and mortality can be 60%. In these situations, ECMO may minimize the trauma caused by mechanical ventilation and might be a therapeutic option for the lungs to be recovered. Nevertheless, at the beginning of ECMO use, most of the trials have shown no advantage of ECMO compared to mechanical ventilation. The complications were mostly caused by severe bleeding due to the use of anticoagulation and weak biocompatibility of the circuits [Schmidt et al., 2012]. In 1979 Zapol et al. made a randomized trial where nine medical centers collaborated in order to find out if ECMO has a benefit as therapy for patients with acute respiratory failure. It has been shown that ECMO did not increase the likelihood of long term survival [Zapol et al., 1979]. In 1994 Morris et al. have shown in a randomized study with ARDS patients that there was no significant difference in survival with use of ECMO compared to mechanical ventilation [Morris et al., 1994]. The early attempts to use ECMO for adult patients were unsuccessful, but the neonatal experience has led to better understanding and improvement in ECMO technology [Betit, 2009]. In 1996 Green et al. made a study for investigating the impact of ECMO in pediatric patients with acute respiratory failure. They have found that ECMO had a positive effect on survival; the mortality in patients treated with ECMO has been reduced [Green et al., 1996]. UK collaborative ECMO trial group has shown the effectiveness of ECMO in neonatal patients. They demonstrated that ECMO should be considered as an option for neonates with severe but potentially reversible respiratory failure [Field et al., 1996]. As early as 1985, it was shown that ECMO improves survival in neonatal patients with severe respiratory failure

compared to conventional ventilation [Bartlett et al., 1985]. However, the patient outcomes in children with respiratory failure associated with hematopoietic stem-cell transplantation have not been found encouraging. The survival in these patients was reported to be poor [Gow et al., 2006]. In the last ten years, outcomes in adult patients have improved. Linden et al. [Linden et al., 2000] have shown a high survival in patients with severe ARDS when treated with ECMO and pressure-supported ventilation [Linden et al., 2000]. In 2004 Hemmila et al. also proved the effectiveness of ECMO in adult patients with ARDS. They have found ECMO as a good option for treatment in cases when patients are not responsive to conventional approach [Hemmila et al., 2004]. Recently, the encouraging results continue to appear mostly due to higher biocompatibility and performance as well as increased durability [Schmidt et al., 2012]. In 2009 after their randomized trial, Peek et al. [Peek et al., 2009] have recommended ECMO as a good option for adult patients with severe but potentially reversible respiratory failure [Peek et al., 2009]. Good outcomes were also reported in patients who received ECMO as a therapy during A(H1N1) influenza pandemic in 2009. Several studies have reported lower mortality in patients who received ECMO than in patients who have not been treated with ECMO [Patroniti et al., 2011, Noah et al., 2011, Roch et al., 2010]. These new encouraging results started an increased interest in ECMO as a treatment for ARDS. In the past, the unsuccessful tries could be caused by a lack of adequately educated and qualified medical, nursing and perfusion staff. The availability of assistant devices such as echocardiography was also limited and the concerns about safety and efficacy were presented [Lindstrom et al., 2009]. A lot of these concerns and deficiencies have been improved in last ten years. The knowledge about ECMO has been developed as well as the experience of the staff. The technology has been improved; devices are miniaturized and therefore more available. All these changes and improved patient's outcomes in last few years signals a strong potential of ECMO application.

2.5 ECMO training

This section is focused on exploring the existing tools for ECMO training with emphasis on model based simulators. The goal is to find what kind of tools, models, simulations and simulators are available for ECMO training.

There are two most used types of ECMO training - computer based simulations and educational courses with hands-on simulations. Computer-based applications can be very realistic and users can learn a lot from them. They also do not need a lot of equipment compared to the other type. On the other hand, simulations where the students or novice learners are using the actual ECMO circuit and mannequin are definitely closer to reality. A disadvantage is that simulation courses like this are available just at a few institutions. On the contrary, for a computer-based simulation you need only a computer and simulation program.

Both ways have their pros and cons. Computer-based learning is definitely more available while hands-on simulation courses are closer to reality.

ECMO is a treatment for a patients with very severe health conditions, but it may cause more harm if the staff is not sufficiently trained. The purpose of all types of simulations is to improve confidence and crisis management during work with ECMO. This research is focused on simulations led by a computer.

2.5.1 Online training applications

The research in this subsection will be centered on online ECMO trainers and simulators. An overview of the applications is important in order to find out what types of simulators already exist and what would be useful to improve during the design of a training application.

ECMOjo

ECMOjo simulator has been developed by the Telehealth Research Institute (TRI), John A. Burns School of Medicine (JABSOM) of the University of Hawaii. It is a computer application implemented in programming language Java. ECMOjo is possible to use for all major operating systems including Windows, Macintosh, Linux and Unix. The application has a graphical user interface (figure 2.7) for training nurses, students and physicians in the basics of ECMO [Aschwanden et al., 2009].

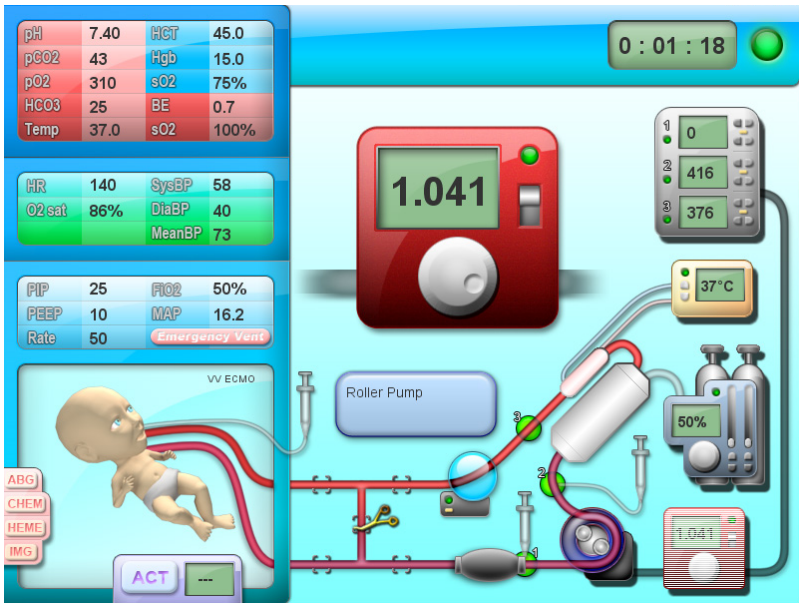


Figure 2.7: Graphical interface of simulator ECMOjo [Aschwanden et al., 2009]

It is possible to download this application online and for free as well as its Java source. ECMOjo simulator consists of a scenario and simulation part. In the scenario part, the developers describe how ECMO in general works, how the simulator is controlled and what is an appropriate solution for different problems in leading an ECMO device. In the simulation part, there are different types of crisis scenarios. During each scenario, some problem arises and the user is supposed to solve the problem by fixing an appropriate part of the circuit or changing certain settings. At the beginning, the user can choose the type of circuit, oxygenator and pump. The application also offers the possibility to have humans or pigs as patients. The program allows users to choose how the patient's lungs work, but only if the function is good or bad. If the user fails during the simulation, the patient dies. If the user succeeds, the patient survives. ECMOjo is suitable for learning how ECMO works but also how to control the device.

The online application works satisfactorily even though sometimes it crashes and the user is not able to run it until the computer is restarted. The mathematical model behind the application has very complex and untransparent structure. Therefore, possible improvements can be made by the programmer only.

MSE simulator

MSE online simulator was developed by a hard- and soft- ware company MSE (Australia) PL in Australia, Sydney. It is a screen-based implementation of a high-fidelity, medical simulation system - "The Modular Simulation Environment" (MSE) (figure 2.8). MSE was developed with an intention to teach the principles of VV and VA ECMO to people working in the fields of

Intensive Care, Anesthesia and Perfusion. MSE simulates both VV and VA ECMO in adults. The simulator was implemented in programming language C# and can be installed on computers with Windows operating system [Pybus, 2009]. MSE simulator is available online and for free. The file which is downloaded together with the simulator includes a number of tutorials in pdf, presentation about the simulator and the group work and few explanatory videos.

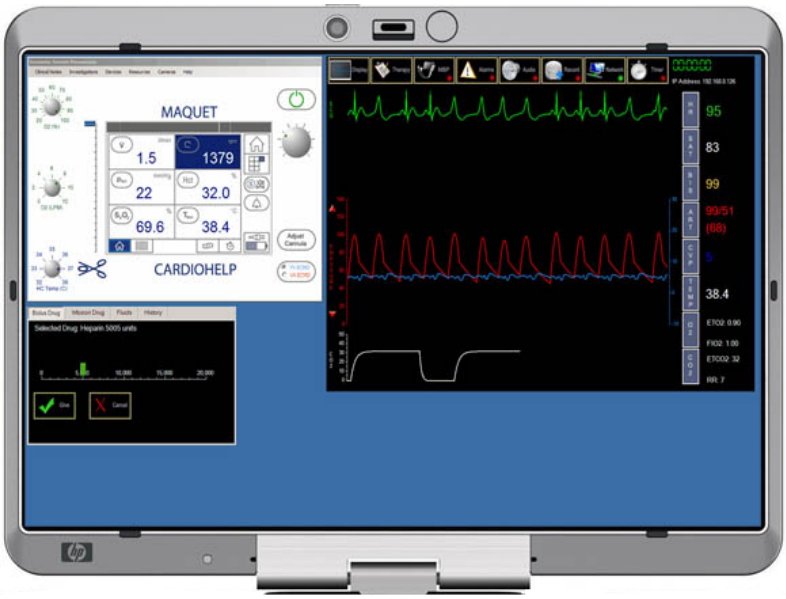


Figure 2.8: Graphical interface of MSE simulator [Pybus, 2009]

The computer model describes the physiology and pharmacology of an adult human as well as the behavior of number of medical devices. It also calculates physiological, pharmacokinetic and mechanical variables in real time. The simulator has a lot of components such as a virtual patient, ECMO system with centrifugal pump, hollow-fibre oxygenator, physiological monitor, ventilator, defibrillator, data recording system, drugs and fluids for treating the virtual patient and a scenario database. The virtual patient consists of 20 real-time models. They can be adjusted by a supervisor in order to express different states of the patient's health condition. The trainee is supposed to treat the patient with any drugs or devices available. The available devices are for instance ventilator, defibrillator, nerve stimulator, stethoscope, ACT machine and of course VV and VA ECMO. The simulation scenario can be controlled by a supervisor who runs a separate application oh his/her PC, PDA, netbook or mobile phone. The supervisor can change patient's clinical state and simulate a wide variety of crisis including oxygenator failure, inlet obstruction, outlet obstruction, fresh gas disconnection, massive blood loss, changes in lung function and changes in cardiac function.

The evaluation version of the simulator is free to download on the MSE home page, but the source is not accessible. However, the simulator fails to start.

ECMO patient simulator

Another simulator available online is ECMO patient simulator (EPS) developed by the company BioMed Simulation from California. EPS is designed to simulate patients before, during and after total or partial ECMO support. It is a programmable, medium-high fidelity simulator system. EPS was designed as an attachment to any ECMO machine circuit. The purpose of developing EPS was to create a tool for teaching and also for evaluating the performance of

ECMO operator during the lead of an ECMO device. This simulator consists of four parts - ICU monitor, controller display, laptop and patient module (figure 2.9) [Tallman, 2012].

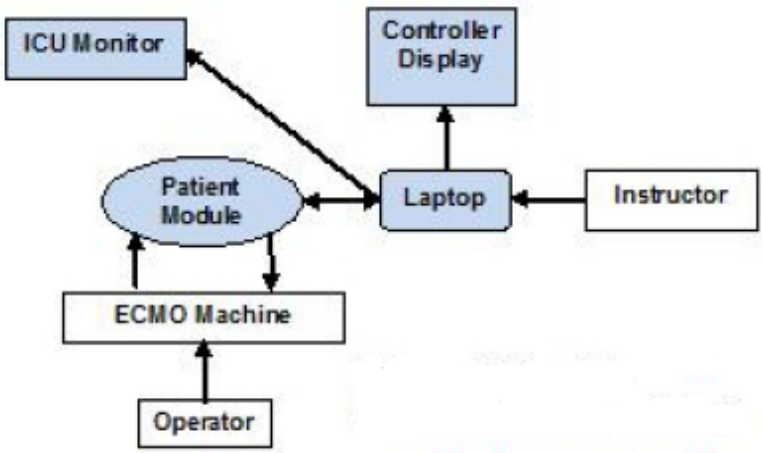


Figure 2.9: Simulator components shown in blue [Tallman, 2012]

The patient module consists of tubing and a reservoir system with transducers attached to a computer with Windows operating system by an A/D converter module. Information from the patient module provides feedback related to the lead of ECMO and is sent back to the computer. The computer uses the information for driving a separate monitor which serves as ICU monitor and displays variety of patient data [Tallman, 2012].

ICU monitor displays a ventilator and also controls the oxygenator values such as sweep rate and oxygen fraction. This monitor is a touch-screen display that offers to ECMO operator the possibility to make visible or hide ventilator and oxygenator settings. The operator is also able to adjust the settings of ventilator and oxygenator. The ICU monitor can also display ECG and a number of additional OR monitors such as Activated Clotting Time (ACT) machine, in-line blood gas monitors or outputs from various POC (point-of-care) devices such as blood gas analyzers [Tallman, 2012].

The controller display which is the computer screen is used by operator or instructor. The operator is able to manipulate with a variety of patient's physiological parameters and control the progress of the scenario via controller display. It allows the instructor or operator to make notes and annotations to the pump record. The controller display has the ability of setting the pre-programmed clinical scenarios. These scenarios are among the most important features of ECMO patient simulator [Tallman, 2012].

ECMO simulation program is an additional program which is identical to EPS with controls for blood flow on the controller display. This program is an opportunity to teach and test ECMO without the actual use of an ECMO machine [Tallman, 2012].

The websites of this simulator display just pictures of the actual simulator and includes very basic description. From the information available online it is not possible to imagine the real program very well.

2.5.2 Other types of simulators

This part of this research will be focused on the other types of simulators and training tools for the ECMO training. The focus in this part was centered on other possibilities how to train ECMO. They were mostly simulators with a mannequin and a real ECMO circuit which were

controlled by a computer. An advantage of this kind of simulators compared to computer applications lies in a more realistic controlling of the device. During hands-on simulation, the user controls ECMO by an actual button instead of clicking in the case of computer application.

ECMOsim

This simulator is in the production prototype phase but it seems the result will be possibly very interesting (figure 2.10). ECMOsim will be a model of a baby in real size as well as the ECMO machine [Antonius and Peeters, 2011]. This is another possibility how to train the leading of ECMO. Trainees can work with the circuit in real sizes and manually try to control all necessary features. No model is ideal, but this is an interesting option for learning how an ECMO machine works.

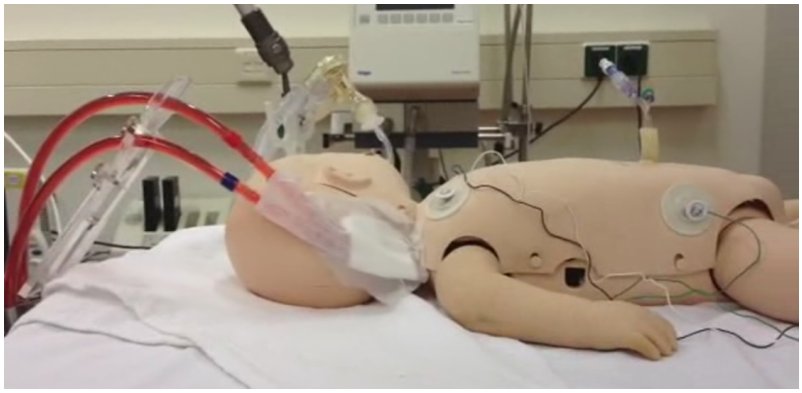


Figure 2.10: The prototype of simulator ECMOsim [Antonius and Peeters, 2011]

ECMO simulation training

The Hawaiian medical center created a video tutorial as an educational tool to show how ECMO simulation can be easily performed using a simulation program, standard ICU equipment and an actual ECMO circuit (figure 2.11). This simulation was created as part of the training program for students. This kind of practice is very good imitation of a real situation of leading ECMO. The team has some prepared scenarios and students are able to try to solve the problem which arises during the conduct of an ECMO. The medical center's website includes also ECMO simulation documentation in pdf which explain some scenarios [Vara, 2012].

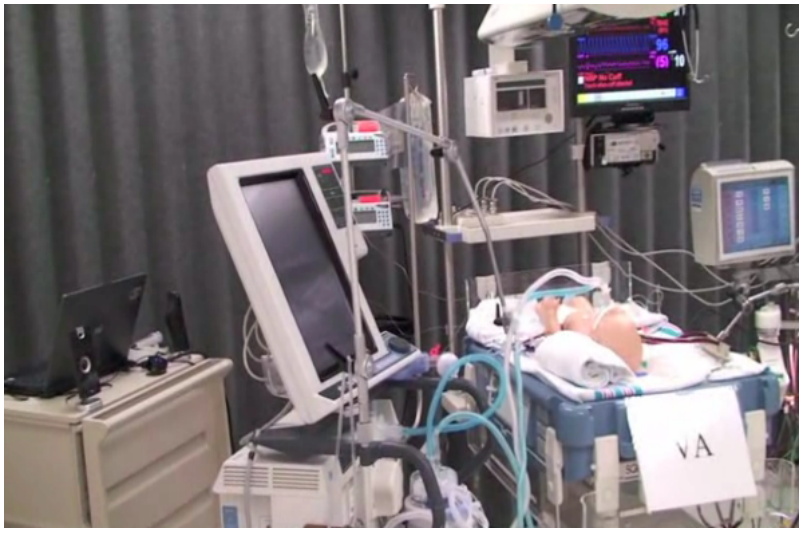


Figure 2.11: ECMO training equipment [Vara, 2012]

ECMO crisis training

In Minnesota's Mayo Clinic, the department of cardiovascular perfusion developed and tested a clinical simulation program for training the conduct of postcardiotomy ECMO. The purpose of the training was to improve confidence, proficiency and crisis management. The role of simulation in the ECMO training of thoracic surgery residents is growing due to concerns for patient safety and limited resident work hours [Burkhart et al., 2013].

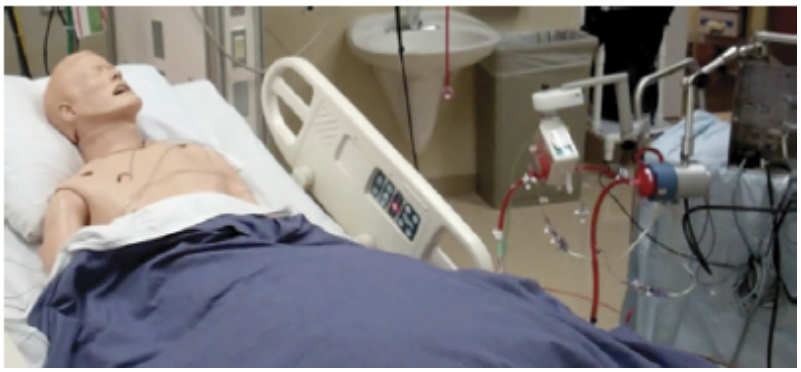


Figure 2.12: Hands-on simulation set-up [Burkhart et al., 2013]

Twenty-three thoracic surgery residents participated in the ECMO training course consisting of didactic lectures and hands-on simulation. The set-up for hands-on simulation included a patient with cardiac and oxygen saturation monitor and postcardiotomy ECMO circuit (figure 2.12). Pretraining and posttraining knowledge and confidence were evaluated. Residents were asked to identify the components of the ECMO circuit and manage crisis scenarios. The didactic part of the course included presentations by specialists about extracorporeal circuit components, evidence-based perfusion techniques, practical aspects of anticoagulation and hemostasis, high-risk patient case reports and about extracorporeal life supports and ventricular assist devices. The hands-on simulation part included focus on common ECMO variances and the diagnosis, patient effects and a safe resolution of the complication. The residents were divided into small groups of 3 to 4 students with roles of anesthesiologist, surgeon and perfu-

sionist. The communication and the team roles were observed, analyzed and built up [Burkhart et al., 2013].

All 23 residents completed the training. The results have shown that before the training the students had a difficulty with identifying ECMO components such as the gas source and flow rate, centrifugal pump head inlet and oxygenator outflow line. The results improved very much after the training. The residents had also difficulties with giving appropriate timely treatment recommendations during the crisis scenario before the training. There were only 22% suitable recommendations. The results improved significantly after the training. Most of the residents were able to manage the crisis scenario correctly and in a timely manner [Burkhart et al., 2013].

It is obvious from this study that after the simulation training programme the residents are more confident and skilled for a conduct of ECMO. This kind of training seems to be appropriate for practicing the management of critical ECMO-related problems. Mayo clinic has excellent facilities for developing such training. The center has four large team training rooms simulating emergency room, ICU patient room and endovascular suite. Each room also has a debriefing and control room [Burkhart et al., 2013].

ECMO education programme

A study about the impact of a simulation-based module on novice learners in ECMO education programme has been made. It was also tested how long the skills acquired during the training were retained. The theory was that the simulation part added to the ECMO curriculum should improve the comfort and confidence among the participants. The participants were physicians, registered nurses, nurse practitioners and respiratory therapists. The curriculum of this training course consisted of didactic lectures, hands-on experience with the ECMO circuit and crisis ECMO scenarios performed on a mannequin [Chan et al., 2013].

For determining the effects of the course on the participant's knowledge, ability and confidence level, pre- and posttraining questionnaires were used. For determining if the skills were retained, the participants were required to take the simulation test again in 6-8 months. By the end of the training, the participants were required to pass a written test (which meant achieving a 90 percent score) and demonstrate that they were able to manage selected crisis scenarios with a team [Chan et al., 2013].

Twenty-four from 26 participants passed the written and practical test. One participant failed the written test and one failed the practical test. Twenty-two participants rated the education program at 4 or higher (5 = very useful) in improving their overall knowledge, ability to fulfill the required critical performance criteria in simulated ECMO crisis scenarios and overall confidence. Twenty participants decided to take the reevaluation test. All of them showed success in the simulated ECMO emergencies and 18 answered the questionnaires completely [Chan et al., 2013].

This kind of training was shown as an effective method for improving knowledge, ability and confidence levels among novice ECMO specialists and physician trainees. A lot of studies have shown that simulation-based training programs seem to be very useful due to the realistic simulation in real time and the clinical cues generated by the mannequin. It also appears to improve team function in a critical clinical situations [Chan et al., 2013].

CHAPTER 3

METHODS

It was shown in the research in the previous section 2.5 that there are several computer applications available online as well as other ECMO training possibilities. It was found that the hands-on simulation training is closer to reality, but much harder to realize. Therefore, it is more realistic to create a computer application than a real size patient simulator with an ECMO circuit. Even though hands-on simulations are better to learn due to a real ECMO device and a mannequin, online applications are also useful for learning and increasing the confidence in working with ECMO. Therefore, I have decided to design a computer application. Only one computer application has the source code available and one is possible to run without troubles. My intention is to make the source and application available online for free use.

