MASTER

Modelling respiratory induced variations in intrathoracic blood flows

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Modelling respiratory induced variations in intrathoracic blood flows

by Emil Verheijen

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Preface

After graduating at the Avans Hogeschool in 's-Hertogenbosch, I decided to continue my study by following the master course Electrical Engineering at the Eindhoven University of Technology. This thesis is a conclusion of the work performed during my graduation project at this university, in close cooperation with the Catharina Hospital in Eindhoven. I would like to thank the people who gave me support and assistance. Without their help, I could not finish the project successfully.

At first, sincere gratitude goes to my supervisor: Prof.dr. Erik Korsten, who introduced me to this interesting topic. His ideas and great enthusiasm made me enthusiastic in the, for an electrical engineer, at first glance strange medical world. Although in the beginning it was hard to understand the medical content, Erik always helped me out. Moreover, he gave me the opportunity to really see the other side of the world. Our trip to Australia was really great and I will never forget!

Furthermore, I would like to thank the other members of the signal processing group. Especially Prof.dr.ir. Bergmans, Dr.ir. Blom, and Ir. Riani who all helped me with the technical aspects during the project, and provided me with critical notes on my thesis. Of course I may also not forget Harry Kuipers for the nice off-topic discussions and giving me the opportunity to organize the Medicast mini-symposium. Also, I want to thank my colleagues at PT 3.31 for their great cooperation, but most of all for the nice working atmosphere.

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Finally, I wish to express my thanks to my family and friends who have supported me during my time at the university. Especially my parents for giving me the chance to continue my study at the university.

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Emil Verheijen
Abstract

Fluid loading is the first-line therapy to improve a patient's hemodynamics by administering additional fluid. Because not every patient responds positively to fluid loading, accurate prediction of a patient's response to fluid loading may be valuable in assisting the clinician with diagnosis and therapy selection. During the last decades, several studies have argued that the variations in blood pressures and flows during mechanical ventilation could serve as a predictor of a patient's response to fluid loading, because these variations might reveal the heart's sensitivity to changes in ventricular preload. However, because of conflicting results, still no consensus has been found on what is the best prediction method.

In this report a method is proposed which may eventually be helpful in predicting a patient's response to fluid loading, based on the variations in intrathoracic blood flows. This method involves the development of a model of the cardiovascular system that contains the respiratory induced influences during mechanical ventilation. When this model is tuned to a patient, it can be used for both getting a better understanding of the variations during mechanical ventilation and predicting a patient's response to fluid loading. The latter can be achieved by performing fluid loading in the model and observing the model's response, assuming that this resembles the patient's response.

First, a coupled model of the cardiovascular and respiratory system is developed, based on existing models found in literature and on physiological knowledge about cardiopulmonary interactions. Here, the main focus is on minimizing the number of unknown parameters while still describing the essential dynamics. Minimizing the number of unknown parameters is important because these parameters have to be estimated based on limited patient data. Next, an experimental set-up is developed that can record intrathoracic blood flows with the use of available equipment. This enables the recording of the patient data for model validation and eventually for providing the model with input signals. Finally, a parameter estimation routine is developed that estimates the patient specific parameters based on recorded patient data.

Simulation results are compared with results found in literature and patient data, and suggest that the model is capable of modelling the respiratory induced influences during mechanical ventilation reliably. Trends in simulated ventricular preload and afterload patterns as well as trends in intrathoracic blood flows during mechanical ventilation are consistent with trends found in literature. Also for varying conditions (i.e. varying ventilator settings and total blood volume), trends in simulated intrathoracic blood flows during mechanical ventilation resemble the trends found in literature and patient recordings. Moreover, the simulations showed that the variations in pulmonary artery flow might be more valuable in predicting a patient's response to fluid loading than currently used measurements. However, no literature confirmed these findings.

Although the developed model is promising in describing the hemodynamical trends during mechanical ventilation, the model validation could not be finished because of two reasons: available literature was sparse and several factors limited patient data acquisition. However, the first preliminary results are promising and warrant further research.
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Chapter 1

Introduction

1.1 Background

Shock is one of the main causes of death in western countries. Shock may be defined as a medical condition where the tissue perfusion is insufficient to meet the required supply of oxygen. Insufficient oxygen supplied to the tissues and organs results in tissue damage and organ failure and can finally lead to death. According to Shoemaker et al. [1999], half of the annual 2.1 million deaths in the United States are due to shock conditions.

The therapeutic goals for counteracting shock are controversial. Still no consensus exists whether the therapeutic goals should be directed towards physiological endpoints of increasing tissue perfusion or towards clinical endpoints such as increasing blood pressure or cardiac output\(^1\) [Astiz and Rackow, 1998]. However, most of the performed studies have been directed towards the clinical endpoints: because blood is the carrier of oxygen within the body, oxygen delivery is directly related to cardiac output. Increasing cardiac output, and thus increasing oxygen delivery, to supranormal levels is therefore a globally accepted therapy towards counteracting shock conditions and hence decreasing mortality [Tuchschmidt et al., 1992].

Increasing cardiac output can be achieved by two types of therapy. The first type is fluid loading. Fluid loading is increasing a patient's total blood volume by administering additional fluid. This fluid consists of blood or red blood cell substitutes that have the same oxygen carrying properties as blood. The additional fluid increases the blood volume that the heart contains before contraction. Because of the positive relationship between cardiac output and the amount of blood that the heart contains before contraction, the expected response to fluid loading is an elevation of cardiac output. The second type of therapy involves the use of medication. This medication increases the efficiency of the heart, resulting in a more powerful pumping function and hence an elevated cardiac output. Medication is, however, only useful when the patient is adequately filled [Beale et al., 2004]. In patients exhibiting a too low blood volume, medication may even have an adverse effect. Therefore, fluid loading is the first-line therapy to increase cardiac output. Still fluid loading is not without risks. Administering of too much fluid may lead to dangerous and harmful situations like volume overload and pulmonary oedema (fluid accumulation in the lungs which can lead to impaired gas exchange).

Unfortunately, determining the filling status of the patient is not trivial. Several methods have been proposed to determine the patient's total blood volume, however the optimal total blood volume differs per patient, so no value can be established that is optimal for all patients. Instead, research is more and more focused on answering the question if we can predict a patient's response to fluid loading. If we can predict how the patient will respond to additional administered fluid, we can determine what the best type of therapy to counteract shock would be for the patient: administering fluid if the patient

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\(^1\)Cardiac output is defined as the blood volume the heart pumps each minute.
Chapter 1. Introduction

will respond positively to fluid loading (i.e. cardiac output will increase with a predefined amount) and administering medication otherwise.

To date, several methods have been proposed to predict the response to fluid loading [Bendjelid and Romand, 2003]. These methods consist of measuring patient specific parameters which serve as an indicator of the patient's filling status. The proposed indicators can be subdivided into static indicators and dynamic indicators [Bendjelid and Romand, 2003]. Static indicators are measurements of cardiac filling pressures and cardiac dimensions, such as right-ventricular end-diastolic volume and left-ventricular end-diastolic volume. Dynamic indicators are measurements of variations in blood pressure and blood flows induced by mechanical ventilation. Mechanical ventilation is a method to assist or replace patient's spontaneous breathing during situations where the patient cannot breath himself. During mechanical ventilation, large variations in intrathoracic pressures occur. These variations influence intrathoracic structures and hence cause variations in intrathoracic blood flows. The latter variations propagate throughout the body and cause (proportional) variations in all blood pressures and flows. The magnitude of these variations could be an indicator of the patient's response to fluid loading.

Examples of dynamic indicators are the magnitude of variations in arterial systolic pressure, arterial pulse pressure and left-ventricular stroke volume during mechanical ventilation. Although dynamic indicators are restricted to mechanically ventilated patients, the majority of the critically ill patients undergo mechanical ventilation so dynamic indicators can be used for almost all patients in potential need of fluid loading [Bendjelid and Romand, 2003].

