Czech Technical University in Prague
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Diploma Thesis

Artificial Ventilation Simulator

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ZADÁNÍ DIPLOMOVÉ PRÁCE

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Obor: Biomedicínské inženýrství

Název tématu: Trenažér umělé plicní ventilace

Zásady pro vypracování:

1. V prostředí Matlab/Simulink vypracujte simulační model umělé plicní ventilace, který bude sloužit jako podklad pro lékařský výukový trenažér. Model bude zahrnovat simulaci výměny krevních plynů v plicích s uvažováním proměnných hodnot ventilace/perfúze v různých kompartmentech plic a jejich vliv na výsledné hodnoty krevních plynů v arteriální krvi a acidobazickou rovnováhu. Model by měl mimo jiné zahrnovat základní prvky mechaniky plic a vliv umělé plicní ventilace na hemodynamické parametry. Při sestavování modelu využijte knihovnu komponent fyziologických modelů (Physiology Blockset) vytvořenou v Biokybernetické laboratoři ÚPF 1.LF UK.
2. Identifikovaný model přeneste z prostředí Matlab/Simulink do prostředí Visual Studio .NET v němž se bude vyvíjet vlastní simulátor. Pro automatizaci tohoto přenosu využijte softwarové nástroje vytvořené v Biokybernetické laboratoři ÚPF 1.LF UK.
3. Vypracujte návrh uživatelského rozhraní pro výukový trenažér. Vizuální animační ztvárnění tohoto trenažéru bude provedeno v prostředí Adobe Flash - pro praktickou realizaci Vašeho návrhu využijte výtvarníky prostřednictvím BAJT servis s.r.o. Naprogramujte vstupně/výstupní komunikaci s animačními prvky v prostředí Flash s využitím ActionScript 3.
4. Vypracujte návrh a implementaci řídicí vrstvy, propojující model s vrstvou uživatelského rozhraní. Pro její návrh využijte softwarové nástroje vytvořené v Biokybernetické laboratoři ÚPF 1.LF UK. Přes řídicí vrstvu propojte uživatelské rozhraní se simulačním modelem a implementujte tak vlastní trenažér v české a anglické jazykové mutaci.
5. Při implementaci trenažéru počítejte s možností dalších jazykových lokalizací a připravte pro to příslušné prostředky.

Seznam odborné literatury: Dodá vedoucí práce.

Vedoucí diplomové práce: MUDr. Jiří Kofránek, CSc.

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Abstract

A lumped-parameter model of the circulatory system was developed in the Simulink environment. The model focused on cardiopulmonary mechanical interaction during artificial lung ventilation. The cardiopulmonary interaction was expressed by terms of changes in pleural and alveolar pressures as well as changes in pulmonary capillary resistance with lung volume variations. Positive (end-expiratory) pressure artificial ventilation increased the pressure in thorax, including pleural pressure and pressure in large systemic veins. Higher lung volumes increased resistance of pulmonary blood vessels. The circulatory model was linked to a model of a lung ventilator to serve as a basis for an intensive-care training simulator. The compound model was tested with different end-expiratory alveolar pressure levels. A decrease in cardiac output was observed in the model, but the reduction was greater than values reported in literature. This might be explained by absence of further autoregulatory mechanisms (as sympaticus stimulation) in the model.

Abstrakt

V prostředí Simulink byl vyvinut model oběhového systému se sousteděnými parametry zaměřený na kardiopulmonární mechanickou interakci při umělé plicní ventilaci. Kardiopulmonární interakce byla vyjádřena změnami v pleurálním a alveolárním tlaku a změnami odporu plicních kapilár s měnícím se objemem plic. Přetlaková ventilace zvyšovala tlak v hrudníku, včetně pleurálního tlaku a tlaku ve velých systémových žilách. Zvýšený objem plic zvětšoval odpor plicních cév. Oběhový model byl propojen s modelem plicního ventilátoru, aby sloužily jako základ simulátoru pro výuku akutní medicíny. Spojený model byl testován při různém endexpiračním tlaku v alveolách. V modelu bylo pozorováno snížení srdečního výdeje, ale tento pokles byl větší než uvádí literatura. Příčinou může být absence autoregulačních mechanismů (např. aktivace sympatiku) v modelu.

Acknowledgements

I would like to thank my supervisor, Jiří Kofránek, from the Institute of Pathological Physiology, 1st Faculty of Medicine, Charles University in Prague, for his help during my work and for educating me in the wonderful field of physiology. Also, I would like to extend my thanks to Stanislav Matoušek, who patiently answered many of my questions and helped to guide the scope of this thesis, to Jan Rusz for close and outstanding collaboration on our project, and to Lenka Lhotská from the Department of Cybernetics for valuable advice on my thesis and for help with my study agenda. Also my thanks to Jakub Brož, Ondřej Vacek, and Martin Rožánek for provided materials. In addition, I want to thank Erik Saudek for proofreading this thesis and to Jan Pipek, Jan Pohanka, and Ondřej Kučera for their assistance with the LaTeX typesetting system. Finally, I would like to thank my parents and friends for their support during my years at the Czech Technical University.

Prohlášení

Prohlašuji, že jsem svou diplomovou práci vypracoval samostatně a použil jsem pouze podklady (literaturu, projekty, SW atd.) uvedené v přiloženém seznamu.

V Praze dne 22. 5. 2008

Jakub Pafl

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Glossary

ARDS	Acute respiratory distress syndrome
FRC	Functional residual capacity
PEEP	Positive end-expiratory pressure
PVR	Pulmonary vascular resistance
TLC	Total lung capacity
ZEEP	Zero end-expiratory pressure
C	Compliance
F	Fluid (blood) flow
L	Inertance
P	Pressure
P_{tm}	Transmural Pressure
Q	Cardiac output
R	Resistance
V	Volume
V_u	Unstressed volume
$\varphi(t)$	Ventricle activation function
E_{max}	Ventricle elastance at maximum contraction
T	Heart period
T_{sys}	Systole duration

part	Pulmonary arterial compartment
pp	Pulmonary peripheral compartment
pao	Pulmonary arteriolar compartment
ps	Pulmonary shunt
pc	Pulmonary capillary compartment
pv	Pulmonary venous compartment
sart	Systemic arterial compartment
sp	Splanchnic peripheral compartment
sv	Splanchnic venous compartment
ep	Extrasplanchnic peripheral compartment
ev	Extrasplanchnic venous compartment
mp	Muscle peripheral compartment
mv	Muscle venous compartment
stv	Systemic thoracic veins compartment
la	Left atrium
lv	Left ventricle
ra	Right atrium
rv	Right ventricle

Chapter 1

Introduction

Artificial lung ventilation of a human patient differs significantly from normal breathing. Non-physiological conditions occur within the ventilated body, and although the artificial ventilation itself often presents a vital and unreplaceable component of modern treatment, its impact on the body may be potentially harmful. The main objective of the *Artificial ventilation simulator* project was to build a computer program based on mathematical models—a training tool, which would help students of medicine (especially those interested in intensive care units) to understand factors accompanying provision of the artificial ventilation and to practice their skills in acute medicine. As a part of the project, this master's thesis focuses on the relation between the respiratory system and the circulatory system under the conditions of artificial ventilation.

1.1 Motivation

There are two basic ways the lung ventilation affects the blood circulation: through gas exchange, which is the main purpose of the respiratory system, and through mechanical means, mainly intrathoracic pressure, i.e., the pressure within the thoracic cavity, which is strongly influenced by the pressure in lungs and which, in turn, influences blood flow.

Air flow is directly proportional to the pressure gradient. Under normal conditions, inspiration is an active process in which the diaphragm and thoracic cage muscles contract while increasing volume of the intrathoracic cavity and lung volume, thus decreasing the alveolar pressure below the atmospheric pressure. That enables the air to enter the lungs. On the other hand, expiration is passive because of the elastic recoil of the lungs, ultimately balancing the alveolar and atmospheric pressure. Due to increased volume of the intrathoracic cavity, the intrathoracic pressure during inspiration is negative. This so-called *thoracic pump* helps to draw blood from systemic veins into the chest [1].

When artificial ventilation is applied, the situation changes dramatically. The muscles are relaxed, and the pressure gradient necessary for breathing is provided by a machine, which literally inflates the lungs using pressure higher than the ambient one (so-called *positive-pressure ventilation*). During inspiration, the mouth pressure is set above the alveolar pressure, and the gas flows inside the lungs, whereas during expiration the process is reversed. The result is positive intrathoracic pressure, which cancels the thoracic pump effect. Moreover, increased lung volume extends pulmonary capillaries [2], therefore reduces their diameter and elevates pulmonary vascular resistance. Both described mechanisms ultimately lead to reduction of *cardiac output*[1], which is not the desired state especially in case of anaesthetized patients. These problems are even augmented if the pressure in the mouth remains above atmospheric pressure during the whole respiratory cycle. This was described by Cournard et al. [3] as early as in 1948, but "[t]he cardiovascular effects of [positive-pressure ventilation] ... continue to cause problems in clinical practice and, after another half century of investigation, the effects remain incompletely elucidated." [1].

1.2 Objectives and Approach

Although the principles of cardiopulmonary interaction under artificial ventilation are well known, details and individual importance of the mechanisms has been discussed until recent time [4], [5]. The complexity of the topic is probably the reason why there are very few published models dealing with the issue. In fact, no suitable model was found, which would describe directly the relation between the circulatory system and the respiratory system with a ventilator. For this reason I decided to enhance a circulatory model that partially takes artificial ventilation into account and to make changes that would allow connection of a lung ventilator model, which was developed simultaneously in another diploma thesis. As gas exchange between the lungs and the pulmonary blood vessels depends strongly on blood flow in pulmonary capillaries, I focused primarily on the mechanical cardiopulmonary interaction, which influences the blood flow. Therefore, the broad assignment of this diploma thesis was ultimately reduced to a more specific objective: to propose and design a model of mechanical cardiopulmonary interaction, which

[1] volume of blood per time unit expelled into the body by heart

would integrate a lung ventilator simulator, and to show how artificial ventilation affects blood circulation, mainly cardiac output.

The thesis describes how the model was evolved from published works and which physiological effects were considered:

- *Chapter 2* summarizes basic principles of blood circulation and respiration. Then, artificial ventilation is introduced and the fundamental difference between spontaneous breathing, and mechanical ventilation is explained. Finally, the two main areas of mechanical cardiopulmonary interaction are detailed: thoracic pump and pulmonary vessels.

- In *Chapter 3* available models are considered. A structure of an adopted model is presented, and lumped parameter concept is explained. Finally, first version of the assembled model—model 1—is implemented and tested. This version focuses mainly on pleural pressure impact.

- *Chapter 4* is devoted to possible model improvements. Parameters of the model are adjusted so that the performance of the new version—model 2 (stage 1)—during spontaneous breathing follows basic physiological data more accurately. In the second part of this chapter roles of lung volume and alveolar pressure are considered in model 2 (stage 2). A function which connects lung volume and hydraulic resistance in pulmonary capillaries is suggested.

- *Chapter 5* describes how the ventilator model was attached to model 2 (stage 2) and the behavior of the compound model. Changes in cardiac output were compared with results published in physiological literature.

- Finally, *Chapter 6* suggests which further steps should be taken for enhancement of the model.

All computer simulations were performed in the Matlab/Simulink environment, and the models can be found on the enclosed CD.

Chapter 2

Physiological Background

Before analysis and improvement of available models, the structure and function of the blood circulatory system and the respiratory system will be briefly summarized. Furthermore, their mutual influence shall be discussed as well as the impact of the artificial ventilation.

2.1 Elementary Hemodynamics

Despite complex physiological relations within the human body, let us focus only on a few physical quantities. For the purpose of this study, elementary physical relations seem to be sufficient, without demand of any deeper discussion of fluid dynamics.

2.1.1 Pressure, Flow, and Resistance

The *rate of fluid flow* F (ml·s^{-1}) between two places in a tube is proportional to the pressure difference[1] ΔP (mmHg) between the two locations:

$$F = \frac{\Delta P}{R} \tag{2.1}$$

where R (mmHg·s·ml^{-1}) denotes the *hydraulic resistance*, in particular the friction between the fluid and tube walls. Assuming laminar flow in (large) blood vessels, one can

[1] All pressure values, unless stated otherwise, will be given relative to the atmospheric pressure. In this thesis the torr (mmHg) is used as a pressure unit—see Appendix A for further details.

derive from *Poiseuille's law* that:

$$R = \frac{8l\eta}{\pi r^4}, \tag{2.2}$$

where l (cm) is the tube length, η (mmHg · s) is the viscosity of blood and r (cm) is the tube diameter. As total circulatory length and blood viscosity change only a little [6], it is apparent how important the vessel diameter is for the resistance and thus for the blood flow.

2.1.2 Pressure, Volume, and Compliance

While blood flow depends on the pressure difference within blood vessels ΔP, the volume of blood V (ml) stored in a vessel is determined by the *transmural pressure* P_{tm}—the pressure difference across the vessel wall, i.e., between the inside and the outside of the vessel. Hence, a very important parameter of a blood vessel is the *compliance* C (ml·mmHg^{-1}), which describes how blood volume changes with change in transmural pressure, that is:

$$C = \frac{dV}{dP_{tm}}. \tag{2.3}$$

Compliance of a vessel is given mainly by the structure of its wall, therefore different vessels (arteries, large veins, etc.) may distend to very different volumes at the same positive transmural pressure.

2.2 Blood Circulation

The continuous function of the cardiovascular system is essential for the human body. It enables material exchange throughout the body, and generally helps to maintain homeostasis of the organism.

2.2.1 The Circulatory System: Structure and Function

The blood circulation connects all body tissues, not only carrying blood gases between the lungs and cells, but also having a prominent role in bringing vital supplies (nutrients) to tissues[2], and taking away cellular wastes. It largely participates on fluid distribution in

[2] It connects the digestive tract and liver, enabling nutrient processing.

close cooperation with the lymphatic system. Moreover, it supports communication within the body through the hormones, it is an integral part of the immune system, and helps to control body temperature.

The cardiovascular system is driven by the heart muscle, a tirelessly working pump divided into two halves, the *left heart* and the *right heart*, each with two chambers: an atrium and a ventricle. Normally, blood moves only from an atrium to a ventricle, and not in the opposite direction. Generally, the one-way direction of the blood flow in the organism (as depicted in Fig. 2.1) is ensured by the system of valves, of which the most notable are inside the heart. The blood vessels connect the right and the left heart by two circulation sets: *pulmonary circulation* and *systemic circulation*.

In the pulmonary circulation the blood flows from the *right ventricle* to the *pulmonary arteries* and further to the lungs. In the *pulmonary capillaries* blood loses carbon dioxide, binds oxygen, and returns to the *left atrium* through the *pulmonary veins*.

The much larger systemic circulation, which takes place between the *left ventricle* and the *right atrium*, brings oxygenated blood to body tissues and extracts carbon dioxide there. Blood from the left ventricle enters the aorta, the largest of the *systemic arteries*. The aorta is gradually left by smaller arteries: The ascending arteries supply upper parts of the body, most notably the brain. The *abdominal aorta* carries blood to lower parts where most of the internal organs are. After passing through the network of *systemic capillaries*, blood returns to the heart via *systemic veins*. The two biggest, *venae cavae*[3] take blood back to the chest and the right atrium. A special part of the systemic circulation, the *coronary circulation* between the aorta and the right atrium, supplies the heart muscle itself.

2.2.2 The Heart

The heart lies in the middle of thorax, behind sternum. It has already been implied that the organ is separated into the left heart and the right heart, and that there is no direct flow between them: Blood from venae cavae enters the right atrium, then flows into the right ventricle, and is ejected to the pulmonary arteries. Blood from the pulmonary veins flows into the left atrium, then to the left ventricle and is expelled to the aorta.

To prevent blood from flowing backwards through the heart, *atrioventricular valves* (*tricuspid valve* in the right heart and *bicuspid*—or *mitral*—*valve* in the left heart) open

[3] *Vena cava inferior* runs from the upper part of a body and *Vena cava superior* comes from the lower parts. Together they collect all blood from the systemic circulation, except from the coronary circulation.

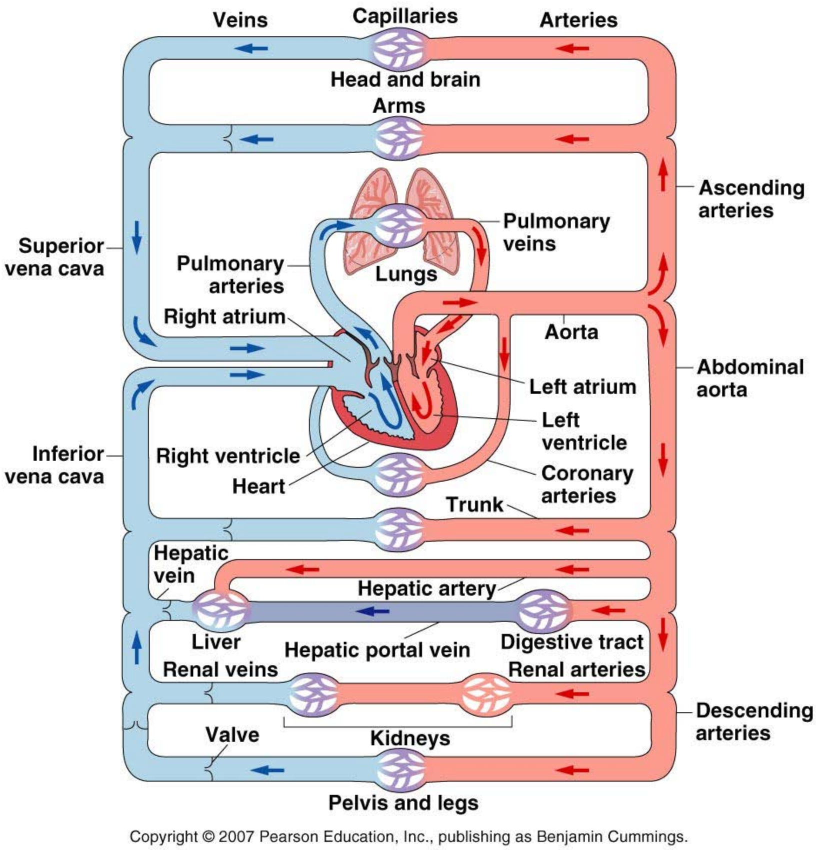

Fig. 2.1. Overview of cardiovascular system anatomy. Printed with permission of Pearson Education, Inc. Source: [7].

only if the pressure within an atrium is bigger than the pressure inside a ventricle. Similarly, *semilunar valves* (*pulmonary valve* and *aortic valve*) close if pressure in the arteries exceeds ventricular pressure.

Regular and repeated contraction of the cardiac muscle cells induces the *cardiac cycle* and propels the blood in the heart, so that it moves in the circulatory system. The mechanism or the origins of the heart muscle cells contraction do not need to be described into detail here. Just let us say that some myocardial cells (called the *autorhythmic cells*) have a special ability to generate action potential spontaneously without signals from the neural system. The pacemaker cells send electrical signal periodically through the electrical conduction system to different parts of the heart. This causes coordinated contractions of the muscle. The heart under normal conditions works as a never-resting pump.

The cardiac cycle

Between two heartbeats, atriums and ventricles undergo a series of events (Fig. 2.2) which ultimately move blood forward in the circulatory system. Both the left and the right heart contract and relax at the same time, even though blood from the left heart is ejected under much bigger pressure than blood from the right heart. The periods of contraction and relaxation are called systole and diastole, respectively.

At the beginning of a new cycle, in late diastole, atriums and ventricles are relaxed. The ventricular pressure decreases below the atrial pressure; blood accumulated in atriums opens the atrioventricular valves and starts filling the ventricles, which increase their volume. Then, atriums contract and push small amount of blood into the relaxed ventricles, which are already partially filled.