3.1 Design of a computer application

The first goal of my master thesis was to create a model with particular functions in order to represent the behavior of the human body when the lungs work insufficiently and their function is supported by an ECMO device and mechanical ventilation. The second goal is to create a design of a computer application which represent these functions also visually and can be used as an educational tool for a deeper understanding of ECMO. In this section, the idea what the computer application should look like in the future will be presented.

3.1.1 Basic functions of the application

As it was shown previously in the chapter 2.5, some computer applications or simulators about ECMO already exist. They have some common aspects and they are different in some other ways. The most important feature which is supported by each of the simulators is the settings of ECMO flow. It is the main property of an ECMO device, so it is necessary for the application to be able to show the dependency of blood properties on ECMO flow. An ECMO device is sometimes used for changing the body temperature of the patient. Therefore, the future training application based on my model will have this function as well. The temperature will be set in ECMO and the temperature change will be seen in the tissues. One of the experiments with the model has shown that the patient is heated up from $25°C$ to the normal temperature around $37°C$ in about one and half hours. Another common function of the ECMO simulators is the settings of oxygen fraction in ECMO oxygenator. This function is also presented in my model, even though one assumption has been made. The oxygen fraction is assumed to be equal to partial pressure, so in the ECMO component, it is possible to change the partial pressure of oxygen and therefore the oxygen fraction. Another feature of some simulators is the lung function setting. It usually has just two possibilities - a bad and a good state of the lungs. My model and consequently the future computer application will allow the user to set the lung function

on a number of different states by changing the pulmonary shunt. Specifically, the user will be able to set the percentage of the venous blood which is mixed with the arterial blood. ECMO function is usually supported by mechanical ventilation with low tidal volume. The ventilator in my model also helps to fulfill the processes of oxygenation and carbon dioxide removal. It will be possible to set the tidal volume, oxygen and carbon dioxide fraction in the inspired air and the breathing rate. Default values of tidal volume, carbon dioxide fraction, oxygen fraction and breathing rate are set to be 0.1l, 0%, 21% and 0.2breaths/s, respectively. In the model of the tissues, it is possible to change the values of carbon dioxide production (VCO_2) and oxygen uptake (VO_2). Therefore, one of the functions of the application may be the possibility to change VCO_2 and VO_2 and observe the changes in arterial blood in relation to ECMO flow. ECMO flow needs to be increased with an enhancement of the activity of the patient's metabolism.

Another important function of a real ECMO device is displaying the blood properties on a screen in order to enable a constant check of the patient's condition. The training application based on my model should display the properties of venous and arterial blood listed in table 3.1.

Blood properties	**Units**
pH	–
pCO_2	kPa
pO_2	kPa
HCO_3	mmol/l
sO_2	%
temperature	$°C$

Table 3.1: Blood properties which should be displayed on the blood monitors

3.1.2 Scenarios

The application should be a nice visual tool where the user is able to change the values of variables and observe how it affects blood properties. It should display how ECMO and mechanical ventilation cooperate in supporting the lung function. The blood properties are going to be displayed on the screens and the user should be able to stabilize the patient by changing the appropriate variable. Examples of some possible scenarios are listed below.

Scenario 1 - ECMO and mechanical ventilation settings

If ECMO flow is decreased and mechanical ventilation settings are changed, so that tidal volume (V_t) is increased, blood properties should be kept at a sufficient level. On the other hand when ECMO flow is increased, V_t can be easily lowered and the oxygenation and carbon dioxide removal should be appropriate. Since ECMO flow is the most important feature of the device, the dependency of all the blood properties on its change should be clear. The model is able to react to ECMO flow changes. Therefore, the user should see blood properties variations after changing the flow. The model allows the user to change the oxygen fraction in the ECMO oxygenator. Therefore, if it is necessary and an increase of ECMO flow is not sufficient for the appropriate oxygenation, oxygen fraction can be increased and it may help during the gas exchange.

Scenario 2 - the change of carbon dioxide production and oxygen uptake

Another function is the change of the carbon dioxide production (VCO_2) and oxygen uptake (VO_2). The scenario can demonstrate how the system reacts if VCO_2 and VO_2 are set to be higher. The user has to solve the problem by changing the appropriate settings.

Scenario 3 - worsening of lung function

Pulmonary function can also be changed by changing the pulmonary shunt and therefore the influence should be seen on the screens. As the pulmonary shunt will be increased, blood properties will be worse and therefore it would be appropriate to increase ECMO flow.

3.1.3 Availability

The application should be available online as a web application and free tool. The main target group is the students of medicine and biomedical engineering as well as new medical staff such as nurses. Therefore, it should be useful as an educational tool for e-learning at home, at universities and at high schools as a supplementary material.

My future application will have one very big advantage compared to others available on the Internet. The underlying model will be available online, so everyone who is going to use it will be able to download the code of the model. Therefore, if a mistake is found, the user can correct it and improve the application. The idea is that in the future, it can become a very advanced and useful training application by cooperating with interested users.

3.1.4 Visual site of the application

Figure 3.1 shows what the visual site of the application may look like. The settings should be adjusted by the buttons on the devices. The flow should be changed by the button under the pump, the oxygen fraction by the buttons on the gas cylinder, and the ventilator settings as well as lung insufficiency on the appropriate screen. The actual arterial and venous blood properties should be displayed on the screens where the user can check the progress of adjusting the settings.

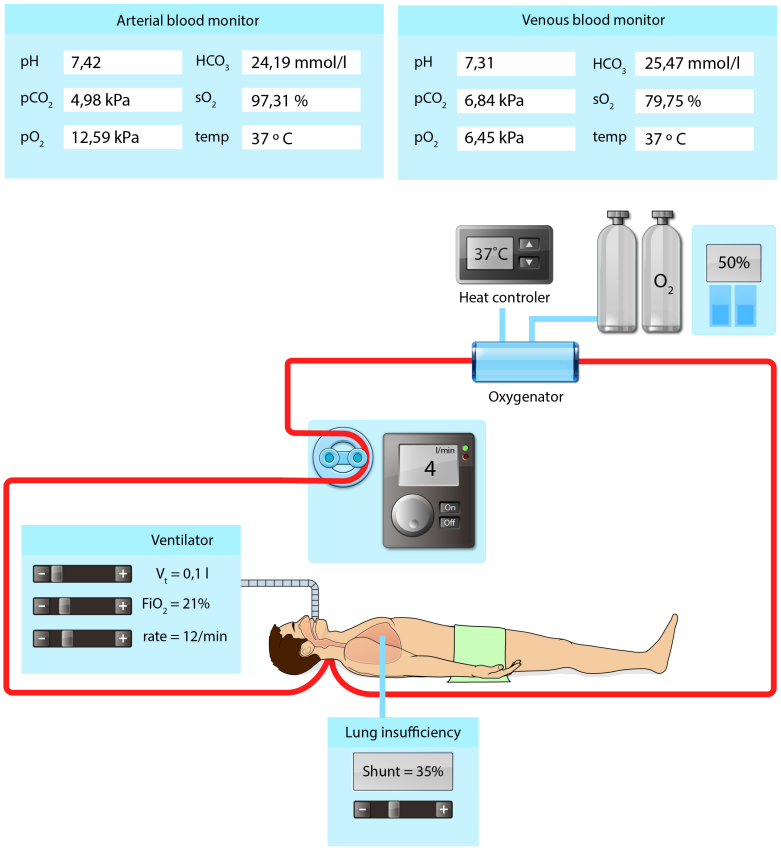


Figure 3.1: The idea of the future application look

3.1.5 Summary

The idea of the design of the training application is that it should represent the dependencies of blood properties on ECMO flow and other ECMO settings, as well as on the mechanical ventilation settings. It should be used for different educational purposes. Trainees should be able to learn how ECMO and mechanical ventilation work and how the settings can affect the blood properties.

Undoubtedly, the model has some limitations and as a result the computer application may have them as well, but it should allow the user to see the most important processes and dependencies during changing the settings.

3.2 Modelica language

As a tool for creating the model, the modeling language called Modelica was used. Modelica simulation environment called Dymola was chosen to create the model in.

The effort to design an object-oriented modeling language was initiated by Hilding Elmqvist in 1978 and started in 1996 within an action of the ESPRIT project "Simulation in Europe Basic Research Working Group" [Otter and Elmqvist, 2001]. The language has been created by the developers of object-oriented modeling languages such as Allan, Dymola, NMF, ObjectMath, Omola, SIDOPS+, Smile as well as practitioners in different domains. The first version used in real application, version 1.3., was finished in December 1999. One year later in December 2000, an update version 1.4. was made [Otter and Elmqvist, 2001].

Modelica is an object-oriented, equation-based programming language. This language specializes in high complex computational applications which require high performance. There are four important features of this programming language which make it powerful and easy to use. Firstly, Modelica is primarily based on equations instead of assignment statements and it allows acausal modeling. Equations do not specify certain data flow direction so Modelica provides a better reuse of classes. A Modelica class is able to adapt to more than one data flow context [Fritzon, 2004]. Secondly, Modelica is a multidomain programming language, meaning that it is possible to describe and connect model parts from varying domains such as electrical, mechanical, thermodynamic, hydraulic, biological, and control applications. Thirdly, Modelica has a general class concept that unifies classes, generics and general subtyping into a single language construct. This feature makes it easier to reuse components and aids in the development of the models. Finally, Modelica has a strong software for designing and connecting components, meaning that this language is suitable for an architectural description of complex physical and software systems [Fritzon, 2004].

A model developed in the Modelica language consists of several submodels with acausal connectors which allow an exchange of out- and incoming information. The Modelica language then works with subcomponents, connected via connectors, which represent instances of classes. The classes in Modelica have a special section called equation where the equations are defined. The character of the equations is different compared to other object-oriented programming languages such as Java, C# and so on. The equations in these types of languages are assignment statements, it means that the result of an assigned command is saved in the variable whereas in Modelica they define the relationship between variables in the same matter as in mathematical or physical equations [Kroček, 2011].

3.2.1 Connectors

Connectors are exactly defined interfaces which connect certain submodels. They define variables which are part of the communication interface and therefore they specify external interfaces for interaction [Fritzon, 2004]. The connection is possible just for the same connector classes and it is resistant to errors. Another advantage is that by connecting the submodels, the connection of sets of equations from each component occurs. In electrotechnics, the voltages of the connected wire ends are the same; it corresponds with the Kirchhoff's first law. The same works for Modelica where by connecting two components, values of the variables are the same. The Kirchhoff's second law also works in Modelica. In the connector, it is possible to define one flow variable so that the sum of all flow variables in the model is zero. It means that the values of flow variables in all components which are connected together will be set in a way that inflow will be equal to outflow. The flow cannot be lost or accumulated in the connection point. In Modelica language, the connection of the parts does not define the calculation procedure but the modelled reality. The way of solving the equations is then "left up to the machines" [Kroček, 2011, Kofránek et al., 2008].

Stream connectors

In the Modelica language, there are different types of variables. *Stream* variables are very useful in case of concentration mixing [Olsson et al., 2012]. The Stream is a special type of connector variable, declared with the prefix Stream. A *stream* variable describes a quantity that is carried by a *flow* variable. The value of the *stream* variable is different than on the connector, *stream* variable is a property close to the boundary assuming that the fluid flows out of the component into the connection point. Stream describes bi-directional transport where one direction is right and one direction is wrong in the sense of the correct functioning of the model. The rule

of *stream* variable is that the user has to describe both directions. As mentioned above, *stream* variables are especially useful for concentration mixing. For instance, there are two jars with different concentrations of the fluid. The jars are connected by tubes, so the concentrations in the connection point will be a mix of concentrations weighted by the flow.

If at least one variable in the connector has the prefix Stream, the connector is called "stream connector". There are several definitions regarding these types of connectors. There has to be only one *flow* variable in the stream connector. The prefix Stream is used only in the connector declaration. For generating the equations in the components, operators inStream() and actualStream() are used. One equation is defined for every *stream* variable [Olsson et al., 2012].

The stream connectors are used in the Modelica Fluid Library. It is a free Modelica package which provides basic interfaces and components for thermo-fluid systems. The purpose of this library is to provide standard connectors which suit to a wide range of needs, show how to realize elements of thermo-hydraulic processes in Modelica and provide a decent number of components which can be changed for the particular user application or used as they are [Casella et al., 2006].

3.2.2 Causal and acausal modeling

A model in block-oriented modeling language can be seen as a connection of individual blocks where each of them has a specific function. Signals are transmitted through connections of individual components. The signals transfer the values of variables from the output of one block to the input of another. Input information is processed in the block to output information. This type of modeling is called causal or block-oriented and languages such as Simulink are used. Thus, the model describes rather the calculation procedure than the very structure of the modelled reality. In complex systems, physical reality of the modelled system can be covered under the computation structure [Kroček, 2011, Kofránek et al., 2008].

Due to the loss of clarity in complex systems, acausal (declarative) modelling techniques start to be used in recent times. Individual parts are directly described as equations and not as an algorithm of the solution. By connecting individual components, the sets of equations become connected with each other. The model developed by acausal approach represents the modelled physical reality by the generalized properties of the real world [Kroček, 2011,Kofránek et al., 2008].

Relationships between all types of variables are similar in each domain. There are variables of generalized effort e(t), generalized flow f(t), generalized momentum p(t) and generalized accumulation q(t). The relationships between them are well explained in picture 3.2. Variables of generalized effort are voltage in electrical diagrams, force in mechanics, pressure in hydraulics etc. Variables of generalized momentum correspond to an integral of generalized effort and they represent kinetic energy. It is for instance flow momentum in hydraulics and induction in electrical diagrams. Third type of variables is generalized flow which is for example current in electrical diagrams, velocity in mechanics, volume flow in hydraulics, heat flow in thermodynamics. Variables of generalized accumulation correspond to an integral of generalized flow and accumulated potential energy. These variables include the extension of a spring in mechanics, volume of the fluid in hydraulics, charge in electrical diagrams and accumulated heat in thermodynamics. It means that we can use similar equations for describing different types of systems [Kofránek and Hozman, 2013].

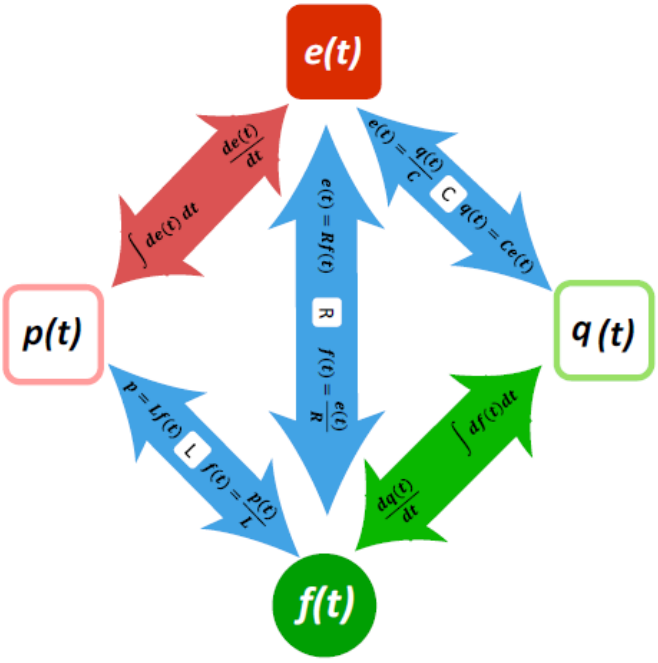


Figure 3.2: Relationships between generalized system properties; R, L and C represent the constants of proportionality between individual generalized system properties - resistance, mass or capacitance

For a better understanding of the difference between causal and acausal approach, simple model of the mass on the spring is shown. An advantage of the acausal modelling is obvious as soon as the model is more complex. This example has one difference compared to the previously explained generalized properties. The effort variable is the position and flow variable is the force. This approach is more useful in the case of this example.

3.2.3 Example of a model of mass on the spring

This simple model consists of three parts as it is shown in picture 3.3. These three parts are the *mass*, the *fix* and the *spring*. The *fix* is used for fixing the *spring*. The *joint* is an interface which connects all the parts together as mentioned previously. The harmonic oscillator works in a very simple way, the *mass* on the end of the *spring* causes periodical movement of the *spring*.

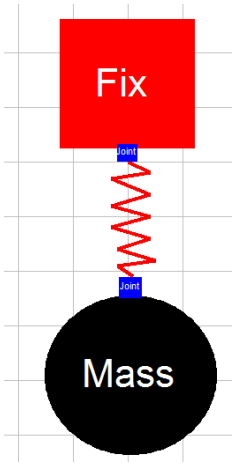


Figure 3.3: Harmonic oscillator in Modelica interface

The harmonic oscillator is a system that experiences the restoring force when it is displaced from its equilibrium position. The restoring force is proportional to the displacement. The equations which describe all four parts of the system are placed in table 3.2.

Model	**Equation**
fix	$y = 0$
spring	$F_1 = F_2$ $F = -k \cdot dy$ $dy = y_2 - y_1$
mass	$F = m \cdot a$ $a = \frac{d^2y}{dt^2}$

Table 3.2: Equations describing harmonic oscillator (y - position, F - force, dy - displacement, a - acceleration, k - stiffness constant, m - mass, t- time)

These kinds of model equations are simple enough to write in both causal and acausal approach. It will be shown below what the equations of each parts of the model look like in the Modelica language. The equation of the subcomponent *fix* is very simple and it says that there is no displacement which means the position stays zero. Picture 3.4 displays the submodel *fix* and its equation written in the Modelica language.

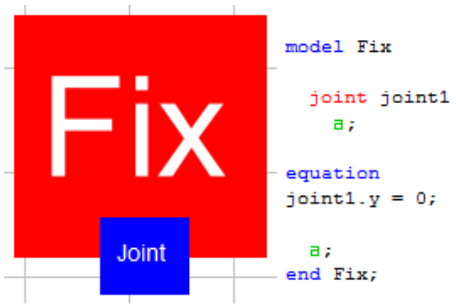


Figure 3.4: Component fix and its equation

The component *spring* is described by three equations as seen in table 3.2. First equation

explains that the forces on both ends of the *spring* are equal. The second equation says that the force can be calculated as multiple of stiffness constant k and displacement dy. The third equation describes the calculation of the displacement, so that it is the difference between joint positions. All three equations are shown in picture 3.5 as written in the Modelica language.

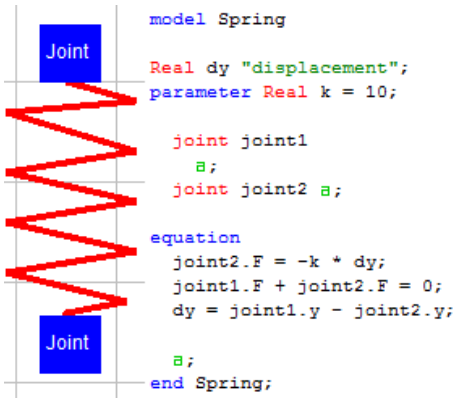


Figure 3.5: Component spring and its equations

The last component named *mass* is described by two equations. First equation is well known from the Newton's second law. This law states that acceleration of the object is directly proportional to the force, which affect the object and inversely proportional to the mass of the object. The force has the same direction as the acceleration. The force can therefore be described as a function of the acceleration as shown in table 3.2 [Jewett and Serway, 2008]. The second equation describing component *mass* is a differential equation which defines the calculation of the acceleration. It says that the acceleration is equal to the second derivative of position divided by the first derivative of time on the power of two. The way of writing differential equations is different in acausal languages compared to the causal approach, see figure 3.6. It is not possible to write the second derivative straight into the Modelica language. Each derivative of high order could be written as a set of the first order. Therefore, the velocity is defined as a first derivative of the position and the acceleration is described as a derivative of velocity.

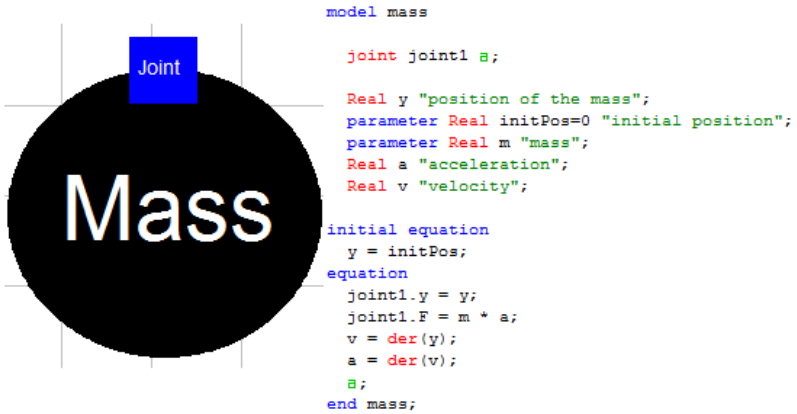


Figure 3.6: Component mass and its equations

The connector *joint* is a very important part of the system. It connects all the parts together. The connection causes that the sets of equations from each part are automatically connected as well. In the connector there are variables which are important to each of the parts and which

are necessary to transfer between all the components. These most important variables are in this case the force and the position. Picture 3.7 shows the way of defining the variables in the connector. The force is in this example the flow variable, so it means that the Kirchhoff's second law is applied on the force as seen in picture 3.5. The second equation says that force on the second joint plus force on the first joint are equal to zero, it means that they are equal, but with opposite direction. It means that the inflowing force is equal to minus outflowing force.