Several authors made a comparative study of static and dynamic indicators [Michard and Teboul, 2002; Reuter et al., 2002b; Preisman et al., 2005]. They concluded that dynamic indicators are superior to static indicators in predicting the response to fluid loading. However, it must be noted that the conditions (e.g. ventilator settings, definition responder versus non-responder) are not exactly the same in all studies. This could lead to misinterpretations because a patient could for example be rated as a responder to fluid loading (i.e. responds positively) in one study while the patient would be a non-responder in another study because of varying definitions of what a responder is. Therefore, research is necessary that gives more insight in the underlying physiological processes, so knowledge can be obtained that eventually can be used to predict a patient's response to fluid loading in all clinical settings.

1.2 Problem definition

Although many studies have been performed on predicting the patient's response to fluid loading, still no consensus has been reached on what is the best prediction method. This thesis focuses on finding an answer to this problem from a point of view that has not been used before: a modelling approach. A model is an abstraction of reality that can be used to gain better understanding of complex phenomena. Using models in clinical practice can give more insight in the underlying physiological processes and may therefore be very valuable.

The goal of this research is the development of a patient specific model which can be used to predict the patient's response to fluid loading. First a model has to be developed which can describe patient's hemodynamics during mechanical ventilation. Based on recorded patient data (i.e. intrathoracic blood flows and airway pressure), the model should next be tuned to the patient so the model describes the hemodynamics for this specific patient. Once the model is tuned to the patient, the model can give us more insight on the patient's filling status and can be used to predict the patient's response to fluid loading. This can be achieved by performing fluid loading in the model and observing the model's response, because the patient's response to fluid loading is assumed to resemble the model's response to fluid loading.

In order to develop and validate the mentioned model, several steps have to be performed. To this end the research has been split up in several parts:
• Develop an experimental set-up for recording and storing intrathoracic blood flows. The intrathoracic blood flows have to be recorded with available equipment. Because this equipment only provides information about the blood velocities, signal processing techniques have to be developed and implemented to construct the blood flow profile.

• Develop a cardiovascular model which includes the respiratory influences induced by mechanical ventilation. The model has to be implemented on a personal computer to be able to perform the model simulations. Next the model has to be validated qualitatively by comparing trends in simulation results with trends in results from literature and patient recordings. Once the model captures the main hemodynamic trends during mechanical ventilation, the influences of mechanical ventilation on the cardiovascular system are assumed to be modelled correctly.

• Develop a parameter estimation algorithm that can estimate the patient specific model parameters based on recorded patient data. The patient data consists of recorded intrathoracic blood flows as well as recorded airway pressure, which is an indirect measure of the intrathoracic pressure. Estimating the model parameters can be done by tuning the model parameters until the modelled blood flows closely resemble the recorded patient blood flows. Once the model parameters have been estimated, the model has to be validated quantitatively. Quantitative validation consists of comparing model simulation results with recorded patient data during changing ventilation settings.

Integration of these parts enables the clinician to tune the model to the patient based on recorded patient data, resulting in a model that describes patient hemodynamics. Next the model can be used to help the clinician with the decision making process of what the patient's hemodynamical status is and what the best therapy would be for this specific patient.

1.3 Report outline

This report will follow the structure corresponding to the mentioned steps. First of all the physiological background of the respiratory induced variations will be discussed in Chapter 2. Before the influences of the respiratory system on the cardiovascular system are explained, an overview of both systems will be provided in order to get a better understanding why the respiratory system influences the cardiovascular system, especially during mechanical ventilation.

In Chapter 3 the development of the experimental set-up for recording and storing the intrathoracic blood flows will be discussed. After a short introduction on flow physics, the development and implementation of techniques to record and store intrathoracic blood flows will be discussed. The chapter will end with the validation of the developed experimental set-up.

Chapter 4 will discuss the development of the model. First individual models of both the cardiovascular and respiratory system will be developed. Next the influences of the respiratory system on the cardiovascular system will be explained, resulting in a coupled model of both systems. Before the model can be validated, it has to be implemented in order to perform the simulations. The model implementation will be dealt with in Chapter 5. The model will be validated qualitatively in Chapter 6. Simulated blood flows during mechanical ventilation will be compared to results from literature and patient recordings. Also for changing conditions (i.e. changing ventilator settings and a changing total blood volume), trends in the simulated signals will be compared with trends found in literature and patient recordings.

In order to fit the model to the patient, the values of the several model parameters have to be estimated. Chapter 7 deals with the parameter estimation algorithm that estimates the unknown parameter values.

Finally, Chapter 8 will summarize the conclusions of the project. This chapter will also provide some recommendations for further research.
Chapter 2

Physiological background

In order to develop a physiologically correct model of the cardiovascular system including the respiratory influences during mechanical ventilation, first the underlying physiology of the cardiovascular and respiratory system have to be understood. However, not all parts of the underlying physiology will be dealt with in detail. Instead, only the relevant parts for the successive modelling chapters will be discussed. For a more detailed overview of the anatomy and physiology of the cardiovascular and respiratory system, the reader is referred to [Guyton and Hall, 2000; Ganong, 1975; Solomon et al., 1990].

This chapter starts with an overview of both physiological systems. Section 2.1 describes the respiratory system and Section 2.2 describes the cardiovascular system. In order to get a better understanding of the respiratory influences on the cardiovascular system during mechanical ventilation, Section 2.3 discusses the causes of the variations in intrathoracic blood flows during mechanical ventilation together with some currently used methods to quantify these variations.

2.1 The respiratory system

The function of the respiratory system is bringing oxygen from the atmosphere into the blood and transporting carbon dioxide from the blood back to the atmosphere. Oxygen is necessary for the organs and tissues to function correctly, carbon dioxide is the waste product of oxidative metabolism and needs to be removed from the body. Based on its function, the respiratory system can be subdivided into two systems: a transport system and a gas exchange system.

The transport system transfers air from the atmosphere to the lungs and vice versa. Figure 2.1 shows a schematic overview of the respiratory system. Air enters the body at the level of the nose and the mouth. Next the air is transported to both lungs via the trachea and the main bronchi. These bronchi successively branch into smaller bronchi. This branching continues until the 23rd generation where the branching ends in small air bubbles, the alveoli. The transport system ends at the 16th generation. From here the gas exchange system begins [Blom, 2004].

From the 17th to the 23rd generation, gas exchange takes place. Oxygen depletes from the air in the alveoli into the circulating blood in the lungs. Carbon dioxide is extracted from the circulating blood into the alveoli. The gas exchange is facilitated by a passive process called diffusion. Because the partial pressure\(^1\) of oxygen in the alveoli exceeds the partial pressure of oxygen in the blood, oxygen diffuses from the alveoli into the blood across a thin permeable membrane. The reverse process holds for carbon dioxide. The partial pressure of carbon dioxide in the blood exceeds the partial pressure in the air so carbon dioxide diffuses into the alveoli.

\(^{1}\text{Partial pressure is defined as the pressure that the gas would have in a certain volume if all other gases were removed.}\)
Chapter 2. Physiological background

2. Main bronchi
   Alveoli

Figure 2.1: Schematic overview of the respiratory system. Air enters the body at the level of the nose and the mouth. Next the air is transported via the trachea to both lungs where gas exchange takes place with the circulating blood.

In order to renew the air in the lungs, an active process called spontaneous respiration takes place. Spontaneous respiration is caused by rhythmic contraction and relaxation of the respiratory muscles surrounding the thorax. During inspiration these muscles contract, causing the thorax to expand. Expansion of the thorax causes the pressure in the alveoli to drop below atmospheric pressure. This pressure drop results in a positive pressure gradient between the pressure in the atmosphere and the lungs and hence an inflow of air into the lungs. During expiration the respiratory muscles relax, causing the thorax to return to its normal volume. As a result, air passively flows out of the lungs back into the atmosphere.