After a brief moment, ventricular volume reaches its maximum, and ventricles begin to contract. The intraventricular pressure rises quickly, and the atrioventricular valves close. Before the ventricular pressure exceeds the pressure in arteries, the semilunar valves are closed as well, the heart muscle tension is increasing, and the contraction is *isovolumic*. Finally, the semilunar valves open, and as the ventricular pressure keeps raising, blood is ejected into arteries.

During ventricular diastole, the ventricular pressure falls below the arterial pressure. Blood, which starts to flow back from arteries to ventricles, now closes the semilunar valves, and the phase of *isovolumic ventricular relaxation* occurs. The atriums and the ventricles are relaxed again.

The cardiac cycle is often described by the pressure-volume relation in the left ventricle (Fig. 2.3) and divided into four stages:

Period of filling. Pressure in the left ventricle is on its minimum slightly above 0 mmHg. Blood starts filling the ventricle and flows in until the end of atrial systole. As the ventricle is in diastole, the intraventricular pressure rises only to about 5 mmHg, but volume of the ventricle increases from 45-65 ml to its maximum of about 115-135 ml[4], which is called the *end-diastolic volume*.

Isovolumic contraction. During systole the pressure rises to about 80 mmHg. Both the atrioventricular valve and the aortic valve are closed, thus the ventricular volume remains unchanged.

[4] The higher values are given by [7] for a 70-kg man at rest. The lower values are given by [6].

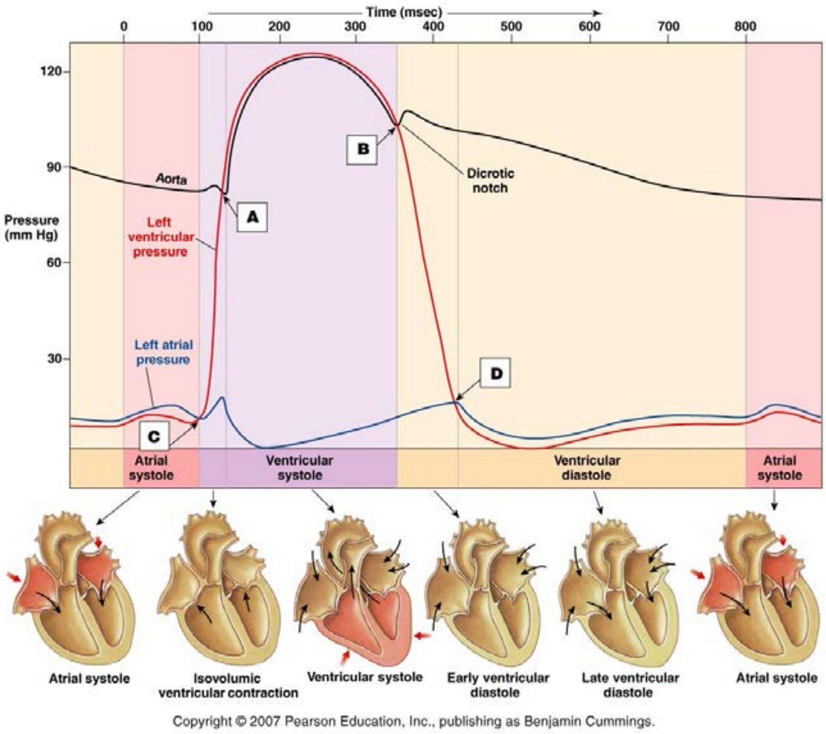

Fig. 2.2. Mechanical events in the heart and the pressure in the aorta, the left ventricle, and the left atrium during the cardiac cycle. A/B: aortic valve opens/closes, C/D: mitral valve closes/opens. Printed with permission of Pearson Education, Inc. Source: [7].

Ejection. Blood is pushed into the aorta. During the ejection phase the intraventricular pressure ascents up to about 120 mmHg. The ventricular volume in the end returns back to its minimum (the *end-systolic volume*).

Isovolumic relaxation. The ventricle is in diastole. The valves are closed again; the volume does not change, and the pressure drops towards 0 mmHg.

The difference between the end-diastolic and the end-systolic volume is the *stroke volume*—the amount of blood that the heart ejects into the aorta in one cardiac cycle. A typical value is 70 ml; however, the more cardiac muscle is stretched, the stronger it contracts, and so, according to *Frank-Starling law of the heart*, the stroke volume rises with the end-diastolic volume. In other words, the more blood comes to the left heart, the greater is the volume that the heart pumps to the aorta within one stroke, and vice versa. This is related to the role of veins that will be discussed later.

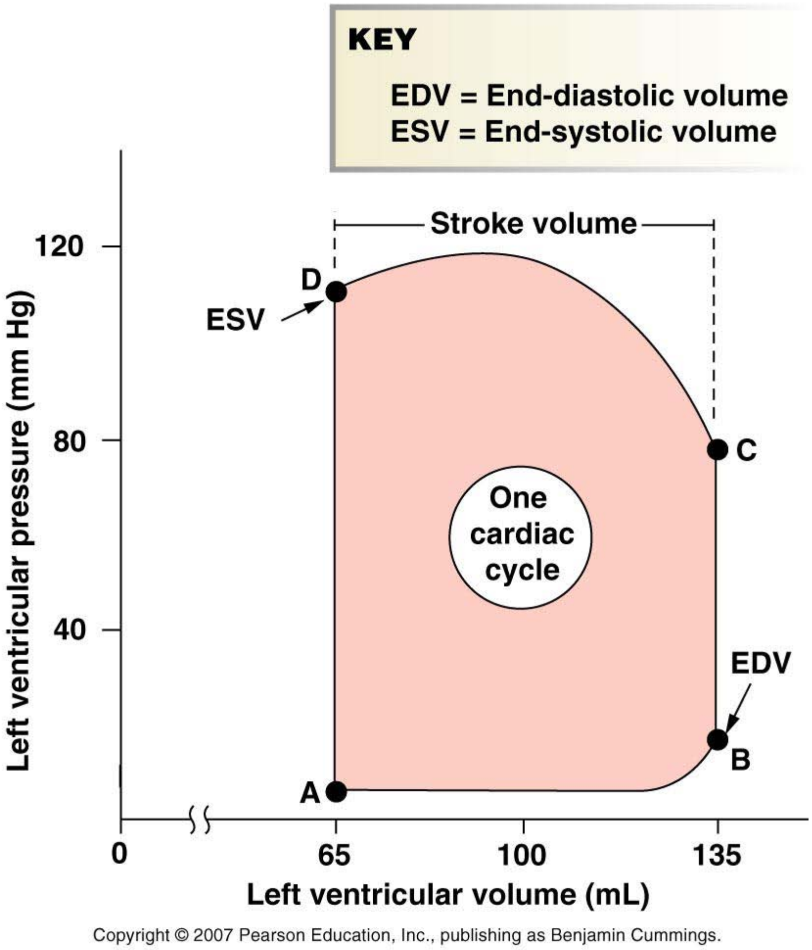

Fig. 2.3. Left ventricular pressure-volume changes during one cardiac cycle. A/B: mitral valve opens/closes, C/D: aortic opens/closes. Printed with permission of Pearson Education, Inc. Source: [7].

2.2.3 Blood Vessels

Blood vessels may be divided according to their composition and function into three major groups: High-pressure *arteries* (and arterioles) take blood away from the heart, thin *capillaries* run through tissues and are the place of material exchange, and low-pressure *veins* (preceded by venules), which return blood back to the heart. The size (diameter) of the blood vessels varies greatly, as can be seen in Table 2.1.

Table 2.1. The average diameter of blood vessels. Source: [7].

Artery	Arteriole	Capillary	Venule	Vein
4.0 mm	30.0 μm	8.0 μm	20.0 μm	5.0 mm

Mechanical properties of blood vessels depend on their tissue composition, in particular on the amount of smooth muscle and elastic fibers in the vessel wall. Vascular smooth muscle is usually partially contracted, but can change its tone and thus alter the diameter of blood vessels (so-called *vasoconstriction* and *vasodilation*). The elastic fibers (and fibrous connective tissue) affect flexibility and recoil of the vessels.

Systemic arteries contain large amount of smooth muscle and elastic and fibrous tissue. This makes their walls tense and stiff. They stretch (only) under high blood pressure originating from the left heart ventricle, and once the ventricle relaxes, the significant elastic recoil of arterial walls pushes blood further to the circulatory system. In other words, the energy stored in arterial walls is used to keep continuous driving pressure at the time of the ventricular filling. The same effect in pulmonary arteries is much smaller as they operate under lower pressure and are less distensible.

Arterioles are high-resistance vessels with very little elastic tissue, but large amount of smooth muscle. The muscle layer enables large-scale constriction and dilation, and in this way the divergent blood flow is controlled and distributed to various body tissues according to their momentary needs. A typical blood distribution in the resting body is in Table 2.2.

Table 2.2. Typical distribution of total blood flow (approximately 5000–5600 ml·min^{-1}) in the body at rest. Sources: [6], [7].

Systemic circulation	Brain	14%
	Coronary circulation	4%
	Liver and digestive tract	27%
	Kidneys	20%
	Skeletal muscle	21%
	Skin	5%
	Bone and other tissues	9%
Pulmonary circulation	Lungs	100%

In a network of about ten billion capillaries [6], water and materials like nutrients or cell waste are exchanged between the plasma, intersticial fluid, and cells. Thin walls of capillaries allow easy diffusion of substances, but contain no muscle or elastic tissue, and so capillaries can hardly change their diameter. In fact, the blood flow through a single capillary is not steady, as the vessel is very narrow and has diameter comparable with red blood cell dimensions. But due to the high number of vessels one can assume that there is some average flow rate and average blood pressure in capillaries.

From tissues, the blood returns to the heart through a convergent system of venules and veins. As vessels diameter increases, elastic tissue and smooth muscle tissue appear again. However, venous walls are thinner than in arteries, have less elastic tissue, and therefore they can swell more freely than arteries. Due to greater flexibility, veins can also collapse more easily and can even shut themselves to blood flow. On the other hand, veins, which are large in size, hold normally more than half of all blood in the body (see Table 2.3), and the vessels serve as blood reservoir in the circulatory system.

Table 2.3. Volumes of blood in different parts of circulation expressed in % of total blood volume. The total blood volume is about 5000 ml. Source: [6].

Systemic vessels	Arteries	13%
	Arterioles and capillaries	7%
	Veins	64%
Heart		7%
Pulmonary vessels		9%

2.2.4 Cardiac Output and Venous Return

Cardiac output Q (ml·s^{-1} or ml·min^{-1}) is the amount of blood pumped by the left ventricle into the aorta[5] in given time. Very often it is expressed in milliliters per minute. All blood in the body has to flow through the heart, so cardiac output is a significant parameter as it represents the overall blood flow through the circulatory system. An average adult person at rest has the cardiac output about 5000–5600 ml/min, but this can raise up to 7 times during exercise [6], [7]. Cardiac output is a product of heart rate (min^{-1}) and stroke volume (ml). It has already been explained how the stroke volume strongly depends on the end-diastolic volume. Therefore, cardiac output is determined primarily by the total blood flow from tissues, or in other words by *venous return*—the inflow from systemic veins to the right atrium.

Like any other flow, venous return depends on pressure gradient, i.e., the difference between the pressures in systemic veins and the right atrial pressure, and on the resistance of vascular vessels. There are many factors that affect venous return. For example, a great impact has a so-called (*skeletal*) *muscle pump*, made by leg muscles which compress veins during movement of the body, increasing peripheral venous pressure and driving

[5] In fact, under standard conditions, the pumped volume should be the same for both ventricles. As one can see in Table 2.2, all the blood flows through pulmonary circulation, so the cardiac output is essentially the pulmonary blood flow.

blood into the heart [7]. A very important *respiratory pump* will be discussed later on in section 2.5.

Low cardiac output

Reduced cardiac output indicates a pathological situation when oxygen supply of the cells and removal of metabolic waste may not be fast enough. Very low cardiac output is closely related to the *circulatory shock*, a serious failure of the circulatory system, when insufficient perfusion of tissues may lead to their progressive damage and ultimately to death. Low cardiac output is often an immediate cause of the failure [6].

The reasons for pathologically low cardiac output are divided into *cardiac abnormalities* and *peripheral factors*. The instances of the former ones may be myocardial infraction or arrhythmias. Low cardiac output due to low venous return has several causes—for example severe bleeding or allergic reaction resulting in vasodilation. Also, high pressure in the right atrium holds blood in the veins. If the right atrial pressure raises up to 7 mmHg, the venous return is stopped entirely [6].

Another important factor of low cardiac output is easy collapse of large veins. Vena cava may collapse if blood pressure inside the vessel falls below the intrathoracic pressure [8]. Similarly, negative pressure (i.e., subatmospheric pressure) in the right atrium does not increase the venous return, because it "sucks the walls of the veins together where they enter the chest" [6].

2.2.5 Blood Pressure

Blood pressure progressively decreases as blood moves through the circulatory system. The highest values are reached in the aorta (during ventricular systole) and systemic arteries. Then the pressure falls down along the way to the right atrium where it is approximately zero as can be seen in Table 2.4.

According to a phase of the cardiac cycle, the pressure in the aorta oscillates between about 120 mmHg (*systolic pressure*) and 80 mmHg (*diastolic pressure*). The difference, called *pulse pressure* is affected by the stroke volume. Due to the inertia of blood, the pressure wave progresses further into the circulatory system, but because of resistance and compliance of blood vessels, the pulsations are damped by the time they reach capillaries. A similar arrangement as in the systemic circulation can be found in the pulmonary circulation, but the pressure amplitude is notably smaller, yielding the *mean pulmonary* *arterial pressure* approximately 15–16 mmHg. Then the pulmonary circulation pressure falls on the way to the left atrium (Table 2.5).

Table 2.4. Typical pressures in the systemic circulation of a recumbent human. Sources: [6], [9].

Vessels	Pressure (mmHg)
Aorta and large arteries	100 (mean)
	120 (systolic)
	80 (diastolic)
Capillaries	17 (average)
	35 (arteriolar end)
	10 (venous end)
Peripheral Veins	4–6
Venae cavae	2
Right Atrium	0–1

Table 2.5. Typical pressures in the pulmonary circulation of a recumbent human. Source: [6].

Vessel	Pressure (mmHg)
Pulmonary artery	15 (mean)
	25 (systolic)
	8 (diastolic)
Capillaries	7 (average)
Veins and left atrium	1–6 (mean: 2)

2.2.6 Circulatory System Regulation

The central mechanism which regulates blood pressure is the *baroreceptor reflex*. Baroreceptors are stretch-sensitive sensors placed in the walls of the carotid arteries[6] and the aorta. A blood pressure change in the vessels causes a change in the rate of a signal that the sensors send to the cardiovascular control center in *medulla oblongata* in the brain. From there, arteriolar vasodilatation/vasoconstriction and the heart rate and contraction are regulated, so that the original blood pressure level is restored. Besides this system,

[6]take blood to the brain

there are various other regulatory mechanisms, either local (arterioles regulate blood flow to tissues) or systemic (for example, the kidneys help to maintain body fluid balance) [7].

2.3 Respiration

Two primary functions of the respiratory system are to provide gas exchange between the atmosphere and the blood and to help regulate body pH through the level of carbon dioxide (CO_2). The human metabolism requires a continuous supply of oxygen (O_2) and removal of CO_2. The bulk of this need is satisfied by breathing. The term *external respiration* is used for the movement of gases between the outer environment and cells of the body[7]. This can be divided [7] into four two-way processes:

1. The exchange of air between the atmosphere and the alveoli (called ventilation, this involves both inspiration and expiration).
2. The exchange of O_2 and CO_2 (and possibly other gases) between the lungs and the blood.
3. The blood transport of O_2 and CO_2.
4. The exchange of gases between blood and cells.

Further, the first stage—ventilation—will be focused.

2.3.1 Anatomy of the Respiratory System

The airways

The respiratory system consists of several parts, divided into the *upper respiratory tract* and the *lower respiratory tract*. The first one includes the mouth, nasal cavity, pharynx, and larynx. The lower respiratory tract, enclosed in the thorax, starts with the *trachea*, which splits into two *primary bronchi*. Each bronchus divides into smaller bronchi as it enters a lung. Trachea and bronchi are semirigid tubes. In the lungs bronchi splits again into collapsible smooth muscle bronchioles which ultimately end in alveoli. The diameter of the airways decreases from 15–25 mm of the trachea to 0.2–0.3 mm in alveoli [7], [10].

[7] Whereas the *cellular respiration* means the intracellular consumption of oxygen and production of carbon dioxide.

The *pulmonary tree* also may be described according to its divisions or generations. The trachea is the generation 0, and in every next generation, a passageway is forked into two or more smaller tubes. The primary bronchi are the generation 1 (first division), smaller bronchi form generations 2-11. Bronchioles farther branches up to the generation 23 where in the respiratory bronchioles the conducting zone changes to the respiratory zone [7].

Alveoli

Alveoli (generation 24) are the primary site of gas exchange realized as a process of diffusion. There are several hundreds of millions alveolar sacks in each lung [11]. Each alveolus is made of a thin layer of epithelial cells and covered by an ample network of pulmonary capillaries. Some of the epithelial cells produce a secretion called surfactant, which is necessary for easy lung expansion into the thorax (see below).

Thoracic cavity and lungs

The *thoracic* (or *chest*) *cavity*, or the thorax, is the space between the spine and the rib cage. The cavity is covered by muscles of which the largest one, the *diaphragm*, shapes the cavity floor. The external and internal intercostal muscles connect the ribs. Besides the *pericardial sack* with the heart, a substantial part of the thoracic cavity is filled with two *pleural cavities*, each containing a lung and surrounded by a *pleural sack*.

The lungs are cone shaped soft-tissue organs with most of their volume occupied by air-filled alveoli. There are no muscles in the lungs, but elastin and collagen fibers maintain elasticity of the organs [7]. The right lung and left lung are divided into three and two macroscopic lobes, respectively. The base of the lungs lies on the diaphragm, but otherwise they practically hang or better float freely in the thoracic cavity.

The pleural sack itself is made of two elastic *pleural membranes* with a very thin pleural fluid in the *intrapleural space* between them. The outer layer of the pleural sack lines the boundaries of the chest cavity, and the inner layer forms the outline of a lung. This double-layer configuration not only allows a lung to slide within the pleural cavity, but also holds a lung always at least partially stretched due to the cohesiveness of the pleural fluid, which holds together the pleural membranes [7].

2.3.2 Mechanics of Breathing

At rest, between breaths, the pressure inside the airways is the same as the atmospheric pressure, that is 0 mmHg[8]. Under normal conditions, respiration is an active process, in which movement of the diaphragm and muscles of the thoracic cage creates pressure gradient, and thus enables air to flow into or out of the lungs following principles similar to those mentioned in section 2.1.

Without any muscles in the lungs, the lung movement cannot be controlled directly. However, the hydrogen bonds in the pleural fluid hold the pleural membranes together, so the lungs basically follow the expanding thorax. This is enhanced by the surfactant in the alveoli which decreases the surface tension of the alveolar fluid. On the other hand, the elastic lung fibers tend to contract if stretched, which creates—together with the air-fluid surface tension in alveoli— a recoil force in the lungs [6].

During inspiration, the diaphragm contracts (Fig. 2.4) and moves downward, therefore increasing volume of the thoracic cavity. This is supported, to much less extent (about 30% of the total volume change), by the external intercostal muscles which pull the rib cage and sternum forward [7]. As the chest and lungs enlarge, *alveolar pressure* (the pressure inside the alveoli) decreases below -1 mmHg, and the air flows into the lung. After about 2 seconds the lungs are filled with air, and the alveolar and atmospheric pressures are balanced again [7].

Expiration, on the other hand, is passive during quiet breathing; the inspiratory muscles relaxe, and due to the elastic recoil the lungs shrink. The alveolar pressure raises to over 1 mmHg and therefore the air leaves the lungs, ultimately leveling the alveolar and atmospheric pressure again. The expiration may be active if the expiratory muscles (the intercostal and abdominal muscles) are employed. For an adult, according to [7], the normal respiratory rate is 12–20 breaths per minute for quiet breathing and up to 30–40 breaths per minute for active expiration.