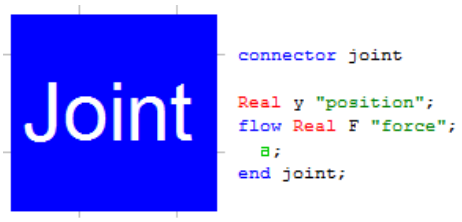


Figure 3.7: Connector joint and the definition of the variables

Equations described previously are simple to write in any programming language using causal and also acausal approach. However, as soon as the equations, especially differential equations, are more complex, it is very complicated to invent and write the algorithm of the calculations in causal programming language. A good example is a double spring mass system where the differential equation is much more complicated than using just one spring in the system. The set of differential equations for a double spring mass system would look like the equations 3.1 and 3.2. It would be more difficult to invent an algorithm for solving those kind of equations by causal approach. As seen in figure 3.8, in the Modelica language the springs are just manually connected and the system connects the sets of equations itself without hard computation effort for the programmer.

$$m_1 \frac{d^2 y_1}{dt^2} - k_2(y_2 - y_1) + k_1 y_1 = 0 \tag{3.1}$$

$$m_2 \frac{d^2 y_2}{dt^2} + k_2(y_2 - y_1) = 0 \tag{3.2}$$

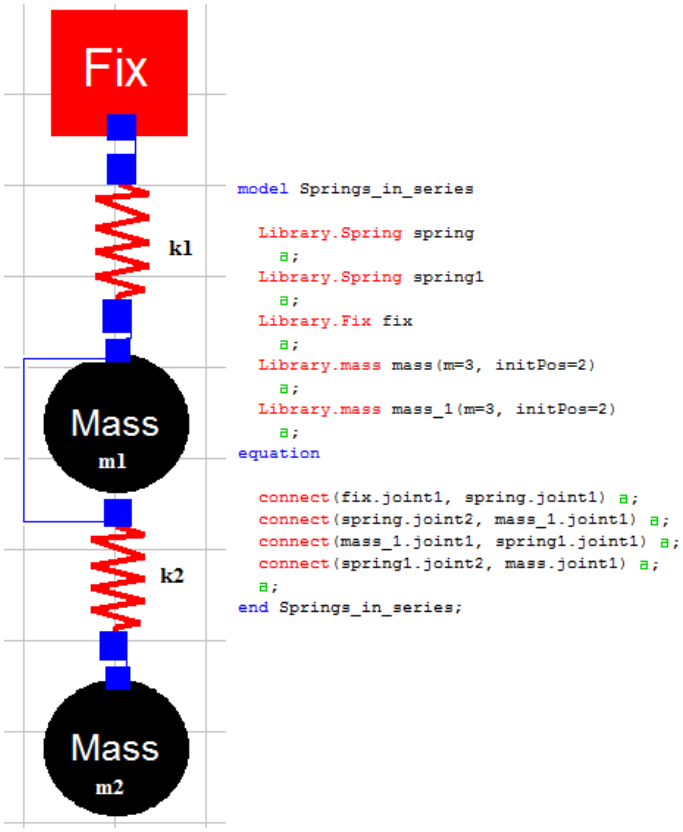


Figure 3.8: Double spring oscillator

For a demonstration, the plots of the mass position change are shown. Before running the simulation, it is necessary to define the initial position of the mass where the ball starts to move. Both balls have the same values of initial position and mass. The initial position is two and the mass is three. It is also necessary to define the simulation time, I chose fifty seconds. Figure 3.9 displays the movement of one single mass on one spring. Figure 3.10 displays the movement of a double mass spring system. It is obvious that the single mass moves faster than the double mass spring system.

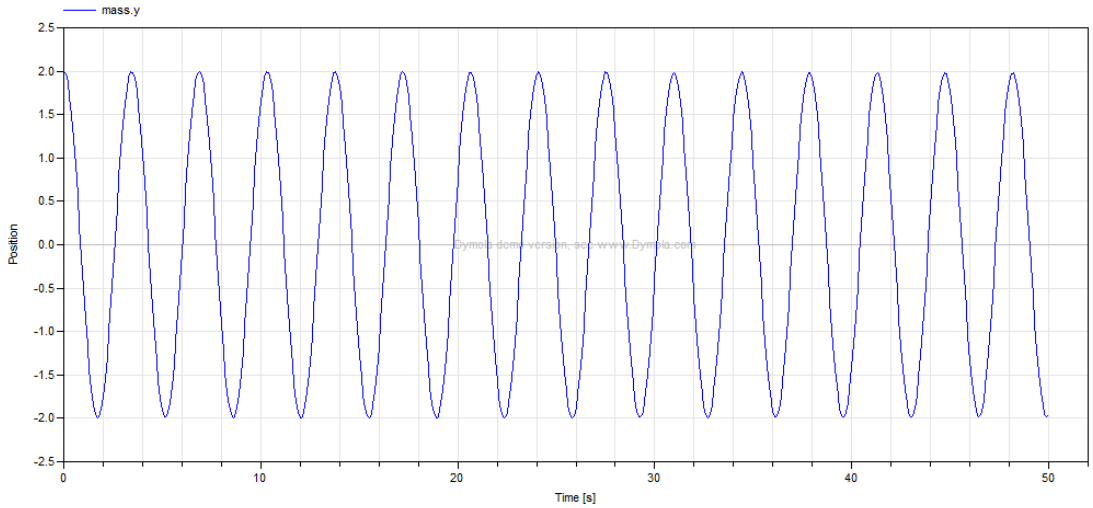


Figure 3.9: Plot of the single mass position change

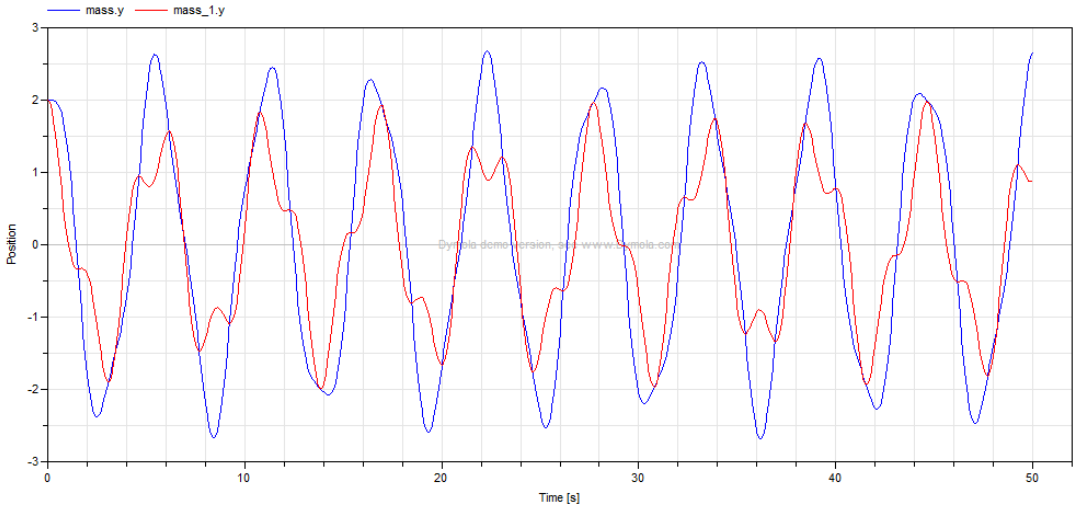


Figure 3.10: Plot of the double spring mass system position change

The acausal approach has a big advantage in the case of complex models and systems. It is more about the understanding of the problem, of the physical laws, of the equations describing it than about inventing an algorithm of the calculation.

3.3 Model

In order to be able to create a design of a computer application, it was necessary to build a model with certain features as it was mentioned previously at the beginning of this thesis. The created model represents the human circulation of blood through pulmonary veins and arteries, systemic veins and arteries and left and right heart, lungs, tissues and an ECMO device. The model of the circulation ensures that blood flows through the system. The pulmonary function is insufficient in the system and therefore mechanical ventilation and VV ECMO is needed in order to support the lungs. Oxygenation and carbon dioxide removal take place in the lungs

and ECMO. In the tissues, oxygen uptake and carbon dioxide production occur. In order to model these processes, the basics of acid-base chemistry of blood are described in the model.

Parts of the description text are taken from my former project [Doležalová, 2013], because some of the model components are the same but most of them are improved and changed.

3.3.1 Expected usage of the model

Since the idea is to make a computer application based on the model created in this master thesis, the expected functions of the model and therefore the application are listed below.

Dependency of blood properties on ECMO flow

The main feature of the model should be the ability of expressing the relationship between ECMO flow and blood properties. ECMO flow is the essential setting variable on ECMO device. The flow determines how much the processes of oxygenation and carbon dioxide removal are supported by ECMO. It should be seen that if the patient has an insufficient pulmonary function and ECMO flow is increased, the blood should be well oxygenated and deprived of carbon dioxide. In other words, the blood properties should be within physiological ranges compared to the tables 2.2 and 2.3 in the section 2.2.1.

Relationship between mechanical ventilation and ECMO settings

Mechanical ventilation supports the pulmonary function together with an ECMO device. It is usually set on a low tidal volume, but if it is necessary to set ECMO flow lower then expected, the tidal volume can be increased and these two devices together should provide good oxygenation and carbon dioxide removal. Therefore, the second important function of the model should be the representation of the dependency of blood properties on the settings of ECMO and mechanical ventilation.

Temperature changes

During the usage of ECMO, it is sometimes necessary to cool down the patient's body in order to slow down some metabolic processes. On the contrary, it is sometimes needed to heat up the blood when it is transported outside the patient's body and therefore the temperature is decreased. The desired temperature is set in an ECMO component of the model and the cooling down or heating up processes should be displayed in the tissues. The next important model function should be the possibility to display the cooling down process.

The time dependencies and time dynamics do not have to be exactly corresponding with the real time. Even though correct units are used and the values of the parameters make physiological sense, it is possible that the dynamical changes do not completely correspond with real time. Although the time dependency is important, during the creating of the model, the focus was centered on the resulting values of blood properties and their trends more than on the time dynamics.

Dependency of blood properties on pulmonary shunt changes

The created model of the lungs has the possibility of expressing pulmonary insufficiency. It was made by creating a pulmonary shunt. The shunt is a pathological state when arterial blood is mixed with venous blood. Another function of the model should be the ability of showing how much the ECMO settings should be changed compared to the seriousness of pulmonary insufficiency.

Dependency of blood properties on carbon dioxide production and oxygen uptake

In the component tissues, carbon dioxide production (VCO_2) and oxygen uptake (VO_2) can be changed. These two variables depend on the physical activity of the patient. The future computer application may have the function of changing VCO_2 and VCO_2. Therefore, the model should be able to show the dependency of arterial blood properties on VCO_2 and VCO_2.

Summary

According to these expected functions, the experiments are designed in order to find out whether the function of the model is adequate as a basis for a training application. All the results are shown in chapter 4 on the corresponding graphs and plots. The results from my model are compared with the literature and it is discussed whether the results are sufficient in order to base the computer application on the model.

3.3.2 Validation and verification of the model

Models are never meant to fully express the reality, but they can be very useful for a better understanding of complex systems. Validation and verification of the model are important parts of the model development process. After validation and verification, it can be decided if the model will actually be accepted and used [Macal, 2005]. The model is usually built for a specific purpose and the validity is determined with respect to that purpose. It was mentioned previously that a set of experiments should be designed in order to find out if the model has the intended behavior. Simply speaking, validation and verification should answer the question whether the model and its results are "correct" [Sargent, 2005].

Verification

Model verification is usually defined as ensuring whether the model is programed and implemented properly. It means that the verification does not ensure that the model solves the important problem or that it correctly reflects the real process, but it ensures that the model does not contain errors in the sense of programming [Macal, 2005, Sargent, 2005].

In order to find out if the model was programmed correctly, each of the components had to be tested separately. As it is shown in figure 3.11, the components have to be tested one by one. This test was performed in order to find out if the *lungs* has the right function of oxygenating blood. The *lungs* were connected with simple *blood source* which defines the values of variables on the connector as a constants. The values were controlled by *blood-meters*. Figures 3.12 and 3.13 display the output of the test. Figure 3.12 shows that outflowing oxygen concentration in blood is higher than inflowing. How much of the oxygen will be exchanged depends on the oxygen concentration in the air and on the tidal volume. Figure 3.12 displays that the output partial pressures in the air and in the blood are equal. The components had to be tested separately and if the function was shown to be correct, it was possible to add them to the circulation. The function of the component had to be tested also in the entire circulation.

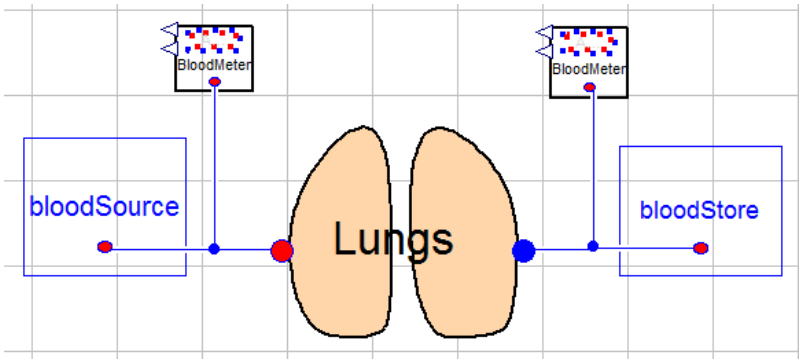


Figure 3.11: Testing of the lungs component

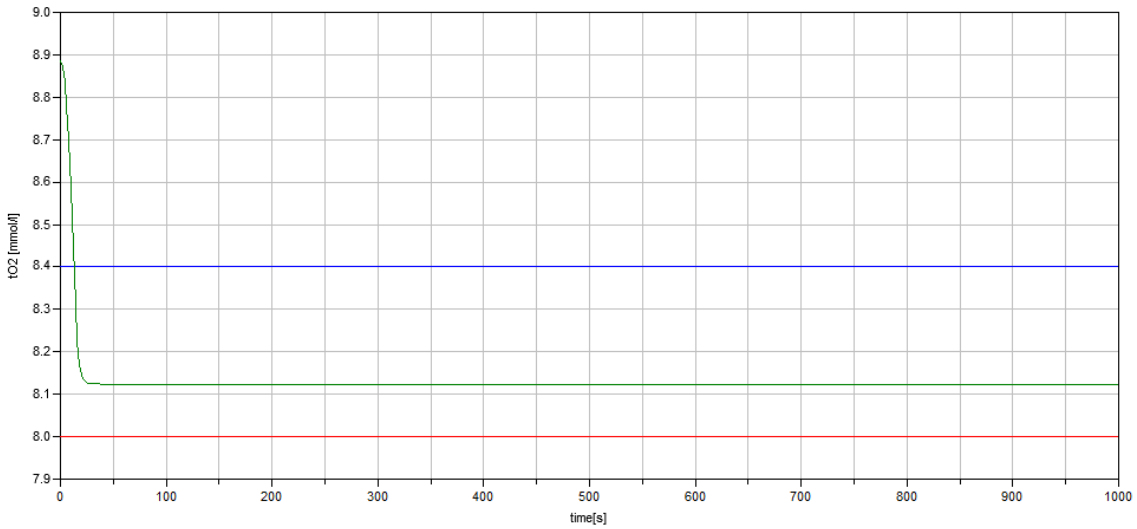


Figure 3.12: Result of the lung testing; blue line represent oxygen concentration in the air, red line represents inflowing oxygen concentration in the blood and green line is the result of the oxygenation - oxygen concentration in the blood leaving the lungs

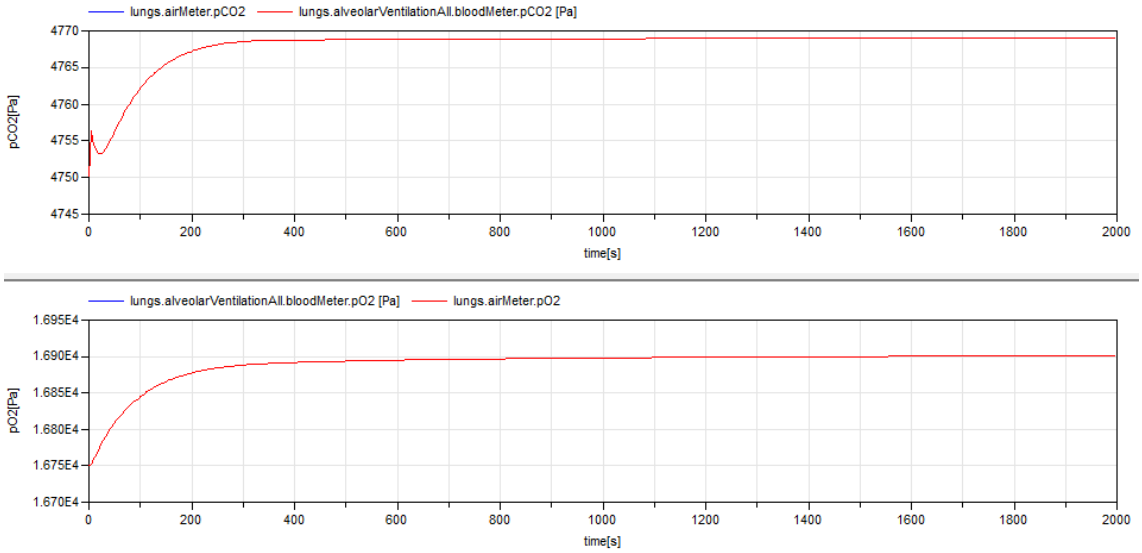


Figure 3.13: Result of the lung testing; on the top the blue line represent carbon dioxide partial pressure in the air, red line represents carbon dioxide partial pressure in the blood; on the bottom blue line represents oxygen partial pressure in the air, red line represents oxygen partial pressure in the blood; partial pressures in the blood and in the air are the same, so the lines overlap

Validation

Model validation is often defined as ensuring whether the model meets its intended requirements for the specific purpose. The main goal of validation is to make the model useful for the intended application and for providing the right information about the system being modelled. It is possible that the model is valid for some experimental conditions and invalid for another [Macal, 2005, Sargent, 2005].

In the case of my model, validation was made expertly according to data known. The data were obtained from the former models and studies of the same topic. The initial conditions were set to be physiological and the resulting plots and graphs have physiological values. Although the validation was made only expertly, the resulting plots are comparable with other studies on patients or on other models, so the model can be considered as validated.

3.3.3 General description of the model

The entire model consists of several major parts as shown in figure 3.14. The first major part is the model of human circulation which includes six segments - pulmonary veins, pulmonary arteries, systemic veins, systemic arteries, left and right heart. The model of human circulation was taken from [Tribula et al., 2013] and reorganized and remade for the purpose of my master thesis. The second main part is the model of the lungs which is composed of four segments - alveolar space, resistor, ventilator and shunt. In the alveolar space, oxygenation and carbon dioxide removal take place and mechanical ventilation helps to fulfill the processes. The compartments shunt and resistor represent the pulmonary shunt, so they define how much of the venous blood is mixed with the arterial blood. The third major part of the system is the compartment tissues where two important processes take place - oxygen uptake and carbon dioxide production. The last main segment of the model is the ECMO compartment where the same processes as in the lungs take place - oxygenation and carbon dioxide removal. ECMO contains

three segments - ECMO, resistor and shunt. These three parts have analogous functions as the subcompartments in the lungs. There is one more compartment which is possible to use anywhere in the system in order to find out blood properties at the exact point in the circulation. This component is called BloodMeter [Doležalová, 2013].

The entire model demonstrates a human whose lungs are not working properly and have to be supported with slight mechanical ventilation and VV ECMO device [Doležalová, 2013].

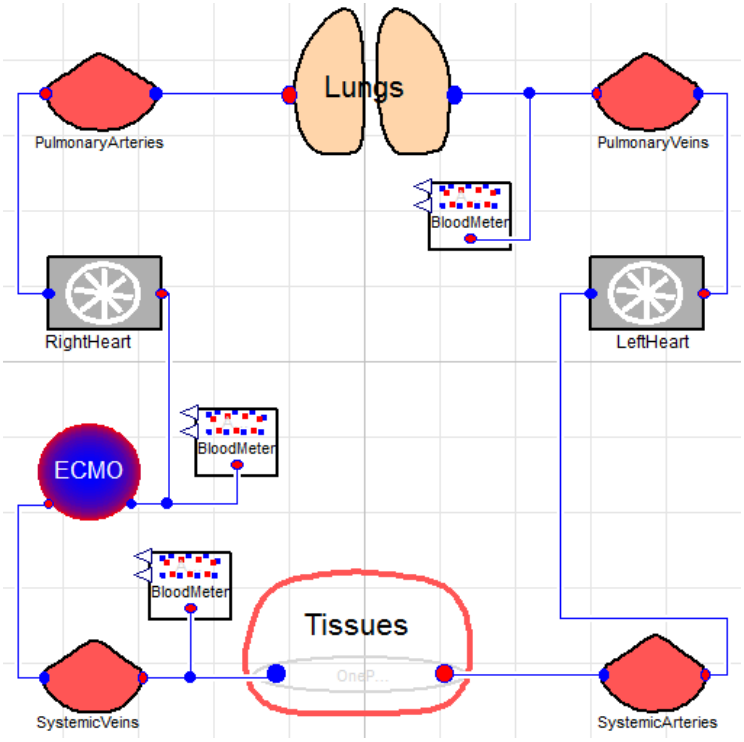


Figure 3.14: The structure of the entire model

Blood connector

As it was explained previously in the section 3.2, the connector is the part of the model that connects all the components together. It is used for transferring the variables between the parts. In the case of this model, the blood connector transfers the blood properties which are the most important in the acid-base balance of the blood. The variables which are defined on the connector are listed in table 3.3 with the units, description and type. The depending variables of acid-base balance are calculated in the certain components by appropriate equations.

Variable	Type	Unit	Description
p	Real	Pa	Blood pressure
Q	flow Real	l/s	Blood flow
h	stream Real	J/l	Enthalpy (concentration of thermal energy)
tCO_2	stream Real	mmol/l	Total concentration of carbon dioxide
tO_2	stream Real	mmol/l	Total concentration of oxygen
tA	stream Real	mmol/l	Total concentration of non-bicarbonate buffer
BB	stream Real	mmol/l	Concentration of buffer base

Table 3.3: Variables with their description, type and units which are defined on the blood connector

Figure 3.15 shows what the description of the variables on the connector look like in the Modelica language. The system knows that in each component there are at least 6 variables (unknowns) that are necessary to calculate. The depending variables are calculated and declared in the certain component.

```
connector BloodFlow

flow Real Q( unit = "l/s") "Blood flow";
Real p( unit = "Pa") "Blood pressure";
stream Real h( unit = "J/l") "Enthalpy (concentration of termal energy)";
stream Real tCO2( unit = "mmol/l") "Total concentration of carbon dioxide";
stream Real tO2( unit = "mmol/l") "Total concentration of oxygen";
stream Real tA( unit = "mmol/l")
    "Total concentration of non-bicarbonate buffer";
stream Real BB( unit = "mmol/l") "Concentration of buffer base";
  a;
end BloodFlow;
```

Figure 3.15: The connector description in Modelica language

Blood

For the purpose of describing the acid-base chemistry of blood the partial model *AcidBaseBasic* was created based on the model by Rees and Andreassen [Rees and Andreassen, 2005]. The description consists of two, nearly separate, parts - carbon dioxide and oxygen part. The two chemical reactions (3.3, 3.4) describe the main processes which occur in plasma. These two reactions can be translated into mathematical domain. Carbon dioxide content is in *AcidBaseBasic* described by six mathematical equations (3.5 - 3.10) which explain the processes in plasma. Values of constants such as $pKHCO_3$, pKA^- ($pKNBB$), α_{CO_2} are listed in the subsection 2.2.1 in table 2.2.

$$H^+ + HCO_3^- \longleftrightarrow CO_2 + H_2O \tag{3.3}$$

$$H^+ + A^- \longleftrightarrow HA^- \tag{3.4}$$

$$pH = pKHCO_3 + log_{10}\frac{HCO_3^-}{CO_2} \tag{3.5}$$

$$pH = pKA^- + log_{10}\frac{A^-}{HA^-} \tag{3.6}$$

$$BB = HCO_3^- + A^- \tag{3.7}$$

$$tCO_2 = HCO_3^- + CO_2 \tag{3.8}$$

$$tA = A^- + HA^- \tag{3.9}$$

$$CO_2 = \alpha_{CO_2} \cdot pCO_2 \tag{3.10}$$

In the case of oxygen, a dissociation curve, which represents the relationship between oxygen saturation and oxygen partial pressure, has been made. Several assumptions have been made in order to make the computations less complex. For instance, concentration of hemoglobin (Hb) was set to be fixed as a parameter with the value 9.3mmol/l and the fraction of methemoglobin ($FMetHb$) and fraction of carboxyhemoglobin ($FCOHb$) were set to be 0. $FMetHb$ is the ratio between the concentration of methemoglobin ($MetHb$) and total concentration of Hb. $FCOHb$ is the ratio between the concentration of carboxyhemoglobin ($COHb$) and total concentration of Hb. The solubility coefficient of oxygen (α_{O_2}) can be calculated by an equation 3.11. The most important relations which describe oxygen status of the blood are equations about free dissolved oxygen (3.12) and total concentration of oxygen (3.13) [Doležalová, 2013].

$$\alpha_{O_2} = e^{ln(\alpha_{O_2}(37))} - \frac{dln(\alpha_{O_2})}{dt} \cdot (t - t_0) + 2 \cdot \frac{d^2 ln(\alpha_{O_2})}{dt} \cdot (t - t_0)^2 \tag{3.11}$$

$$O_2 = \alpha_{O_2} \cdot pO_2 \tag{3.12}$$

$$tO_2 = O_2 + sO_2 \cdot (Hb - (FMetHb \cdot Hb) - (FCOHb \cdot Hb)) \tag{3.13}$$

Since the solubility of oxygen depends on the temperature, it is necessary to convert the enthalpy, which is defined in the connector, to the temperature. For this purpose, equation 3.14 is used where t is a temperature, h is an enthalpy, cb is a specific heat capacity of blood. The units of the temperature are Kelvins.

$$t = \frac{h}{cb} \tag{3.14}$$

Partial model *AcidBaseBasic* is used in each part of the model where is necessary to calculate the blood properties. All of the equations describing the carbon dioxide (3.5 - 3.10) and oxygen (3.11 - 3.13) content are used in this partial model. The use of *AcidBaseBasic* is provided by an inheritance, so the user does not have to use the same equations over and over again and they are placed only on one place of the system. The function *extend* causes that all the components, where *AcidBaseBasic* is used, inherit all the equations from it. *AcidBaseBasic* is inherited by *blood-meter*, *lungs* and *ECMO*.