In sedated patients the muscles in the body become paralyzed because of administered medication. As a result, the respiratory muscles do not contract anymore, stopping the process of spontaneous respiration. In order to ensure oxygen supply and removal of carbon dioxide, patients have to be artificially ventilated. During artificial ventilation the work of the respiratory muscles is replaced by an externally driven pressure generated by a ventilator. Inspiration is caused by raising the ventilator pressure above atmospheric pressure. This will result in a positive pressure gradient between ventilator pressure and the pressure in the lungs and in an inflow of air into the lungs. The air volume forced into the lungs during inspiration is called the tidal volume. Expiration is caused by decreasing the ventilator pressure, causing a negative pressure gradient and outflow of air from the lungs back to the ventilator. Although during expiration the ventilator pressure could be decreased to atmospheric pressure, normally it will decrease to a positive pressure referenced to atmospheric pressure. This positive end-expiratory pressure (PEEP) ensures a positive pressure in the alveoli, preventing the possibility of alveolar collapse [Blom, 2004].

2.2 The cardiovascular system

2.2.1 The heart

The heart, located in the thorax between both lungs, is the main muscle of the cardiovascular system and takes care of pumping the blood throughout the circulation. Without this pumping mechanism, oxygen enriched blood from the lungs would not be transported to the periphery and carbon dioxide enriched blood in the periphery would not be transported back to the lungs. Eventually, this might result in irreversible damage to organs and finally to death.

A schematic overview of the heart is shown in Figure 2.2. The heart consists of two separately working
2.2. The cardiovascular system

The cardiovascular system consists of two pumps, the left and the right heart. The right heart pumps carbon dioxide enriched blood from the periphery to the lungs. The left heart pumps oxygen enriched blood from the lungs to the peripheral organs, supplying the organs with oxygen. Each heart side consists of two chambers: an atrium and a ventricle, separated by a one-way valve which ensures unidirectional blood flow from the atrium to the ventricle. Both the atrium and the ventricle are active chambers which contract by applying wall stress, supplying its pumping function. However, most of the pumping work is done by the ventricles. In fact, the atria only function as a primary pump to help move blood into the ventricles. Normally 75 percent of the blood flows into the ventricles even before atrial contraction [Guyton and Hall, 2000]. The atria thus increase ventricle efficiency at most about 25 percent. So malfunctioning atria do not have to be lethal because the pumping work of the heart relies mainly on the pumping function of the ventricles [Guyton and Hall, 2000].

The heart is encapsuled by a rather stiff wall called the pericardium [Glantz and Parmley, 1978]. During contraction, when the walls of the chambers expand, the pericardium acts as an outer constraint causing the chamber walls only to expand inside. In turn, this expansion causes a pressure rise inside the chambers which forces the blood to flow out. Moreover, the pericardium together with the septum (i.e. the flexible wall that separates the left and right heart) gives rise to interaction between both ventricles. This ventricular interaction can affect the pumping function of the heart. For example, right ventricular overload causes the septum to be pushed into the left ventricle because the pericardium acts as a stiff outer constraint. This leftward shift of the septum leads to a decrease in left ventricular efficiency because the left ventricular size is decreased and therefore cannot be maximally filled. The effects of ventricular interaction during mechanical ventilation will be further explained in Section 4.2.

The pumping action of both ventricles is roughly the same and consists of four phases: filling, contraction, ejection and relaxation. This process is usually illustrated in a pressure-volume loop (PV-loop) of a ventricle. Figure 2.3 shows such a PV-loop.

At the end of diastole ($t_1$), which is the relaxing phase of the heart's pumping cycle, the pressure in the atrium exceeds the pressure in the ventricle. This positive pressure gradient results in opening of the inflow valve (i.e. the valve between the atrium and the ventricle) and blood flow from the atrium to the ventricle starts. Now, the ventricle fills up with blood. During this phase of filling, the ventricular volume increases and causes the ventricular pressure to increase slightly as well. At the begin of systole ($t_2$), which is the contraction phase of the heart's pumping cycle, the inflow valve closes and ventricular pressure starts to rise. Once the ventricular pressure exceeds the arterial pressure ($t_3$), the outflow valve (i.e. the valve between the ventricle and the circulation) opens. This causes an
Figure 2.3: Example of a ventricular pressure-volume loop. The four phases that occur every cardiac cycle are denoted together with the action of the valves during the transitions of the cardiac phases.

outflow of blood from the ventricle into the circulation, called the ejection phase. This ejection phase holds on until the ventricular pressure equals the arterial pressure. When the ejection phase ends (t4), the outflow valve closes and the outflow stops. Next, the ventricle isovolumetrically relaxes until the atrial pressure exceeds the ventricular pressure. This phase is called the relaxation phase. When the relaxation phase ends, the cardiac cycle starts again.

2.2.2 The circulation

The circulation can roughly be subdivided into two parts2: the pulmonary circulation and the systemic circulation [Guyton and Hall, 2000]. Both parts transport blood from one side of the heart to the other side via peripheral tissues where oxygen and carbon dioxide will be exchanged. Figure 2.4 shows a schematic overview of the cardiovascular system, and shows where the two parts are located.

Blood enters the pulmonary circulation in the pulmonary artery, connected by the pulmonary valve with the right ventricle. The pulmonary artery transports carbon dioxide enriched blood from the right side of the heart to the lungs. In the lungs, the pulmonary artery successively branches into smaller vessels. These small vessels, the capillaries, interact with the alveoli in the lungs and exchange oxygen and carbon dioxide as explained in Section 2.1. After the gas exchange, the capillaries successively bundle into larger vessels and ultimately end up in the pulmonary veins. The pulmonary veins transport the oxygen enriched blood from the lungs back to the left side of the heart.

After passing the left side of the heart, blood enters the systemic circulation. Just like the pulmonary circulation, the systemic circulation can roughly be subdivided into three parts. First, oxygen enriched blood enters the systemic circulation in the aorta. The aorta successively branches into smaller vessels ultimately ending in the capillaries. In the tissues the reverse process of the gas exchange takes place. Oxygen depletes from the blood in the capillaries into the tissues and carbon dioxide is attracted back from the tissues. After the gas exchange, the vessels successively bundle into larger vessels ultimately ending up in the vena cava. Finally, the vena cava transports the carbon dioxide enriched blood back to the right heart.

Besides the difference in gas exchange between the pulmonary and systemic circulation, another difference is important in this research. Although all parts of the pulmonary circulation are located in the thorax, the systemic circulation is only partially located in the thorax. This has consequences during

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2Actually a third part, the coronary circulation which provides oxygen to the heart, can be denoted. However, the coronary circulation will not be dealt with in this research.
2.3 Respiratory induced variations in intrathoracic blood flows

2.3.1 Physiological background

Although spontaneous respiration also induces intrathoracic pressure changes, intrathoracic pressure changes are different during mechanical ventilation because of two reasons. First of all, during mechanical ventilation the alveolar and intrathoracic pressure increase at inspiration because of a forced inflow of air into the lungs. This in contrast to spontaneous respiration where the alveolar and intrathoracic pressure decrease during inspiration because of the expanding thorax. Secondly, the magnitude of the intrathoracic pressure changes is much larger during mechanical ventilation than during spontaneous respiration. The intrathoracic pressure changes will therefore have a much bigger impact on the cardiovascular system during mechanical ventilation than during spontaneous respiration.