Pleural pressure

The lung ability to stretch with expanding thorax (*lung compliance*[9]) and to collapse back (*elasticity*) affects *pleural pressure* in the intrapleural space[10] (Fig. 2.5). At the beginning

[8] All pressure values, unless stated otherwise, will be given relative to the atmospheric pressure.

[9] The meaning of this parameter is the same as in 2.1. Here, the transmural pressure is called transpulmonary pressure

[10] Called *intrathoracic pressure*, too.

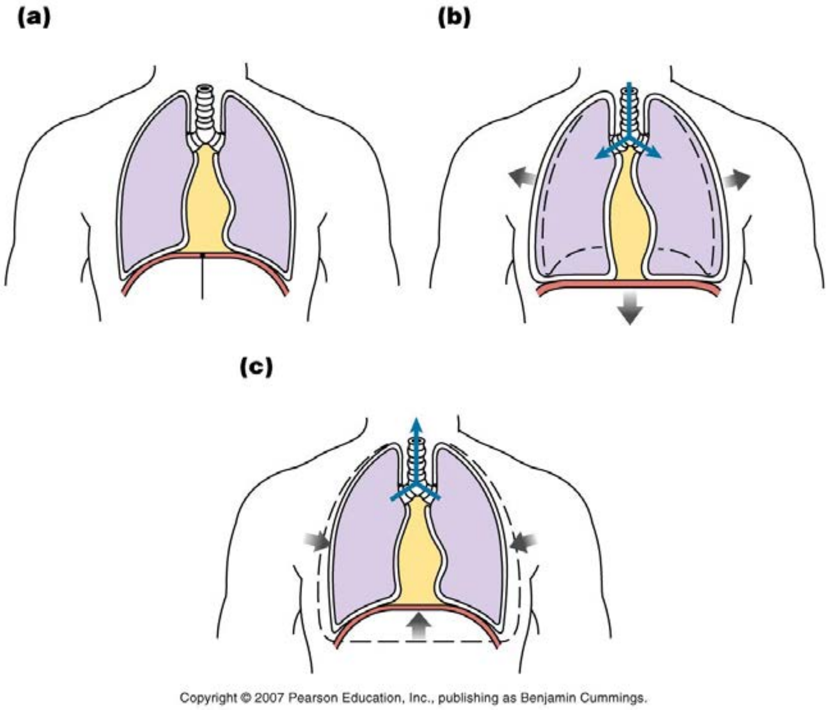

Fig. 2.4. Movement of the diaphragm during breathing. a: at rest, b: inspiration, c: expiration. Printed with permission of Pearson Education, Inc. Source: [7].

of inspiration, the antagonizing fluid bonds and recoil forces plus a slight suction of excess fluid [6] causes that the pleural pressure is about -3 mmHg. When the thorax moves outwards, the resisting recoil forces increase, and the pleural pressure is lowered down to -6 mmHg (at rest). The pressure returns back to -3 mmHg at the end of the respiratory cycle, but remains always negative because of the sealed intrapleural space [7].

2.3.3 Lung Volumes

The total volume of air in the lungs or *total lung capacity* can be divided into four parts. During quiet breathing, there is actually only a small change of lung volume. The difference between normal inspiration and expiration is the *tidal volume*. The *inspiratory reserve volume* is added if a person inspires with full force. The *expiratory reserve volume*, on the other hand, is the volume of the remaining air that can expired forcefully. But even after that there is some air left in the lungs—the *residual volume*. Often, the term *functional residual capacity* (FRC) is used for the volume of air remaining in the lungs at the end of normal expiration. Typical FRC values can be found in Table 2.6.

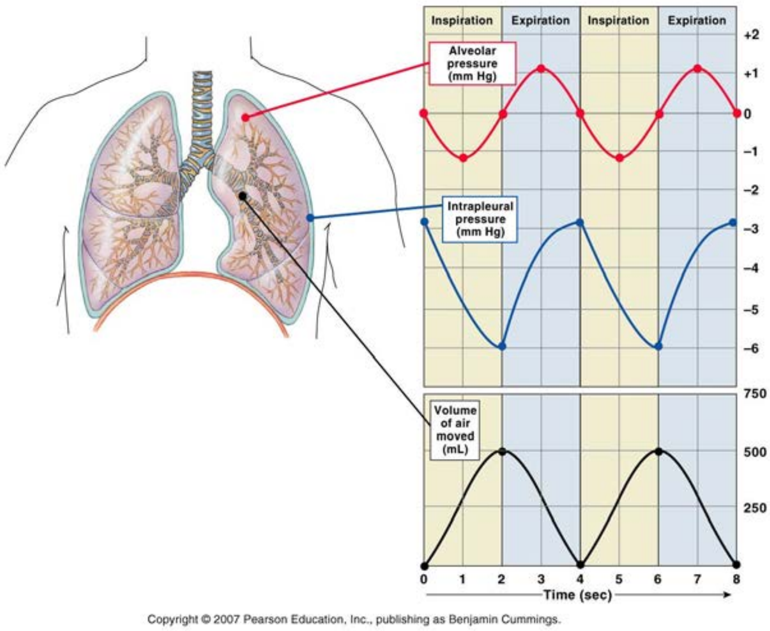

Fig. 2.5. Pressure changes during quiet breathing. Printed with permission of Pearson Education, Inc. Source: [7].

Table 2.6. Typical lung volumes and capacities for a 70-kg man with total lung capacity of 5800 ml. Source: [7].

Inspiratory reserve volume:	3000 ml	3500 ml
Tidal volume:	500 ml	(inspiratory capacity)
Expiratory reserve volume:	1100 ml	2300 ml
Residual volume:	1200 ml	(functional residual capacity)

2.4 Artificial Ventilation

Artificial ventilation is a substitution or a support of spontaneous breathing by external forces when respiratory muscles are not working properly or blood oxygenation is insufficient. A machine (ventilator) is employed in case of anesthesia with paralysis, intensive care, or treatment of chronic ventilatory failure. When possible, the artificial ventilation is applied in such a way that it assists rather than completely replaces patient's own breathing. However, in all the three mentioned situations the basic method is *intermittent positive pressure ventilation* [1].

2.4.1 Principle of Positive Pressure Ventilation

During inspiration, the ventilator provides the necessary pressure gradient by setting mouth or airway pressure above alveolar pressure, allowing air to flow into lungs. The process is reversed during expiration—the pressure in the mouth is decreased below the alveolar pressure [1]. No matter if the airway pressure at the end of expiration is leveled with the ambient pressure or if it is higher, note the principal difference between the mechanics of spontaneous breathing and positive pressure ventilation:

Normally, the necessary pressure gradient for air flow is acquired as a **result** of thorax expansion and recoil; the alveolar pressure oscillates around 0 mmHg, and the intrathoracic pressure falls deeply into negative. During positive pressure ventilation, however, the thorax movement is **caused** by lung inflation. Alveoli are inflated above ambient pressure, and pressure in lungs does not fall under zero. Expanding lungs push thorax away, and pleural pressure is higher than under physiological conditions [12]. If normally the change of alveolar pressure depends on the change of pleural pressure, during artificial ventilation the situation is reversed, and it is the pressure in alveoli that determines intrathoracic pressure.

2.4.2 Patterns and Modes of Artificial Ventilation

The inspiration/expiration control may be based on time, volume, or pressure cycling[11] [1], and so there are various patterns of air delivery during artificial ventilation. The mouth pressure curve may have for example a simple square wave (constant pressure) or sine wave profile. Widely used is the constant flow rate pattern. Currently, electronically controlled ventilators offer more advanced modes with greater cooperation with the patient and with accurate control of the gas pressure and flow. Also, *high frequency ventilation* (HFV) with frequencies 1-50 Hz [1] is a subject to research as it might be more protective towards the respiratory system due to lower pressure amplitudes [13].

PEEP

The situation when the pressure in the upper airways remains always positive (related to the atmospheric pressure), even at the end of expiration, may be induced in order to prevent decrease in the functional residual capacity which is common during general anaesthesia. By contrast, *intrinsic PEEP*[12] occurs when residual end-expiratory alveolar pressure re-

[11] The machine terminates inspiration when a watched parameter reaches preset value.

[12] It is alseo called *dynamic hyperinflation*.

mains raised because of inadequate expiration time during artificial ventilation [1].

PEEP helps to prevent collapse of the alveoli, and thus engages more lung units and improves arterial oxygenation. Enhancing distribution of lung ventilation, it also improves lung compliance [14]. For these reasons, the application of PEEP may also be considered as a treatment of the *Acute respiratory distress syndrome* (ARDS).

2.4.3 Acute Respiratory Distress Syndrome

Acute lung injury is a kind of parenchymal (inflammatory) lung disease. It can lead to pulmonary edema (flooding of alveoli) and therefore to severe gas exchange problems which evolve hypoxemia[13], and may result in multiple organ failure. The worst form, ARDS, has estimated mortality around 50 per cent [1]. During the development of ARDS, the integrity of the blood-gas barrier is harmed, and fluid leaks from capillaries to alveoli. Surfactant production is limited, and some areas of alveoli collapse with impact on ventilation and perfusion. The lung compliance is reduced as well. Artificial ventilation is a necessary component of ARDS treatment [1], [15].

2.4.4 Risks of Artificial Ventilation

Positive pressure which occurs during the artificial ventilation in lungs and chest cavity is quite different from physiological conditions. That is to say, besides therapeutical advantages, PEEP, and especially intrinsic PEEP, poses some risks for a patient. The governing parameters seem to be mean alveolar pressure and mean intrathoracic pressure [1].

Barotrauma, i.e., lung damage caused by high transmural pressure gradient, may appear after long high airway pressure ventilation. Barotrauma or volutrauma (i.e., damage by excess volume) may be a result of intrinsic PEEP as alveoli can safely enlarge only to certain volume [14]. On the other hand, a wise application of moderate PEEP reduces the risk of barotrauma [1]. Significant cardiovascular consequences of positive pressure ventilation will be discussed in the next section.

[13] insufficient oxygen supply

2.5 Cardiopulmonary Interactions

The relation between respiratory and circulatory system consists not only of their functional connection (i.e., in gas exchange), but, naturally, also of their physical proximity inside the thorax. The cardiopulmonary mechanical interaction plays its vital role during spontaneous breathing, but also transfers non-physiological conditions in artificially ventilated lungs into the circulatory system.

There are two main reasons why mechanical interaction shall be considered: First, pulmonary vessels and large systemic veins are susceptible to external pressure. Second, change of lung volume affects shape and resistance of pulmonary vessels. As a result, during positive pressure ventilation, especially with PEEP, increased alveolar pressure and subsequent positive mean intrathoracic pressure may cause undesirable obstruction to the left heart filling. Consequently, cardiac output, importance of which was explained in section 2.2, is reduced, since “the heart cannot pump blood that does not flow into it” [6]. Systemic arterial pressure decreases, too [12].

2.5.1 Thoracic Pump

During spontaneous inspiration, the contracting diaphragm compresses abdomen and therefore raises pressure in abdominal veins. More importantly, as thorax expands, pleural pressure decreases and so does the pressure in the inferior vena cava. The result is the higher pressure gradient between abdomen and thoracic cavity. This so-called *respiratory* (or *thoracic*) *pump* helps to draw blood from systemic veins into the thorax and the right atrium [7].

However, during positive-pressure ventilation the elevated intrathoracic pressure is transferred to large systemic veins within thorax, so the pressure inside inferior vena cava is higher. Therefore the thoracic pump effect is canceled, and venous return reduced. The right-ventricle filling is decreased; consequently, blood flow towards the left heart is lower. Left ventricular end-diastolic volume is reduced, and the cardiac output falls [1].

2.5.2 Pulmonary Circulation and Breathing

As can be seen from Tables 2.2 and 2.5, the pulmonary circulation is normally a high flow, low-pressure system, which implies low *pulmonary vascular resistance* (*PVR*). However, pulmonary vessels are usually passive and highly susceptible to outer mechanical factors, and the resistance changes with variations in external pressure and lung volume.

External pressure and pulmonary vessels

Due to their high compliance, which is about seven times higher than in the systemic circulatory vessels [16], a change in transmural pressure, caused by the external pressure, largely influences pulmonary vessels' diameter and thus their volume and resistance. According to their location in the lungs, the pulmonary vessels can be divided to alveolar and extraalveolar. The alveolar vessels, mostly capillaries, lie within alveolar walls and therefore are largely influenced by the alveolar pressure. An increase in the alveolar pressure decreases the transmural pressure gradient, hence raises the resistance of alveolar vessels [2], [17]. The extraalveolar vessels, i.e., mainly pulmonary arteries and veins, are placed in the space between alveoli, being more sensitive to alteration in the pleural pressure, rather than in the alveolar pressure [8], [16].

Lung volume effect on pulmonary vascular resistance

Since the pulmonary circulation is tightly connected with lungs, changes in lung volume play an important, yet complicated role in PVR. During lung inflation, the alveolar vessels are stretched as expanding alveoli increase volume; the vessel diameter decreases and resistance grows. On the other hand, walls of extraalveolar vessels are drawn apart as they hang between alveoli [2], and their diameter enlarges (Fig. 2.6). When lung volume decreases, the effect is opposite: now resistance of the extraalveolar vessels raises as they collapse, but the alveolar vessels have larger diameter.

The contradicting behavior of lung vessels produces so-called U-shape relationship between PVR and lung volume. Above FRC, extraalveolar resistance does not change as much as the resistance of alveolar vessels, and the total PVR grows with increasing lung volume. Below FRC, however, the collapse of extraalveolar vessels outweighs distension of alveolar vessels and thus PVR grows with decreasing lung volume [16], [17].

PVR during positive-pressure ventilation

The relation between lung volume and total PVR changes when positive-pressure ventilation is applied. The falling part of U-shape curve is missing, and with increasing lung volume the pulmonary resistance only raises. In addition, this growth of the total resistance is steeper than in case of normal breathing because of the greater compression of alveolar vessels [16].

Elevated PVR leads to higher blood accumulation in the right ventricle. Systolic pressure in the thin-walled chamber is not high enough to overcome increased resistance, the

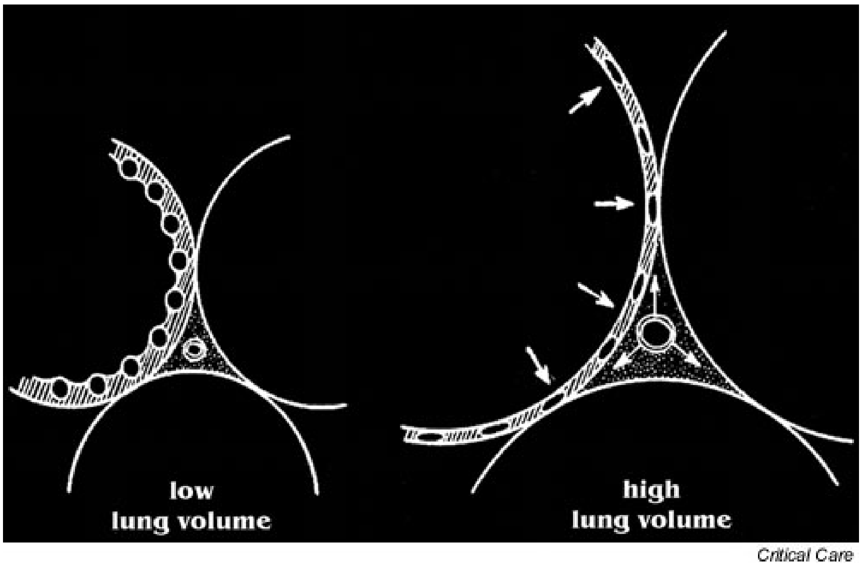

Fig. 2.6. Influence of lung expansion on alveolar and extra-alveolar vasculature. Source: [18].

right-ventricle output is lower, and as a result the left heart filling decreases. In this way high airway pressure, PEEP, or lung hyperinflation further contribute to cardiac output reduction [1], [16].

Chapter 3

Basic Model Assembling

The first steps in building a new model of cardiopulmonary interaction were to find, adopt, and test a proper model which had already been published. In this chapter such a model will be presented and described. Some minor changes, clarifications, and corrections were made based on other models, and the model was implemented as *model 1*.

3.1 Available Models

Lung ventilation as well as the circulatory system have been depicted in many elaborated models. Still, it appears that not many published models have dealt with the complexity of the cardiopulmonary interaction. There are many models of the respiratory system; some of them work under physiological conditions, for example the model of Renotte et al. [19], others, like the model of Polak and Mroczka [20] or the model of Rožánek [13], consider the effect of artificial ventilation. Unfortunately, these models usually do not extend their concern to blood circulation. Likewise, broad research has been conducted in the field of blood circulation modeling, but many models (e.g., the model of Korakianitis and Shi [21] or the model of Danielsen and Ottesen [22]) do not take ventilation into account at all. And in the field of cardiopulmonary interaction, more attention has been paid to gas exchange (for example in the model of Christiansen and Dræby [10] or in the model of Chiari et al. [23]) than to mechanical effects and relations.

Therefore, it turned out to be a rather difficult task to find published models that would attempt to describe how the thoracic and alveolar pressure affects hemodynamic parameters during positive-pressure artificial ventilation. Finally, I chose two models (or better two groups of models) for closer analysis and further work:

First, De Lazzari et al. [12] studied the compound effect of mechanical ventilation and Hemopump[1] assistance in a lumped parameter model of blood circulation, where the mean pleural (intrathoracic) pressure P_{pl} is brought to compartments inside the thoracic cavity. Two blood circulation models precede [12]: Ursino [24] provided the basic structure and parameter values for most parts of the model in [12]. This was further developed by Magosso et al. [25] mainly by detaching the systemic thoracic veins section placed in a thoracic chamber, which is subject to intrathoracic pressure.

Second, the large model of Lu et al. [8] is claimed by its authors to be "...the first example of a truly integrative model of the cardiopulmonary system." This model employs previous models of airway mechanics [26], gas exchange [27], and blood circulation [28] by the same group of authors. The primary purpose of the model was to test the response of the cardiopulmonary system to Valsalva maneuver, which can be described as forced expiration against a glottis[2] closed for about 30 seconds. Increased airway pressure leads to *Valsalva effect*—a phased circulatory response including reduced ventricular filling [1]. This model was used as the main basis for the set of models developed at the University of Washington [29].

3.1.1 Model Selection

The basic feature of both models which made them interesting for this work is that they detach a special section of thoracic veins (or venae cavae). The model of Lu et al. [8] has obviously some advantages over the models of De Lazzari et al. [12] or Magosso [25]. Beside the gas exchange issue, it particularly offers more detailed description of vein behavior (nonlinear pressure-volume characteristics) and focuses more thoroughly on pulmonary circulation. Nonetheless, I found the model of De Lazzari et al. to be more suitable as an initial background model for the purpose of my work for three reasons:

Artificial ventilation. Although Valsalva response targeted in the model of Lu et al. is in some way similar to the effect of positive-pressure ventilation (increased airway and pleural pressures), the model of De Lazzari et al. was used explicitly to investigate the role of artificial ventilation.

Modularity. The model of De Lazzari et al. has simpler structure than model of Lu et al. This might appear as an disadvantage, but in fact for the scope of my work it seemed

[1] A mechanical heart support in a form of a miniature rotary pump in the left ventricle.

[2] The space between vocal folds.

to be more reasonable to start with limited concept and gradually extend it, if possible. The series of models of which [12] is the last one contains some features that are not essential for the function of the basic structure, but which were added and tested in some of the models. For example, pleural pressure P_{pl} is not presented by Ursino [24], is constant in [12], and is time-dependent in the model of Magosso et al. [25]. If a new airway model was planned to test, the open-structure concept seemed beneficial.