The acid-base chemistry of the blood described in the model is simplified. The focus is centered on oxygenation and carbon dioxide removal. Since the strong base is left out from the description, BB and tA are assumed to be constant in the entire circulation (see the section 2.2.1). Carbon dioxide content is described just in the plasma; the content in erythrocytes is ignored. Oxygen content is defined in the blood in general [Doležalová, 2013].

3.3.4 Circulation

For the purpose of creating a model of *circulation*, a simple model from Tribula was used [Tribula et al., 2013]. This model was adjusted and upgraded for my own use. Units were recalculated, a different connector was used, and therefore different initial values were defined.

The model of the *circulation* is based on the assumption that vessels in the human body are divided into four groups - pulmonary veins and arteries and systemic veins and arteries. The heart pump is also divided into two parts - left and right heart. Right heart pumps blood through pulmonary arteries to the lungs. Then the blood flows from the lungs through the pulmonary veins to the left heart. Left heart pumps the blood through system arteries to the entire body and the loop ends up with system veins which transport blood to the right heart again. Picture 3.16 shows the order of the components.

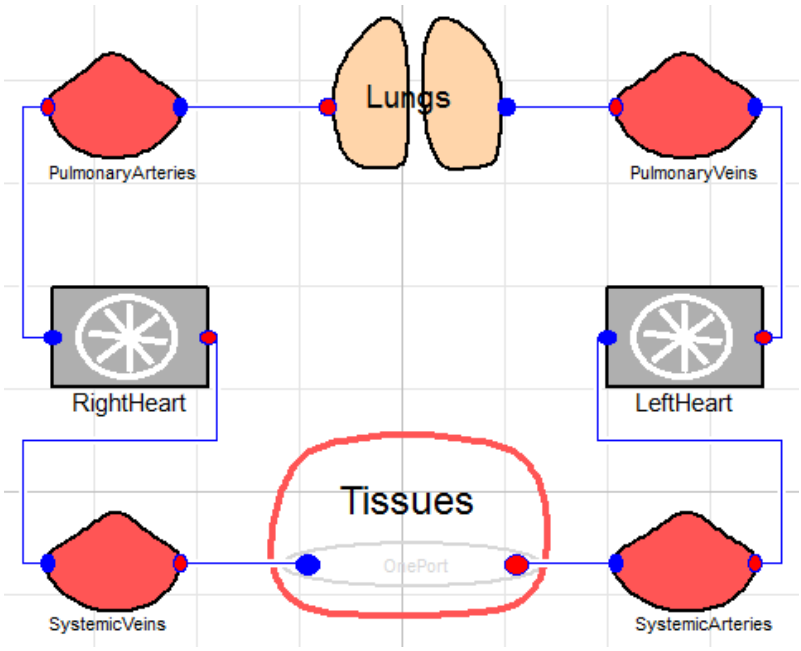


Figure 3.16: Model of the circulation with its six components

The *circulation* consists of six parts - *pulmonary veins*, *pulmonary arteries*, *systemic veins*, *systemic arteries*, *left heart* and *right heart*. All four blood-vessel compartments (pulmonary veins, pulmonary arteries, systemic veins and systemic arteries) have the same basis, but they have different initial values and different values of the parameters; all of the them are shown in table 3.4. In these compartments, change of the total volume (V_{total}) is described as sum of inflow (Q_{in}) and outflow (Q_{out}) (equation 3.15). The blood-vessels have unstressed volume (V_U), the volume when the transmural pressure is equal to zero. The stressed volume (V_S) means the remainder of the volume when the transmural pressure is above zero (figure 3.17). V_U is a parameter defined in each of the four blood-vessel compartments, V_{total} is a variable which is initialized and then calculated as previously mentioned and V_S is a variable which is computed by subtracting V_U from V_{total} (equation 3.16). The next variable which is defined in the blood-vessel compartments is pressure (p) which is calculated by dividing V_S and compliance (C) (equation 3.17). There is one assumption that has been made in the context of the blood-vessel compartments - the concentration of the blood properties which are transported through the connector to the entire system is not changed by passing through the veins and arteries. There are just different initial values of the concentrations of CO_2, O_2, tA and BB. In each of the blood-

vessel compartments, the change of the mass is calculated as a multiple of Q_{in} and inflowing concentration (c_{in}) plus multiple of Q_{out} and outflowing concentration (c_{out}) (equation 3.18). The last important equation to be mentioned is the calculation of concentration (c) which is described as a division of M by V_{total} (equation 3.19) [Doležalová, 2013].

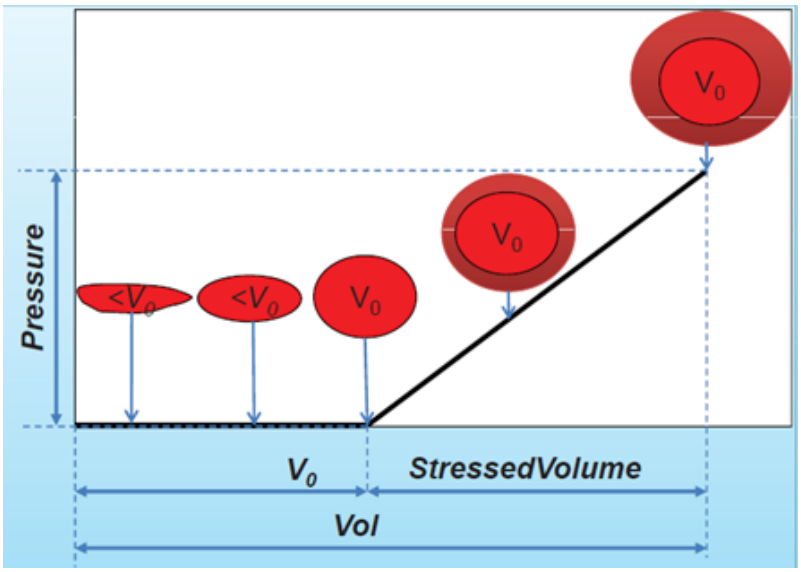


Figure 3.17: Definition of stressed and unstressed volume (V_0) [Mateják, 2013]

$$\frac{d(V_{total})}{dt} = Q_{in} + Q_{out} \tag{3.15}$$

$$V_S = V_{total} - V_U \tag{3.16}$$

$$p = \frac{V_S}{C} \tag{3.17}$$

$$\frac{d(M)}{dt} = Q_{in} \cdot c_{in} + Q_{out} \cdot c_{out} \tag{3.18}$$

$$c = \frac{M}{V_{total}} \tag{3.19}$$

Variable	Unit	Pulmonary veins	System arteries	System veins	Pulmonary arteries
Compliance	l/Pa	0.000225	0.000012	0.0015	0.0000225
Initial volume	l	0.7	0.67	3.9	0.37
Unstressed volume	l	0.4	0.5	2.7	0.3
Initial concentration of CO_2	mmol/l	25.30	25.30	27	25.72
Initial concentration of O_2	mmol/l	9.18	9.18	7.48	8.85
Initial concentration of tA	mmol/l	23.5	23.5	23.5	23.5
Initial concentration of BB	mmol/l	41.7	41.7	41.7	41.7

Table 3.4: Parameters and their values which have been used for modeling blood-vessels [Tribula et al., 2013]

The *left* and *right heart* are similar and very simple segments of the *circulation*. They use the pressure (p_{in}) produced by veins to build the flow (Q) in the whole system. The equations in the *left* and *right heart* have one common parameter - starling slope (SS). SS is approximated by the linear relationship between p_{in} and cardiac output (Q) (equation 3.20) [Tribula et al., 2013]. The values of SS for both *left* and *right heart* are listed in table 3.5 [Doležalová, 2013].

$$Q = p_{in} \cdot SS \tag{3.20}$$

Side of the heart	Starling Slope Value [l/Pa.s]
Right	0.00012751
Left	0.00007501

Table 3.5: Values of the starling slope in both sides of the heart [Tribula et al., 2013]

3.3.5 Blood-meter

Blood-meter is a very important component of the system. It is universal part of the model which can be used everywhere in the circulation in order to find out the blood properties at the exact point of the system. All of the blood properties which can be calculated by the *blood-meter* are listed in table 3.6. It uses the values of the connector variables at the certain point of the circulation and it calculates all the important blood properties. *Blood-meter* uses all the acid-base chemistry equations (3.5 - 3.13), which are inherited from the partial model *AcidBaseBasic*, for calculating the blood properties.

Blood-meter is also used in lungs where it has a slightly different function. The *blood-meter* has two real outputs - the partial pressures of carbon dioxide and oxygen. In this case, *blood-meter* provides an equality of outflowing partial pressures in the blood and in the air going out of the *alveolar ventilation*. This system is explained in detail in section 3.3.7.

Variable	Unit	Description
pH	–	Potential of hydrogen
tCO_2	mmol/l	Concentration of carbon dioxide
tO_2	mmol/l	Concentration of oxygen
$NBB(A)$	mmol/l	Concentration of non-bicarbonate buffer
$HNBB(HA)$	mmol/l	Concentration of non-bicarbonate buffer
tA	mmol/l	Concentration of non-bicarbonate buffer
BB	mmol/l	Concentration of buffer base
HCO_3^-	mmol/l	Concentration of bicarbonate buffer
CO_2	mmol/l	Concentration of free carbon dioxide
O_2	mmol/l	Concentration of free oxygen
pCO_2	kPa	Carbon dioxide partial pressure
pO_2	kPa	Oxygen partial pressure
sO_2	%	Oxygen saturation
cHb	mmol/l	Concentration of hemoglobin
Hct	%	Hematocrit
h	J/l	Concentration of thermal energy (enthalpy)
t	°C	Temperature

Table 3.6: Variables which can be measured by the blood-meter

3.3.6 Tissues

Two very important processes take place in the *tissues* - oxygen uptake and carbon dioxide production. These two processes are described by two equations 3.21 and 3.23. The other two equations define the total outflowing concentrations of oxygen and carbon dioxide (equations 3.22 and 3.24) [Doležalová, 2013].

The amount of carbon dioxide which is added to the blood from *tissues* ($addCO_2$) is calculated by dividing the production of carbon dioxide (VCO_2) with the cardiac output (Q) (equation 3.21). Therefore, the resulting outflowing concentration of carbon dioxide (tCO_2) is inflowing concentration ($tCO_{2,inflow}$) plus $addCO_2$ (equation 3.22) [Doležalová, 2013].

$$addCO_2 = \frac{VCO_2}{Q} \tag{3.21}$$

$$tCO_2 = tCO_{2,inflow} + addCO_2 \tag{3.22}$$

In contrast with carbon dioxide, oxygen is in the *tissues* removed from the blood. Two equations describe this process. Firstly, the amount of oxygen which is removed from the blood ($remO_2$) is defined as a division of oxygen uptake (VO_2) by cardiac output (Q) (equation 3.23). Secondly, the final outflowing concentration of oxygen (tO_2) is calculated as the subtraction of $remO_2$ from the inflowing concentration ($tO_{2,inflow}$) (equation 3.24) [Doležalová, 2013].

$$remO_2 = \frac{VO_2}{Q} \tag{3.23}$$

$$tO_2 = tO_{2,inflow} - remO_2 \tag{3.24}$$

VCO_2 and VO_2 are assumed to be equal - 10mmol/min; it means that the respiratory quotient (RQ) is equal to 1. RQ is the ratio between VCO_2 and VO_2 (equation 3.25 [Silbernagl and Despopoulos, 2009]) and it varies between 0.7 and 1. If RQ is equal to 1, the patient's body is burning carbohydrates (figure 3.18) [Doležalová, 2013].

$$RQ = \frac{VCO_2}{VO_2} \tag{3.25}$$

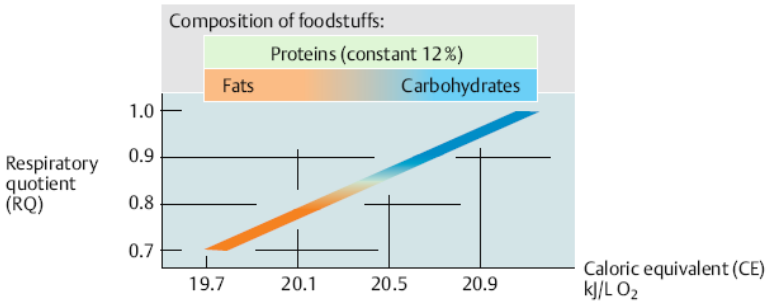


Figure 3.18: Relationship between respiratory quotient and caloric equivalent [Silbernagl and Despopoulos, 2009]

In contrast with my former model, *tissues* has another function - they accumulate heat. An ECMO device is able to set the desired temperature of the patient's body (t). Due to various reasons, it is sometimes required to change the temperature. For instance, the blood is colder because of the transport through the ECMO circuit outside the body so it is required to increase

the temperature. On the contrary, in order to reduce the activity of human metabolism it is necessary to decrease blood temperature. The desired temperature is set in *ECMO* and the progress of changing the temperature in the *tissues* is described by three equations. The first equation 3.26 defines the change of the heat (U) as a multiple of inflowing enthalpy (h_{in}) and blood inflow (Q_{in}) minus outflowing enthalpy (h_{out}) and blood outflow (Q_{out}). The second equation 3.27 describes heat as a multiple of human body volume (V) which is 50l, specific heat capacity of human tissue (cb) which is 4200J/(l.K) and temperature. The last equation 3.28 describes the translation of enthalpy to the temperature. It is calculated as h divided by cb. Common units of specific heat capacity are J/(kg.K), but the assumption that 50kg of human weight is equal to volume of 50l has been made. The units were transferred according to the assumption, so J/(l.K) was used.

$$der(U) = h_{in} \cdot Q_{in} - h_{out} \cdot Q_{out} \tag{3.26}$$

$$U = V \cdot cb \cdot t \tag{3.27}$$

$$t = \frac{h}{cb} \tag{3.28}$$

The blood coming out of the *tissues* is deoxygenated (venous) blood with new values of concentrations and thus pH, partial pressures and oxygen saturation. Concentration and partial pressure of carbon dioxide are higher, oxygen concentration, saturation and partial pressure are lower and pH is lower than in arterial blood. Venous blood needs to be oxygenated and deprived of carbon dioxide in *ECMO* and later on in the *lungs* [Doležalová, 2013].

3.3.7 Lungs

Gas exchange in the *lungs* in the present model is insufficient and therefore their function has to be supported by mechanical ventilation with low V_t.

The *lung* compartment consists of four segments - *alveolar ventilation*, *resistor*, *shunt* and *ventilator* (figure 3.19). In the *alveolar ventilation* the oxygenation and carbon dioxide removal take place. An inheritance is used in this compartment and therefore *alveolar ventilation* inherit all the equations from *AcidBaseBasic* as was mentioned previously. *Alveolar ventilation* contains the equations of gas exchange which is supported by mechanical ventilation. The equations are mainly used for the calculation of partial pressures of carbon dioxide and oxygen. Parameters of mechanical ventilation are listed in table 3.7.

Parameter	Unit	Value	Description
FiO_2	%	21	Fraction of inspired oxygen
$FiCO_2$	%	0	Fraction of inspired carbon dioxide
V_t	l	0.1	Tidal volume
f	breaths/s	0.2	Frequency of breathing
V_{lungs}	l	2	Volume of the lungs

Table 3.7: Values of the mechanical ventilation parameters

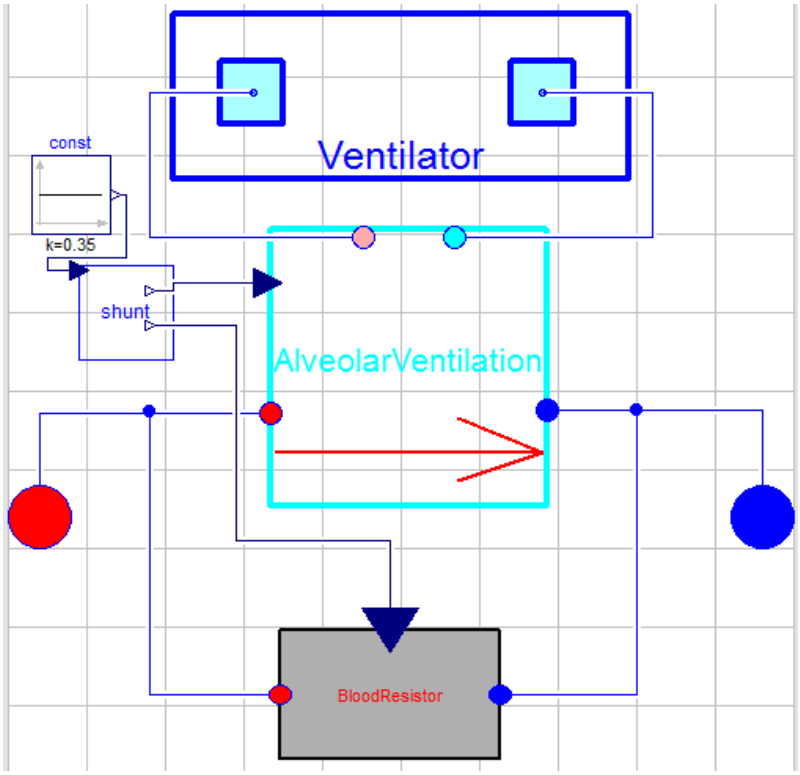


Figure 3.19: Model of the lungs with its components

Alveolar ventilation

The component *alveolar ventilation* has two different types of connectors as you can see in figure 3.20. There are two blood connectors which are used in all the other parts of the model and also two air connectors. The air connectors create a link between the *ventilator* and *alveolar ventilation* and they transport different variables than the blood connectors. The air connector variables are listed in table 3.8. The process in the *alveolar ventilation* is the gas exchange between the air and the blood. The process is simplified in order to describe it with few mathematical equations. The blood takes over some of the oxygen from the air, and carbon dioxide is removed from the blood. The concentration of oxygen is increased and concentration of carbon dioxide is decreased in the blood. In the air, concentration of carbon dioxide is increased and concentration of oxygen is decreased. The outflowing partial pressures of oxygen and carbon dioxide in blood and in the air are equal.

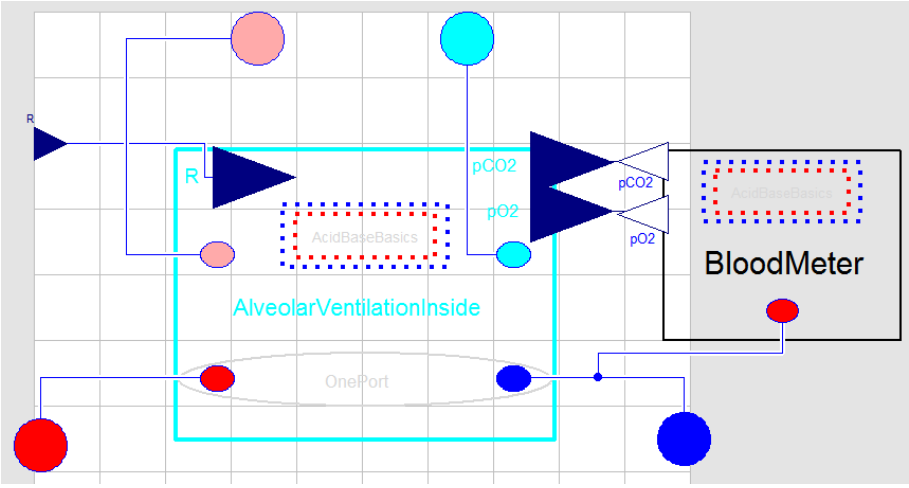


Figure 3.20: Component alveolar ventilation and its internal structure

Variable	Unit	Description
tCO_2	mmol/l	Concentration of carbon dioxide in the air
tO_2	mmol/l	Concentration of oxygen in the air
Q	l/s	Air flow
p	Pa	Air pressure

Table 3.8: Variables transferred by the air connector

The first two equations in the alveolar ventilation compartment describe the equality between fraction and partial pressures (3.29, 3.30). The fraction of alveolar oxygen (FAO_2) and carbon dioxide ($FACO_2$) are considered to be equal with partial pressures, so if pCO_2 or pO_2 is 5kPa, the fraction is 5%. Therefore, the fraction is multiplied by atmospheric pressure which is approximately 100,000Pa in order to obtain the values of the partial pressures in Pa. The next two calculations are based on the ideal gas law (equation 3.31), where p is pressure of the gas, V is volume of the gas, n is the amount of substance of gas (measured in moles), T is the absolute temperature of the gas and R is a universal gas constant. Equation 3.32 is an analogy to the ideal gas law for carbon dioxide, where pCO_2 is partial pressure of carbon dioxide, V_{lungs} is the volume of the lungs, M_{CO_2} is alveolar mass of carbon dioxide, R is a universal gas constant (8.314J/(K.mol)) and T temperature of the gas (chosen to be 300.7K). Equation 3.33 is the equivalent to equation 3.32 for oxygen. There are two equations which describe the addition of oxygen (mVO_2) and removal of carbon dioxide ($mVCO_2$) to/from the blood, that is the difference between the concentrations inflowing ($tO_{2,in}$ and $tCO_{2,in}$) multiplied with Q_{in} and outflowing concentrations ($tO_{2,out}$ and $tCO_{2,out}$) multiplied with Q_{out} (3.34, 3.35). The next couple of equations define the final change of mass dependent on inspired (inflowing) concentration in the air ($tO_{2,in-air}$ and $tCO_{2,in-air}$), alveolar (outflowing) concentration ($tO_{2,out-air}$ and $tCO_{2,out-air}$) , Q and also addition or removal of the substance (3.36, 3.37). The last couple of equations define total concentration of carbon dioxide ($tCO_{2,air}$) and oxygen ($tO_{2,air}$) in the air by dividing alveolar mass by the volume of the lungs (3.38, 3.39).

$$pCO_2 = p_{atm} \cdot FACO_2 \tag{3.29}$$

$$pO_2 = p_{atm} \cdot FAO_2 \tag{3.30}$$

$$p \cdot V = n \cdot R \cdot T \tag{3.31}$$

$$p_{CO_2} \cdot V_{lungs} = M_{CO_2} \cdot R \cdot T \tag{3.32}$$

$$p_{O_2} \cdot V_{lungs} = M_{O_2} \cdot R \cdot T \tag{3.33}$$

$$mVCO_2 = Q_{in} \cdot tCO_{2,in} - Q_{out} \cdot tCO_{2,out} \tag{3.34}$$

$$mVO_2 = Q_{in} \cdot tO_{2,in} - Q_{out} \cdot tO_{2,out} \tag{3.35}$$

$$\frac{d(M_{CO_2})}{dt} = Q_{in-air} \cdot tCO_{2,in-air} - Q_{out-air} \cdot tCO_{2,out-air} + mVCO_2 \tag{3.36}$$

$$\frac{d(M_{O_2})}{dt} = Q_{in-air} \cdot tO_{2,in-air} - Q_{out-air} \cdot tO_{2,out-air} + mVO_2 \tag{3.37}$$

$$tCO_{2,air} = \frac{M_{CO_2}}{V_{lungs}} \tag{3.38}$$

$$tO_{2,air} = \frac{M_{O_2}}{V_{lungs}} \tag{3.39}$$

As it is seen in figure 3.20, *blood-meter* is used in the *alveolar ventilation*. All the equations which are used in *blood-meter* are also used in *alveolar ventilation*. The real outputs from the *blood-meter* provide partial pressures of carbon dioxide and oxygen. After the mixing, the loop goes from the *blood-meter* back to *alveolar ventilation*. It has been made in order to set the partial pressures equal in outflowing blood and air. This shows the great advantage of the acausal approach. It is possible to use the same equations twice and the system is able to handle and compute the calculations.