The ventricular stroke volume, the blood volume a ventricle ejects during one cardiac cycle, depends on the ventricular preload. Ventricular preload is defined as the myocardial wall stress at the end of diastole, just before the ventricle starts contracting [Guyton and Hall, 2000]. Because this wall stress is difficult to measure, surrogates such as end-diastolic pressure and end-diastolic volume are usually used in clinical practice. The relation between ventricular preload, measured as end-diastolic pressure, and ventricular stroke volume is known as the Frank-Starling relation [Guyton and Hall, 2000]. This relation is depicted in Figure 2.5. As can be seen, variations in stroke volume caused by variations in intrathoracic blood flows, reflect variations in ventricular preloads.
Chapter 2. Physiological background

Figure 2.5: Frank-Starling relation of a ventricle. The Frank-Starling relation denotes the relation between ventricular preload and ventricular stroke volume. As can be seen, different phases in the curve can be distinguished corresponding to the relative change in ventricular stroke volume due to a small change in ventricular preload. On the 'steep' portion of the curve small changes in preload result in large changes in stroke volume whereas on the 'plateau' portion small changes in preload result in small changes in stroke volume.

According to an extensive review of Michard [2005] about variations in arterial pressure during mechanical ventilation, four key mechanisms contribute to the ventricular preload variations:

1. Because of the increasing intrathoracic pressure at inspiration, the pressure on the outside of the heart increases. This results in an increasing transmural pressure across the heart walls and thus in an increasing right atrial pressure. Because of this increased right atrial pressure, the pressure gradient for venous return, which is defined as the right atrial pressure minus the mean venous pressure, increases. This results in a decreased venous return because the blood faces more resistance to flow to the right atrium [Guyton et al., 1957], and finally in a decreased right ventricular preload during inspiration.

2. During inspiration the increase of pressure surrounding the pulmonary capillaries is greater than the increase of pressure surrounding the pulmonary vessels. This results in an increasing resistance to blood flow from the pulmonary arteries into the pulmonary capillaries, and hence in blood accumulation in the pulmonary arteries. As a result, the pulmonary artery pressure rises and the right ventricular afterload increases [Vieillard-Baron et al., 1999]. Afterload is defined as the load against which the muscle exerts its contractile force [Guyton and Hall, 2000]. The increasing afterload thus impedes right ventricular outflow during inspiration.

3. During inspiration, the increase in alveolar pressure increases the tension on the intrathoracic vessel walls. This results in compressing the pulmonary capillaries, initially squeezing the blood present in these capillaries towards the left side of the heart [Vieillard-Baron et al., 2003]. This results in an initial increase of left ventricular preload during inspiration.

4. Left ventricular afterload decreases during inspiration. The elevated intrathoracic pressure increases the tension on the left ventricular walls. This assists left ventricular ejection and thus reduces left ventricular afterload, so left ventricular stroke volume increases at the same ventricular preload [Fessler et al., 1985].

Summarizing, during inspiration the left ventricular outflow initially increases because of an elevated left ventricular preload together with a decreased left ventricular afterload. At the same time the right ventricular preload decreases and right ventricular afterload increases, resulting in a decreased right ventricular outflow. Because of the pulmonary transit time of blood (approximately 2 sec [Jardin et al., 1983]), the decrease in right ventricular outflow will result in a decrease in left ventricular preload after a few heartbeats. This decreased left ventricular preload will finally result in a decreased left
ventricular outflow. During mechanical ventilation cyclic variations in intrathoracic blood flows can thus be observed.

2.3.2 Methods to quantify the variations

In order to quantify the variations in intrathoracic blood flows, several methods have been proposed. Because variations in left ventricular stroke volume will eventually result in variations in arterial blood pressure as well, also two methods have been proposed to quantify the variations in arterial blood pressure. The first method involves evaluating the magnitude of the variation in systolic peaks during one ventilation period, called systolic pressure variation [Perel et al., 1987]. The second method involves evaluating the magnitude of the variation in pulse pressure (i.e. the difference between systolic and preceding diastolic pressure) during one ventilation period, called pulse pressure variation [Michard et al., 1999]. Recently, the variations during mechanical ventilation in vena cava diameter [Feissel et al., 2004] and ventricular pre-ejection period [Bendjeldid et al., 2004] have also been investigated. Our research, however, is focused on the variations in intrathoracic blood flows. Therefore only quantification methods regarding the variations in intrathoracic blood flows will be discussed here.

Peak velocity variation (PVV)

Because aortic blood flow may be assumed directly proportional to left ventricular stroke volume, variations in aortic blood velocity might provide an accurate estimation of the respiratory induced variations in left ventricular stroke volume [Feissel et al., 2001]. The respiratory induced variations in aortic peak velocity ($\Delta V_{\text{peak}}$) are calculated according to:

$$\Delta V_{\text{peak}}(\%) = 100 \cdot \frac{V_{\text{peak,max}} - V_{\text{peak,min}}}{0.5 \cdot (V_{\text{peak,max}} + V_{\text{peak,min}})}$$

where $V_{\text{peak,max}}$ and $V_{\text{peak,min}}$ are the maximum and minimum aortic peak velocity during one ventilation period, respectively. The blood velocities are measured with the use of ultrasound. Chapter 3 will give a more detailed description of how blood velocities are measured with the use of ultrasound.

Velocity time integral variation (VTIV)

Supposing that all the blood cells are moving at the same velocity, which can be assumed at the outflow valves of the ventricles [Savage and Aronson, 2005], the area under the aortic velocity curve represents the stroke distance of the blood (i.e. the distance a column of blood travelled). Slama et al. [2002] used this approach to quantify the respiratory induced variations in aortic stroke distance according to:

$$\Delta VTI_{ao}(\%) = 100 \cdot \frac{VTI_{ao,max} - VTI_{ao,min}}{0.5 \cdot (VTI_{ao,max} + VTI_{ao,min})}$$

where $VTI_{ao,max}$ and $VTI_{ao,min}$ are the maximum and minimum area under the aortic curve during one ventilation period, respectively.

Stroke volume variation (SVV)

Although the peak velocity variation method and the velocity time integral variation method are based on several assumptions in order to approximate the variations in blood flows, the most direct method is measuring the variations in blood flows itself [Reuter et al., 2002a]. Several methods have been proposed to measure left ventricular stroke volume beat-by-beat. The pulse contour method calculates stroke volume based on the arterial pressure wave [Wesseling et al., 1983], the Doppler method calculates stroke volume with use of ultrasound [Roeck et al., 2003; Monnet et al., 2005]. The stroke volume variations (SVV) are quantified according to:

$$\Delta SVV(\%) = 100 \cdot \frac{SVV_{max} - SVV_{min}}{0.5 \cdot (SVV_{max} + SVV_{min})}$$

where $SVV_{max}$ and $SVV_{min}$ are the maximum and minimum stroke volume during one ventilation period, respectively.

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2.3.3 Factors that influence the methods to quantify the variations

As explained before, the magnitude of the variations in intrathoracic blood flows (or velocities) might serve as an indicator of the patient's response to fluid loading. Several authors proposed threshold values to discriminate between responders and non-responders to fluid loading [Feissel et al., 2001; Slama et al., 2002; Reuter et al., 2002a; Michard, 2005]. Although the proposed threshold values show good correlation in their studies, still they cannot easily be transferred into a golden standard for all clinical settings because of several problems.

Inconsistent successive values

Because the systolic peaks in blood flows and pressures have different timings with respect to the beginning of each ventilation period, the values of the indicators can fluctuate highly between successive ventilation periods [Diepen et al., 2005]. Figure 2.6 shows an example of the fluctuations in systolic pressure variation (SPV) between two successive ventilation periods. Every ventilation period the difference between the highest and lowest systolic peak is calculated. As can be seen in the figure, the SPV-value for the first period is much larger than the SPV-value for the second period. This will lead to misinterpretations in the results. When, for example, the threshold value is defined in between both calculated SPV-values, the patient would be rated as a responder during the first ventilation period and as a non-responder during the second ventilation period.