Clear description. The description of some model elements and parameters in the model of Lu et al. [8] is a little ambiguous. In particular, it is not clear if the interaction of pleural pressure and the vena cava compartment is examined and what the magnitude of pulmonary capillary resistance is . On the other hand, the simple structure of [12] with description provided by [24] and [25] suggested reduced risk of misunderstanding.

Having that said, some parts of the model of Lu et al. were still important and useful for further development of the model.

3.2 RLC Lumped Parameter Concept

Regardless of the construction specifications of considered models, all of them are lumped parameter models. They divide circulatory system into finite number of distinct sections described by several scalar parameters. Spatial variations inside a compartment are ignored. In studied models, the basic element is an RLC or RC compartment. That is, each section is characterized by a hydraulic resistance R, a compliance C, and sometimes an inertance L (mmHg·s^2·ml^{-1}). The meaning of hydraulic resistance and compliance can be derived from section 2.1. Relations within a compartment and between adjacent compartments are represented by equations[3] for blood flow F, volume V, and pressure P.

The resistance R_i reflects pressure energy losses [24] between compartments i and $i+1$ with pressures P_i and P_{i+1}, respectively. The inertance L_i accounts for the effect of blood flow inertia. Therefore, balance of forces in the ith compartment can be stated for blood outflow F_i as:

$$\frac{dF_i}{dt} = \frac{1}{L_i} \cdot (P_i - P_{i+1} - RF_i) \tag{3.1}$$

[3] The equations are principally the same in all mentioned models, varying only in details.

Usually, inertance vanishes in compartments with supposed low blood acceleration. Then, (3.1) changes to a form similar to (2.1):

$$F_i = \frac{P_i - P_{i+1}}{R_i}. \tag{3.2}$$

The compliance C_i describes relation between pressure inside the ith compartment and stored blood volume. Assuming constant compliance, it comes immediately from (2.3) that:

$$V_i = C_i P_{tm,i} + V_{u,i} \tag{3.3}$$

where $V_{u,i}$ is unstressed volume, and transmural pressure $P_{tm,i}$ is the difference between pressure P_i inside a compartment and external pressure P_{ext}:

$$P_{tm,i} = P_i - P_{ext}. \tag{3.4}$$

Conservation of mass in the compartment i is expressed as:

$$\frac{dV_i}{dt} = F_{i-1} - F_i \tag{3.5}$$

where F_{i-1} is inflow from a preceding compartment $i-1$. From (3.3) and (3.5) is:

$$\frac{dP_{tm,i}}{dt} = \frac{1}{C_i} \cdot (F_{i-1} - F_i) \tag{3.6}$$

and therefore

$$\frac{dP_i}{dt} = \frac{1}{C_i} \cdot (F_{i-1} - F_i) \tag{3.7}$$

for constant external pressure P_{ext}.

3.2.1 Electrical Analogy

Although the RLC compartment concept is basically a hydraulic model, and we will keep original names of parameters and variables will be kept. One can see a clear electrical analogy here: voltage replaced by pressure, current as flow rate, electric charge in role of volume. Compliance and inertance may be substituted by capacitance and inductance, respectively. Resistances have the same role in both approaches. An RLC compartment is shown in Fig. 3.1. For lungs, an electroacoustical analogy can be used in the same way [13].

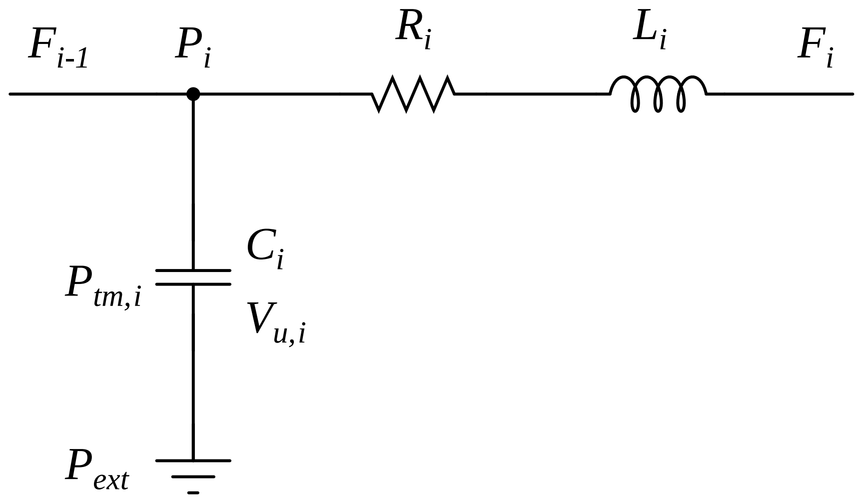

Fig. 3.1. RLC compartment scheme. See text for closer description.

3.3 Adopted Model Description

The model presented in [12] is a closed-loop circulatory model consisting of seven main sections. The right heart section and the left heart section are connected through the pulmonary section. Systemic circulation is divided into the systemic section and the systemic thoracic veins section. The coronary section is parallel to the two systemic sections and connects the heart sections directly as does the coronary bed in a real body. The hemopump section, which mimics the mechanical heart assistance, is connected to the left ventricle.

3.3.1 Heart Sections

The left and the right heart sections have identical structure and differ only in parameter values. Each heart section is divided into an atrial compartment and a ventricular compartment. The atrial compartments are normal RC compartments, only with added valves (i.e., diodes in the electrical analogy) between atriums and ventricles. In other words, in this model both atriums are passive. The ventricles, on the other hand, are the true motor of the circulatory system model. They exhibit contractile activity and are described by a time-varying elastance[4] and resistance for which I used functions provided in [24]:

In the model, the heart is shown as a pulsatile pump with the isometric ventricular pressure:

$$P_{max} = \varphi(t) \cdot E_{max} \cdot (V_v - V_{u,v}) + [1 - \varphi(t)] \cdot P_0 \cdot (e^{k_E \cdot V_v} - 1) \tag{3.8}$$

where E_{max} is the ventricle elastance at maximum contraction, V_v is the ventricle instantaneous volume, $V_{u,v}$ is the ventricle unstressed volume, and P_0 and k_E are constant parameters characterizing an exponential function. The first term in (3.8) refers to the linear pressure-volume function at the end systole (the maximum contraction), and the second term describes the exponential run during diastole.

Propulsion of the heart pump (the pacemaker) comes from $\varphi(t)$, called "the ventricle activation function", in this case a squared half-sine wave:

$$\varphi(t) = \begin{cases} sin^2\left[\frac{\pi \cdot T}{T_{sys}} \cdot u(t)\right] & \text{for } 0 \leq u(t) \leq T_{sys}/T \\ 0 & \text{for } T_{sys}/T \leq u(t) \leq 1 \end{cases} \tag{3.9}$$

where T is the heart period and T_{sys} is the duration of systole. Finally, $u(t)$ is a dimensionless variable, having $u = 0$ at the beginning of systole. The $u(t)$ rises linearly to $u = 1$ throughout the cardiac cycle, then resets back to zero and so on. Heart rate was assumed to be constant in this adaptation.

The instantaneous ventricular pressure P_v is given as:

$$P_v = P_{max} - R_v F_v \tag{3.10}$$

where R_v is viscous resistance of the ventricle, and F_v is the ventricular output (cardiac output in case of the left ventricle). The ventricular resistance R_v is proportional to P_{max}, that is:

$$R_v = k_R \cdot P_{max}. \tag{3.11}$$

The outflow F_v is set to zero if P_{max} is not greater than pressure in an arterial compartment P_{art}. This simulates an ideal semilunar valve. Similarly, flow F_a from an atrium with

[4] Elastance is just a reciprocal of compliance.

pressure P_a is non-zero only if $P_a > P_v$ which mimics an atrioventricular valve. Note that since the non-zero ventricular output is defined as:

$$F_v = \frac{P_{max} - P_{art}}{R_v}, \tag{3.12}$$

from 3.10 comes $P_v = P_{art}$ if $F_v > 0$ and $P_v = P_{max}$ else.

3.3.2 Blood Vessel Sections

For the scope of this work, the hemopump section was clearly redundant and I also left out the coronary section as unimportant, thus the simplified structure was almost the same as given in [25] (Fig. 3.2). The pulmonary section is divided into one RLC compartment (pulmonary arterial) and two RC compartments (pulmonary peripheral and pulmonary venous) in a series. The systemic section is made of the systemic arterial compartment (RLC) followed by a combination of three parallel branches (splanchnic, extrasplanchnic and active muscle). Each branch consists of two RC compartments: peripheral (capillaries) and venous. Flow from all the branches converge at the systemic thoracic veins section—a single RC compartment—and continues to the right heart section.

Pressure in every RLC or RC section is governed by (3.6) except for the pressure in the splanchnic venous compartment where:

$$P_{sv} = \frac{1}{C_{sv}} \left[V_t - V_{u,sv} - \sum_{i \neq sv} V_i \right]. \tag{3.13}$$

Here, V_t is the total amount of blood in the body (the sum of all volumes in the model), $V_{u,sv}$ is unstressed volume in the splanchnic venous compartment, and V_i comes from (3.3). The total blood circulation volume is held constant at $V_t = 5300$ ml.

3.3.3 External Pressure

The systemic thoracic veins section along with all the heart and pulmonary sections are placed inside the thoracic chamber (Fig. 3.2). That means their external pressure P_{ext} equals the pleural pressure P_{pl}, whereas other sections have external pressure equal to the atmospheric pressure, that is 0 mmHg. In [12], the mean (constant) intrathoracic pressure is applied.

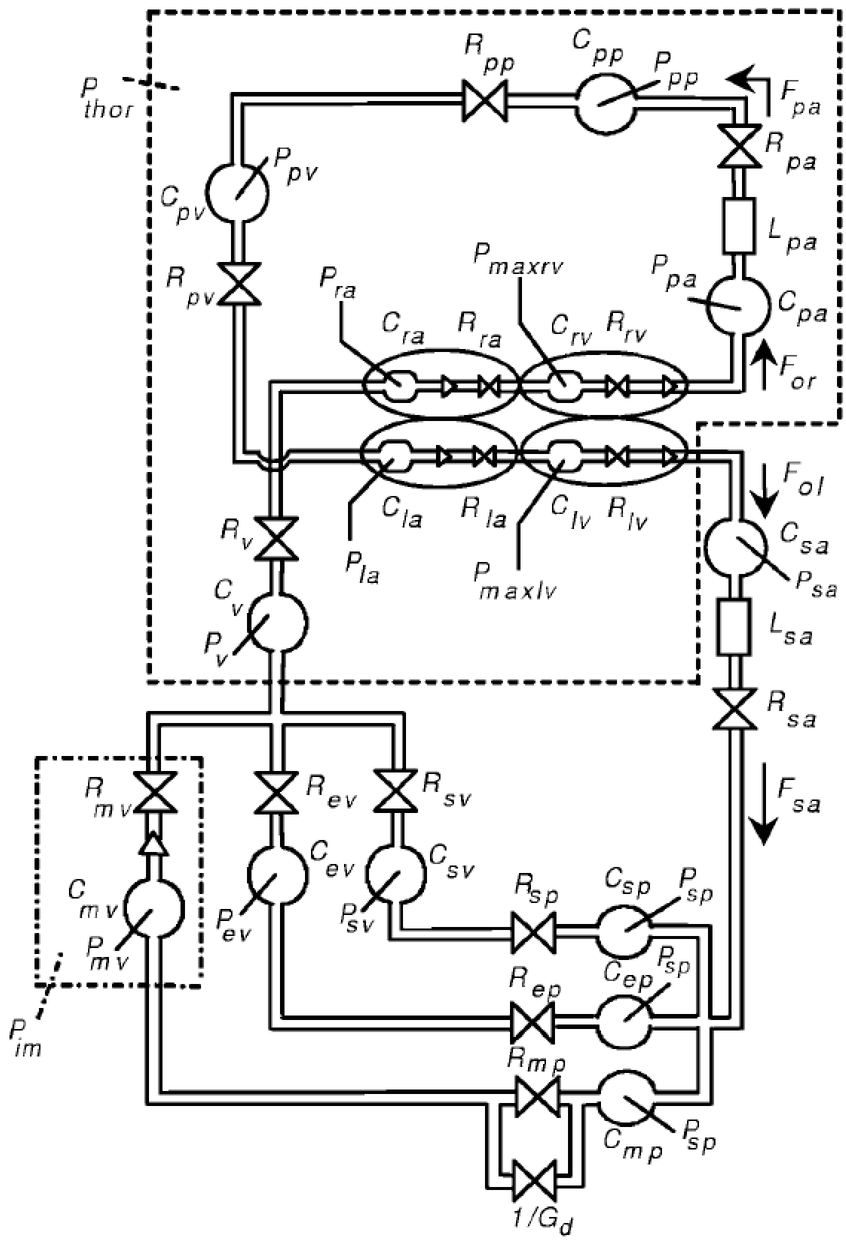

Fig. 3.2. Structure of circulatory model with intrathoracic pressure (P_{thor} in the picture) and three branches in the systemic section. Depicted conductance G_d and intramuscular pressure P_{im} were not used in the assembled model. Source: [25].

The equations in [12] follow (3.6), but volume in sections within the thorax is obtained as:

$$V_i = C_i(P_{tm,i} + P_{pl}) + V_{u,i}. \tag{3.14}$$

In other words, it is not the transmural pressure, but the pressure inside the blood vessels that is used for the volume calculation. This would actually cause increase in blood volume with increasing pressure outside the vessels, and this does not seem to correspond with physical reality. I assumed this to be, most likely, a typographical error in the published article, and I further adhered to (3.3) as this is supported for example by [28].

3.4 Implementation of Model 1

For computer implementation of model 1, the Matlab/Simulink environment was used. The model may be found in a file `model1.mdl` on an enclosed CD. The model composition keeps the structure described above; there are five main sections further divided into compartments and the ventricle activation block, which generates functions $u(t)$ and then $\varphi(t)$ (Fig. 3.3).

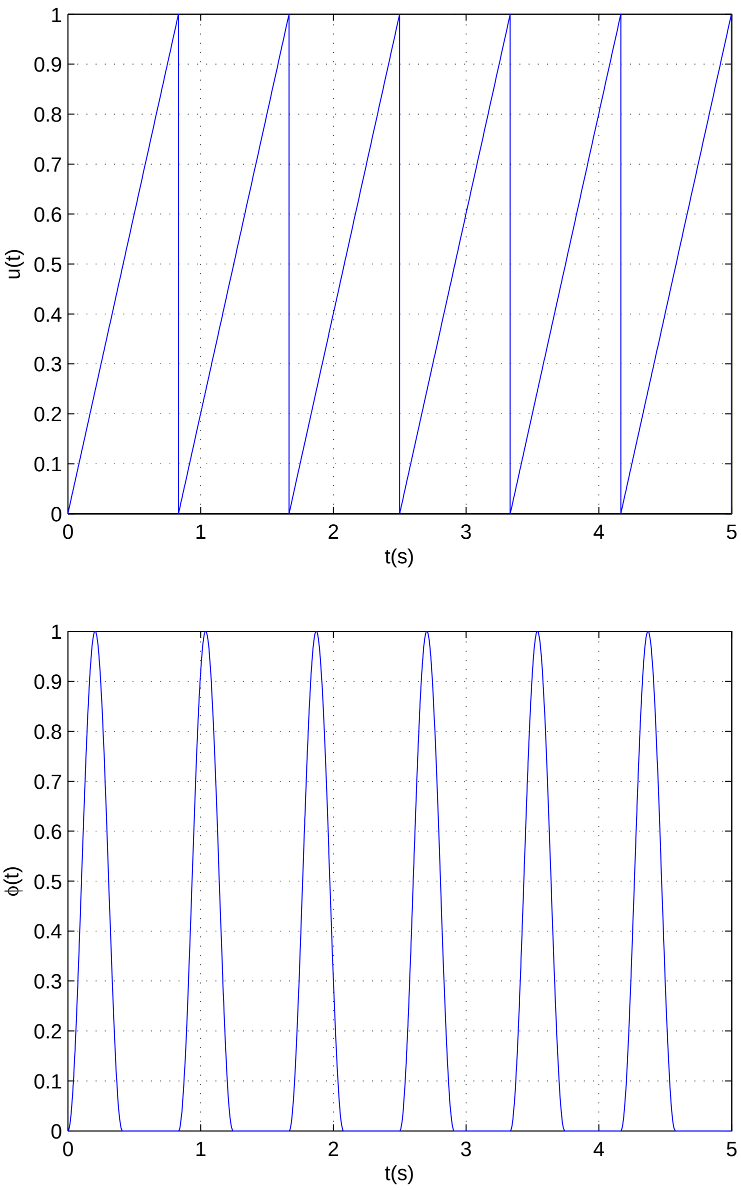

Fig. 3.3. Ventricle activation functions $u(t)$ and $\varphi(t)$—a 5-s run. Heart period set to $T = 0.833$ s. See text for further description.

Functions in every compartment are based on definitions from section 3.2. Transmural pressures were used as state variables as in [28]. A block communicates with its precursor by sending back the pressure signal P_i and with its successor by sending forward blood flow signal F_i. Due to their parallel connection to the systemic arterial compartment, all systemic peripheral compartments are assumed to have the same pressure P_{sp}. Every block also sends its total volume V_i to the splanchnic venous section for the calculation of P_{sv}. Due to ambiguities in referred articles, all equations used are summarized in Appendix B.

Most R, L, and C parameter values in this model are taken from [24] as well as values of constants in the heart sections. Some of the parameters were altered or added in [25]. All used parameters and variables with their values are listed in Appendix D.

3.4.1 Role of Ventricular Pressures

It was unclear if ventricular pressures from (3.8) and (3.10) should be treated as intramural or transmural. The article [24], from which the equations come, does not make any difference in this as it does not use intrathoracic pressure at all. The heart chamber description in [12] is very short, but in the equation for cardiac output there is pleural pressure added to the instantaneous left ventricular pressure, which suggests that the ventricular pressure is transmural. The difference between *transmural* and *intramural version* may be clarified through selected equations for the left heart presented in Table 3.1.

Table 3.1. Selected equations of the left heart section in the *transmural* (left) and *intramural* (right) *version*, i.e., with isometric and instantaneous pressures treated as transmural or intramural. See Appendix B and sections 3.2 and 3.3 for detailed explanation of variables and constants used.

Transmural version	Intramural version
$P_{tm,lv} = P_{max,lv} - R_{lv}F_{lv}$	$P_{lv} = P_{max,lv} - R_{lv}F_{lv}$
$F_{la} = (P_{tm,la} - P_{tm,lv})/R_{la}$	$F_{la} = (P_{tm,la} + P_{pl} - P_{lv})/R_{la}$
$F_{lv} = (P_{max,lv} + P_{pl} - P_{sart})/R_{lv}$	$F_{lv} = (P_{max,lv} - P_{sart})/R_{lv}$

Although the difference in equations does not seem to be fundamental, the results of tests conducted for both variants (Table 3.2) showed that the intramural version was unacceptable as all measured parameters rise with rising pleural pressure, and values for normal conditions of $P_{pl} = -4$ mmHg were too low. This was most likely caused by left-atrial flow F_{la}; in the transmural version there is:

$$F_{la} = \frac{P_{tm,la} - P_{tm,lv}}{R_{la}} = \frac{P_{tm,la} + R_{lv}F_{lv} - P_{max,lv}}{R_{la}}, \tag{3.15}$$

whereas in the intramural version the flow is:

$$F_{la} = \frac{P_{tm,la} + P_{pl} - P_{lv}}{R_{la}} = \frac{P_{tm,la} + P_{pl} + R_{lv}F_{lv} - P_{max,lv}}{R_{la}}. \quad (3.16)$$

The calculation of $P_{max,lv}$ is the same in both versions, but with increasing pleural pressure P_{pl} the left-atrial flow raises in the intramural version of the model, which has the unfavorable effect of increased pressures and volumes. Therefore, ventricular isometric and instantaneous pressures were treated as transmural pressures in the final version of model 1.