Ventilator

The *ventilator* consist of two parts. The *air source* is the first part and it transports the air to the alveolar space. The air is enriched with oxygen and it has zero concentration of carbon dioxide. The oxygen passes from the air to blood and then flows to the second part of the *ventilator* called *air store*. In the *air source* there are a few important equations which describe the outflowing air. The air flow is described by an equation 3.40 as a multiple of breathing frequency (f) and tidal volume (V_t). The next two calculations (3.41, 3.42) describe the partial pressures of carbon dioxide and oxygen (pCO_2, pO_2) as atmospheric pressure (p_{atm}) which is around 100,000Pa multiplied by a fraction of carbon dioxide and oxygen ($FiCO_2$, FiO_2) in the inspired air. The next two equations (3.43, 3.44) are an analogy to the ideal gas law as was mentioned previously. pCO_2 and pO_2 are multiplied by volume (V) and set to be equal to the multiple of the masses ($massCO_2$, $massO_2$), universal gas constant (R) and temperature of the gas (T). The concentrations of oxygen and carbon dioxide (tCO_2, tO_2) in the air is derived from the equations 3.46 and 3.45. tCO_2 and tO_2 are $massCO_2$ and $massO_2$ divided by V. Fractions of carbon dioxide and oxygen and volume are set to be 0, 21% and 2l, respectively.

$$Q = f \cdot V_t \tag{3.40}$$

$$pCO_2 = p_{atm} \cdot FiCO_2 \tag{3.41}$$

$$pO_2 = p_{atm} \cdot FiO_2 \tag{3.42}$$

$$p_{CO_2} \cdot V = massCO_2 \cdot R \cdot T \tag{3.43}$$

$$p_{O_2} \cdot V = massO_2 \cdot R \cdot T \tag{3.44}$$

$$tCO2 = \frac{MassCO2}{V} \tag{3.45}$$

$$tO2 = \frac{MassO2}{V} \tag{3.46}$$

Shunt

In order to represent lung failure in the system, it was necessary to model the insufficiency of gas exchange. This was provided by creating pulmonary shunt. Pulmonary shunt is a pathological state of the lungs when deoxygenated blood is mixed with oxygenated blood and thereby the overall efficiency of gas exchange in the lungs is reduced [Lovering and Goodman, 2012]. The shunt was modeled as two parallel resistances, the first resistance was incorporated to the alveolar ventilation compartment and the second was simply made as a resistor (figure 3.19). The compartment shunt is a control panel which sets the values of resistances in the alveolar ventilation and the resistor according to pulmonary shunt. The total pulmonary resistance is known (9333 [(Pa.s)/l] [Tribula et al., 2013]) and the shunt computes the resistances for the alveolar space and the resistor according to pulmonary shunt. Based on parallel resistors rule, if the pulmonary shunt is 50% both resistances are 18666 (Pa.s)/l. The function of the compartment shunt is described by two equations (3.47, 3.48).

$$\frac{1}{R_{total}} = \frac{1}{R_{alveolar}} + \frac{1}{R_{resistor}} \tag{3.47}$$

$$shunt \cdot R_{resistor} = (1 - shunt) \cdot R_{alveolar} \tag{3.48}$$

The resistor is one of the necessary parts for building a pulmonary shunt. The function of this segment is expressed by two equations. The first equation (3.49) is definition of the pressure drop (pD), which is the difference between inflow pressure (p_{in}) and outflow pressure (p_{out}). The second equation (3.50) is an analogy to the Ohm's law where voltage is represented as pD, resistance is simply blood resistance ($bloodR$) with units Pa.s/l and finally the current is defined as the blood flow (Q) [Doležalová, 2013].

$$pD = p_{in} - p_{out} \tag{3.49}$$

$$pD = bloodR \cdot Q \tag{3.50}$$

3.3.8 ECMO

The last part of the model is the *ECMO* compartment (figure 3.21). It has similar functions and structure as the model of the *lungs*. This segment is composed of three subcompartments - *ECMOoxygenation*, *resistor* and *shunt*. In the *ECMOoxygenation*, the oxygenation and carbon dioxide removal take place. Except for one difference, it is structured as the *alveolar ventilation* in the *lungs*. Partial pressures in the *alveolar ventilation* are calculated from mechanical ventilation, however in the *ECMOoxygenation* they are set to be parameters. pCO_2 and pO_2 are set to be 4.5kPa and 45kPa, respectively. The process which takes place in *ECMO* is equilibrium of the blood balance towards new partial pressures of oxygen and carbon dioxide. An inheritance is used in this component, so all the equations about acid-base chemistry of blood from *AcidBaseBasic* are used (equations 3.5 - 3.14). *ECMO* is used as a control panel for setting the blood temperature. It was mentioned previously that sometimes it is needed to change the blood temperature [Doležalová, 2013].

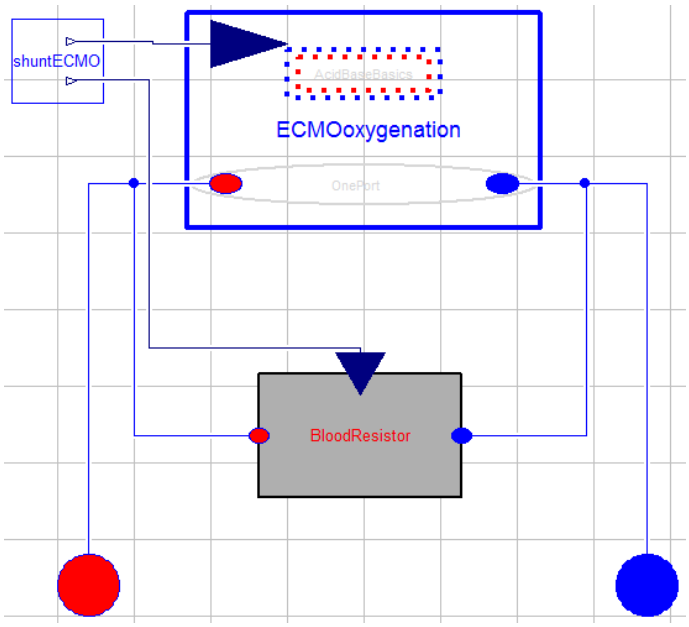


Figure 3.21: ECMO compartment and its parts

The *shunt* and a *resistor* are used in similar way as in the *lungs*. The *resistor* is in parallel with the *ECMO* subcompartment and both have their own resistance. The *shunt* is a control panel which sets the resistances in the *resistor* and *ECMO* according to the needed ECMO flow. For instance, the desired ECMO flow is 50% and total resistance is 500 Pa.s/l, therefore resistance in both the *resistor* and the *ECMO* subcompartment is 1000 Pa.s/l. The function of the *shunt* is described by two simple equations (3.51, 3.52).

$$\frac{1}{R_{total}} = \frac{1}{R_{ECMO}} + \frac{1}{R_{resistor}} \tag{3.51}$$

$$shunt \cdot R_{ECMO} = (1 - shunt) \cdot R_{resistor} \tag{3.52}$$

The output from the *ECMO* compartment is made of partly oxygenated blood deprived of carbon dioxide which continues to the *lungs* where oxygenation and carbon dioxide removal are fulfilled. The levels of oxygenation and carbon dioxide removal depend on ECMO flow.

ECMO can be also used when there is no lung function left. It can provide very good oxygenation, but the higher ECMO flow is the higher is the pressure around cannulas and the risk of a rupture of the vessel is bigger. The goal is to set ECMO flow as low as possible, but on the level when it provides good oxygenation and carbon dioxide removal.

CHAPTER 4

RESULTS

The set of simulation experiments was designed and performed in order to investigate whether the model behaves within physiological standards and whether it is comparable with the results from the former experiments and studies.

The goal of the first three experiments was to investigate the dependency of arterial blood properties on ECMO flow. In the case of the first experiment, it was specifically the dependency of oxygen saturation on ECMO flow. The second experiment was performed in order to describe the dependency of oxygen partial pressure on ECMO flow. The third experiment was carried out in order to investigate how carbon dioxide partial pressure depends on ECMO flow. Those three experiments were also performed in the study by Schmidt et al. [Schmidt et al., 2012] and therefore I was able to compare my results with their findings.

Another experiment has been made in order to show how the settings of mechanical ventilation and ECMO flow affect the arterial blood properties. From the results from experiment 4 it should be seen how mechanical ventilation and ECMO work together during the supporting lung function.

Experiment 5 was performed with a goal to show the ability of the model to change the patient's body temperature. From the result it should be obvious that the patient is cooled down to the desired temperature in some time. The opposite process of heating up the body can be performed.

Next experiment 6 was carried out in order to express the dependency of arterial oxygen saturation (sO_2) on ECMO flow and on the level of pulmonary shunt. This experiment should show that with a lower shunt, a lower ECMO flow is necessary to keep sO_2 at normal level. Normal arterial oxygen saturation is considered to be >97%.

The goal of experiment 7 is to show the dependency of arterial sO_2 on the changes of oxygen uptake (VO_2) and carbon dioxide removal (VCO_2). ECMO flow will probably be necessary to change in order to reach a sufficient level of arterial sO_2.

The last experiment 8 was performed as an observation of the model behavior. The results from this experiment should show whether the model behaves in accordance to the expected outcomes. The resulting blood properties can be compared with the values listed in tables 2.2 and 2.3 in the section 2.2.1.

4.1 Experiment 1 - oxygen saturation (sO_2) in relation to ECMO flow

In experiment 1, the relation between sO_2 and ECMO flow was investigated. Settings of mechanical ventilation were as follows. Tidal volume V_t and pulmonary shunt were set to be 100ml and 35%, respectively. Figure 4.1 shows that sO_2 is highly dependent on ECMO flow. When ECMO flow is 20% of cardiac output (1.2 l/min), sO_2 is low in both pulmonary and peripheral artery. Specifically, sO_2 is 73% in pulmonary artery and 84% in peripheral artery. As

ECMO flow is increased, sO_2 also increases. Well saturated blood sO_2 of >97% in pulmonary artery is achieved when ECMO flow is more than 70% of cardiac output. In peripheral artery the desired sO_2 is achieved when ECMO flow is 60%.

Schmidt et al. [Schmidt et al., 2012] have performed similar trial with patients. They have shown that as soon as ECMO flow/cardiac output is above 60%, sO_2 in peripheral artery is always above 90% (figure 4.3). It was also shown that the behavior of sO_2 is the same in different parts of the circulation, specifically in right atrium and pulmonary and peripheral artery. sO_2 rises with an increase of ECMO flow/cardiac output (figure 4.2) [Schmidt et al., 2012]. Results from my mathematical model follows the same pattern as in the study by Schmidt et al. [Schmidt et al., 2012], but sO_2 of >90% in peripheral artery occurs earlier than during ECMO flow of 60%. sO_2 of >90% in peripheral artery is achieved when ECMO flow is only 30%.

Figure 4.1 displays the comparison of the results from the present project and from the study by Schmidt et al. [Schmidt et al., 2012]. The results from both experiments follow the same pattern, but sO_2 is obviously higher in the case of the mathematical model. It could be caused by an excessive efficiency of the model. Figure 4.2 also shows that the plots have a very wide range of values due to a number of the patients whose data were used. Median values from the article by Schmidt et al. [Schmidt et al., 2012] were used for a comparison of the present study (figure 4.1).

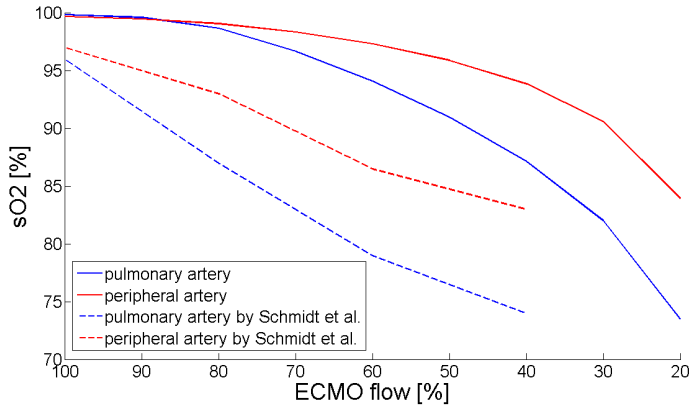


Figure 4.1: Experiment 1 - Relationship between oxygen saturation (sO_2) in the peripheral and pulmonary artery and ECMO flow; tidal volume (V_t) is 100ml, pulmonary shunt is 35%

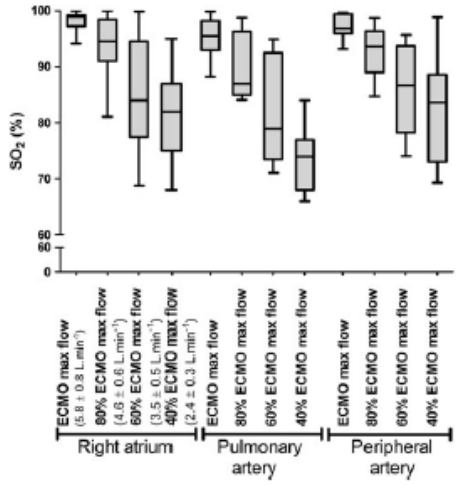


Figure 4.2: Impact of ECMO flow reduction on oxygen saturation (sO_2) in the right atrium, pulmonary artery and peripheral artery [Schmidt et al., 2012]

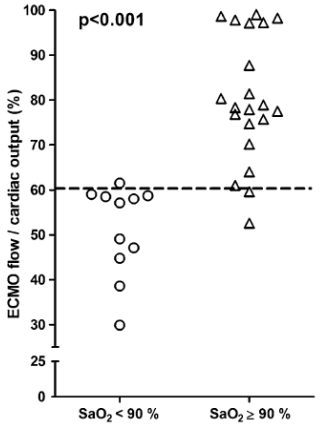


Figure 4.3: Relationship between ECMO flow/cardiac output and oxygen saturation (sO_2) in the peripheral artery [Schmidt et al., 2012]

4.2 Experiment 2 - oxygen partial pressure (pO_2) in relation to ECMO flow

Experiment 2 was performed in order to investigate the relation between ECMO flow and pO_2. It is related to experiment 1, because both pO_2 and sO_2 describe oxygenation of blood. V_t and the pulmonary shunt are set to be 100ml and 35%, respectively. Results from this experiment have shown that pO_2 is also dependent on ECMO flow. pO_2 increases with an enhancement of ECMO flow (figure 4.4). The normal value of pO_2 is around 13kPa or 100mmHg. pO_2 of 13kPa in pulmonary and peripheral artery is achieved when ECMO flow is 73% and 62%, respectively. Study by Schmidt at al. [Schmidt et al., 2012] has shown that pO_2 rises slightly with an increase of ECMO flow in all the parts of the circulation (figure 4.5). However, pO_2 of 13kPa is not reached.

Figure 4.4 displays the results both from the present project and from study by Schmidt et al. [Schmidt et al., 2012]. The results differ probably due to the same reasons as in experiment

1. Specifically, due to an excessive efficiency of the model function and a wide range of the results from the study by Schmidt et al. [Schmidt et al., 2012] (figure 4.5).

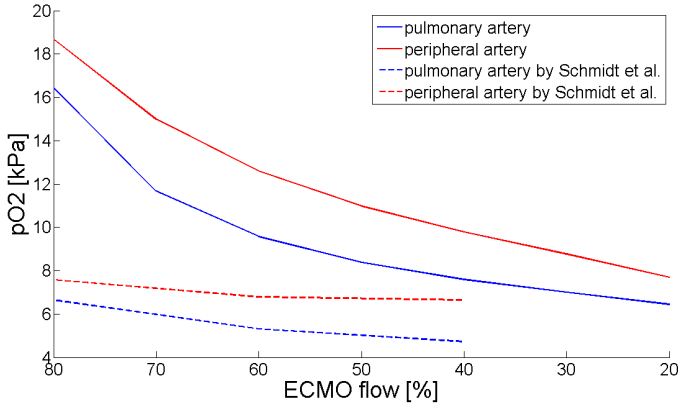


Figure 4.4: Experiment 2 - Relationship between oxygen partial pressure (pO_2) in the peripheral and pulmonary artery and ECMO flow; tidal volume (V_t) is 0.1l, pulmonary shunt is 35%

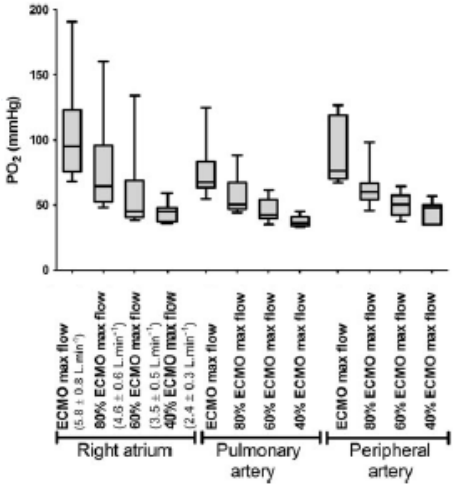


Figure 4.5: Impact of ECMO flow reduction on oxygen partial pressure (pO_2) in the right atrium, pulmonary artery and peripheral artery [Schmidt et al., 2012]

4.3 Experiment 3 - carbon dioxide partial pressure (pCO_2) in relation to ECMO flow

In experiment 3, the relationship between pCO_2 and ECMO flow was investigated. V_t and pulmonary shunt are set to be 100ml and 35%, respectively. Schmidt et al. [Schmidt et al., 2012] have shown that pCO_2 is not affected by a change of ECMO flow (figure 4.7). Results from experiment 3 have shown that pCO_2 decreases with an increase of ECMO flow in both pulmonary and peripheral arteries (figure 4.6). When ECMO flow is low - only 20%, pCO_2 is 9.4 in the pulmonary and 8.5kPa in the peripheral artery. With an increase of ECMO flow, pCO_2 decreases towards the value which is set in ECMO for 4.5kPa. The normal value of pCO_2 is around 5kPa or 37mmHg. Since the default value of pCO_2 in ECMO is set to be 4.5kPa, pCO_2 reaches a nor-

mal value during ECMO flow of 70% in the pulmonary and 60% in the peripheral artery. The results from the study by Schmidt et al. [Schmidt et al., 2012] have shown that ECMO flow of 40% is sufficient in order to achieve a normal value of pCO_2 in both pulmonary and peripheral arteries.

Figure 4.6 compares the results from present experiment and the experiment made by Schmidt et al. [Schmidt et al., 2012]. The difference between the results could be caused by partial pressure settings in the *ECMO* compartment or by the facts mentioned above in the sections 4.1 and 4.2.

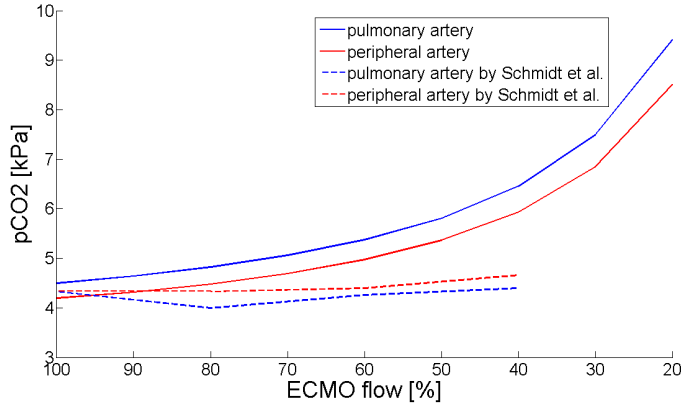


Figure 4.6: Experiment 3 - Relationship between carbon dioxide partial pressure (pCO_2) in the peripheral and pulmonary artery and ECMO flow; tidal volume (V_t) is 0.1l, pulmonary shunt is 35%

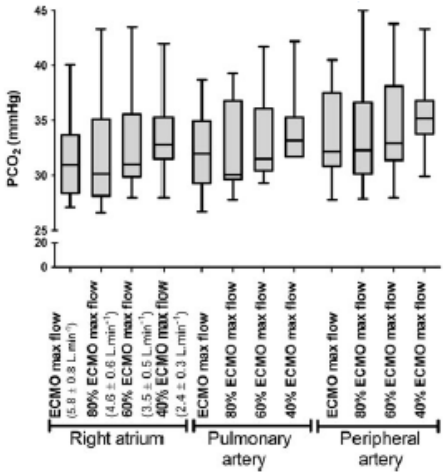


Figure 4.7: Impact of ECMO flow reduction on carbon dioxide partial pressure (pCO_2) in the right atrium, pulmonary artery and peripheral artery [Schmidt et al., 2012]

4.4 Experiment 4 - pH in relation to ECMO flow and settings of mechanical ventilation

In experiment 4, the influence of ECMO flow and settings of mechanical ventilation on pH was investigated. Figure 4.8 shows the dependency of pH on ECMO and mechanical ventilation

settings. It is obvious that the higher ECMO flow is set, the lower tidal volume (V_t) is needed. A normal range of pH values in arterial blood is between 7.35 and 7.45, the average pH value for the healthy human is 7.4. The plot displays that when ECMO flow is only 10%, V_t of 0.4l is necessary for reaching the pH of 7.4. As ECMO flow is increased, lower V_t is sufficient for getting the normal value of pH in arterial blood. If ECMO flow is 50%, V_t of 0.1l is adequate mechanical ventilation support.