![Figure 2.6: Example of inconsistent successive values when calculating the systolic pressure variation (SPV). The top graph shows the systolic peaks in arterial blood pressure (P_{abp}) and the bottom graph shows the airway pressure (P_{aw}). Because the systolic peaks in both ventilation periods have different timings with respect to the beginning of the ventilation period, successive calculated SPV-values can fluctuate highly.](image)

Inconsistent values between successive ventilation periods occur with all indicators. Diepen et al. [2005] proposed a method to reduce the fluctuations in arterial blood pressure based on a modulation approach, called systolic pressure modulation. This method assumes that the systolic peaks in arterial blood pressure can be seen as samples of a modulation envelope, induced by the changing intrathoracic pressure. Because the samples are probably not exactly located on the maximum and minimum of the envelope every ventilation period, the value of the used indicator can fluctuate between successive ventilation periods. By calculating the envelope (e.g. by curve fitting), the maximum and minimum of the envelope can be used to quantify the variations in arterial blood pressure. Because the envelope does probably not change significantly between successive ventilation periods, the value of the indicator fluctuates less. The modulation approach could probably also be used for the methods that quantify the variations in intrathoracic blood flows, however, this assumption still has to be investigated.
2.3. Respiratory induced variations in intrathoracic blood flows

Influence of changing ventilator settings

The variations in intrathoracic blood flows are caused by changes in intrathoracic pressure due to changes in ventilator pressure. The ventilator pressure is determined by the ventilator settings. Varying ventilator settings thus result in varying ventilator pressure curves and play an important role in how the respiratory system influences the cardiovascular system. Recently, the influences of varying tidal volume on the pulse pressure variation method [Backer et al., 2005], systolic pressure variation method [Jones et al., 2004] and stroke volume variation method [Reuter et al., 2003] have been investigated. All studies concluded that the used methods are sensitive to the magnitude of the applied tidal volume, and that this should be kept in mind when using these methods to predict a patient’s response to fluid loading.

The proposed threshold values may thus give good prediction at the specific ventilator settings used, but need not give a good prediction for all ventilator settings. In clinical settings where different ventilator settings are used, different ventilator pressures curves (shape as well as magnitude) are generated and the influences of the respiratory system on the cardiovascular system are different, probably resulting in different threshold values.

The exact relation between ventilator settings and its influence on intrathoracic blood flows is yet unknown. One part of this research, however, is modelling these influences in order to get a better understanding of the influences. If the influences are better understood, the proposed threshold values may also be explained. Moreover, it might be possible to transfer the proposed threshold values into ventilator dependent values, so the threshold values will be a function of the ventilator settings and can be used in all clinical settings.

Oscillations induced by neural influences

As explained, intrathoracic pressure changes induce changes in venous return. These changes are detected by baroreceptors in the body. A baroreceptor is a pressure-sensitive nerve ending in the wall of a vessel. Baroreceptors detect changes in blood pressure and can send messages to the central nervous system to increase or decrease total peripheral resistance and cardiac output in order to counteract these blood pressure changes. These neural influences also act on the cardiovascular system by inducing small oscillations in blood pressure [Malpas, 2002]. Guyton and Harris [1951] found that these oscillations were in the frequency range of 0.03-0.06 Hz. Because changes in blood pressure result in changing blood flows, these neural influences do also affect the variations in intrathoracic blood flows. When, for example, the aortic pressure rises, the left ventricular outflow faces more resistance to flow into the aorta and as a results decreases.

Although neural influences are usually neglected, they also influence the proposed indicators. The induced oscillations may result in small changes in blood pressures and flows between several ventilation periods. A possible method to cancel out these variations (partially) is using a high-pass filter before processing the blood flow data. Because the frequency range of the oscillations is out of the frequency range of mechanical ventilation (0.1-0.2 Hz), tuning the high-pass filter to the correct frequency will cancel out the oscillations induced by the neural influences without distorting the variations induced by mechanical ventilation.
Chapter 3

Recording intrathoracic blood flows

As described in the introduction, recording intrathoracic blood flows in patients is necessary in order to be able to evaluate the variations during mechanical ventilation, and eventually to provide the developed model with input signals. Since no system exists that can record and store intrathoracic blood flows automatically, a new system has to be developed. Because of considerations about money and time, use have to be made of available equipment. This equipment provides information about blood velocities in the body by making use of ultrasound. Ultrasound waves are sent into the body and are reflected by the moving blood. The reflections are detected and because signal properties of the reflected waves are changed, the reflections provide information about the blood velocities.

This chapter gives an overview of the performed steps to record intrathoracic blood flows (calculated from the velocity information) in patients. First some basic flow physics will be explained in order to get a better understanding of how blood flow profiles look and how the reflected waves have to be interpreted. Next, the interaction between ultrasound and blood will be dealt with. Because the exact interaction is very complex, only some properties will be explained which are important with respect to the blood flow recordings. For a more detailed overview about the interaction between ultrasound and blood, the reader is referred to [McDicken, 1991; Kremkau, 1998]. When the interaction between ultrasound and blood is understood, the two different techniques for measuring blood flow using ultrasound will be explained. This chapter will end with the implementation of how the blood flow profiles are extracted from the ultrasound data, and with the comparison between manually and automatically calculated flow profiles.

3.1 Physics of blood flow

Blood flow throughout the cardiovascular system is very complex. Therefore first the simplest flow type will be treated: steady laminar flow in a rigid tube. Steady flow means that all flow conditions are constant at any point in time. Laminar flow means that all the particles in the fluid move along smooth paths (layers) in time. These layers are adjacent and do not cross. This in contrast to turbulent or disturbed flow where the particles follow chaotic paths that cross each other so no organized flow patterns occur. An indicator which denotes roughly if a flow is laminar or turbulent is defined by the dimensionless Reynolds number [Oates, 2001]:

\[ Re = \frac{2R\rho \bar{v}}{\mu} \]  

(3.1)

where \( R \) is the tube radius, \( \rho \) the fluid density, \( \bar{v} \) the average velocity and \( \mu \) the fluid viscosity. Reynolds numbers below 2000 indicate laminar flow while Reynolds numbers above 2500 indicate turbulent flow. Values in between indicate the transition state where the flow starts to become more and more turbulent. However, measured Reynolds numbers have to be interpreted with care. In carefully constructed circumstances Reynolds numbers of 50000 have been measured while still laminar flow was observed.
Chapter 3. Recording intrathoracic blood flows

Figure 3.1: Entrance effects of flow entering a rigid tube. The flow profile will initially be flat and gradually, with the distance travelled, transform into the parabolic flow profile.

Fortunately, in normal conditions blood flows within the cardiovascular system always appear to have Reynolds numbers below 2000 which implies that all blood flows within the cardiovascular system may be assumed laminar [Evans and McDicken, 2000]. However, exceptions can occur due to several reasons. Turbulence can, for example, occur when the vascular lumen is heavily decreased due to calcification. Also in the initial segment of the aorta or near heart valves, where very large velocities can occur, sometimes some turbulence is observed. However, normally no turbulence occurs in the cardiovascular system so turbulence usually indicates some abnormality.

When a steady blood flow flows through a vessel, frictional forces between the moving blood and the vessel walls occur. These frictional forces make the blood flow more difficult near the walls than in the center of the vessel because layers near the walls face more frictional forces than layers near the center. The fully developed flow profile of steady flow is parabolic. The relation between velocity and radius of a parabolic flow profile can be described as [Evans and McDicken, 2000]:

\[ v(x) = v_{\text{max}} \cdot \left(1 - \frac{x^2}{r^2}\right) \]  

where \( v_{\text{max}} \) is the velocity in the center of the vessel, \( r \) the radius of the vessel and \( x \) the radius of a particular layer from the center of the vessel. Parabolic flow has the nice property that the number of red blood cells moving at each velocity is constant, and thus also the blood volume flowing at each velocity [Oates, 2001]. This, as will be explained in next sections, has consequences for the signal properties of the reflected signals.