Table 3.2. Maximal left ventricular pressure $P_{lv,max}$ and end-diastolic volume $V_{lv,ed}$ produced by model 1 in transmural and ventricular version of the heart equations. Tested for both negative and positive mean pleural pressure P_{pl}.

P_{pl} (mmHg)	Parameter	Transmural	Intramural
-4	$P_{lv,max}$ (mmHg)	141.8	106.5
	$V_{lv,ed}$ (ml)	145.5	108.5
4	$P_{lv,max}$ (mmHg)	118.3	151
	$V_{lv,ed}$ (ml)	115.7	150.5

3.4.2 Test of Model 1

Before further model enhancement, the basic function of model 1 needed to be verified. Model behavior was tested under physiological conditions and with increasing intrathoracic pressure. Normal value of mean pleural pressure in the body without positive-pressure ventilation was assumed to be $P_{pl} = -4$ mmHg. This value is given in [6] and roughly corresponds to the graph in Fig. 2.5. Mean pleural pressure was then raised in steps of 1 mmHg up to 5 mmHg, which is the value suggested by [12] according to experimental results from [30]. In Simulink, each simulation was run for 120 s of simulation time with ode45 (Dormand-Price) solver and variable step with maximum step size 0.01 s. Under zero initial conditions, the model needed about 30 seconds of simulation time to reach steady state.

First, pressure P_{lv} and volume V_{lv} in the left ventricle were observed under normal conditions together with systemic arterial pressure P_{sart}. The resulting left-ventricular and systemic atrial pressure graph depicted in Fig. 3.4 and the pressure-volume diagram in Fig 3.5 may be compared with Fig. 2.2 and Fig. 2.3, respectively, in section 2.2.

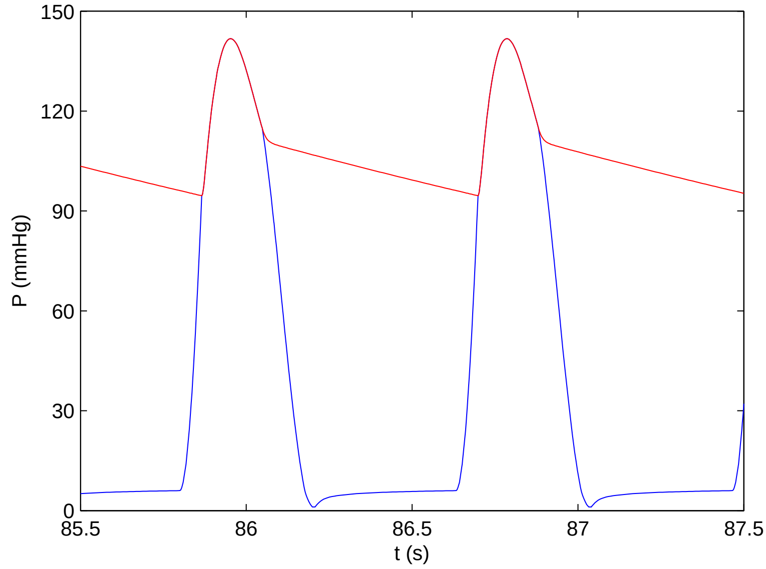

Fig. 3.4. Left-ventricular pressure P_{lv} (blue) and systemic arterial pressure P_{sart} (red) in model 1. Simulation with mean pleural pressure $P_{pl} = -4$ mmHg.

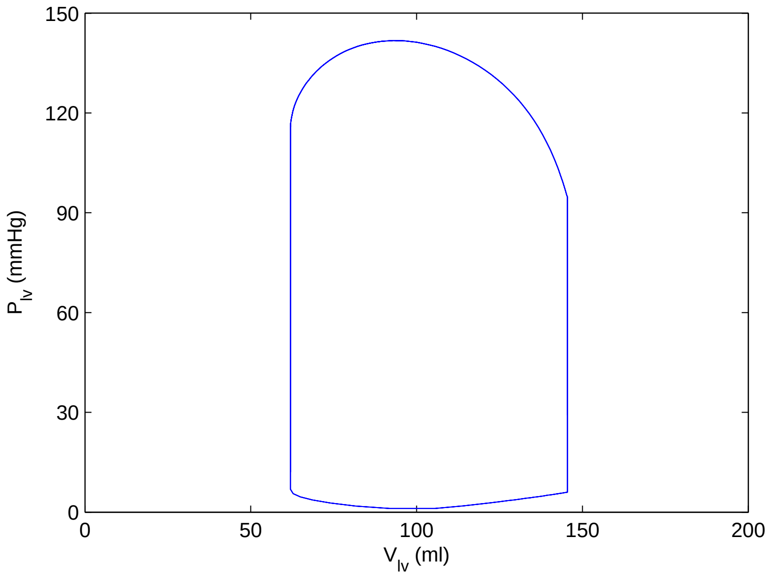

Fig. 3.5. Left-ventricular pressure-volume diagram for model 1. Mean pleural pressure $P_{pl} = -4$ mmHg. Data taken between time $t_1 = 80$ s and $t_2 = 82$ s of simulation.

Second, the reaction of model 1 to increased pleural pressure was observed. Left end-diastolic volume, cardiac output[5] and mean systemic arterial pressure were taken. Mean systemic arterial pressure was estimated as $\overline{P}_{sart} = P_{sart,d} + (P_{sart,s} - P_{sart,d})/3$. $P_{sart,s}$ and $P_{sart,d}$ are systolic and diastolic arterial pressure, respectively. The results can be found in Table 3.3 and may be compared with data in section 2.2.

Table 3.3. Static characteristics for mean pleural pressure P_{pl} changing between -4 and $+4$ mmHg in model 1: End-diastolic volume $V_{lv,ed}$, cardiac output Q, and mean systemic arterial pressure $\overline{P}_{sart}$.

P_{pl} (mmHg)	$V_{lv,ed}$ (ml)	Q (ml·min^{-1})	$\overline{P}_{sart}$ (mmHg)
-4	141.8	6016	110.3
-3	142.3	5873	108.5
-2	138.9	5724	106.7
-1	135.4	5568	104.7
0	131.8	5405	102.6
+1	128.0	5234	100.3
+2	124.0	5057	97.9
+3	120.0	4872	95.4
+4	115.7	4576	92.8
+5	111.3	4474	89.9

Performed tests showed that model 1 worked with exaggerated rates of the observed parameters. The supposed trend of decreasing cardiac output and systemic arterial pressure was followed (Fig. 3.6), but further improvements were necessary.

[5]In this work, the instantaneous outflow from the left ventricle is denoted F_{lv}. Cardiac output Q is total outflow for certain time period, calculated from F_{lv}.

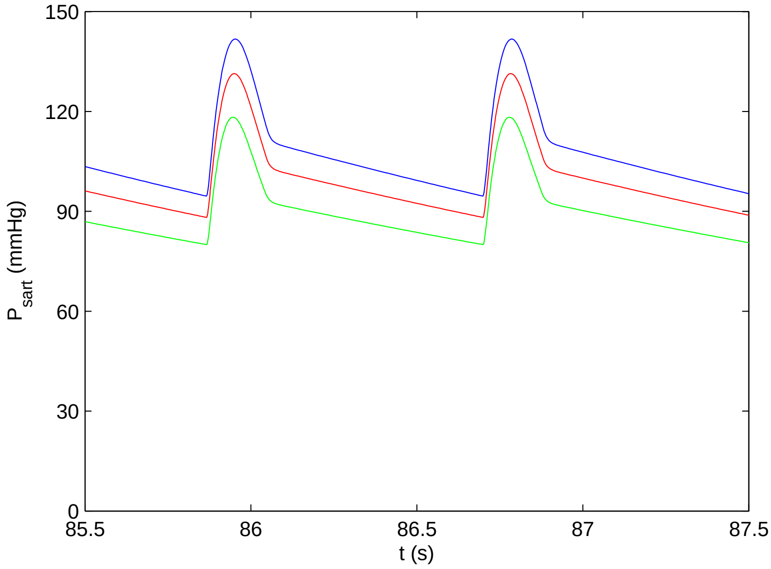

Fig. 3.6. Systemic arterial pressure in model 1. Simulation with mean pleural pressure -4 mmHg (blue), 0 mmHg (red), and +4 mmHg (green).

Chapter 4

Model Enhancement

Tests run on model 1 showed that changes in parameter values and possibly in structure were necessary. Also, the cardiopulmonary relation was represented rather weakly only by mean (constant) pleural pressure P_{pl}. Therefore, I attempted to improve the model performance and accuracy in several steps, which involved both structural and parameter changes. A new model, *model 2*, was developed in two phases: *stage 1* and *stage 2*[1]. In the first stage, the objective was to simplify the model where it was impractically complex, and to reach better correspondence between results generated by the model and standard parameter values reported in physiological sources for normal breathing. In the second stage, more complex connection between the respiratory system and the circulatory system was suggested and implemented. The equations describing the model are summarized in Appendix C. In Appendix D, all new parameter values can be found and compared with the old ones. The final circulatory model structure is depicted in Fig. F.1 in Appendix F.

4.1 Stage 1: Model Performance Correction

In the first phase, some constant parameter values were altered, and minor to medium-scale structure changes were conducted. No outer factor other than the pleural pressure P_{pl} was used.

4.1.1 Simplification of the Systemic Section

The active muscle compartments (peripheral and venous) were not important for the objective of the model. Therefore, in order to make the model as plain and fast as possible,

[1]Implemented models can be found as `model2_1.mdl` and `model2_2.mdl` on the enclosed CD.

I decided to leave these out. The new structure of systemic circulation is the same as published in [31], only without special abdominal pressure. As for the combination of the systemic thoracic veins section and two parallel branches within the systemic section (splanchnic and extrasplanchnic compartments) there were no extra list of parameter values (R, L, V_u) published, I derived them from [24] and [25] so that:

1. The systemic thoracic veins compartment remains unchanged.

2. Resistances in the systemic section were set to the same values as in [24]. Adding small R_{stv} in a series only slightly changes total resistance of the systemic circulation between systemic arteries and the right atrium, which is called *total peripheral vascular resistance*, from 1.058 mmHg·s·ml^{-1} to 1.063 mmHg·s·ml^{-1}. This fully matches the value given in [6], which is 1 mmHg·s·ml^{-1}.

3. Compliances in extrasplanchnic and active muscle peripheral compartments were summed to form new extrasplanchnic peripheral compliance. New extrasplanchnic venous compliance was set in an analogous way. Now extrasplanchnic compliances are the same as in [24], and the sum of all systemic compliances is equal in model 2 and in [24], too.

4. Unstressed volumes have the same values as in [24]. That means that extrasplanchnic and active muscle values were merged.

4.1.2 Parameter Adjustment

Results obtained in section 3.4 showed too high levels of cardiac output and systemic arterial pressure for $P_{pl} = -4$ mmHg (basal conditions). The standard values for these parameters are supposed to be about 5400 ml·min^{-1} instead of 6016 ml·min^{-1} and 100 mmHg instead of 110.3 mmHg. One can see in Table 3.3 that the desired values generates the model at $P_{pl} = 0$ mmHg or slightly more. In other words, despite being used by De Lazzari et al. [12] and in [25], the parameter values adopted from [24] do not properly reflect pressure differences between thorax and the rest of the body. Therefore, before turning one's attention to the cardiopulmonary interaction itself, it seemed necessary to attempt better parameter adjustment. Although composed mostly of first-order ordinary differential equations, the model built contains some non-linear functions in the heart, and it turned out to be rather tricky to reach the desired output. The final settings are a result of many trials; however, the intentions and steps taken for the change of parameters can be described at least.

The presented model certainly cannot simulate the work of blood circulation system into precise details. Nevertheless, I tried to reach at least fair performance in basic physiological parameters, keeping in mind the cardiopulmonary scope of the model. The objectives for $P_{pl} = -4$ mmHg basically followed data from Chapter 2 and additional information found in [6]. The priorities were to reach:

1. cardiac output about 5400 ml·min^{-1} (90 ml·s^{-1});
2. mean systemic atrial pressure $\overline{P}_{sart} = 100$ mmHg and left ventricle pressure-volume relation similar to Fig. 2.3;
3. pulmonary capillary pressure (represented by P_{pp}) about 7 mmHg;
4. pressure in venae cavae P_{stv} about 2 mmHg;
5. pulmonary capillary volume (represented by V_{pp}) about 70 ml.

Starting with the data describing model 1 performance (Tables 4.1 and 4.2), I gradually improved the model behavior in four areas: systemic circulation, the pulmonary section, volumes, and left-heart parameters. If possible, the compliances were not changed. Resistances were estimated in a similar way as in [32]: as the (expected) pressure drop divided by cardiac output.

Table 4.1. Intramural pressure in compartments of model 1. Presented is the lowest (min), highest (max), or average (avg) pressure in last 23 s of the simulation (120 s).

	P (mmHg)		
	min	max	avg
lv	1.1	141.8	
sart	94.6	141.8	110.3
sp	–	–	102.2
sv/ev	–	–	3.6/3.6
stv	–	–	2.4
ra	–	–	1.9
rv	-1.0	27.0	–
part	11.6	27.0	16.4
pp	–	–	15.4
pv	–	–	6.4
la	–	–	5.9

Table 4.2. Blood flow (cardiac output) Q (ml·min^{-1}) and selected volumes (ml) in model 1: end-systolic ($V_{lv,es}$) and end-diastolic ($V_{lv,ed}$) volume in the left ventricle, total volume in the heart (V_{heart}); total volume in systemic arteries (V_{sart}) and veins (V_v); pulmonary arterial (V_{part}), peripheral (V_{pp}) and venous volume (V_{pv}).

$V_{lv,es}$	62.1
$V_{lv,ed}$	145.5
V_{heart}	655.5
V_{sart}	30.4
V_v	2848.8
V_{part}	16.5
V_{pp}	235.6
V_{pv}	385.2
Q	6016

Changes in Systemic Circulation

Preserving blood flow of about 90 ml·s^{-1} while adding 4 mmHg to the pressure gradient between systemic arteries and the right atrium required to increase the total peripheral vascular resistance by about 0.044 mmHg·s·ml^{-1}. At the same time, the desired pressure drop between systemic thoracic veins and the right atrium was 1–2 mmHg which yielded $R_{stv} \approx 0.013$ mmHg·s·ml^{-1}. Pressure in venae cavae should have been about 2 mmHg; hence, some changes in systemic arterial and venous resistances were necessary. Finally, the changes were: $R_{sart} = 0.055$ mmHg·s·ml^{-1}, $R_{sv} = 0.132$ mmHg·s·ml^{-1}, $R_{ev} = 0.056$ mmHg·s·ml^{-1}, and $R_{stv} = 0.014$ mmHg·s·ml^{-1}. The total peripheral vascular resistance was raised from 1.063 mmHg·s·ml^{-1} to 1.095 mmHg·s·ml^{-1}.

Changes in Pulmonary Circulation

In model 1, the total pulmonary resistance is 0.118 mmHg·s·ml^{-1}. This seemed satisfactory although [6] reports a little higher value (0.14–0.16 mmHg·s·ml^{-1}). The real problem was high pulmonary peripheral pressure P_{pp}, which was intended to be used for expression of pressure in the pulmonary capillaries. Simple increase in pulmonary arterial resistance R_{part} with concurrent decrease of R_{pp} only raised systolic pressure in the right ventricle and did not bring the desired effect. In the end, I decided to split the pulmonary peripheral compartment into two parts: the pulmonary arterioles (*pao*) and pulmonary capillaries (*pc*). Such an arrangement, originating from [28], not only allowed finer control of pressure drop across the pulmonary circulation, but also opened the possibility of future pulmonary shunt modeling. In the pulmonary compartments, resistances were changed to $R_{part} = 0.04$ mmHg·s·ml^{-1}, $R_{pao} = 0.045$ mmHg·s·ml^{-1}, $R_{pc} = 0.025$ mmHg·s·ml^{-1}, and $R_{pv} = 0.015$ mmHg·s·ml^{-1}, which yields the total pulmonary vascular resistance 0.125 mmHg·s·ml^{-1}. To keep a reasonable blood flow, both compliances of the two middle compartments (C_{pao} and C_{pc}) had to be decreased from $C_{pp} = 5.80$ ml·mmHg^{-1} to 4.0 ml·mmHg^{-1}.

Changes in Volumes

According to [6], blood volume in the lungs is about 9% of the total blood volume in the body, that is 450 ml out of 5000 ml. Of that volume, about 70 ml is in pulmonary capillaries, and the rest is equally distributed in arteries and veins. As the model has the total blood volume 5300 ml, of which 9% is 477 ml, I assumed 77 ml in the pulmonary capillaries, 200 ml in the pulmonary veins, and 200 ml together in pulmonary arteries and arterioles. In order to reach that objective, unstressed volume in the pulmonary arteries was kept zero, $V_{u,pao} = 123$ ml (transferred from V_{pp}), $V_{u,pc} = 30$ ml, and $V_{u,pv} = 0$ ml. To balance such settings, remaining 50 ml were divided among systemic splanchnic and extrasplanchnic venous compartments.

Changes in Heart Parameters

Only one parameter in the heart sections was changed: In the left ventricle I raised $P_{0,lv}$ from 1.5 to 1.57 to avoid negative left-ventricular diastolic pressure.

4.1.3 Upgraded Model Performance

For $P_{pl} = -4$ mmHg, the new version of the model, *model 2 (stage 1)*, exhibits performance more similar to standard physiological values presented in Chapter 2 than model 1. This can be verified by data in Tables 4.3 and 4.4. The left-atrial pressure-volume diagram (Fig 4.1) may be compared with the results of model 1 (Fig. 3.5). The new parameter settings maintains the trend of systemic arterial pressure decrease with increasing pleural pressure (Fig. 4.2 and Table 4.5).

Table 4.3. Intramural pressure in compartments of model 2 (stage 1). Presented is the lowest (min), highest (max), or average (avg) pressure in the last 23 s of the simulation (120 s).

	P (mmHg)		
	min	max	avg
lv	0.1	127.3	–
sart	86.8	127.3	100.3
sp	–	–	93.6
sv/ev	–	–	5.9/5.9
stv	–	–	2.4
ra	–	–	1.1
rv	-1.4	28.6	–
part	8.1	28.6	15.0
pao	–	–	11.7
pc	–	–	7.7
pv	–	–	5.5
la	–	–	4.0

Table 4.4. Blood flow (cardiac output) Q (ml·min^{-1}) and selected volumes (ml) in model 2 (stage 1): end-systolic ($V_{lv,es}$) and end-diastolic ($V_{lv,ed}$) volume in the left ventricle, total volume in the heart (V_{heart}); total volume in systemic arteries (V_{sart}) and veins (V_v); pulmonary arterial (V_{part}), arteriolar (V_{pao}, capillary (V_{pc}) and venous volume (V_{pv}).

$V_{lv,es}$	57.1
$V_{lv,ed}$	131.1
V_{heart}	578.5
V_{sart}	27.6
V_v	3084.4
$V_{part} + V_{pao}$	200.4
V_{pc}	76.8
V_{pv}	240.6
Q	5333

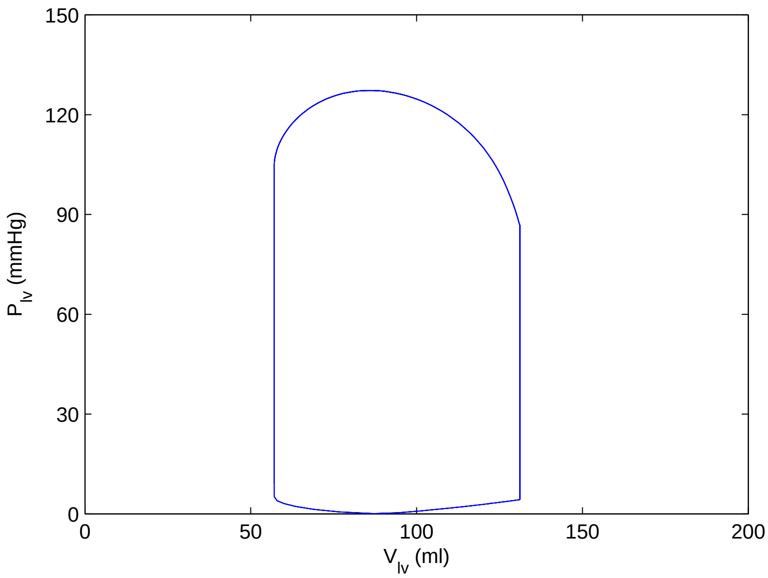

Fig. 4.1. Left-ventricular pressure-volume diagram for model 2 (stage 1). Mean pleural pressure $P_{pl} = -4$ mmHg. Data taken in time from $t_1 = 80$ s to $t_2 = 82$ s of the simulation.