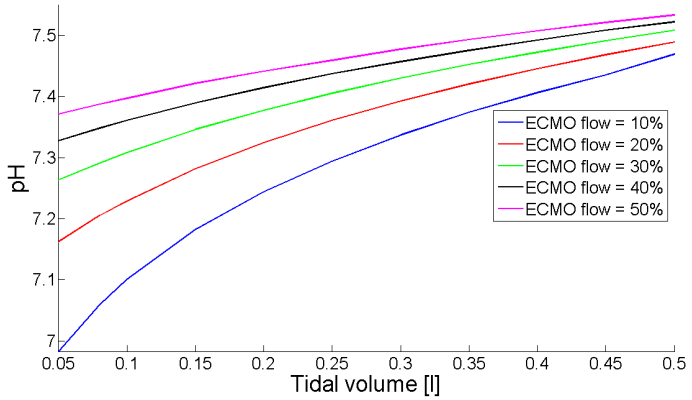


Figure 4.8: Experiment 4 - Relationship between arterial pH, ECMO flow and settings of mechanical ventilation; pulmonary shunt is 35%

4.5 Experiment 5 - temperature change

In experiment 5, the process of a temperature change was investigated. The goal of this experiment was to investigate how fast the patient body with the volume of 50l can be cooled down from the normal body temperature around 37°C towards 25°C. Figure 4.9 displays how the temperature in the tissues is changed during the time. It was shown that the desired temperature is almost reached after 5,000s (around 1.38hours). The desired temperature is not reached completely, because the temperature has exponential progress. However, the result was shown to be reasonable.

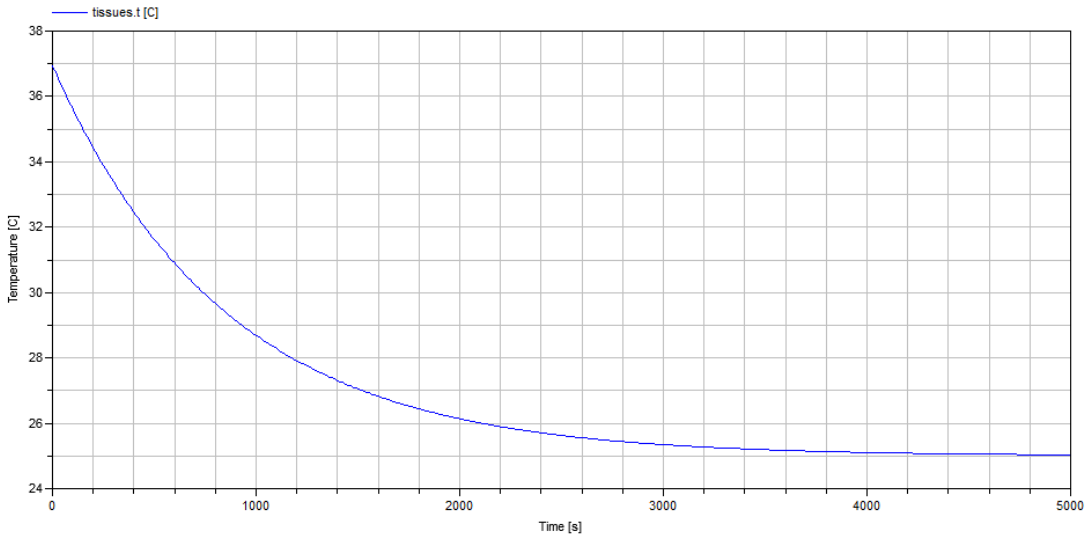


Figure 4.9: Experiment 5 - The process of cool down of the patient from 37°C towards 25°C

4.6 Experiment 6 - oxygen saturation (sO_2) in relation to ECMO flow and pulmonary shunt

In experiment 6, the dependency of sO_2 on ECMO flow and pulmonary shunt was investigated. Pulmonary shunt is a pathological condition when venous blood is mixed with arterial blood and the efficiency of gas exchange is affected [Lovering and Goodman, 2012]. The theory is that the lower pulmonary shunt is, the lower ECMO flow is necessary in order to keep sO_2 on the value >97%. The results have confirmed the theory. Figure 4.10 shows that the lower the shunt is, the lower ECMO flow is sufficient in order to reach sO_2 of >97%. When the shunt is physiologically normal around 10%, ECMO flow around 35% is needed in order to keep sO_2 sufficiently high. As soon as the state of the lungs gets worse and pulmonary shunt is 50%, ECMO flow of 60% is needed to keep sO_2 at a sufficient level.

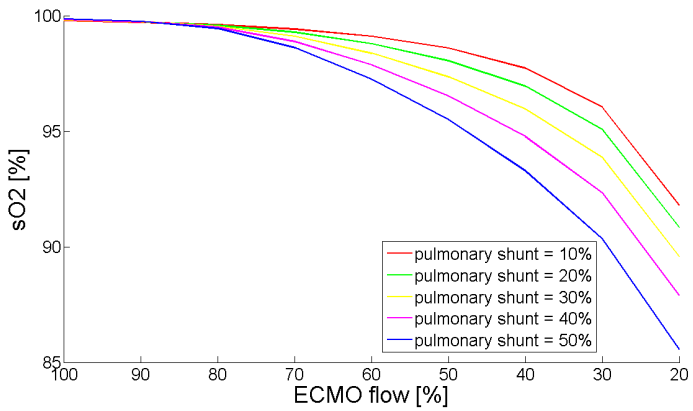


Figure 4.10: Experiment 6 - Relationship between arterial oxygen saturation (sO_2), ECMO flow and pulmonary shunt

4.7 Experiment 7 - oxygen saturation (sO_2) in relation to ECMO flow and carbon dioxide production (VCO_2) and oxygen uptake (VO_2)

In experiment 7, the dependency of arterial sO_2 on VCO_2 and VO_2 was investigated. The theory is that a higher ECMO flow is necessary to keep arterial sO_2 at a sufficient level during an increase of VCO_2 and VO_2. The results have confirmed such a theory. As it is shown in figure 4.11 a higher ECMO flow is necessary for reaching sO_2 of >97% with an enhancement of VCO_2 and VO_2. Specifically, when VCO_2 and VO_2 are 10mmol/min, ECMO flow of 60% is sufficient for arterial sO_2 of >97%. When VCO_2 and VO_2 are increased towards 15mmol/min, ECMO flow of 70% is needed for a sufficient value of arterial sO_2. In the case of VCO_2 and VO_2 equal to 22mmol/min, ECMO flow of 80% is necessary.

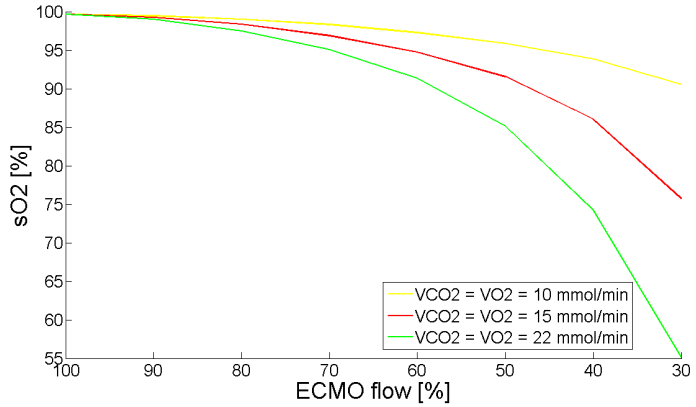


Figure 4.11: Experiment 7 - Relationship between arterial oxygen saturation (sO_2), ECMO flow, carbon dioxide production (VCO_2) and oxygen uptake (VO_2); pulmonary shunt is 35% and tidal volume (V_t) is 0.1l

4.8 Experiment 8 - behavior of the model

In experiment 8, the behavior of the model has been observed. The changes of blood properties such as sO_2, pO_2, pCO_2, tO_2, tCO_2 and pH were observed during the passage through the circulation. Pulmonary shunt, V_t and ECMO flow were set to be 35%, 0.1l and 60%, respectively. The results are listed in table 4.1. In comparison with the tables 2.2 and 2.3 in the section 2.2.1, the behavior can be considered as physiological. The results have shown values of arterial blood properties which are consistent with values suggested by Rees and Andreassen [Rees and Andreassen, 2005] and Martin [Martin, 1999].

	sO_2 [%]	pO_2 [kPa]	pCO_2 [kPa]	tO_2 [mmol/l]	tCO_2 [mmol/l]	pH
Venous blood	79.76	6.45	6.84	7.48	27.04	7.31
ECMO	99.84	45.00	4.50	9.76	24.86	7.46
After ECMO	94.07	9.58	5.38	8.85	25.73	7.39
Alveolar space	98.76	16.90	4.77	9.36	25.14	7.44
Arterial blood	97.31	12.60	4.98	9.18	25.34	7.42

Table 4.1: Experiment 8 - Summary of blood properties in different parts of circulation under following settings; pulmonary shunt is 35%, V_t is 0.1l, ECMO flow is 60%, $pCO_{2,ecmo}$ is 4.5kPa and $pO_{2,ecmo}$ is 45kPa

4.9 Results summary

In summary, the results from the experiments have shown that arterial blood properties are dependent on ECMO flow. Specifically, ECMO flow between 60 and 70% is usually associated with good arterial blood properties. On the contrary, experiment 7 has shown that ECMO flow of 80% is necessary for keeping arterial sO_2 at a sufficient level if VO_2 and VCO_2 are increased towards 22mmol/min. Nevertheless, under a normal conditions when VO_2 and VCO_2 are equal to 10mmol/l, ECMO flow of 60% is sufficient. The results from experiment 5 have shown that the model is able to display the temperature change of the patient body. Experiment 6 has shown that with an increase of pulmonary shunt, a higher ECMO flow is necessary for reaching good arterial blood properties. Experiment 8 has observed the behavior of the model and it can be considered as satisfactory.

4.10 Comparison of the results

It is relevant to compare the results from the present master thesis with my former project. The results have shown very similar behavior despite a number of changes in the model (figure 4.12). The model has been upgraded and the function and structure were improved from the programming point of view. However, the purpose of these two projects was different. The objective of the former project was to design a computer model of blood circulation, lungs, tissues and VV ECMO in order to find out which ECMO settings are optimal for achieving sufficient oxygenation and carbon dioxide removal in different states of lung function presented. The aim of the master thesis was to improve and upgrade this model and create a design of a computer application. During my master thesis, I worked on the functional improvement of the model, so it can be used in the future as a basis for the training application.

However, the results from the experiments which were necessary to perform in order to find out whether the model works as it is expected have shown similar behavior of the model. It was shown that the most important indicator of sufficient oxygenation and carbon dioxide removal is ECMO flow and that 60% of the systemic blood flow is usually associated with good arterial blood properties.

Figure 4.12 compares the results from the former and present project. The performed experiment has shown the dependency of sO_2 on ECMO flow. It is shown that the plots follow the same pattern, but the results of the present project are slightly shifted towards lower values.

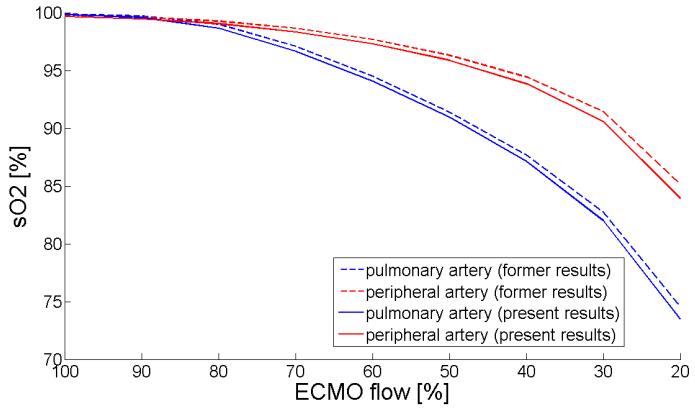


Figure 4.12: Dependency of oxygen saturation (sO_2) on ECMO flow - comparison of the results from the former and present project; tidal volume (V_t) is 100ml, pulmonary shunt is 35%

CHAPTER 5

DISCUSSION

Two important findings have emerged from this master thesis. Firstly, the model was shown to work within physiological standards and therefore it can be used as a basis for a future computer application. Secondly, the results from the experiments have shown that for a patient with insufficient lung function (pulmonary shunt = 35%) and slight support by mechanical ventilation (V_t = 0.1l) the optimal ECMO flow is between 60% and 70% (3.5 - 4.1l/min). Partial pressures in ECMO are set to be pCO_2 of 4.5kPa and pO_2 of 45kPa. Under these conditions, arterial blood is well saturated and deprived of carbon dioxide.

A former study has investigated that using femoro-jugular ECMO settings and ECMO flow of >60% of systemic blood flow is associated with arterial sO_2 of >90% [Schmidt et al., 2012]. Results from the present project confirm this finding. However, sO_2 in the peripheral artery of 90% is achieved already when ECMO flow is 30% of cardiac output. sO_2 in the pulmonary artery was found to be lower than in the peripheral artery under the same conditions of ECMO flow [Schmidt et al., 2012]. The same finding has emerged from the present experiment. Specifically, sO_2 in the pulmonary and peripheral artery of >90% is achieved when ECMO flow is set to be 50% and 30%, respectively. Nevertheless, sO_2 of >97% in both the pulmonary and peripheral artery is achieved when ECMO flow is 70% [Doležalová, 2013].

The previous study by Schmidt et al. [Schmidt et al., 2012] has observed that ECMO flow of >60% of systemic blood flow is associated with arterial pO_2 of >60mmHg (8kPa). It was shown that pO_2 is lower in the pulmonary than in the peripheral artery under the same conditions of ECMO flow [Schmidt et al., 2012]. Similar findings have emerged from the present project. However, pO_2 of >60mmHg (8kPa) occurs in the pulmonary artery and in the peripheral artery when ECMO flow is 50% and 30%, respectively. Optimal pO_2 of 100mmHg (13kPa) is achieved in pulmonary and peripheral artery when ECMO flow is 73% and 62%, respectively [Doležalová, 2013].

Schmidt et al. [Schmidt et al., 2012] have shown that during ECMO flow reduction to 40%, pCO_2 is unaffected. The finding differs in the present project. It has emerged that ECMO flow of 70% in pulmonary artery and 60% in peripheral artery provides normal values of pCO_2 (37mmHg or 5kPa). The reason is probably the settings of partial pressures in the ECMO compartment. The default value of pCO_2 in the ECMO compartment is set to be 4.5kPa. Therefore, pCO_2 is in all parts of the circulation at least 4.5kPa. When ECMO flow increases pCO_2 decreases towards the default value.

The results from the experiments 1, 2 and 3 were shown to be different compared to the results from the study by Schmidt et al. [Schmidt et al., 2012]. The difference between the results from the present project and the results from study by Schmidt et al. [Schmidt et al., 2012] may be caused by an excessive efficiency of the model and a wide range of the values from the study by Schmidt et al. [Schmidt et al., 2012]. However, the model was made as a basis for the computer application, so the focus was centered on the trends of the variables more than the exact

values.

Experiment 4 has observed an effect of ECMO flow and mechanical ventilation settings on arterial pH. Both mechanical ventilation and an ECMO device are often used in combination. The goal is to make the settings sufficient in order to keep arterial pH between 7.35 and 7.45. The results from the experiment have shown that with an increase of ECMO flow, lower V_t is needed for maintaining the pH on the desired level. Mechanical ventilation can cause harm on lung tissue, but ECMO can also have lasting effects on the patient body. Therefore, these kinds of support are the last opportunity in very severe cases.

Experiment 5 has investigated the progress of temperature change. An ECMO device is able to change the body temperature by changing the blood temperature. The patient's body was cooled down from 37°C towards 25°C. The condition when the human body has a temperature below the required temperature for normal metabolism (around 37°C), is called hypothermia. Under these circumstances, the metabolic demands are reduced, the oxygen demands are decreased, the brain is protected from hypoperfusion and hypoxia and the tissue energy reserves are saved. Therefore, hypothermia is sometimes used during an ECMO treatment. Hypothermia may also have negative effects, but in some cases it is a necessary approach. The condition when the human body temperature is between 32°C and 25°C, is called moderate hypothermia [Pavlík, 2012]. The results from experiment 5 have shown that the patient's body temperature is the closest to the desired temperature of 25°C in 5000s (1.38hours). The results can be considered as reasonable.

As it was mentioned previously, pulmonary shunt is a pathological condition which is caused by mixing venous blood with arterial blood. The efficiency of gas exchange is therefore affected [Lovering and Goodman, 2012]. The higher the shunt is, the worse the patient's condition is expected to be. The results from the experiment 6 have confirmed such a statement. It was shown that with an increase of pulmonary shunt, a higher ECMO flow is needed in order to provide sO_2 on the normal value (>97%). When pulmonary shunt is around 10%, ECMO flow of 35% is sufficient for arterial sO_2 of >97%. As soon as pulmonary shunt is increased towards 50%, ECMO flow of 60% is needed for keeping the arterial sO_2 high enough.

During strenuous exercise the human body requires up to 500 times more oxygen than when at rest. At the same time, the body has to eliminate carbon dioxide and other metabolic products whose production suddenly significantly increases [Silbernagl and Despopoulos, 2009]. Experiment 7 has investigated the influence of the changes of VCO_2 and VO_2 on arterial sO_2. An increase of VCO_2 and VO_2 means an increase of the patient's metabolism. Even though patients on ECMO are usually bedridden and their physical activity does not increase a lot, a small change is possible. For instance, if the patient is sedated and after some time the sedation is decreased and the patient is allowed to communicate with relatives and medical staff. Under normal conditions, VCO_2 and VO_2 are equal to 10mmol/min. As it was mentioned previously in the section 3.3.6 the ratio between VCO_2 and VO_2 is called respiratory quotient (RQ) and it varies between 0.7 and 1. I chose RQ to be 1, so the patient body burns carbohydrates. The results from this experiment have shown that with an increase of the activity of the patient's metabolism, a higher ECMO flow is needed in order to keep arterial sO_2 >97%.

Experiment 8 has investigated the behavior of the model. The change of the most important blood properties such as sO_2, pO_2, pCO_2, tO_2, tCO_2 and pH were observed at several exact points of the circulation. The results have shown that the model behaves in accordance with the expected results. In the venous blood, tCO_2 is high together with pCO_2, the rest of the blood properties are low, because of a low concentration of oxygen. ECMO oxygenates blood and deprives it of carbon dioxide, therefore the values of mentioned blood properties are opposite. Specifically, sO_2 and pO_2 are extremely high, pCO_2 and tCO_2 are low and pH is in normal range. After ECMO, the blood flowing from ECMO is mixed with venous blood, because ECMO

flow is 60%. In alveolar space, mechanical ventilation helps to fulfill oxygenation and carbon dioxide removal. The blood properties are in normal ranges. Finally, arterial blood properties are a mix of blood going from ECMO and alveolar ventilation according to the pulmonary shunt. In this case, the pulmonary shut is set to be 35%. Therefore, arterial blood properties are closer to the values from alveolar space.

A previous study has suggested that ECMO flow is the main determinant of blood oxygenation. It was shown that ECMO flow of >60% of systemic blood flow obtains adequate arterial oxygenation. ECMO flow of 4 to 7 l/min is usually required to achieve sO_2 of >88-90% depending on the patient size, cardiac output, oxygen consumption and lung shunt. Safe ventilation supports the pulmonary function while on ECMO [Schmidt et al., 2012]. The present experiments do not consider all of the conditions. The goal during most of the experiments is to achieve sO_2 of >97% and cardiac output in the model is 5.8l/min. Under these circumstances, the ideal ECMO flow is between 60 and 70%. All of the present experiments have shown that ECMO flow is the major determinant of blood oxygenation [Doležalová, 2013].

5.1 Limitations

Mathematical or computer model is never able to fully substitute or express the real system, but it may be very useful in describing and explaining basic processes and functions of any system. My intention in this master thesis was to try to reproduce the behavior of human blood circulation when the lungs are not working properly and it is necessary to support their function with slight mechanical ventilation and an ECMO device. I started to work on the model during my stay in Denmark where I was working on a similar topic with different purposes. The model which was created before has now been improved, the basis was changed and some parts were added. After building the model which expresses the behavior of human body, the goal was to create a design of a computer application based on the model. Even though the model was upgraded and its function improved and it works satisfactorily, there are still similar limitations which are necessary to mention.

5.1.1 Acid-base chemistry

The first limitation is an imperfect buffering system in the model. Since a strong base is not considered as a blood component in the model, concentrations of tA (tNBB) and BB are assumed to be constants in the system. The initial values are set and the equations define that these variables are not change in the circulation.

Next inaccuracy is the description of oxygen and carbon dioxide content in the blood. Each of these two substances are described almost separately and in different ways. Carbon dioxide content is described only in plasma, its part in erythrocytes is ignored. Therefore, tCO_2 in the model means total concentration in plasma. Oxygen content is defined in the entire blood volume, since Hb concentration was set to be 9.3mmol/l, which is oxygen carrying capacity of hemoglobin per liter of blood. As you can see, the ways of describing oxygen and carbon dioxide are not completely consistent. In summary, acid-base chemistry in the model is simplified. However, it shows the most important behaviors, processes and dependencies of concentrations, partial pressures and saturation in the lungs, tissues and ECMO [Doležalová, 2013].

5.1.2 ECMO

The next limitation is the simplified structure of the ECMO compartment. In real ECMO device, air supply is an independent unit with its own flow. The air unit sets the fraction of oxygen and carbon dioxide. In the model, oxygen and carbon dioxide are incorporated to the ECMO

subcompartment without any additional flow settings. I assume that fractions of the gases are analogous to partial pressures. Therefore the settings of oxygen and carbon dioxide fraction are changed by changing partial pressures [Doležalová, 2013].