Another important aspect are the entrance effects of blood flow entering a vessel. Although steady flow in a long tube can be considered parabolic when the flow profile is fully established, the cardiovascular system does not consist of one long rigid tube. Instead, it is a network of tubes which branch and are mutually separated by heart valves. These branches and valves introduce distortion to the parabolic flow profile. When, for example, the left ventricular pressure exceeds the aortic pressure during contraction, the aortic valve opens and suddenly a blood flow enters the aorta. Here, other effects have to be accounted for because the parabolic flow profile is not fully established yet. Initially a flat flow profile can be observed when the flow enters the tube. In a flat profile all particles are moving at the same velocity. Gradually, with the distance travelled, the flat profile will change into the parabolic flow profile. This is illustrated in Figure 3.1.

Of course blood flow within the cardiovascular system is not steady but pulsatile due to the pulsatile nature of the beating heart. Moreover, the vessel walls are elastic which implies that the vessel diameter depends on the pressure in the vessel. Especially at the arterial side of the cardiovascular system pulsatile flow can be observed. The venous side acts more as a buffer receiving continuous blood flow from the organs, so less pulsatile blood flows occur and steady blood flow may be assumed. The combination of pulsatile flow and elastic vessel walls implies the need for adaptations to the assumed velocity profiles of steady flows. Pulsatile flow can be described as steady flow with a superimposed pulsatile component. The calculation of the exact flow profile of pulsatile flow is, however, very complex. An indicator of how pulsatile a flow is, is defined by the dimensionless Womersley number [Oates, 2001]:
3.2 Ultrasound’s interaction with blood

\[ \alpha = r \sqrt{\frac{\omega \rho}{\mu}} \] (3.3)

where \( r \) is the radius of the vessel, \( \omega \) the angular oscillation frequency \((2\pi f)\) which is determined by the heart rate, \( \rho \) the fluid density and \( \mu \) the fluid viscosity. The most important result of the Womersley number is its relation to the velocity profile. As for steady flow the velocity profile may be assumed parabolic, for pulsatile flow the velocity profile is a function of the Womersley number [Evans and McDicken, 2000]. The larger the Womersley number, the more the velocity profile tends towards the flat profile instead of the parabolic profile. This has consequences for the velocity profiles within the cardiovascular system. For example in the ascending aorta, its large radius results in a large Womersley number and velocity profiles may be assumed flat. Further away in the cardiovascular system the vessel’s radius decreases, so smaller Womersley numbers are observed and velocity profiles become more parabolic.

No unique flow profile occurs within the cardiovascular system. Not only do flow profiles differ between arterial and venous sections, also flow profiles within the arterial section differ from place to place. This will have consequences when interpreting the reflected signals from different places. Reflections from places where flow profiles can be assumed flat need other calculations than reflections from places where flow profiles are assumed to be parabolic. This will be explained in next sections.

3.2 Ultrasound’s interaction with blood

Ultrasound is sound with a frequency above the audible range. Ultrasound used in medicine usually uses frequencies in the range between 2 MHz and 10 MHz. These limits are set because of two reasons [Evans and McDicken, 2000]. The lower limit is set because of problems with a too poor spatial resolution. The wavelength of a signal is inversely proportional to its frequency. The lower the frequency, the longer the wavelength and hence the poorer the spatial resolution. Frequencies below 2 MHz have too long wavelengths so the spatial resolution drops below acceptable levels. The upper limit is set because of problems with patient safety. Attenuation increases with increasing frequency which means that higher frequencies need more power transmitted into the body in order to get enough reflections back. However, high power levels can be harmful for the patient because of possible tissue damage. Therefore, frequencies above 10 MHz are not acceptable because they need a too much power transmitted.

During an ultrasound examination, an ultrasound transducer transmits a beam of ultrasound waves into the body. These ultrasound waves interacts with ultrasound targets in the body (e.g. bones, vessel walls and blood), and produce reflections in all directions. A small part of these reflections is collected. Because some signal properties of the reflected signals are changed compared to the transmitted signals, conclusions about the movement of the ultrasound targets can be drawn.

For a stationary ultrasound target, the frequency of the reflected signals equals the transmitted frequency. Moving targets, however, introduce a shift in the frequency of the reflected signals. This is called the Doppler effect. For targets moving towards the transducer the frequency of the reflected signals is higher than the transmitted frequency, while for targets moving away from the transducer the frequency of the reflected signals is lower than the transmitted frequency. The relation between the velocity of the moving ultrasound target and the introduced frequency shift can be approximated by [Oates, 2001]:

\[ v(f_d) = \frac{c \cdot f_d}{2f_0 \cos(\theta_d)} \] (3.4)

where \( c \) is the propagation velocity of sound waves in the body (approximately 1540 m/s [Thrush and Hartshorne, 2005]), \( f_0 \) the transmitted frequency, \( \theta_d \) the angle between the transmitted beam and the moving ultrasound target, \( v \) the velocity of the moving target and \( f_d \) the frequency shift.
Chapter 3. Recording intrathoracic blood flows

According to Equation (3.4), several parameters influence the relation between the measured frequency shift and calculated velocity. The main source of error in estimating true velocities is the estimation of the angle between the ultrasound beam and the ultrasound target [Jones, 1993]. Although knowledge about anatomy provides valuable information about the approximate angle between the ultrasound beam and the ultrasound target, small errors in the angle estimation can have big impact. Since not the angle itself but the cosine of the angle affects the calculation of the velocity from the frequency shift, analysis of the cosine function gives information about the introduced error. The shape of the cosine varies mostly around $90^\circ$. Hence small errors in the angle estimation around $90^\circ$ induce large errors in the cosine function and in the calculation of blood velocities. To introduce acceptable errors, measurements may therefore only be performed using angles below $60^\circ$ [Oates, 2001].

For this research, blood is the ultrasound target of interest. Blood consists of red blood cells, white blood cells and placelets suspended in plasma. Because of the large number of red blood cells compared to the number of white blood cells and placelets, the red blood cells are assumed to be responsible for the reflected signals [Oates, 2001]. By assuming that the velocity of blood equals the velocity of the red blood cells, the frequency shift of the reflected signals caused by the red blood cells can be used to calculate the blood velocity. One should remark that blood is of course not the only ultrasound target. Other ultrasound targets that are located along the direction of the ultrasound beam like bones and moving vessel walls do produce reflected signals as well. Fortunately, the velocities of these targets are very low compared to blood velocities, so signal processing techniques can be used to remove these unwanted components out of the reflected signals.1

3.3 Type of Doppler systems

Two main types of Doppler systems can be discriminated that use ultrasound and the Doppler effect to measure blood velocities [Evans and McDicken, 2000]. Both systems use the fact that transmitted signals in the body are reflected by the moving blood and that the velocity profile can be calculated from the reflected signals. The difference between both systems is the way the system deals with transmitting and receiving ultrasound waves.

The simplest Doppler system is the continuous wave system. The continuous wave system consists of two crystals (the ultrasound transducers) integrated in one probe of which one acts as a transmitter and the other acts as a receiver. The transmitter is continuously transmitting and the receiver is continuously receiving ultrasound signals. The continuously transmitted waves are propagated in the body and reflected by the body's ultrasound targets which produce the frequency shifts in the reflected signal that are detected by the receiver. The disadvantage of the continuous wave system is its inability to relate frequency shifts to the depth where the shifts originated. All moving ultrasound targets along the direction of the ultrasound beam produce reflections. The reflected signals thus contain information about all the velocities of ultrasound targets along the direction of the ultrasound beam. This can lead to misinterpretations of the results because unexpected velocity profiles may be observed. If, for example, two heart chambers are located along the direction of the ultrasound beam, the reflected signal will not be representative for the velocities in one heart chamber, but instead it will represent all velocities (positive as well as negative) present in both heart chambers.