Table 4.5. Static characteristics for mean pleural pressure P_{pl} changing between -4 and $+4$ mmHg in model 2 (stage 1): End-diastolic volume $V_{lv,ed}$, cardiac output Q, and mean systemic arterial pressure $\overline{P}_{sart}$.

P_{pl} (mmHg)	$V_{lv,ed}$ (ml)	Q (ml·min^{-1})	$\overline{P}_{sart}$ (mmHg)
-4	131.1	5333	100.3
-3	127.9	5190	98.5
-2	124.6	5041	96.6
-1	121.2	4888	94.5
0	117.7	4729	92.4
+1	114.0	4565	90.2
+2	110.3	4395	87.9
+3	106.5	4219	85.5
+4	102.5	4038	83.0
+5	98.4	3851	80.4

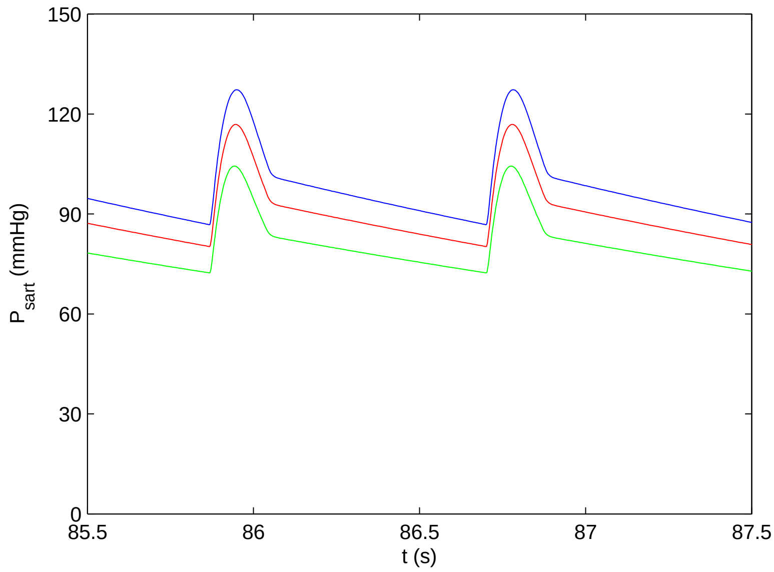

Fig. 4.2. Systemic arterial pressure in model 2 (stage 1). Simulation with mean pleural pressure -4 mmHg (blue), 0 mmHg (red), and +4 mmHg (green).

4.2 Stage 2: Lung Influence Modelling

In section 2.5, two main areas of cardiopulmonary mechanical interaction are described. With the basic model functioning and mimicking the thoracic pump, the next step was to look closely at the pulmonary circulation section. In this phase, lung volume and alveolar pressure effect was incorporated into the model, and the concept of *pulmonary shunt* was taken into account, too.

4.2.1 Alveolar Pressure

As stated in section 2.5, alveolar vessels are more influenced by alveolar pressure than by pleural pressure. Thus, in the pulmonary capillary compartment alveolar pressure P_{alv} was employed as the external pressure in the same way as in [27]. Now the pulmonary capillary intramural pressure P_{pc} is:

$$P_{pc} = P_{tm,pc} + P_{alv} \tag{4.1}$$

where $P_{tm,pc}$ is the pulmonary capillary transmural pressure. In all other pulmonary compartments, pleural pressure R_{pl} remains in a role of the external pressure.

4.2.2 Pulmonary Shunt

A part of blood passing through the pulmonary capillaries is not oxygenated due to low *ventilation/perfusion ratio*[2], that is, because lung ventilation is inadequate for blood flow in some parts of the lungs. Even under normal ventilation/perfusion ratio, a fraction of blood—about 2%—in the pulmonary circulation flows through bronchial vessels and not through alveolar capillaries. This is called the *physiologic shunt* [6].

The pulmonary shunt was modeled in [28] and [8] as an additional branch connecting directly the pulmonary arteriolar and pulmonary venous compartment. The only element in this branch is a hydraulic resistance. I adopted this concept (the new structure is in Fig. 4.3), therefore the outflow from the pulmonary arteriolar compartment is divided into $F_{pao,pv}$, which mimics the shunted blood, and $F_{pao,pc}$, which leads towards the pulmonary capillaries. In [28], the ratio of the flows is about 0.011. Keeping the same relation together with unchanged values of R_{pao} and R_{pc} yielded pulmonary shunt resistance $R_{ps} =$ 6.43 mmHg·s·ml^{-1}.

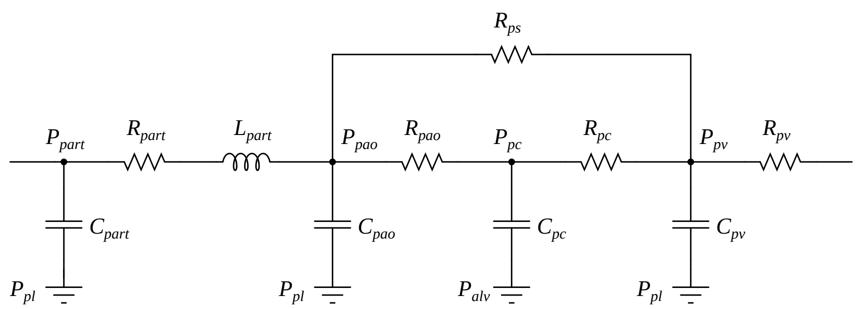

Fig. 4.3. Structure of the pulmonary section in model 2 (stage 2). See text for closer description.

4.2.3 Lung volume and PVR

The final change in the model regards lung air volume and its relation to pulmonary vascular resistance (PVR). It was explained in section 2.5 how PVR raises with increased lung volume. According to the results of experiments published in [33], the changes in resistance are by far the greatest in the middle segment of the pulmonary vessels. This conclusion was reflected in [8] where the capillary resistance R_{pc} is a function of the alveolar

[2]The concept of the ventilation/perfusion ratio matches alveolar ventilation and blood flow in pulmonary capillaries.

volume[3] V_A:

$$R_{pc} = R_{pc,0} \left(\frac{V_A}{V_{A,max}} \right)^2. \tag{4.2}$$

Here, $R_{pc,0}$ is called the *magnitude of pulmonary capillary resistance* and $V_{A,max}$ is the maximal alveolar volume. Though corresponding with the U-shape relationship mentioned above, this formula has serious disadvantages: First, it designates an upper bound for the capillary resistance most likely without considering the artificial ventilation option. Second, values of $R_{pc,0}$ and $V_{A,max}$ are not provided in [8]. Because of these ambiguities I decided to derive a new function, which would describe the volume–resistance relation.

The rise of pulmonary vascular resistance with lung inflation has been examined for a long time[4]; however, in many published articles PVR is plotted as a function of transpulmonary pressure (for instance in [33], [34], [35]) rather than lung volume. Nevertheless, in [36] the direct relation between PVR and lung volume is presented in the form of a plot of relative pulmonary vascular resistance as a function of relative lung volume (in percent of total lung capacity TLC). From this curve I attempted to estimate the pulmonary capillary resistance as a function of lung volume $R_{pc}(V_{lung})$:

1. Coordinates of nine points from the plot were taken, starting from volume of 0.4·TLC, which should be the volume of functional residual capacity (2300 ml out of 5800 ml, see Table 2.6).

2. Absolute values were estimated from acquired relative values: In x-axis, TLC was supposed to be 5800 ml. In y-axis, PVR in model 2 settled on 0.124 mmHg·s·ml^{-1} after previous improvements. As this simulated normal breathing, I estimated the lung volume to be equal to FRC plus half of the tidal volume, hence 2550 ml (0.44·TLC). This corresponds to relative PVR of 0.3850 in the original graph.

3. A second-degree polynomial that fits the data best in a least-square sense was found using a Matlab script.

4. The relation between PVR (R_{pulm}) and the pulmonary capillary resistance R_{pc} is

$$R_{pulm} = R_{part} + \frac{(R_{pao} + R_{pc})R_{ps}}{R_{pao} + R_{pc} + R_{ps}} + R_{pv}. \tag{4.3}$$

[3]The alveolar volume is volume in the alveolar region (compartment) of the airway/lung mechanics model used in [8].

[4]usually on dogs or cats

Since $R_{ps} \gg (R_{pao} + R_{pc})$, the equation (4.3) can be simplified to

$$R_{pulm} = R_{part} + R_{pao} + R_{pc} + R_{pv}, \tag{4.4}$$

and so $R_{pc}(V_{lung})$ can be derived from R_{PVR} by subtracting a constant value of resistance.

The final formula for the pulmonary capillary resistance was therefore estimated as:

$$R_{pc}(V_{lung}) = 2.89922 \cdot 10^{-7} V_{lung}^2 - 1.35128 \cdot 10^{-3} V_{lung} + 1.58430 \tag{4.5}$$

where V_{lung} is the instantaneous total lung volume. The estimated function is in Fig. 4.4. A script used for the polynomial calculation is attached in Appendix E.

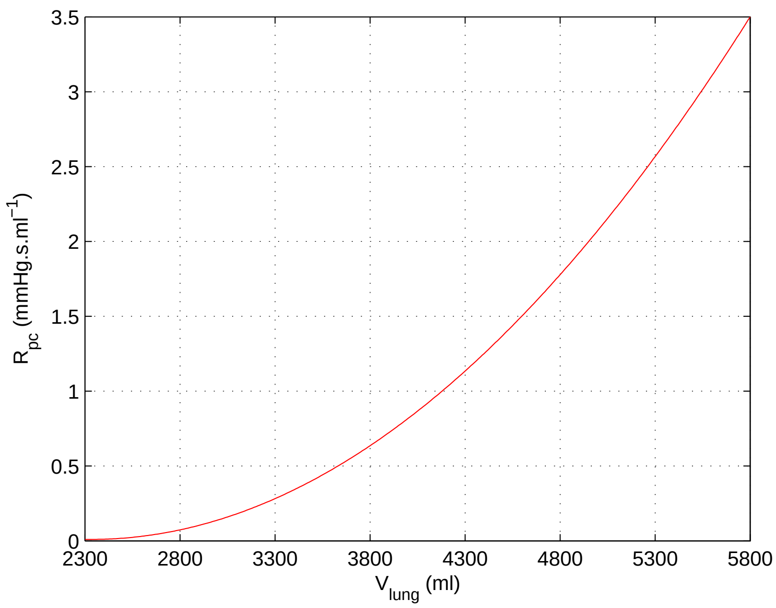

Fig. 4.4. Pulmonary capillary resistance as a function of lung volume in model 2 (stage 2).

4.2.4 Test of Stage 2

Model 2 (stage 2) was first tested without any model of lungs or ventilation available. For the test of normal breathing, I left $P_{pl} = -4$ mmHg. Alveolar pressure was set at $P_{alv} = 0$ mmHg, and lung volume was held at constant value $V_{lung} = 2550$ ml. As can be seen in Tables 4.6 and 4.7, the results of model 2 (stage 2) are almost identical to stage 1. The recent changes did not worsen the performance of the model.

Table 4.6. Intramural pressure in compartments of model 2 (stage 2). Presented is the lowest (min), highest (max), or average (avg) pressure in last 23 s of the simulation (120 s).

	P (mmHg)		
	min	max	avg
lv	0.1	128.0	–
sart	87.3	128.0	100.9
sp	–	–	94.2
sv/ev	–	–	6.0/5.9
stv	–	–	2.4
ra	–	–	1.2
rv	-1.3	28.7	–
part	8.1	28.7	15.0
pao	–	–	11.7
pc	–	–	7.7
pv	–	–	5.6
la	–	–	4.2

Table 4.7. Blood flow (cardiac output) Q (ml·min^{-1}) and selected volumes (ml) in model 2 (stage 2): end-systolic ($V_{lv,es}$) and end-diastolic ($V_{lv,ed}$) volume in the left ventricle, total volume in the heart (V_{heart}); total volume in the systemic arteries (V_{sart}) and veins (V_v); pulmonary arterial (V_{part}), arteriolar (V_{pao}, capillary (V_{pc}) and venous volume (V_{pv}).

$V_{lv,es}$ (ml)	57.3
$V_{lv,ed}$ (ml)	131.8
V_{heart} (ml)	582.6
V_{sart} (ml)	27.8
V_v (ml)	3071.7
$V_{part} + V_{pao}$ (ml)	200.3
V_{pc} (ml)	76.8
V_{pv} (ml)	243.2
Q (ml·min^{-1})	5365

Chapter 5

Model Test and Evaluation

After final modifications described in the previous chapter, the performance of model 2 (stage 2) needed to be evaluated, mainly its ability to react to changes in lung ventilation. The model requires three basic input variables: the pleural pressure P_{pl}, the alveolar pressure P_{alv}, and the lung volume P_{alv}. In thorax, pleural and alveolar pressures are related in a non-trivial manner; hence, at this stage tests could not have been executed without a model of lung ventilation. First, a simple simulation of normal breathing was added to model 2. Second, a reaction of the model to positive-pressure ventilation was examined. At this point, the circulatory system model was connected to a model of artificial lung ventilation by Rusz [37] called the *linear ventilator*.

5.1 Test Objectives and Methods

The purpose of the experiment was to inspect how model 2 simulates cardiopulmonary mechanical interaction during artificial ventilation; that is, how the cardiac output and some other variables in the circulatory model change if spontaneous breathing is replaced by mechanical ventilation. As for the observed variables, besides the cardiac output Q, the average pulmonary capillary pressure $\overline{P}_{pc}$ and the systemic arterial pressure P_{sart} were measured as model 2 output with respect to the end-expiratory alveolar pressure $P_{alv,EE}$. Moreover, from lung ventilation parameters the average pleural pressure $\overline{P}_{pl}$ was also recorded as well as lung volumes at the end of expiration and inspiration, $V_{lung,exp}$ and $V_{lung,insp}$, respectively. The test had three parts:

1. Spontaneous breathing was simulated in order to obtain basic (reference) values of the parameters. In comparison with tests in the previous chapter, this time the inputs

were time-varying functions.

2. Linear ventilator was attached to the circulatory model, and the model internal parameters were adjusted so that the air volume in the lungs was similar to the volume set during the spontaneous breathing . Then, artificial ventilation with zero end-expiratory pressure (ZEEP) was simulated.

3. The ventilator setting was changed so that positive-end expiratory pressure (PEEP) was induced.

In all the steps, a simulation ran for 120 s (of the simulation time) and the data were taken in the last 60 s.

5.1.1 Spontaneous Breathing

As the lung ventilator does not simulate spontaneous breathing, a brief test how model 2 can handle time-dependent inputs required to build some functions mimicking P_{pl}, P_{alv}, and V_{lung}. I tried to make these functions similar to the form presented in Fig. 2.5. The alveolar pressure function P_{alv} was simulated as a sine wave with the mean value of 0 mmHg and an amplitude 1.1 mmHg. Also, the lung volume V_{lung} was modeled as a sine wave function with the mean value of 2550 ml and an amplitude of 250 ml, so the end-expiratory lung volume corresponds with typical functional residual capacity, and the tidal volume is 500 ml. For the pleural pressure P_{pl}, a function used in [25] was adapted:

$$P_{pl}(t) = \begin{cases} P_{pl,insp} & \text{for } 0 \leq s(t) \leq T_i/T_{resp} \\ P_{pl,exp} & \text{for } T_i/T_{resp} < s(t) \leq (T_i + T_e)/T_{resp} \\ P_{pl,max} & \text{for } (T_i + T_e)/T_{resp} < s(t) \leq 1 \end{cases} \tag{5.1}$$

where

$$P_{pl,insp} = P_{pl,max} - (P_{pl,max} - P_{pl,min}) \cdot \frac{T_{resp}}{T_i} \cdot s(t)$$
$$P_{pl,exp} = P_{pl,max} - \frac{(P_{pl,max} - P_{pl,min})}{T_e} \cdot (T_i + T_e - s(t) \cdot T_{resp})$$

are pleural pressures during inspiration and expiration, respectively. In (5.1), there is:

$$P_{pl,max} = -2.9\text{mmHg}\ldots \text{the maximal pleural pressure}$$
$$P_{pl,min} = -6\text{mmHg}\ldots \text{the minimal pleural pressure}$$
$$T_{resp} = 4\text{s}\ldots \text{the respiratory period}$$
$$T_i = 1.6\text{s}\ldots \text{the inspiration time}$$
$$T_e = 1.4\text{s}\ldots \text{the expiration time}$$

The function $s(t)$ periodically rises from 0 to 1 in the same way as $u(t)$ in section 3.3. At the beginning of inspiration $s = 0$.

5.1.2 The Ventilator

The *linear ventilator* model by Jan Rusz combines a model of a lung ventilator and a model of the respiratory system. Four ventilator parameters (the inspiration time, inspiration pause, expiration time, and one cycle flow) and two lung parameters (the pulmonary pressure and the chest wall pressure) may be adjusted. Other 18 parameters are considered internal. The Simulink file with model 2 (stage 2) `model2_2.mdl` was altered so that a subsystem block with the linear ventilator was attached. Now it is possible to switch between the spontaneous breathing block and the linear ventilator block. In the linear ventilator a few minor adjustments were made: The chest wall pressure P_{HS} was changed from 2.14 kPa to 1.45 kPa and an internal constant C_p was changed from 2.4 l·kPa^{-1} to 3 l·kPa^{-1} for better adjustment of initial lung volume. Names of output variables were altered to match with the description used in the circulatory part of model 2, and one cycle flow input parameter was renamed from Q_max to CF_max because of possible confusion with the cardiac output Q.

The default setting of the ventilator produced intermittent positive-pressure ventilation with zero end-expiratory pressure; that is, with respiratory pressure and alveolar pressure returning to ambient pressure at the end of each respiratory cycle. This was used for the initial measurement with the ventilator. As the ventilator does not offer easy switch to positive end-expiratory pressure, I reached such an output by prolonging the inspiration time T_i, shortening the expiration time T_e, and changing the cycle flow CF_{max}. In this way, the end-expiratory alveolar pressure was raised to values up to 15 cmH$_2$O while lung volume was changing only within a 1-liter range.

5.2 Results

Table 5.1 shows settings of the ventilator, which were used for reaching desired end-expiratory alveolar pressure, and lung volumes produced by the ventilator or the spontaneous breathing module. In Table 5.2, there are mean pressures in the pleural cavity, pulmonary capillary compartment, and systemic arterial compartment listed together with resulting cardiac output. The units of alveolar pressure (cmH_2O) were chosen as the most typical ones used in cited source materials.

In Figure 5.1, cardiac output produced by the model with the lung ventilator attached (for various ZEEP or PEEP settings) is related to the output measured in the spontaneous breathing mode. Figure 5.2 shows systemic arterial pressure as produced by model 2 (stage 2) for three levels of the pleural pressure P_{pl}. The highest pressure was measured during the spontaneous breathing simulation, the other two runs were acquired when the lung ventilator and PEEP were applied.

Table 5.1. End-expiratory alveolar pressure $P_{alv,EE}$ and lung end-expiratory and end-inspiratory volumes $V_{lung,exp}$ and $V_{lung,insp}$ as results of various ventilator settings of inspiration time T_i, expiration time T_e, and cycle flow CF_{max}. In the first line, the output of the spontaneous breathing module is given. The second line presents the default ventilator setting (ZEEP).