5.1.3 Shunt

Another limitation which I want to mention is the mixing of venous blood in pulmonary shunt and the shunt in the ECMO compartment. At some point, the oxygenation in the lungs does not make physiological sense. This occurs specifically if the entire blood volume is going through ECMO. The blood is well oxygenated with the appropriate concentration of carbon dioxide after passing through ECMO. Since the model represents VV modality and blood from ECMO is returned to the venous bloodstream, venous blood becomes well oxygenated and deprived of carbon dioxide. After passing through ECMO, venous blood comes to the lungs and it is supposed to be more oxygenated and deprived of carbon dioxide. However, it is not possible, because it already is very well saturated with oxygen and carbon dioxide concentration is appropriate. The next problem arises with pulmonary shunt when the entire blood volume is going through ECMO. Pulmonary shunt is a pathological state when oxygenated blood is mixed with deoxygenated blood. The higher pulmonary shunt is, the more of the venous blood is mixed with the arterial blood and the worse the patient's condition is expected to be. However, since venous blood in the model is under mentioned conditions well saturated and deprived of carbon dioxide, it is actually better to have higher shunt which does not make any physiological sense. Nevertheless, it is not that common even in real ECMO device, that the entire blood volume is going through, since drainage is most often located in femoral vein or inferior or superior vena cava [Doležalová, 2013].

5.1.4 Validity

The last limitation is that the model is valid in a particular range of values. Under normal conditions, the model works satisfactorily, but as soon as the initial values are completely out of the physiological range, the model crashes. The biggest problem arises when the shunt is set to be zero, the system is not able to compute with zero. The same applies also to the shunt in the lungs. If the shunt is set to be zero, the model cannot handle the calculations with zero. However, the normal physiological value of pulmonary shunt is around 2%, so there is no reason in the simulation to set the pulmonary shunt to zero.

A problem arises also with wrong initial values. The model is built for physiological values. Therefore, when the initial values of some variables are completely out of range, the system cannot handle the calculations.

5.1.5 Limitations summary

These limitations are still presented, but the model has appropriate properties which allow us to possibly create a computer application which should be able to express the most important functions of VV ECMO and mechanical ventilation. Even though the limitations are the same as in the former model, the connector was changed and settings of temperature in ECMO were added together with the model of mechanical ventilation. Therefore, the functioning of the model is more realistic and it can be used as a basis for a training computer application which was mentioned previously. There are still a lot of possibilities how to expand and elaborate the model in the future and therefore make more advanced application. It would be very interesting to try to cooperate with hospitals and find out if it is possible to express or anticipate

the function of ECMO on particular patients by fixing the parameters and settings according to specific details of their body.

CHAPTER 6

CONCLUSION

The aim of this master thesis was to improve and upgrade the computer model of blood circulation, lungs, tissues and venovenous extracorporeal membrane oxygenation (VV ECMO) from my former project. My second goal was to create a design of a training application including the explicatory text.

According to the master thesis assignment, an overview of tools for ECMO training with emphasize on model-based simulators was made. A model of human blood circulation and blood gases transport was chosen and the present model is based on it. The model was implemented in the Modelica language and based on Modelica Fluid library principles. A simple model of mechanical ventilator was added and temperature settings were incorporated to the ECMO component. Although a design of the training computer application was made, the explicatory text is not included. For creating the explicatory text, further discussions with doctors and developers of the application would be necessary.

The present master thesis can conclude that the results from the performed experiments have shown that the model works satisfactorily and within desired physiological standards despite some limitations. Therefore it could be considered as a sound basis for creating a computer application which should be used as an educational tool. The future training application will be able to demonstrate basic behavior of human circulation, processes in tissues, lungs and VV ECMO. The application will express the dependencies of blood properties on the changes of ECMO and mechanical ventilation settings. The user will be able to see how the settings have to be changed when the level of lung function decreases.

The future computer application will help students of medicine and biomedical engineering and other medical staff develop a deeper understanding of the function of ECMO. The model can be easily modified, improved and extended. The model is distributed under the Modelica License Version 2 [1].

[1] https://modelica.org/licenses/ModelicaLicense2

BIBLIOGRAPHY

[Antonius and Peeters, 2011] Antonius, T. and Peeters, T. (2011). Ecmo simulation. Accessed: 2013-09-09. Available from: http://ecmosim.com/.

[Aschwanden et al., 2009] Aschwanden, C., Wang, K., and Tanaka, L. (2008 - 2009). Ecmojo - online ecmo simulator. Accessed: 2013-09-07. Available from: http://ecmojo.sourceforge.net/index.php.

[Bartlett et al., 1985] Bartlett, R., Roloff, D., Andrews, R. C. A., Dillon, P., and Zwischenberger, J. (1985). Extracorporeal circulation in neonatal respiratory failure: a prospective randomized study. *Pediatrics*, 76:479–487.

[Betit, 2009] Betit, P. (2009). Extracorporeal membrane oxygenation: Quo vadis? *Respiratory Care*, 54:948–957.

[Burkhart et al., 2013] Burkhart, H., Riley, J., Lynch, J., Suri, R., Greason, K., L.D.Joyce, Nuttall, G., Schaff, J. S. H., and Dearani, J. (2013). Simulation-based postcardiotomy extracorporeal membrane oxygenation crisis training for thoracic surgery residents. *The Annals for thoracic Surgery*, 95:901–906.

[Casella et al., 2006] Casella, F., Otter, M., Proelss, K., Richter, C., and Tummescheit, H. (2006). The modelica fluid and media library for modeling of incompressible and compressible thermo-fluid pipe networks. pages 631–640. Accessed: 2013-12-09. Available from: https://www.modelica.org/events/modelica2006/Proceedings/sessions/Session6b1.pdf.

[Chan et al., 2013] Chan, S., Figueroa, M., Spentzas, T., Powell, A., Holloway, R., and Shah, S. (2013). Prospective assessment of novice learners in a simulation-based extracorporeal membrane oxygenation (ecmo) education program. *Pediatric Cardiology*, 34:543–552.

[Churg et al., 2005] Churg, A., Myers, J., Tazelaar, H., and Wright, J. (2005). *Thurlbeck's Pathology of the Lung*. Thieme, third edition.

[Curley and Moloney-Harmon, 2001] Curley, M. and Moloney-Harmon, P. (2001). *Critical Care Nursing of Infants and Children*. second edition. Accessed: 2013-09-13. Available from: http://repository.upenn.edu/miscellaneous_papers/4/.

[Darling, 1999] Darling, D. (1999). Circulatory system. Accessed: 2013-09-12. Available from: http://www.daviddarling.info/encyclopedia/C/circulatory_system.html.

[Doležalová, 2013] Doležalová, A. (2013). Mathematical model for optimizing ecmo settings in case of respiratory failure. pages 1–44. Available from: http://patf-biokyb.lf1.cuni.cz/wiki/_media/projekty/ecmo_dolezalova_aalborg.pdf.

[Elišková and Naňka, 2006] Elišková, M. and Naňka, O. (2006). *Přehled anatomie*. Univerzita Karlova v Praze, first edition.

[Field et al., 1996] Field, D., Davis, C., nad A. Grant, D. E., Johnson, A., and Macrae, D. (1996). Uk collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *The Lancet*, 348:75–82.

[Fritzon, 2004] Fritzon, P. (2004). *Principles of object-oriented modeling and simulation with Modelica 2.1*. John Wiley and Sons, INC.

[Gow et al., 2006] Gow, K., Wulkan, M., Heiss, K., Haight, A., Heard, M., and Fortenberry, P. R. J. (2006). Extracorporeal membrane oxygenation for support of children after hematopoietic stem cell transplantation: the extracorporeal life support organization experience. *J Pediatr Surg*, 41:662–667.

[Green et al., 1996] Green, T., Timmons, O., Fackler, J., Moler, F., Thompson, A., and Sweeney, M. (1996). The impact of extracorporeal membrane oxygenation on survival in pediatric patiens with acute respiratory failure. pediatric critical care study group. *Crit Care Med*, 24:323–329.

[Hemmila et al., 2004] Hemmila, M., Rowe, S., Boules, T., Miskulin, J., McGillicuddy, J., Schuerer, D., Haft, J., Swaniker, F., Arbabi, S., Hirschl, R., and Bartlett, R. H. (2004). Extracorporeal life support for severe acute respiratory distress syndrome in adults. *Annals of Surgery*, 240:595–607.

[Jewett and Serway, 2008] Jewett, J. and Serway, R. (2008). *Physics for scientists and engineers with modern physics*. Brooks/Cole Cengage Learning, seventh edition.

[Katyal and Gajic, 2013] Katyal, P. and Gajic, O. (2013). Pathophysiology of respiratory failure and use of mechanical ventilation. Accessed: 2013-10-15. Available from: http://www.thoracic.org/clinical/critical-care/clinical-education/respiratory-failure-mechanical-ventilation.pdf.

[Kofránek and Hozman, 2013] Kofránek, J. and Hozman, J. (2013). *Pacientské simulátory*. Creative Connections s.r.o., first edition.

[Kofránek et al., 2008] Kofránek, J., Mateják, M., and Tribula, M. (2008). Causal or acausal modeling: Labour for humans or labour for machines. *Technical Computing Prague conference*, pages 1–16.

[Kroček, 2011] Kroček, T. (2011). Implementace rozsáhlého modelu fyziologických funkcí v prostředí jazyka modelica. pages 1–108. Accessed: 2013-09-09. Available from: http://cyber.felk.cvut.cz/research/theses/detail.phtml?id=181.

[Langmeier et al., 2009] Langmeier, M., Kittnar, O., Marešová, D., and Pokorný, J. (2009). *Základy lékařské fyziologie*. Grada Publishing, a.s., first edition.

[Linden et al., 2000] Linden, V., Palmer, K., Reinhard, J., Westman, R., Ehren, H., Granholm, T., and Frenckner, B. (2000). High survival in adult patients with acute respiratory distress syndrome treated by extracorporeal membrane oxygenation, minimal sedation, and pressure supported ventilation. *Intensive Care Med*, 26:1630–1637.

[Lindstrom et al., 2009] Lindstrom, S., Pellegrino, V., and Butt, W. (2009). Extracorporeal membrane oxygenation. *MJA*, 191:178–182.

[Lovering and Goodman, 2012] Lovering, A. and Goodman, R. (2012). Detection of intracardiac and intrapulmonary shunts at rest and during exercise using saline contrast echocardiography. *Intech*, pages 160–175. Accessed: 2013-04-27. Available from: http://cdn.intechopen.com/pdfs/35866/InTech-Detection_of_intracardiac_and_intrapulmonary_shunts_at_rest_and_during_exercise_using_saline_contrast_echocardiography.pdf.

[Macal, 2005] Macal, C. (2005). Model verification and validation. Accessed: 2013-11-26. Available from: http://jtac.uchicago.edu/conferences/05/resources/V&V_macal_pres.pdf.

[Martin, 1999] Martin, L. (1999). *All You Really Need to Know to Interpret Arterial Blood Gases*. Lippincott Williams and Wilkins, second edition.

[Mateják, 2013] Mateják, M. (2013). Physiolibrary. Accessed: 2013-12-12. Available from: https://cw.felk.cvut.cz/wiki/courses/a6m33mos/prednasky.

[Morris et al., 1994] Morris, A., Wallace, C., Menlove, R., Clemmer, T., Jr, J. O., Weaver, L., Dean, N., Thomas, F., East, T., nad M.R. Suchyta, N. P., Beck, E., Bombino, M., Bohm, D. S. S., Hoffmann, B., Becks, H., Butler, S., Pearl, J., and Rasmusson, B. (1994). Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal co2 removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med*, 149:295–305.

[Noah et al., 2011] Noah, M., Peek, G., Finney, S., Griffiths, M., Harrison, D., nad M.Z. Sadique, R. G., Sekhon, J., McAuley, D., Firmin, R., Harvey, C., Cordingley, J., Price, S., Vuylsteke, A., Jenkins, D., Noble, D., Bloomfield, R., Walsh, T., Perkins, G., Menon, D., Taylor, B., and Rowan, K. (2011). Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza a(h1n1). *JAMA*, 306:1659–1668.

[Olsson et al., 2012] Olsson, H., Elmqvist, H., and Otter, M. (2012). Modelica - a unified object-oriented language for systems modeling, language specification, version 3.3. Accessed: 2013-12-09. Available from: https://www.modelica.org/documents/ModelicaSpec33.pdf.

[Oshima et al., 2010] Oshima, K., Kunimoto, F., Hinohara, H., Ohkawa, M., Mita, N., and Tajima, Y. (2010). Extracorporeal membrane oxygenation for respiratory failure: Comparison of venovenous versus venoarterial bypass. *Surg Today*, 40:216–222.

[Otter and Elmqvist, 2001] Otter, M. and Elmqvist, H. (2001). Modelica language, libraries, tools, workshop and eu-project realsim. pages 1–8. Accessed: 2013-04-20. Available from: https://modelica.org/documents/ModelicaOverview14.pdf.

[Patroniti et al., 2011] Patroniti, N., Zangrillo, A., Pappalardo, F., Peris, A., Cianchi, G., Braschi, A., Iotti, G., Arcadipane, A., Panarello, G., Ranieri, M., nad M. Antonelli, P. T., Gattinoni, L., Oleari, F., and Pesenti, A. (2011). The italian ecmo network experience during the 2009 influenza a(h1n1) pandemic: preparation for severe respiratory emergency outbreaks. *Intensive Care Med*, 37:1447–1457.

[Pavlík, 2012] Pavlík, P. (2012). Mimotělní oběh, hypotermie. Accessed: 2013-12-12. Available from: http://www.fsps.muni.cz/zachranavzime/sbornik/ct/8_mimotelniobeh_Pavlik.pdf.

[Peek et al., 2009] Peek, G., Mugford, M., Tiruvoipati, R., Wilson, A., Allen, E., Thalanany, M., Hibbert, C., Truesdale, A., Clemens, F., Cooper, N., Firmin, R., and trial collaboration, D. E. C. (2009). Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (cesar): a multicentre randomised controlled trial. *Lancet*, 374:1351–1363.

[Petty and Newman, 1978] Petty, T. and Newman, J. (1978). Adult respiratory distress syndrome. *Medical Progress*, 128:399–407.

[Pybus, 2009] Pybus, D. (2009). Adult ecmo simulator. Accessed: 2013-09-09. Available from: http://www.ecmosimulation.com/index.html.

[Rees and Andreassen, 2005] Rees, S. E. and Andreassen, S. (2005). Mathematical models of oxygen and carbon dioxide storage and transport:the acid-base chemistry of blood. *Critical reviews in biomedical engineering*, 33:209–264.

[Roch et al., 2010] Roch, A., Lepaul-Ercole, R., Grisoli, D., Bessereau, J., Brissy, O., Castanier, M., Dizier, S., Forel, J.-M., Guervilly, C., Gariboldi, V., Collart, F., Michelet, P., Perrin, G., Charrel, R., and Papazian, L. (2010). Extracorporeal membrane oxygenation for severe influenza a(h1n1) acute respiratory distress syndrome: a prospective observational comparative study. *Intensive Care Med*.

[Rodriguez-Cruz, 2011] Rodriguez-Cruz, E. (2011). Extracorporeal membrane oxygenation. *Medscape Reference*.

[Sargent, 2005] Sargent, R. (2005). Verification and validation of simulation models. *Winter Simulation Conference*, pages 130–143.

[Schmidt et al., 2012] Schmidt, M., Tachon, G., anf G. Muller, C. D., Hekimian, G., Brechot, N., Merceron, S., Luyt, C., Trouillet, J.-L., Chastre, J., Leprince, P., and Combes, A. (2012). Blood oxygenation and decarboxylation determinants during venovenous ecmo for respiratory failure in adults. *Intensive Care Med*.

[Siggaard-Andersen, 2005] Siggaard-Andersen, O. (2005). Acid-base balance. *Encyclopedia of respiratory medicine*, pages 1–6.

[Siggaard-Andersen et al., 1987] Siggaard-Andersen, O., Durst, R., and Maas, A. (1987). Acid-base and oxygen status of the blood. Accessed: 2013-05-01. Available from: http://www.siggaard-andersen.dk/OsaTextbook.htm#LctCO2P2.

[Silbernagl and Despopoulos, 2009] Silbernagl, S. and Despopoulos, A. (2009). *Color Atlas of Physiology*. Thieme, sixth edition.

[Simmons et al., 1979] Simmons, D., Nash, G., and Brigham, K. (1979). Adult respiratory distress syndrome. *Clinical Case Conference*, 130:218–235.

[Tallman, 2012] Tallman, R. (2012). Ecmo patient simulator. Accessed: 2013-09-08. Available from: http://www.biomedsimulation.com/ECMO.htm.

[Tribula et al., 2013] Tribula, M., Jezek, F., Kofranek, P. P. J., and Kolman, J. (2013). Webovy vyukovy simulator krevniho obehu. *Sbornik prispevku MEDSOFT 2013*, pages 197–204. Accessed: 2013-04-28. Available from: http://creativeconnections.cz/medsoft/2013/Medsoft_2013_Tribula.pdf.

[Vara, 2012] Vara, R. (2012). Ecmo simulation training. Accessed: 2013-09-08. Available from: http://www.kapiolani.org/women-and-children/health-services-for-children/simulation-videos.aspx.

[Varjavand et al., 2000] Varjavand, N., Kaye, J., Wang, S., and Primiano, F. (2000). The interactive oxyhemoglobin dissociation curve. Accessed: 2013-10-14. Available from: http://www.ventworld.com/resources/oxydisso/dissoc.html.

[Wikimedia.Commons, 2013a] Wikimedia.Commons (2013a). Diagram of human heart. Accessed: 2013-09-12. Available from: http://commons.wikimedia.org/wiki/File:Diagram_of_the_human_heart_(cropped).svg.

[Wikimedia.Commons, 2013b] Wikimedia.Commons (2013b). Oxyheamoglobin dissociation curve. Accessed: 2013-09-12. Available from: http://en.wikipedia.org/wiki/File:Oxyhaemoglobin_dissociation_curve.png.

[Zapol et al., 1979] Zapol, W., Snider, M., Hill, J., Fallat, R., Bartlett, R., Edmunds, L., Morris, A., Peirce, E., nad H.J. Proctor, A. T., Drinker, P., Pratt, P., and nad R.G. Miller, A. B. (1979). Extracorporeal membrane oxygenation in severe acute respiratory failure; a randomized prospective study. *JAMA*, 242:2193–2196.

APPENDIX

As an appendix, the documentation of the model is included. The documentation was generated straight from Dymola. As it was mentioned previously, Dymola is one of the Modelica simulation environments. The documentation consists of a description of all the components, models and testing packages. The pictures of the all the components and models are included as well.

Circulation

Practical part of the master thesis

Information

The model was created as a practical part of the project called *Mathematical model for optimizing ECMO settings in case of respiratory failure* and the master thesis called *Design of a model for ECMO demonstration and teaching*.

The work on the model was started in Denmark during an ERASMUS stay. The model was improved and upgraded for the master thesis. It is a model of human circulation, tissues, lungs and VV ECMO. Lungs do not work sufficiently, so they are supported by mechanical ventilation and VV ECMO. The model reproduce the function of an ECMO device and it is the basis for a computer application for educational purposes.

Last update by Anna Dolezalova 2013-12-26

Licensed by Anna Dolezalova under the Modelica License 2

Copyright © 2013-2020, Anna Dolezalova

Package Content

Name	Description
MasterThesis	Package with the final model
Components	Package of the components for the final model
Testing_acidbase	Testing the acid-base function
Testing_ventilation	Testing of the lung and ventilator function
Testing_tissues	Testing of the tissue function
Testing_ECMO	Test of the ECMO function
Testing_circulation	Testing of the circulation

Circulation.MasterThesis

Package with the final model

Information

The final model is the complete *circulation* together with *lungs*, *tissues* and *VV ECMO*. All the experiments were performed on this model. The results presented in my master thesis were obtained from the simulations on this model.

Package Content

Name	Description
Circulation_final	Final model for the master thesis

Circulation.MasterThesis.Circulation_final

Final model for the master thesis

Information

The final model consists of several parts - *circulatory system*, *lungs*, *tissues* and *VV ECMO*. *Circulation* consists of six parts - *pulmonary arteries*, *pulmonary veins*, *system arteries*, *system veins*, *left heart* and *right heart*. Model

of the *circulation* mediates the flow in the system. *Lungs* consists of four parts which is *alveolar ventilation* where the gas exchange take place, *ventilatior* which supports the pulmonary function, *shunt* and *resistor* which set the level of pulmonary shunt (how much of the venous blood is mixed with arterial blood). In the *tissues,* oxygen uptake and carbon dioxide removal take place. Finally, *ECMO* supports the function of the lungs as well as the mechanical ventilation.

Blood-meters measure blood properties at the exact points of the circulation.

Circulation.Components

Package of the components for the final model

Information

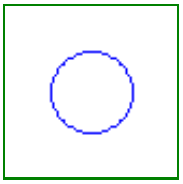
The package with all the components which are used in the final model.

Package Content

Name	Description
BloodFlow	Blood connector
BloodInflow	Blood connector for an inflow
BloodOutflow	Blood connector for an outflow
AirFlow	Air connector
AirInflow	Air connector for an inflow
AirOutflow	Air connector for an outflow
acidBaseBasics	Acid-base chemistry of the blood
BloodMeter	Blood-meter
BloodSource	Source of the variables for testing components
OnePort	Model for the flow through components
BasicResistor	The basis for the blood resistor and heart pump
BloodResistor	Blood resistance
HeartPump	Model of the heart pump
AirSource	Source of the air for mechanical ventilation
AirOutput	The output of mechanical ventilation
AirMeter	Air-meter
Shunt	Pulmonary shunt
ShuntECMO	ECMO flow
BloodElastic	Model of the blood-vessels
AlveolarVentilation	Gas exchange itself
AlveolarVentilationAll	Alveolar space
ECMOoxygenation	A support of oxygenation and carbon dioxide removal
Lungs	Model of the lungs
Tissues	Model of the tissues
ECMO	ECMO model

Circulation.Components.BloodFlow

Blood connector



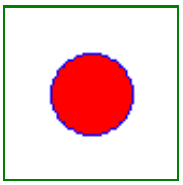
Information

BloodFlow transports the blood variables listed in the table below.

Contents

Name	Description
Q	Blood flow [l/s]
p	Blood pressure [Pa]
h	Enthalpy (concentration of thermal energy) [J/l]
tCO2	Total concentration of carbon dioxide [mmol/l]
tO2	Total concentration of oxygen [mmol/l]
tA	Total concentration of non-bicarbonate buffer [mmol/l]
BB	Concentration of buffer base [mmol/l]

Circulation.Components.BloodInflow



Blood connector for an inflow

Information

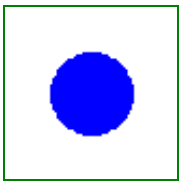
Connector which transports the same variables as *BloodFlow*. *BloodInflow* is used only as an input to the component.

Extends from Circulation.Components.BloodFlow (Blood connector).

Contents

Name	Description
Q	Blood flow [l/s]
p	Blood pressure [Pa]
h	Enthalpy (concentration of thermal energy) [J/l]
tCO2	Total concentration of carbon dioxide [mmol/l]
tO2	Total concentration of oxygen [mmol/l]
tA	Total concentration of non-bicarbonate buffer [mmol/l]
BB	Concentration of buffer base [mmol/l]

Circulation.Components.BloodOutflow



Blood connector for an outflow

Information

BloodOutflow transports the same variables as *BloodFlow*, but it is used only as an output from the component.