The second type of Doppler systems is the pulse wave system. The pulse wave system consists of only one crystal which alternatively functions as transmitter and receiver. Contrary to the continuous wave system, short bursts of ultrasound waves are transmitted instead of a continuous ultrasound wave. After a selected time delay, the reflected signals are sampled. Because the propagation velocity of sound waves in the body is known and assumed to be constant, a linear relation exists between

1A common way to remove the unwanted reflections from the slow-moving ultrasound targets is using a high-pass filter. The high-pass filter passes high frequencies (reflections from the red blood cells) and blocks low frequencies (unwanted reflections from the slow-moving ultrasound targets).
3.4 Blood flow recordings

3.4.1 Velocity profile estimation

As explained, the frequency of the reflected signals is changed according to the velocities at which the numerous ultrasound targets are moving. When the transmitted frequency is subtracted from the received signals (e.g. by demodulation), a signal remains that only contains the frequency shifts between the transmitted and received signal. These frequency shifts are proportional to the blood velocities of the ultrasound targets and therefore have to be calculated from the reflected time signal in order to obtain the velocity profile of the blood flow.

The more ultrasound targets are moving at a certain velocity, the more this velocity contributes to the reflected signals. Ideally, the power in a particular frequency band of the spectrum is proportional to the number of ultrasound targets moving with the velocity that produce frequencies in that band. Thus, the power spectrum of the reflected signals should have the same shape as the velocity profile of the flow. This implies that, for example, the power spectrum of a flat profile should have much power concentrated around one frequency because all red blood cells are moving at approximately the same velocity. This in contrast to the power spectrum of a parabolic flow profile which should be rather flat because the number of red blood cells moving at each velocity is approximately the same.

Because the velocity profile of blood flow varies over time, important to know is how the power spectrum varies over time. This can be evaluated by dividing the reflected signal into small time intervals and determining the power spectrum of each time interval (e.g. by taking the squared modulus of the Fourier transform). When these power spectra are plotted over time, the variation of the power spectrum over time can be analyzed. Figure 3.2 shows a plot of the variation of the power spectrum as function of time, which is called a sonogram. The horizontal axis displays time, the vertical axis displays the frequency shift, and the intensity at a particular frequency shift and time indicates the spectral power at that frequency shift and time. Because the frequency shift is linearly related to the velocity, the y-axis can also be seen as a velocity axis and the sonogram thus visualizes how the velocity profile varies over time.

Dividing the reflected signal into time intervals requires a tradeoff between spectral and temporal resolution according to:

$$\Delta f = \frac{1}{\Delta t}$$

where $\Delta t$ is the time interval which determines the temporal resolution and $\Delta f$ is the frequency in-
Chapter 3. Recording intrathoracic blood flows

Figure 3.2: Construction of a sonogram (adapted from Thrush and Hartshorne [2005]). Every time interval \( \Delta t \) the power spectrum of the reflected signal is calculated and added as a vertical line in the sonogram. The intensity at a particular frequency and time is related to the spectral power at that frequency and time. In this example, a grey scale determines the power at a particular frequency. Black denotes much power while white denotes no power. Equation (3.4) can be used to transform the frequency shifts on the y-axis into velocities.

A method to improve the spectral resolution is using time windows [Evans and McDicken, 2000]. Before the power spectrum is calculated, the data of the time interval is multiplied with a non-rectangular weighting function (the window). This is called windowing. Windowing reduces the effective data length and hence improves the spectral resolution. However, if the window and the Fourier transform are applied to non-overlapping data segments, a part of the data is ignored because the window dims the values near the boundaries of a data segment. To avoid this loss of data, usually overlapping data segments are used. This overlap improves the calculated spectra, but requires more computational power to process the data because more spectra have to be calculated.

To construct the sonogram from the frequency shifts, we adapted the settings of Illindala et al. [1996]. They acquired and analyzed mitral and aortic flows in 7 normal subjects, and found good correlation between manual and automated detection of velocity spectra. They used a sample frequency of 20000 Hz, a 256 point Hamming window (12.8 ms) with 128 point (6.4 ms) overlap, and a smoothing low-pass filter with a cut-off frequency of 15 Hz in order to remove unwanted noise components afterwards. According to Equation (3.5), this results in a spectral resolution of approximately 78 Hz. Because the ultrasound machine uses a transmitter frequency of 4.4 MHz, the corresponding velocity resolution is approximately 1.37 cm/s.
3.4. Blood flow recordings

3.4.2 Flow profile estimation

Although the sonogram shows how the velocity distribution varies over time, the variation of the flow profile is our subject of interest. The blood flow through a vessel can be estimated according to:

\[ Q(t) = A(t) \cdot \bar{v}(t) \]  \hspace{1cm} (3.6)

where \( A(t) \) is the cross-sectional area of the vessel, and \( \bar{v}(t) \) the mean blood velocity. Although the cross-sectional area of the vessel varies over time, at some places it may be assumed constant during ejection. Maslow et al. [1996] and Darmon et al. [1994] used this assumption for measuring aortic and pulmonary artery flow, respectively. Both authors found high correlation when comparing Doppler cardiac output measurements with thermodilution cardiac output measurements (which is widespread used as the 'reference' technique for cardiac output measurements). As will be explained later on, we only focus on these two flows. Therefore, we may assume constant cross-sectional vessel areas in the recordings, and only the measurement of the mean blood velocities remains. Two important estimators are commonly used to estimate the mean velocity: the mean velocity estimator and the maximum velocity estimator.

The mean velocity estimator is used at places where high velocities do not occur, and the pulse wave system can be used. By placing the sample volume along the diameter of the vessel, the reflected signal contains information about all the velocities across the diameter. The mean velocity estimator estimates the velocity that the blood travels on average, by calculating the mean frequency shift in the reflected signals. The most obvious way of estimating the mean velocity is calculating the intensity weight frequency according to [Evans and McDicken, 2000]:

\[ \bar{T}(t) = \frac{\int f P(f) df}{\int f P(f) df} \]  \hspace{1cm} (3.7)

where \( P(f) \) is the spectral power at a particular frequency \( f \). By using Equation (3.4), the intensity weight frequency can be transferred into the mean velocity.

At places where the pulse wave system cannot be used, the continuous wave system has to be used. Because the reflected signals contain velocity information of all ultrasound targets along the ultrasound beam, the mean velocity will not be representative for the mean velocity of the blood in the vessel under interest. Instead, the maximum velocity estimator has to be used here. The maximum velocity estimator estimates the maximum frequency in the reflected signals at which a certain power level is reflected. If a flat velocity profile can be assumed (e.g. in the ascending aorta), the maximum frequency approximately equals the mean blood velocity, so it can be used to calculate the mean velocity. Several methods have been proposed to extract the maximum frequency from the reflected signals [Evans and McDicken, 2000]:

- The percentile method defines the maximum frequency as the frequency where the integrated power spectrum exceeds a certain threshold value. This makes the percentile method very sensitive to the signal-to-noise-ratio (SNR), which is the power ratio between signal and background noise. For a very high SNR the threshold value can be between 95%-99%, while for a lower SNR the threshold value can be significantly lower.

- The simple threshold method uses a predefined threshold value to define the transition from signal to noise. The method starts at the highest analyzed frequency and determines at which frequency this threshold value is crossed. A small modification to the simple threshold method is the threshold-crossing method which calculates the threshold value automatically based on the spectral power in the tail of the power spectrum. Moreover, the threshold-crossing method states that the spectral power of several successive frequency intervals should have crossed the threshold value instead of only one interval. Another improvement to the simple threshold is the adaptive threshold method which updates the threshold value every cardiac cycle, dependent on the SNR of the previous cycle.
Chapter 3. Recording intrathoracic blood flows

- The geometric method tries to find the 'knee' in the integrated power spectrum by geometrical ways. The 'knee' is assumed to indicate the transition from signal to noise. This method was improved later on by solving some small disadvantages of the geometric method, resulting in the modified geometric method which produces better results.