T_i [s]	T_e (s)	CF_{max} (l.s^{-1})	$V_{lung,exp}$ (ml)	$V_{lung,insp}$ (ml)	$P_{alv,EE}$ (cmH_2O)
–	–	–	2300	2800	0
1.00	2.50	0.50	2329	2679	0.2
1.50	2.00	0.40	2399	2871	0.5
2.00	1.50	0.40	2545	3174	1.1
2.33	1.17	0.40	2695	3385	1.9
2.45	1.05	0.40	2765	3464	2.4
2.85	0.65	0.40	3085	3730	4.9
3.05	0.45	0.40	3315	3865	7.2
3.10	0.40	0.50	3669	4308	10.0
3.20	0.30	0.50	3862	4393	12.2
3.25	0.25	0.55	4144	4653	15.0

Table 5.2. The mean pulmonary capillary pressure $\overline{P}_{pc}$, mean systemic arterial pressure $\overline{P}_{sart}$, and cardiac output Q as results of various end-expiratory alveolar pressure $P_{alv,EE}$ settings. The mean pleural pressure P_{pl} is also listed. In the first line, $P_{alv,EE}$ and P_{pl} are produced by the spontaneous breathing section. Further, the linear ventilator section was employed. The second line presents the default ventilator setting (ZEEP) although the end-expiratory pressure did not fall exactly to zero.

$P_{alv,EE}$ (cmH_2O)	$\overline{P}_{pl}$ (mmHg)	$\overline{P}_{pc}$ (mmHg)	$\overline{P}_{sart}$ (mmHg)	Q (ml·min^{-1})
0	-4.1	8.2	98.9	5352
0.2	-0.9	9.0	93.1	4902
0.5	-0.2	10.8	90.6	4734
1.1	1.0	15.3	85.4	4388
1.9	2.0	19.7	80.3	4066
2.4	2.4	21.8	78.0	3924
4.9	3.8	30.2	68.9	3362
7.2	4.5	34.8	63.9	3051
10.0	6.4	42.7	53.8	2414
12.2	6.9	44.6	51.2	2249
15.0	8.1	47.5	46.2	1922

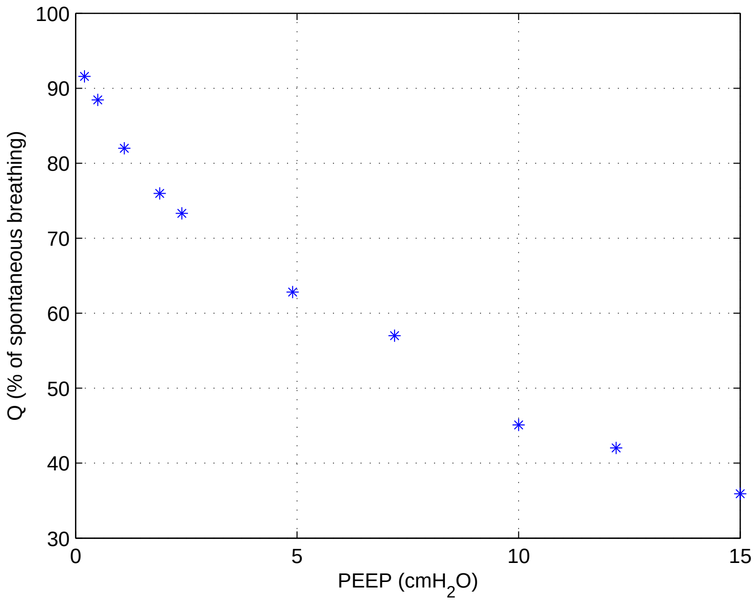

Fig. 5.1. The cardiac output Q (related to the cardiac output value during spontaneous breathing, 5352 ml·min^{-}1) as a function of positive end-expiratory pressure .

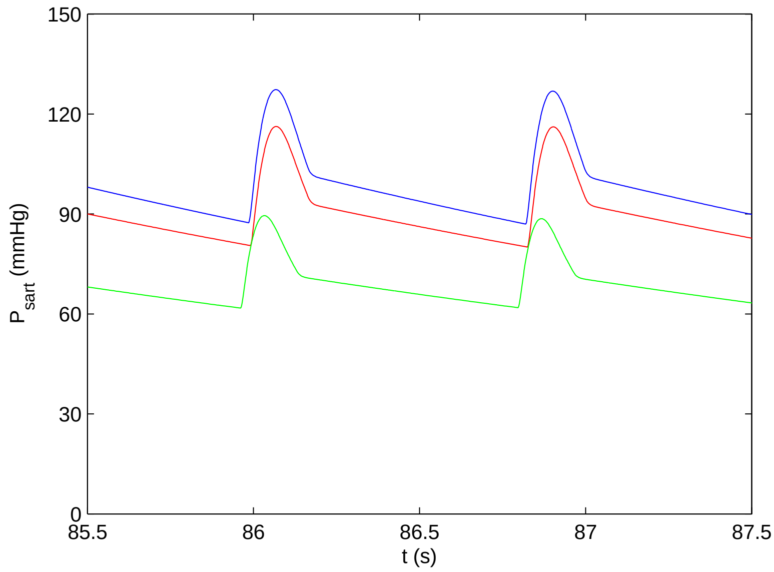

Fig. 5.2. Systemic arterial pressure in model 2 (stage 2) combined with the linear ventilator. Simulation with mean pleural pressure of -4 mmHg (blue), 0 mmHg (red) and +4 mmHg (green). Data taken from tests of spontaneous breathing, PEEP 0.5 cmH_2, and PEEP 4.9 cmH_2O, respectively.

5.3 Discussion

The pulmonary capillary resistance curve $R_{pc}(V_{lung})$ yields for $V_{lung} = 2550$ ml lower resistance than 0.04 mmHg·s·ml^{-1} supposed during the original construction of model 2. That explains minor differences between the results for spontaneous breathing in sections 4.2 and 5.2. Cardiac output $Q = 5352$ ml·min^{-1}, however, can be considered as a satisfactory reference value.

The model exhibits decreasing cardiac output (and systemic arterial pressure). For ZEEP or very low PEEP, the model shows about 8.4% decrease in cardiac output compared to spontaneous breathing. This is similar, yet smaller, decrease than the published values: 10% in anaesthetized patients without pulmonary pathology [1] and 11% in normal dogs [38]. For higher PEEP values, results of model 2 (stage 2) differ significantly from reported values—predicted cardiac output falls faster than laboratory experiments had suggested: In the classic paper of Cournard et al. [3], PEEP of about 5.5 cmH_2O caused cardiac output decrease of about 15%. Lumb [1] mentions 18% and 36% fall for PEEP of 9 cmH_2O and PEEP of 16 cmH_2O, respectively. Cassidy et al. reported 20% cardiac output decrease for PEEP of 10 cmH_2O in healthy adult humans [39]. In normal dogs, the decrease was 26% with PEEP of 5 cmH_2O, 42% with PEEP of 10 cmH_2O, and

49% with PEEP of 15 cmH_2O. On the contrary, the model shows decrease of 38% with PEEP 5 cmH_2O, 55% with PEEP 10 cmH_2O, and 64% with PEEP 15 cmH_2O (Fig. 5.1).

I conclude that a very important factor that contributes to the excessive cardiac output decrease is the large lung volume produced by linear ventilator. According to [1], PEEP of 10 cmH_2O increases functional residual capacity by about 500 ml, depending on lung compliance. For the same level of PEEP, FRC in the model is increased by more than 1300 ml. The impact of lung volume is also apparent from values of the mean pleural pressure. For the same pleural pressure, cardiac output and the mean systemic arterial pressure fall faster in model 2 (stage 2) than in model 2 (stage 1), which does not consider volume-dependent pulmonary resistance (Tables 4.5 and 5.2).

The linear ventilator provides a very good simulation of artificial ventilation with zero end-expiratory pressure. Nevertheless, it does not offer any simple setting for PEEP. Changes in the inspiratory/expiratory (I/E) ratio were used for reaching such a mode. In fact, inverse I/E ratio induces intrinsic PEEP, so this way is not illogical. In [40], the I/E ratio of 2:1 was compared to the normal artificial ventilation with I/E ratio of 1:2, and the reported decrease in cardiac output was about 20%. In a similar situation the model shows a decrease of 17%. However, for PEEP higher than 5 cmH_2O extremely short expiratory times were utilized which might have contributed to overly high lung volume.

Finally, the reaction of the circulatory system to the cardiac output reduction might have been seriously distorted in the model. The role of the baroreceptor regulation in the circulatory system in maintaining homeostasis was completely omitted as, according to [1], PEEP causes inhibition of cardiovascular regulatory centers. However, a partial recovering of cardiac output within 60 minutes was observed after initial decrease [39] due to increased heart rate. Since the heart rate was kept constant in the presented model, such a partial cardiac output recovery was impossible here.

Chapter 6

Conclusions

A functional model of the cardiopulmonary circulation has been assembled by integrating a circulatory model with a model of a mechanical ventilator. The circulatory model design was the primary objective of this thesis; the model of a mechanical ventilator and respiratory system was provided by Jan Rusz. The circulatory model incorporated two major features: pleural pressure influencing transmural pressure of blood vessels within thorax and the pulmonary capillary compartment, which is affected by alveolar pressure and lung volume. Whereas the concept of extramural pressures in thorax could have been adopted from published articles, a function that connects lung volume and pulmonary capillary resistance had to be estimated from physiological data as no such suitable function was available.

Parameters of the circulatory model were adjusted so that its basic variables (cardiac output, arterial pressures, etc.) adhere to typical physiological values during a spontaneous breathing test. A simulation of artificial ventilation confirmed the expected trend: cardiac output and systemic arterial pressure were decreasing with rising end-expiratory alveolar pressure and pleural pressure. For zero end-expiratory pressure the model predicted 8.4% decrease in cardiac output. Compared to about 10% decrease reported in literature, I find this result satisfactory considering that the cardiopulmonary interaction was simplified to two effects and that the circulatory system was discretized into a few compartments. On the other hand, the experiments with elevated end-expiratory pressure provided results significantly different from desired values—the cardiac output decrease in the model was more than two times larger than reported in literature. Besides the missing baroreceptor regulation this may be a result of either exaggerated lung volume produced by the linear ventilator or too sensitive reaction of the pulmonary resistance to lung volume increase. However, as the circulatory model cannot be properly tested without the model of a ventilator, the possible causes cannot be separated. In this sense the results are inconclusive.

6.1 Future Work Recommendations

For further development of the artificial ventilation simulator, the following recommendations on future work are suggested:

- Possibly the greatest simplification of the model presented in this thesis is a constant resistance of systemic blood vessels, mainly of the large veins. In the model, all obstacles to blood flow in thoracic veins are concentrated into elevated pressure, as in [12] and [25]. Some experiments indicate that PEEP reduces venous return by increasing venous resistance rather than lowering driving pressure gradient [4], [5] although there are contradictory conclusions on the rate of large vein collapse. Therefore further research of pressure-varying venous resistance is recommended for model enhancement.

- The role of pressure in abdomen during spontaneous breathing and positive-pressure ventilation might be considered as its change is an integral part of the thoracic pump. The systemic section division in splanchnic and extrasplanchnic branch provides a basis for the abdominal pressure addition.

- The reaction of the heart to artificial ventilation might be examined and modeled. Although contractility of the left ventricle is probably not affected by positive intrathoracic pressure, interventricular septum[1] may shift to the left due to increased pulmonary circulatory resistance causing decrease in left-ventricular compliance [1].

- The heart rate has been kept constant so far, and the role of the baroreceptor reflex in the circulatory system has been ignored. The absence of autoregulatory mechanisms such as sympathetic activation might have contributed to excessive fall in cardiac output; thus, integration of the baroreceptor regulation might be considered. There is no regulation presented in the model of De Lazzari et al. [12], but the baroreceptor reflex was modeled by Ursino [24].

- Cerebral flow was excluded from the circulatory model. However, PEEP increases intracranial pressure [14]; hence, a more complex simulator should pay attention to blood flow to the brain, which takes about 14% of the overall blood flow (Table 2.2.

[1]The wall separating heart ventricles.

- Greater integration of individual model components is vital for further model improvement. Spontaneous breathing and mechanical ventilation should utilize a common respiratory system model; therefore, the comparison of both types of breathing may be more precise, and the effect of varying pulmonary compliance on cardiac output may be studied. For example, PEEP effect on cardiac output is different in healthy lungs and in patients with ARDS as diseased lungs have reduced pulmonary compliance, which limits the rise in pleural pressure [1]. Ventilation-induced lung injuries—barotrauma, volutrauma, or structural damage to the pulmonary vascular wall [16]—might be simulated.

- The linear ventilator used for simulations works outstandingly with zero-end expiratory pressure option. However, as it does not provide easy selection of any PEEP mode, the ventilator settings utilized for the experiments might have been dissimilar to the settings typically used. Enhancing functions of the ventilator may contribute to more accurate simulation of PEEP ventilation and its cardiovascular impact.

- Regional differences and contribution of gravity were omitted in the presented model, which assumes a ventilated human in the supine position. But positive-pressure inflation enhances these differences [16] along vertical axis of the recumbent human, so regional division of lungs should be considered. More importantly, more detailed division of lungs, both from the respiratory and from the circulatory side, would allow simulating various pathological conditions which influence the ventilation/perfusion ratio in various lung regions.

- Finally, gas exchange is a great part of the cardiopulmonary interaction topic. Artificial ventilation does not change arterial oxygenation significantly in patients with healthy lungs [1], but as was described in section 2.4, PEEP recruits collapsed lung units and improves blood oxygenation during lung diseases like ARDS.

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Appendix A

Pressure Unit Conversion

There are several units used for expressing pressure values. The pascal (Pa) is the standard SI unit; however, in physiology and medicine, the millimeter of mercury (mmHg)—also called the torr (Torr)—seems to be the most common unit. Sometimes, for example in [6], the centimeter of water (cmH_2O) is used, too. In Table A.1 below, the mutual conversion between the units is provided.

Table A.1. Approximate unit conversion for the millimeter of mercury (conventional), pascal, centimeter of water (conventional) and the standard atmosphere. Source: [41].

mmHg	Pa	cmH_2O	atm
1	133.32	1.36	$1.32\cdot 10^{-3}$
$7.50\cdot 10^{-3}$	1	0.01	$9.87\cdot 10^{-6}$
$7.36\cdot 10^{-1}$	98.07	1	$9.68\cdot 10^{-4}$
760	$101.33\cdot 10^{3}$	1033.23	1

Appendix B

Equations of Model 1

The equations given below completely describe model 1. The meaning of the variables and parameters is explained in sections 3.2 and 3.3. Parameter values are provided in Appendix D.

B.1 Blood Vessel Sections

B.1.1 Pulmonary section

$$V_p = V_{part} + V_{pp} + V_{pv}$$

Pulmonary arterial compartment

$$\frac{dP_{tm,part}}{dt} = \frac{1}{C_{part}} \cdot (F_{rart} - F_{part}) \qquad V_{part} = C_{part} P_{tm,part} + V_{u,part}$$

$$\frac{dF_{part}}{dt} = \frac{1}{L_{part}} \cdot (P_{tm,part} - P_{tm,pp} - R_{part} F_{part})$$

Pulmonary peripheral compartment

$$\frac{dP_{tm,pp}}{dt} = \frac{1}{C_{pp}} \cdot (F_{part} - F_{pp}) \qquad V_{pp} = C_{pp} P_{tm,pp} + V_{u,pp}$$

$$F_{pp} = \frac{P_{tm,pp} - P_{tm,pv}}{R_{pp}}$$

Pulmonary venous compartment

$$\frac{dP_{tm,pv}}{dt} = \frac{1}{C_{pv}} \cdot (F_{pp} - F_{pv}) \qquad V_{pv} = C_{pv}P_{tm,pv} + V_{u,pv}$$

$$F_{pv} = \frac{P_{tm,pv} - P_{tm,la}}{R_{pv}}$$

B.1.2 Systemic Section

$$F_s = F_{sv} + F_{ev} + F_{mv}$$

Systemic arterial compartment

$$\frac{dP_{tm,sart}}{dt} = \frac{1}{C_{sart}} \cdot (F_{lv} - F_{sart}) \qquad P_{sart} = P_{tm,sart}$$

$$V_{sart} = C_{sart}P_{sart} + V_{u,sart} \qquad \frac{dF_{sart}}{dt} = \frac{1}{L_{sart}} \cdot (P_{sart} - P_{sp} - R_{sart}F_{sart})$$

Splanchnic peripheral compartment

$$\frac{dP_{tm,sp}}{dt} = \frac{1}{C_{sp} + C_{ep} + C_{mp}} \cdot (F_{sart} - F_{sp} - F_{ep} - F_{mp}) \qquad P_{sp} = P_{tm,sp}$$

$$V_{sp} = C_{sp}P_{sp} + V_{u,stv} \qquad F_{sp} = \frac{P_{sp} - P_{sv}}{R_{sp}}$$

Extrasplanchnic peripheral compartment

$$P_{ep} = P_{sp} \qquad P_{ep} = P_{tm,ep}$$

$$V_{ep} = C_{ep}P_{sp} + V_{u,ep} \qquad F_{ep} = \frac{P_{sp} - P_{ev}}{R_{ep}}$$

Active muscle peripheral compartment

$$P_{mp} = P_{sp} \qquad P_{mp} = P_{tm,mp}$$

$$V_{mp} = C_{mp}P_{sp} + V_{u,mp} \qquad F_{mp} = \frac{P_{sp} - P_{mv}}{R_{mp}}$$

Active muscle venous compartment

$$\frac{dP_{tm,mv}}{dt} = \frac{1}{C_{mv}} \cdot (F_{mp} - F_{mv}) \qquad P_{mv} = P_{tm,mv}$$

$$V_{pv} = C_{mv}P_{mv} + V_{u,mv} \qquad F_{mv} = \frac{P_{mv} - P_{stv}}{R_{mv}}$$

Extrasplanchnic venous compartment

$$\frac{dP_{tm,ev}}{dt} = \frac{1}{C_{ev}} \cdot (F_{ep} - F_{ev}) \qquad P_{ev} = P_{tm,ev}$$

$$V_{ev} = C_{ev}P_{ev} + V_{u,ev} \qquad F_{ev} = \frac{P_{ev} - P_{stv}}{R_{ev}}$$

Splanchnic venous compartment

$$V_{sv} = V_{rest} - V_{sart} - V_{mp} - V_{mv} - V_{ep} - V_{ev} - V_{sp}$$

$$P_{tm,sv} = \frac{1}{C_{sv}} \cdot (V_{sv} - V_{u,sv}) \qquad V_{rest} = V_t - V_l - V_r - V_p - V_{stv}$$

$$P_{sv} = P_{tm,sv} \qquad F_{sv} = \frac{P_{sv} - P_{stv}}{R_{sv}}$$

B.1.3 Systemic Thoracic Veins Section

Systemic thoracic veins compartment

$$\frac{dP_{tm,stv}}{dt} = \frac{1}{C_{pv}} \cdot (F_s - F_{stv}) \qquad P_{stv} = P_{tm,stv} + P_{pl}$$

$$V_{stv} = C_{stv}P_{tm,stv} + V_{u,stv} \qquad F_{stv} = \frac{P_{tm,stv} - P_{tm,ra}}{R_{stv}}$$