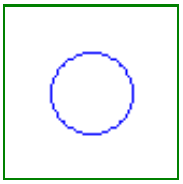
Extends from Circulation.Components.BloodFlow (Blood connector).

Contents

Name	Description
Q	Blood flow [l/s]
p	Blood pressure [Pa]
h	Enthalpy (concentration of thermal energy) [J/l]

tCO2	Total concentration of carbon dioxide [mmol/l]
tO2	Total concentration of oxygen [mmol/l]
tA	Total concentration of non-bicarbonate buffer [mmol/l]
BB	Concentration of buffer base [mmol/l]

Circulation.Components.AirFlow



Air connector

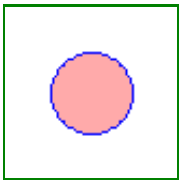
Information

Connector that transports all the important variables for the air, see the table below.

Contents

Name	Description
Q	Air flow [l/s]
p	Pressure of the air [Pa]
tCO2	Total concentration of carbon dioxide in the air [mmol/l]
tO2	Total concentration of oxygen in the air [mmol/l]

Circulation.Components.AirInflow



Air connector for an inflow

Information

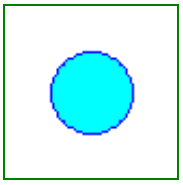
AirInflow transports the same values as *AirFlow*, but it is used only as an inflow.

Extends from Circulation.Components.AirFlow (Air connector).

Contents

Name	Description
Q	Air flow [l/s]
p	Pressure of the air [Pa]
tCO2	Total concentration of carbon dioxide in the air [mmol/l]
tO2	Total concentration of oxygen in the air [mmol/l]

Circulation.Components.AirOutflow



Air connector for an outflow

Information

AirlOutlow transports the same values as *AirFlow*, but it is used only as an outflow.

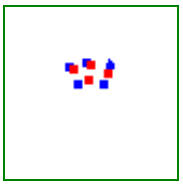
Extends from Circulation.Components.AirFlow (Air connector).

Contents

Name	Description
Q	Air flow [l/s]
p	Pressure of the air [Pa]
tCO2	Total concentration of carbon dioxide in the air [mmol/l]

tO2	Total concentration of oxygen in the air [mmol/l]

Circulation.Components.acidBaseBasics



Acid-base chemistry of the blood

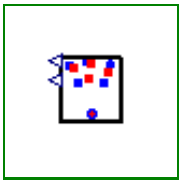
Information

AcidBaseBasic consits of all the important equations for the calculating acid-base chemistry of blood. It is partial model and can be inherited by all the components where the acid-base chemistry equations are needed.

Parameters

Name	Description
pK_A	Dissociation constant for non-bicarbonate buffers in plasma
pK_HCO3	Dissociation constant for bicarbonate in plasma
co2Solubility	Solubility coefficient of carbon dioxide [mmol/(l.Pa)]
Hb	Concentration of hemoglobin in blood [mmol/l]
FMetHb	Fraction of methemoglobin in blood - ratio between methemoglobin and total heamoglobin
FCOHb	Fraction of carboxyhemoglobin in blood - ratio between carboxyhemoglobin and total heamoglobin
cDPG	Concentration of 2,3 - diphosphoglycerate in blood [mmol/l]
cb	Constant for conversion of enthalpy to temperature [J/(l.K)]

Circulation.Components.BloodMeter



Blood-meter

Information

BloodMeter can be used anywhere in the circulation for measuring the blood properties.

Extends from Circulation.Components.acidBaseBasics (Acid-base chemistry of the blood).

Parameters

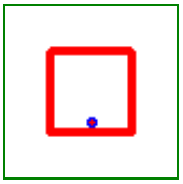
Name	Description
pK_A	Dissociation constant for non-bicarbonate buffers in plasma
pK_HCO3	Dissociation constant for bicarbonate in plasma
co2Solubility	Solubility coefficient of carbon dioxide [mmol/(l.Pa)]
Hb	Concentration of hemoglobin in blood [mmol/l]
FMetHb	Fraction of methemoglobin in blood - ratio between methemoglobin and total heamoglobin
FCOHb	Fraction of carboxyhemoglobin in blood - ratio between carboxyhemoglobin and total heamoglobin
cDPG	Concentration of 2,3 - diphosphoglycerate in blood [mmol/l]
cb	Constant for conversion of enthalpy to temperature [J/(l.K)]

Connectors

Name	Description
bloodInflow	Connector BloodInflow
partial_pressureCO2	Carbon dioxide partial pressure [Pa]
partial_pressureO2	Oxygen partial pressure [Pa]

Circulation.Components.BloodSource

Source of the variables for testing components



Information

Simple component which can be used as a source when testing the components without entire circulation. The variables on the conenctor are set to be parameters, see the table below.

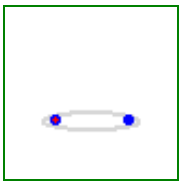
Parameters

Name	Description
co2	Concentration of carbon dioxide [mmol/l]
o2	Concentration of xygen [mmol/l]
h	Enthalpy [J/l]
a	Concentration of non-bicarbonate buffer [mmol/l]
bb	Concentration of buffer base [mmol/l]
pressure	Pressure [Pa]

Connectors

Name	Description
bloodInflow	Connector BloodInflow

Circulation.Components.OnePort



Model for the flow through components

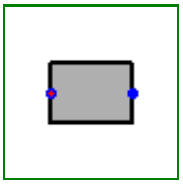
Information

OnePort is described by simple and necessary equations for the component that contains output and input. It is a partial model and it can be inherited by all the components where the blood goes through.

Connectors

Name	Description
bloodInflow	Connector BloodInflow
bloodOutflow	Connector BloodOutflow

Circulation.Components.BasicResistor



The basis for the blood resistor and heart pump

Information

BasicResistor is a partial model which is the basis for creating *BloodResistor* and *HeartPump*. It is defined by simple equations for flow and pressure drop.

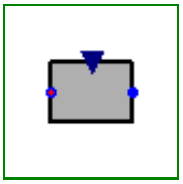
Connectors

Name	Description
bloodInflow	Connector BloodInflow
bloodOutflow	Connector BloodOutflow

Circulation.Components.BloodResistor

Blood resistance

Information



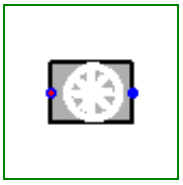
BloodResistor defines the resistance in particular part of the circulation.

Extends from Circulation.Components.BasicResistor (The basis for the blood resistor and heart pump).

Connectors

Name	Description
bloodInflow	Connector BloodInflow
bloodOutflow	Connector BloodOutflow
BloodResistance	[(Pa.s)/l]

Circulation.Components.HeartPump



Model of the heart pump

Information

HeartPump mediates the flow by the pressure which is produced by blood-vessels.

Extends from Circulation.Components.BasicResistor (The basis for the blood resistor and heart pump).

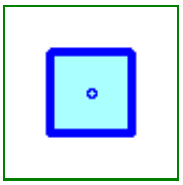
Parameters

Name	Description
StarlingSlope	[l/(Pa.s)]

Connectors

Name	Description
bloodInflow	Connector BloodInflow
bloodOutflow	Connector BloodOutflow

Circulation.Components.AirSource



Source of the air for mechanical ventilation

Information

The source of the air for mechanical ventilation. The air is enriched with oxygen and concentration of carbon dioxide is zero.

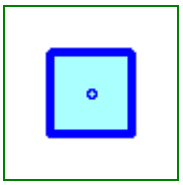
Parameters

Name	Description
FiCO2	Fraction of carbon dioxide in the inspired air
FiO2	Fraction of oxygen in the inspired air
V	Volume of the air [l]
Vt	Tidal volume [l]
f	Frequency of breathing in breaths/s
atm_p	Atmospheric pressure [Pa]
R_t	Universal gas constant [J/(mol.K)]
temp	Temperature of valid calculation [K]

Connectors

Name	Description
airFlow	Connector AirFlow

Circulation.Components.AirOutput



The output of mechanical ventilation

Information

AirOutput is used as a store for the expired air.

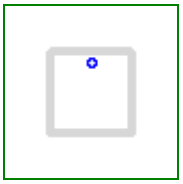
Parameters

Name	Description
pressure	Pressure [Pa]
tCO2	Concentration of carbon dioxide [mmol/l]
tO2	Concentration of oxygen [mmol/l]

Connectors

Name	Description
airFlow	Connector AirFlow

Circulation.Components.AirMeter



Air-meter

Information

AirMeter is used for measuring air properties.

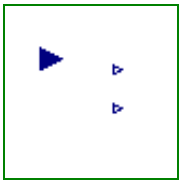
Parameters

Name	Description
atm_p	Atmospheric pressure [Pa]
R_t	Universal gas constant [J/(mol.K)]
temp	Temperature of valid calculation [K]
V	Volume [l]

Connectors

Name	Description
airFlow	Connector AirFlow

Circulation.Components.Shunt



Pulmonary shunt

Information

The *shunt* divides the resistance between *alveolar ventilation* and *blood resistor* according to desired pulmonary shunt. It defines what percentage of venous blood will be mixed with arterial blood.

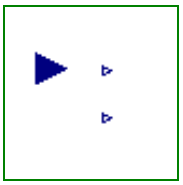
Parameters

Name	Description
R_total	Total resistance of the lungs [(Pa.s)/l]

Connectors

Name	Description
R_alveolar	Alveolar resistance [(Pa.s)/l]
R_resistor	Resistance of the resistor [(Pa.s)/l]
shunt	Percentage of venous blood mixing with arterial

Circulation.Components.ShuntECMO



ECMO flow

Information

ShuntECMO sets the ECMO flow by settings how much of the blood goes through the device.

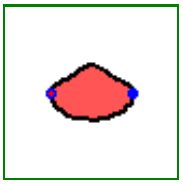
Parameters

Name	Description
R_total	Total resistance of ECMO machine [(Pa.s)/l]

Connectors

Name	Description
R_ECMO	Resistance of ECMO [(Pa.s)/l]
R_resistor	Resistance of the resistor [(Pa.s)/l]
shunt	ECMO flow

Circulation.Components.BloodElastic



Model of the blood-vessels

Information

BloodElastic describes the most important features of the blood-vessels. It defines the stressed volume, unstressed volume and pressure.

Parameters

Name	Description
Compliance	Compliance of the blood-vessel [l/Pa]
InitialVolume	Initial volume [l]
UnstressedVolume	Unstressed volume [l]
cCO2	Initial concentration of carbon dioxide [mmol/l]
cO2	Initial concentration of oxygen [mmol/l]
cTA	Initial concentration of total non-bicarbonate buffer [mmol/l]
cBB	Initial concentration of buffer base [mmol/l]

Connectors

Name	Description
bloodInflow	Connector BloodInflow

bloodOutflow	Connector BloodOutflow

Circulation.Components.AlveolarVentilation

Gas exchange itself

Information

AlveolarVentilation describes the processes of oxygenation and carbon dioxide removal. Pulmonary shunt is defined by component *shunt* by the percentage of venous blood that is mixed with arterial. It contains mechanical ventilation that support the processes of oxygenation and carbon dioxide removal. *AlveolarVentilation* inherits all the equations from the *acidBaseBasic,* so the equations of the acid-base chemistry are used here.

Extends from Circulation.Components.acidBaseBasics (Acid-base chemistry of the blood), Circulation.Components.OnePort (Model for the flow through components).

Parameters

Name	Description
pK_A	Dissociation constant for non-bicarbonate buffers in plasma
pK_HCO3	Dissociation constant for bicarbonate in plasma
co2Solubility	Solubility coefficient of carbon dioxide [mmol/(l.Pa)]
Hb	Concentration of hemoglobin in blood [mmol/l]
FMetHb	Fraction of methemoglobin in blood - ratio between methemoglobin and total heamoglobin
FCOHb	Fraction of carboxyhemoglobin in blood - ratio between carboxyhemoglobin and total heamoglobin
cDPG	Concentration of 2,3 - diphosphoglycerate in blood [mmol/l]
cb	Constant for conversion of enthalpy to temperature [J/(l.K)]
V_lungs	Volume of the entire lungs [l]
atm_p	Atmospheric pressure [Pa]
R_t	Universal gas constant [J/(mol.K)]
temp	Temperature of valid calculation [K]
Initialization	
inFlow_tCO2	Inflow concentration of carbon dioxide [mmol/l]
inFlow_tO2	Inflow concentration of oxygen [mmol/l]
inFlow_tA	Inflow concentration of total non-bicarbonate buffer [mmol/l]
inFlow_BB	Inflow concentration of buffer base [mmol/l]

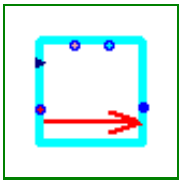
Connectors

Name	Description
bloodInflow	Connector BloodInflow
bloodOutflow	Connector BloodOutflow
R	Resistance of alveolar ventilation [(Pa.s)/l]
airInflow	Connector AirInflow
airOutflow	Connector AirOutflow
partial_pressureCO2	Carbon dioxide partial pressure [Pa]
partial_pressureO2	Oxygen partial pressure [Pa]

Circulation.Components.AlveolarVentilationAll

Alveolar space

Information



This component consists of *alveolarVentilation* and *blood-meter.* It connects these two components together in order to set the partial pressures of carbon dioxide and oxygen in the blood and in the air to be equal.

Connectors

Name	Description
R	Resistance of alveolar ventilation [(Pa.s)/l]
airInflow	Connector AirInflow
airOutflow	Connector AirOutflow
bloodInflow	Connector BloodInflow
bloodOutflow	Connector BloodOutflow

Circulation.Components.ECMOoxygenation

A support of oxygenation and carbon dioxide removal

Information

Part of *ECMO* compartment where the oxygenation and carbon dioxide removal take place. The processes are in other words an equilibrium to the new partial pressures. The desired temperature of the human body is set in *ECMOoxygenation*.

Extends from Circulation.Components.acidBaseBasics (Acid-base chemistry of the blood), Circulation.Components.OnePort (Model for the flow through components).

Parameters

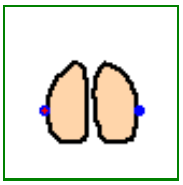
Name	Description
pK_A	Dissociation constant for non-bicarbonate buffers in plasma
pK_HCO3	Dissociation constant for bicarbonate in plasma
co2Solubility	Solubility coefficient of carbon dioxide [mmol/(l.Pa)]
Hb	Concentration of hemoglobin in blood [mmol/l]
FMetHb	Fraction of methemoglobin in blood - ratio between methemoglobin and total heamoglobin
FCOHb	Fraction of carboxyhemoglobin in blood - ratio between carboxyhemoglobin and total heamoglobin
cDPG	Concentration of 2,3 - diphosphoglycerate in blood [mmol/l]
cb	Constant for conversion of enthalpy to temperature [J/(l.K)]
pCO2_ECMO	Partial pressure of carbon dioxide in ECMO machine [Pa]
pO2_ECMO	Partial pressure of oxygen in ECMO machine [Pa]
Temperature	Desired temperature of the blood [K]
Initialization	
inFlow_tCO2	Inflow concentration of carbon dioxide [mmol/l]
inFlow_tO2	Inflow concentration of oxygen [mmol/l]
inFlow_tA	Inflow concentration of total non-bicarbonate buffer [mmol/l]
inFlow_BB	Inflow concentration of buffer base [mmol/l]

Connectors

Name	Description
bloodInflow	Connector BloodInflow
bloodOutflow	Connector BloodOutflow

R	Resistance of ECMOoxygenation [(Pa.s)/l]

Circulation.Components.Lungs



Model of the lungs

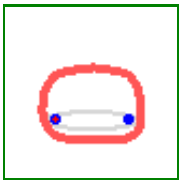
Information

Complex model which consists of four parts - *alveolar ventilation*, *ventilator*, *shunt*, *blood resistor*. The most important processes happening here are oxygenation and carbon dioxide removal. The *lungs* are not working properly, so their function is supported by mechanical ventilation. The insufficient function of the *lungs* is caused by pulmonary shunt.

Connectors

Name	Description
bloodInflow	Connector BloodInflow
bloodOutflow	Connector BloodOutflow

Circulation.Components.Tissues



Model of the tissues

Information

Two important processes take place in the *tissues* - oxygen uptake and carbon dioxide production. Carbon dioxide is added to the blood and oxygen is removed. The heat is accumulated in the *tissues*.

Extends from Circulation.Components.OnePort (Model for the flow through components).

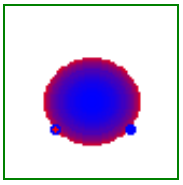
Parameters

Name	Description
VCO2	Carbon dioxide production (10 mmol/min) [mmol/s]
VO2	Oxygen removal (10mmol/min) - burning carbohydrates [mmol/s]
R	Total tissue resistance [(Pa.s)/l]
V	Volume of human body [l]
Initialization	
inFlow_tCO2	Inflow concentration of carbon dioxide [mmol/l]
inFlow_tO2	Inflow concentration of oxygen [mmol/l]
inFlow_tA	Inflow concentration of total non-bicarbonate buffer [mmol/l]
inFlow_BB	Inflow concentration of buffer base [mmol/l]

Connectors

Name	Description
bloodInflow	Connector BloodInflow
bloodOutflow	Connector BloodOutflow

Circulation.Components.ECMO



ECMO model

Information

Supports the oxygenation and carbon dioxide removal by an equilibrium on the new partial pressures. *ECMO* consists of three parts - *ECMOoxygenation*, *blood resistor* and *shunt*. *ECMOoxygenation* is a component where the equilibrium takes place. Oxygen partial pressure (pO2) and carbon dioxide partial pressure (pCO2) are set to be 45 and 4.5kPa, respectively. *Blood resistor* and *shunt* are components that set ECMO flow (how much of the blood go through ECMO).

Connectors

Name	Description
bloodInflow	Connector BloodInflow
bloodOutflow	Connector BloodOutflow

Circulation.Testing_acidbase

Testing the acid-base function

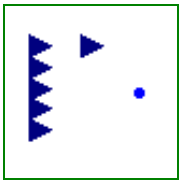
Information

This test was used as a control of the *blood-meter* function and therefore the function of acid-base equations. *Blood-meter* inherit all the equations of the acid-base balance from the partial model called *AcidBaseBasic*.

Package Content

Name	Description
src	The source of the values
testAcidBase	Circuit for acid-base testing

Circulation.Testing_acidbase.src



The source of the values

Information

This model serves as a source for the values of the important variables which are necessary to know in order to test the function of the *blood-meter.*

Connectors

Name	Description
tO2	Concentration of oxygen [mmol/l]
tCO2	Concentration of carbon dioxide [mmol/l]
tA	Concentration of non-bicarbonate buffer [mmol/l]
BB	Concentration of buffer base [mmol/l]
h	Enthalpy [J/l]
p	Pressure [Pa]
bloodOutflow	Connector BloodOutflow

Circulation.Testing_acidbase.testAcidBase

Circuit for acid-base testing

Information

The circuit for the acid-base testing consists of two components *src, blood resistor* and *blood-meter. Src1* is the source of the values of the variables, s*rc2* is a store where the values end. *Blood resistor* set the resistance between the components and *blood-meter* computes all the needed properties of the blood. This test was

performed in order to find out whether *blood-meter* works correctly.

Circulation.Testing_ventilation

Testing of the lung and ventilator function

Information

This test was performed in order to investigate if the *alveolar ventilation* and the *lungs* work correctly. Firstly, the *alveolar ventilation* was connected with *ventilator* and *blood sources* and its function was observed. Secondly, the *lungs* were connected with the *blood sources* and its function was observed by *blood-meters*.

Package Content

Name	Description
TestingAlveolarVentilation	Test of the alveolar ventilation function
Test_lungs	Test of the lung function

Circulation.Testing_ventilation.TestingAlveolarVentilation

Test of the alveolar ventilation function

Information

AlveolarVentilation was tested in this circuit. It was connected with *blood sources, ventilator* and *blood-meters*. *Blood source* sets the values of the varialbes on the connector and ensures that the flow has the right direction. *Ventilator* has two parts - *air source* and *air store*. *Air source* provides the air enriched with oxygen and with zero concentration of carbon dioxide. The expired air flows to the *air store*.

Circulation.Testing_ventilation.Test_lungs

Test of the lung function

Information

The entire component *lungs* is connected with *blood sources* and the function is checked by *blood-meters*. If the function is correct, the component can be tested in the circulation.

Circulation.Testing_tissues

Testing of the tissue function

Information

The function of the component *tissues* was tested. Firstly, *tissues* were connected only with *blood sources*. Secondly, *tissues* were connected with the circulation and its function of heat accumulation was tested.

Package Content

Name	Description
Test_tissues	Tissue function test
Circulation_heatTrial	Testing of the temperature behavior in the tissues

Circulation.Testing_tissues.Test_tissues

Tissue function test

Information

The function of oxygen uptake and carbon dioxide production was tested. The blood on the input should be arterial blood (well oxygenated and deprived of carbon dioxide). The blood on the output from the *tissues* should have higher concentration of carbon dioxide and lower concentration of oxygen.

Circulation.Testing_tissues.Circulation_heatTrial

Testing of the temperature behavior in the tissues

Information

Oxygen uptake and carbon dioxide production was tested in the circulation together with the heat accumulation. The heat was initialized and the progress of the temperature was observed. The temperture should almost reach the desired value that is set in the *ECMO* compartment.

Circulation.Testing_ECMO

Test of the ECMO function

Information

Test of the *ECMO* function was performed by connecting *ECMO* with *blood sources*. *ECMO* should have similar function as *lungs* - carbon dioxide removal and oxygenation. The values were observed by connecting with *blood-meters* on the input and output.

Package Content

Name	Description
ECMO_test	The circuit for ECMO testing

Circulation.Testing_ECMO.ECMO_test

The circuit for ECMO testing

Information

ECMO is connected with *bloodSources*. The first one is source of the concentrations. The concentration of carbon dioxide is set to be high and oxygen concentration is set to be low. On the output, the concentration of carbon dioxide should be lower and concentration of oxygen should be higher.

Circulation.Testing_circulation

Testing of the circulation

Information

The function of *circulation* together with *lungs* and *tissues* were tested. All four blood-vessels components (*pulmonary veins, pulmonary arteries*, *systemic veins, systemic arteries*) were connected together with *left heart, right heart, lungs* and *tissues.* The direction of the flow was observed as well as oxygenation, carbon dioxide removal in the *lungs* and carbon dioxide production and oxygen uptake in the *tissues* .

Package Content

Name	Description
Circulation_cut	Circulation without ECMO device

Circulation.Testing_circulation.Circulation_cut

Circulation without ECMO device

Information

The simple circuit without *ECMO*. It represents a patient whose lungs do not work sufficiently and their function is supported only by mechanical ventilation. The function of the *circulation*, *lungs* and *tissues* were tested. The flow should be mediated by blood-vessels and *right* and *left heart*. Blood should be oxygenated and deprived of carbon dioxide in the *lungs* and in the *tissues* the processes of carbon dioxide production and oxygen uptake should take place.

Automatically generated Thu Dec 26 15:52:16 2013.