B.2 Heart Sections

B.2.1 Ventricle Activation

$$\varphi(t) = \begin{cases} sin^2\left[\frac{\pi \cdot T}{T_{sys}} \cdot u(t)\right] & \text{for } 0 \le u(t) \le T_{sys}/T \\ 0 & \text{for } T_{sys}/T \le u(t) \le 1 \end{cases}$$

$$u(t) = \text{frac}\left[\int \frac{1}{T}\,\mathrm{d}t\right] \quad \text{where} \quad \text{frac}\,(x) \equiv x - \lfloor x \rfloor \quad \text{for } x \ge 0$$

$$u(0) = 0$$

B.2.2 Right Heart Section

$$V_r = V_{ra} + V_{rv}$$

Right atrial compartment

$$\frac{dP_{tm,ra}}{dt} = \frac{1}{C_{ra}} \cdot (F_{stv} - F_{ra}) \qquad V_{ra} = C_{ra} P_{tm,ra} + V_{u,ra}$$

$$F_{ra} = \frac{P_{tm,ra} - P_{tm,rv}}{R_{ra}} \quad \text{if } P_{tm,ra} > P_{tm,rv}, \text{ otherwise } F_{ra} = 0$$

Right ventricular compartment

$$P_{max,rv} = \varphi(t) \cdot E_{max,rv} \cdot (V_{rv} - V_{u,rv}) + [1 - \varphi(t)] \cdot P_{0,rv} \cdot (e^{k_{E,rv} \cdot V_{rv}} - 1)$$

$$\frac{dV_{rv}}{dt} = F_{ra} - F_{rv} \qquad R_{rv} = k_{R,rv} \cdot P_{max,rv}$$

$$P_{tm,rv} = P_{max,rv} - R_{rv} F_{rv}$$

$$F_{rv} = \frac{P_{max,rv} - P_{tm,part}}{R_{rv}} \quad \text{if } P_{max,rv} > P_{tm,part}, \text{ otherwise } F_{ra} = 0$$

B.2.3 Left Heart Section

$$V_l = V_{la} + V_{lv}$$

Left atrial compartment

$$\frac{dP_{tm,la}}{dt} = \frac{1}{C_{la}} \cdot (F_{pv} - F_{la}) \qquad V_{la} = C_{la} P_{tm,la} + V_{u,la}$$

$$F_{la} = \frac{P_{tm,la} - P_{tm,lv}}{R_{la}} \quad \text{if } P_{tm,la} > P_{tm,lv}, \text{ otherwise } F_{la} = 0$$

Left ventricular compartment

$$P_{max,lv} = \varphi(t) \cdot E_{max,lv} \cdot (V_{lv} - V_{u,lv}) + [1 - \varphi(t)] \cdot P_{0,lv} \cdot (e^{k_{E,lv} \cdot V_{lv}} - 1)$$

$$\frac{dV_{lv}}{dt} = F_{la} - F_{lv} \qquad R_{lv} = k_{R,lv} \cdot P_{max,lv}$$

$$P_{tm,lv} = P_{max,lv} - R_{lv} F_{lv} \qquad P_{pl} = P_{tm,lv} + P_{pl}$$

$$F_{lv} = \frac{(P_{max,lv} + P_{pl}) - P_{sart}}{R_{lv}} \quad \text{if } (P_{max,lv} + P_{pl}) > P_{sart}, \text{ otherwise } F_{la} = 0$$

Appendix C

Equations of Model 2

The equations given below describe the pulmonary section and the systemic section of model 2. The systemic thoracic section and both heart sections are not included as their structure is identical with model 1 (see Appendix B). The meaning of the variables and parameters is explained in sections 3.2 and 3.3. Parameter values are provided in Appendix D. In the pulmonary section, the model structure is different for model 2 (stage 1) and model 2 (stage 2). This is reflected in the corresponding equations.

C.1 Blood Vessel Sections

C.1.1 Pulmonary section

$$V_p = V_{part} + V_{pao} + V_{pc} + V_{pv}$$

Pulmonary arterial compartment

$$\frac{dP_{tm,part}}{dt} = \frac{1}{C_{part}} \cdot (F_{rart} - F_{part}) \qquad V_{part} = C_{part} P_{tm,part} + V_{u,part}$$

$$\frac{dF_{part}}{dt} = \frac{1}{L_{part}} \cdot (P_{tm,part} - P_{tm,pp} - R_{part} F_{part})$$

Pulmonary arteriolar compartment

Stage 1

$$\frac{dP_{tm,pao}}{dt} = \frac{1}{C_{pao}} \cdot (F_{part} - F_{pao}) \qquad V_{pao} = C_{pao}P_{tm,pao} + V_{u,pao}$$

$$F_{pao} = \frac{P_{tm,pao} - P_{tm,pc}}{R_{pao}}$$

Stage 2

$$\frac{dP_{tm,pao}}{dt} = \frac{1}{C_{pao}} \cdot (F_{part} - F_{pao,pv} - F_{pao,pc}) \qquad V_{pao} = C_{pao}P_{tm,pao} + V_{u,pao}$$

$$F_{pao,pv} = \frac{(P_{tm,pao} + P_{pl}) - P_{pv}}{R_{ps}} \qquad F_{pao,pc} = \frac{(P_{tm,pao} + P_{pl}) - P_{pc}}{R_{ps}}$$

Pulmonary capillary compartment

Stage 1

$$\frac{dP_{tm,pc}}{dt} = \frac{1}{C_{pc}} \cdot (F_{pao} - F_{pc}) \qquad V_{pc} = C_{pc}P_{tm,pc} + V_{u,pc}$$

$$F_{pc} = \frac{P_{tm,pc} - P_{tm,pv}}{R_{pc}}$$

Stage 2

$$\frac{dP_{tm,pc}}{dt} = \frac{1}{C_{pc}} \cdot (F_{pao,pc} - F_{pc}) \qquad V_{pc} = C_{pc}P_{tm,pc} + V_{u,pc}$$

$$F_{pc} = \frac{P_{pc} - P_{pv}}{R_{pc}(V_{lung})} \qquad P_{pc} = P_{tm,pc} + P_{alv}$$

$$R_{pc}(V_{lung}) = 2.89922 \cdot 10^{-7} V_{lung}^2 - 1.35128 \cdot 10^{-3} V_{lung} + 1.58430$$

Pulmonary venous compartment

Stage 1

$$\frac{dP_{tm,pv}}{dt} = \frac{1}{C_{pv}} \cdot (F_{pc} - F_{pv}) \qquad V_{pv} = C_{pv}P_{tm,pv} + V_{u,pv}$$

$$F_{pv} = \frac{P_{tm,pv} - P_{tm,la}}{R_{pv}}$$

Stage 2

$$\frac{dP_{tm,pv}}{dt} = \frac{1}{C_{pv}} \cdot (F_{pc} + F_{pao,pv} - F_{pv}) \qquad V_{pv} = C_{pv}P_{tm,pv} + V_{u,pv}$$

$$F_{pv} = \frac{P_{tm,pv} - P_{tm,la}}{R_{pv}} \qquad P_{pv} = P_{tm,pv} + P_{pl}$$

C.1.2 Systemic Section

$$F_s = F_{sv} + F_{ev}$$

Systemic arterial compartment

$$\frac{dP_{tm,sart}}{dt} = \frac{1}{C_{sart}} \cdot (F_{lv} - F_{sart}) \qquad P_{sart} = P_{tm,sart}$$

$$V_{sart} = C_{sart}P_{sart} + V_{u,sart} \qquad \frac{dF_{sart}}{dt} = \frac{1}{L_{sart}} \cdot (P_{sart} - P_{sp} - R_{sart}F_{sart})$$

Splanchnic peripheral compartment

$$\frac{dP_{tm,sp}}{dt} = \frac{1}{C_{sp} + C_{ep}} \cdot (F_{sart} - F_{sp} - F_{ep}) \qquad P_{sp} = P_{tm,sp}$$

$$V_{sp} = C_{sp}P_{sp} + V_{u,stv} \qquad F_{sp} = \frac{P_{sp} - P_{sv}}{R_{sp}}$$

Extrasplanchnic peripheral compartment

$$P_{ep} = P_{sp} \qquad P_{ep} = P_{tm,ep}$$

$$V_{ep} = C_{ep}P_{sp} + V_{u,ep} \qquad F_{ep} = \frac{P_{sp} - P_{ev}}{R_{ep}}$$

Extrasplanchnic venous compartment

$$\frac{dP_{tm,ev}}{dt} = \frac{1}{C_{ev}} \cdot (F_{ep} - F_{ev}) \qquad P_{ev} = P_{tm,ev}$$

$$V_{ev} = C_{ev}P_{ev} + V_{u,ev} \qquad F_{ev} = \frac{P_{ev} - P_{stv}}{R_{ev}}$$

Splanchnic venous compartment

$$V_{sv} = V_{rest} - V_{sart} - V_{ep} - V_{ev} - V_{sp}$$

$$P_{tm,sv} = \frac{1}{C_{sv}} \cdot (V_{sv} - V_{u,sv})$$

$$P_{sv} = P_{tm,sv}$$

$$V_{rest} = V_t - V_l - V_r - V_p - V_{stv}$$

$$F_{sv} = \frac{P_{sv} - P_{stv}}{R_{sv}}$$

C.1.3 Systemic Thoracic Veins Section

This section is identical to model 1 (see Appendix B).

C.2 Heart Sections

These section are identical to model 1 (see Appendix B).

Appendix D

Values of Model Parameters

In Tables D.1, D.2, and D.3, the parameter values used in model 1 and model 2 are provided. Only parameters that do have a constant value at least in one of the models are listed. In model 2, some parameters are different for stage 1 and stage 2 (please see Chapter 4 for details). In such a case both values are provided. Most of the values for model 1 were taken from [24] and [25]. The values were adopted from older papers and published experiments on humans and dogs, and rescaled to 70-kg body weight. Some parameters were changed in model 2 for better performance.

Table D.1. Parameters in pulmonary arterial (*part*), peripheral (*pp*), arteriolar (*pao*), capillary (*pc*) and venous (*pv*) compartments within the pulmonary section for model 1 and model 2 (stage 1/stage 2). The arteriolar compartment may include the pulmonary shunt (*ps*). Listed are values of unstressed volumes V_u (ml), hydraulic resistances R (mmHg·s·ml^{-1}), compliances C (ml·mmHg^{-1}), and an inertance L (mmHg·s^2·ml^{-1}).

	Parameter	Model 1	Model 2
Pulmonary section	$V_{u,part}$	0	0
	R_{part}	0.023	0.04
	C_{part}	0.76	0.76
	L_{part}	$0.18 \cdot 10^{-3}$	$0.18 \cdot 10^{-3}$
	$V_{u,pp}$	123	–
	R_{pp}	0.0894	–
	C_{pp}	5.80	–
	$V_{u,pao}$	–	123
	R_{pao}	–	0.045
	C_{pao}	–	4.0
	R_{ps}	–	–/6.43
	$V_{u,pc}$	–	30/46
	R_{pc}	–	0.025/$R_{pc}(V_{lung})$
	C_{pc}	–	4.0
	$V_{u,pv}$	120	0
	R_{pv}	0.0056	0.015
	C_{pv}	25.37	25.37

Table D.2. Parameters in systemic circulation of model 1 and model 2 (stage 1/stage 2). The systemic section contains systemic arterial (*sart*), splanchnic peripheral (*sp*), splanchnic venous (*sv*), extrasplanchnic peripheral (*ep*), and extrasplanchnic venous (*ev*) compartments. In model 1, muscle peripheral (*mp*) and muscle venous (*mv*) compartments are also included. The systemic thoracic veins section has only a single compartment (*stv*). Listed are values of unstressed volumes V_u (ml), hydraulic resistances R (mmHg·s·ml^{-1}), compliances C (ml·mmHg^{-1}), and an inertance L (mmHg·s^2·ml^{-1}).

	Parameter	Model 1	Model 2
Systemic section	$V_{u,sart}$ (ml)	0	0
	R_{sart}	0.06	0.055
	C_{sart}	0.28	0.28
	L_{sart}	$0.22 \cdot 10^{-3}$	$0.22 \cdot 10^{-3}$
	$V_{u,sp}$	274.4	274.4
	R_{sp}	3.307	3.307
	C_{sp}	2.05	2.05
	$V_{u,sv}$	1121	1144/1137
	R_{sv}	0.038	0.132
	C_{sv}	43.11	43.11
	$V_{u,ep}$	274.1	336.6
	R_{ep}	1.725	1.407
	C_{ep}	1.36	1.67
	$V_{u,ev}$	1120	1402/1393
	R_{ev}	0.0197	0.056
	C_{ev}	28.4	35.0
	$V_{u,mp}$	62.5	–
	R_{mp}	7.423	–
	C_{mp}	0.31	–
	$V_{u,mv}$	255	–
	R_{mv}	0.0848	–
	C_{mv}	6.6	–
Systemic thoracic veins sec.	$V_{u,stv}$	0	0
	R_{stv}	0.0054	0.014
	C_{stv}	33	33

Table D.3. Parameters the ventricle activation function, heart sections—left atrium (*la*), left ventricle (*lv*), right atrium (*ra*), right ventricle (*ra*)—and total blood circulation volume. See section 3.3 for explanation.

	Parameter	Model 1	Model 2	Units
Ventricle activation	T	0.833	0.833	s
	T_{sys}	0.41	0.41	s
Left heart section	$V_{u,la}$	25	25	ml
	R_{la}	$2.5 \cdot 10^{-3}$	$2.5 \cdot 10^{-3}$	mmHg·s·ml^{-1}
	C_{la}	19.23	19.23	ml·mmHg^{-1}
	$V_{u,lv}$	16.77	16.77	ml
	$E_{max,lv}$	2.95	2.95	mmHg·ml^{-1}
	$P_{0,lv}$	1.5	1.57	mmHg
	$k_{E,lv}$	0.014	0.014	ml^{-1}
	$k_{R,lv}$	$3.75 \cdot 10^{-4}$	$3.75 \cdot 10^{-4}$	s·ml^{-1}
Right heart section	$V_{u,ra}$	25	25	ml
	R_{ra}	$2.5 \cdot 10^{-3}$	$2.5 \cdot 10^{-3}$	mmHg·s·ml^{-1}
	C_{ra}	31.25	31.25	ml·mmHg^{-1}
	$V_{u,rv}$	40.8	40.8	ml
	$E_{max,rv}$	1.75	1.75	mmHg·ml^{-1}
	$P_{0,rv}$	1.5	1.57	mmHg
	$k_{E,rv}$	0.011	0.011	ml^{-1}
	$k_{R,rv}$	$1.4 \cdot 10^{-3}$	$1.4 \cdot 10^{-3}$	s·ml^{-1}
Total blood volume	V_t	5300	5300	ml

Appendix E

Estimation of the Capillary Resistance Function

```
% Based on entered data in tlc and pvr, this m-file estimates the pulmonary
% capillary resistance Rpc as a function of lung volume Vlung

% Coeffitients of a second-degree polynomial:
%       PVR...pulmonary vascular resistance
%       Rpc...pulmonary capillary resistance

close all;
clear all;
clc;

TLC = 5800; %total lung capacity

tlc = [0.4 0.45 0.5 0.53 0.6 0.7 0.8]; %fraction of total lung capacity
pvr = [0.46 0.39 0.54 0.65 1.62 3.24 5.03]; %relative pulm.vasc.resistance

tlc_abs = tlc*TLC;  %absolute values of lung volume
pvr_abs = (0.124/0.3850)*pvr; %absolute values of pulm.vasc.resistance

PVR = polyfit(tlc_abs,pvr_abs,2);
%finds coefficients of a second-degree polynomial
```

```
Rpc = PVR;
Rpc(3) = Rpc(3) - 0.100;
%constant resistance of the other pulmonary vessels subtracted

x = 0:10:TLC;
y = polyval(PVR,x);

% figure;
% plot(tlc_abs,pvr_abs,'rx');
% hold on;
% plot(x,y,'b-');
%
% figure;
% plot(x,y-0.100,'r');

figure;
plot(x,y-0.100,'r');
axis([2300 TLC 0 3.5]);
set(gca,'XTick',2300:500:TLC)
xlabel('V_{lung} (ml)');
ylabel('R_{pc} (mmHg.s.ml^{-1})');
grid on;
```

Appendix F

Model 2 Final Structure

On the next page, the final structure of model 2 (stage 2) is provided in a form of an electrical circuit diagram. See Appendix C for the corresponding equations and Appendix D for the parameter values and section names.

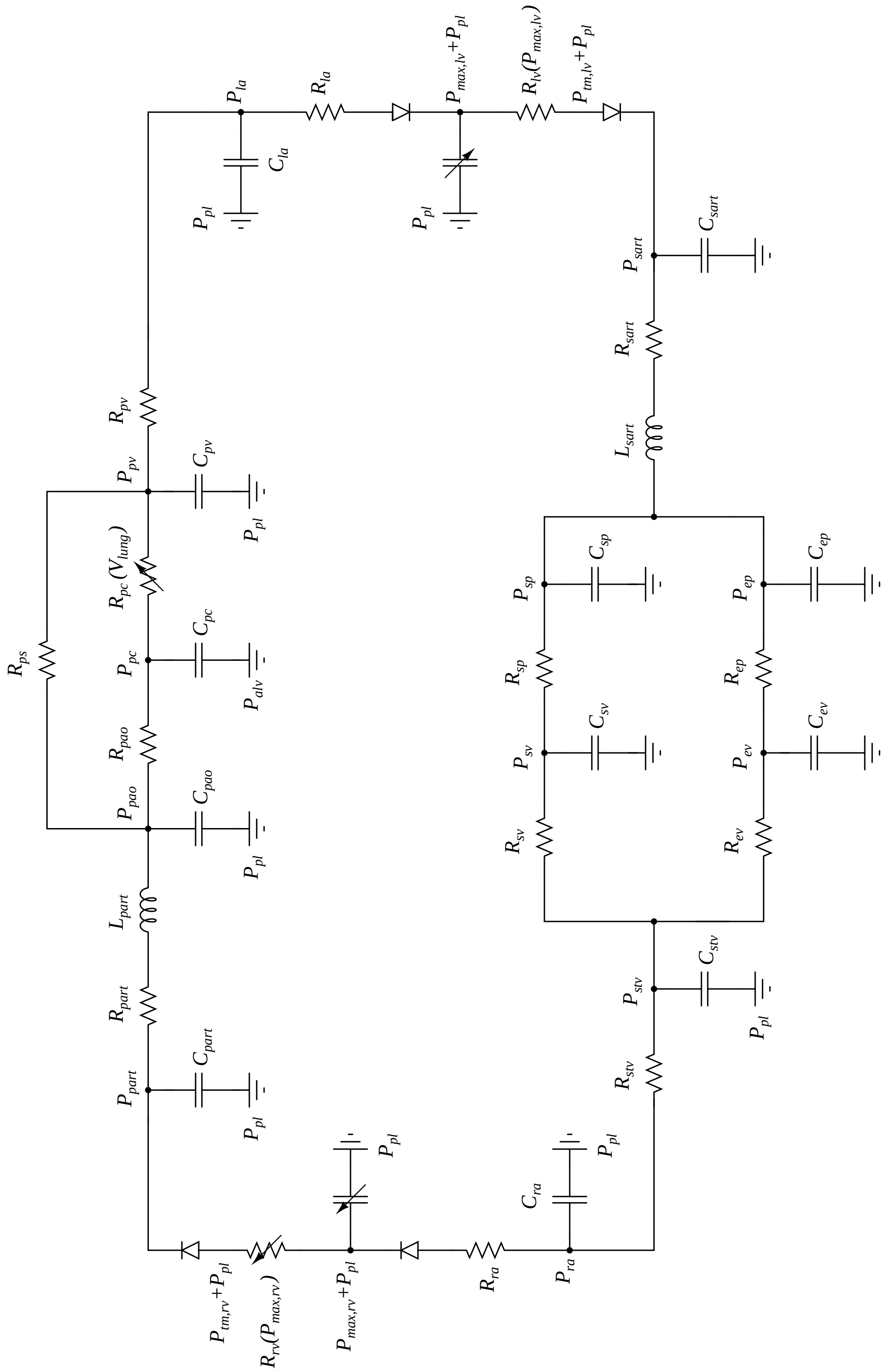

Fig. F.1. The final structure of model 2 (stage 2). An electrical analogy was used for the hydraulic system modelling.