Several authors made a comparative study of different maximum velocity estimators [Mo et al., 1988; Cloutier et al., 1990; Steinman et al., 2000]. They all concluded that the choice of the best estimator is dependent on the type of application. While the percentile method is, for example, preferable when a very high SNR is present, the simple threshold method is preferable for off-line applications where several thresholds can be tried. However, unfortunately not one maximum velocity estimator can be assigned as the best during all conditions.

In this research, both the mean and maximum velocity estimator are used. When using the pulse wave system (i.e. measuring the pulmonary artery flow), the mean velocity estimator is used. When using the continuous wave system (i.e. measuring the aortic flow), the maximum velocity estimator is used. Remains the choice of the maximum velocity estimator. Because the SNR will probably differ per recording, the simple threshold method is chosen because it can be manually adjusted for each recording until the best results are found. This requires manual intervention, but ensures an optimal Doppler spectrum for each recording.

3.5 Results

Before the system can be used to record and store intrathoracic blood flows, the system has to be validated. This can, for example, be done by using an in-vitro set-up of which the flow can be manually set to a predefined value. However, because such set-up was not available, the validation was limited to comparing automatically calculated blood flows with manually obtained values, calculated by a trained clinician.

Simultaneously, audio and video doppler data were recorded during a transesophageal Doppler examination of normal patients. The examination was performed using a Sonos 5500 ultrasound machine (Hewlett Packard) equipped with a 4.4 Mhz transesophageal probe. The probe was introduced into the patient's esophagus in supine position. The position of the probe was adjusted until the brightest sonogram was obtained, which implies an optimal Doppler signal. For recordings of the aortic flow, the continuous wave system was used. For recordings of the pulmonary artery flow, the pulse wave system was used.

The forward and reverse audio doppler data were digitized separately by sampling the audio signals at 20000 KHz using a multifunction data acquisition board NI PCI-6220 (National Instruments). The audio data was split into data segments of 256 samples with an overlap of 128 samples, and multiplied with a Hamming window. By using the short-time Fourier transform, the power spectra of the 256 point data segments were calculated and concatenated, resulting in the sonogram. Figure 3.3 and 3.4 show the constructed sonograms for the aortic and pulmonary artery flow, compared with the original sonograms of the Sonos. As can be seen in the figures, the constructed sonograms of the developed system are similar to the original sonograms of the (FDA-approved2) Sonos ultrasound machine. This enables us to process the sonogram and use if for the flow calculations.

Next, the mean velocity was estimated. For the pulse wave recordings the mean velocity was calculating as the intensity weight frequency. For the continuous wave recordings the mean velocity was calculated using the simple threshold method. At the start of the recordings, the threshold was manually adjusted until an optimal envelope was traced, based on visually inspections. In order to reduce unwanted noise

2The Food and Drug Administration (FDA) is an agency of the united states department of health and human services and is responsible for all radiation emitting medical devices.
3.5. Results

Figure 3.3: Comparison between the constructed sonogram of the aortic flow (left) and the sonogram constructed by the Sonos ultrasound machine (right).

Figure 3.4: Comparison between the constructed sonogram of the pulmonary artery flow (left) and the sonogram constructed by the Sonos ultrasound machine (right).

components, the envelopes were smoothed using a fifth-order Butterworth low-pass filter with a cutoff frequency of 15 Hz. Figure 3.5 and 3.6 show the results of the used mean velocity estimators for the aortic and pulmonary artery flow, respectively.

Figure 3.5: Comparison of the maximum velocity estimator (left) and the sonogram constructed by the Sonos ultrasound machine (right).

Figure 3.6: Comparison of the mean velocity estimator (left) and the sonogram constructed by the Sonos ultrasound machine (right).
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In order to validate the algorithm that constructs the envelopes of the mean blood velocities, the area under the envelope was automatically integrated for several heartbeats and compared to areas that were manually traced and calculated by a trained clinician. This area is called the velocity-time integral (VTI), and is an indicator of the stroke distance (i.e. the mean distance that the blood travels during one cardiac cycle) at places where flat velocity profiles may be assumed. Table 3.1 lists the manually and automatically calculated VTI's of ten heartbeats. The results indicate that, for almost all heartbeats, the implemented algorithm produces an estimate of the area under the envelope within an error of 5%, which is within the required accuracy. However, one remark should be made. Although the manual obtained results are calculated by a trained clinician, it is yet not clear whether the made error is due to the algorithm, artifacts, or imprecise envelope tracing of the clinician.

Table 3.1: Manually and automatically calculated VTI's of ten heartbeats.

<table>
<thead>
<tr>
<th>Heartbeat</th>
<th>Manual (cm)</th>
<th>Automatic (cm)</th>
<th>Error (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28.5</td>
<td>28.2</td>
<td>-1.05</td>
</tr>
<tr>
<td>2</td>
<td>26.1</td>
<td>25.7</td>
<td>-1.53</td>
</tr>
<tr>
<td>3</td>
<td>25.3</td>
<td>24.8</td>
<td>-1.98</td>
</tr>
<tr>
<td>4</td>
<td>26.5</td>
<td>25.9</td>
<td>-2.26</td>
</tr>
<tr>
<td>5</td>
<td>24.0</td>
<td>23.8</td>
<td>-0.83</td>
</tr>
<tr>
<td>6</td>
<td>26.0</td>
<td>25.6</td>
<td>-1.54</td>
</tr>
<tr>
<td>7</td>
<td>28.8</td>
<td>28.9</td>
<td>0.35</td>
</tr>
<tr>
<td>8</td>
<td>28.2</td>
<td>27.6</td>
<td>-2.13</td>
</tr>
<tr>
<td>9</td>
<td>29.7</td>
<td>28.0</td>
<td>-5.72</td>
</tr>
<tr>
<td>10</td>
<td>29.2</td>
<td>28.8</td>
<td>-1.37</td>
</tr>
</tbody>
</table>

Concluding, an algorithm is developed in order to automatically measure blood flow profiles. First the sonogram, which is a representation of the velocity distribution over time, is constructed from the sampled audio doppler data. Next, the mean velocity is calculated from the sonogram, resulting in the velocity profile of the blood flow in the vessel under interest. Because constant cross-sectional vessel areas may be assumed, the shape of the velocity profile can be assumed to resemble the flow profile, and is used to calculate the variations in intrathoracic blood flows during mechanical ventilation. However, although the results show good correlation between automatically and manually obtained values, it is recommended to validate the system further by comparing calculated flows to predefined flows in an in-vitro set-up.
Chapter 4

Modelling respiratory induced variations in blood flows

The main goal of this research is modelling the variations of the intrathoracic blood flows induced by mechanical ventilation. This chapter provides an overview of the development that finally results in a coupled model of the respiratory and cardiovascular system. The development is performed in close cooperation with Diepen [2006]. The difference between both studies is the focus on the output signals used for modelling the variations. Diepen [2006] focused on modelling respiratory induced variations in blood pressure while here the focus is on modelling the respiratory induced variations in intrathoracic blood flows.

This chapter starts with an introduction to the modelling of physiological systems. The purpose of modelling physiological systems is explained, some considerations are made regarding model complexity and a description is given of how physiological systems, which are in this case fluid transport systems, can be modelled. Next, the modelling parts of the cardiovascular system and the respiratory system are explained. This chapter ends with the explanation of how both models are coupled in order to model the respiratory influences on the cardiovascular system during mechanical ventilation.

4.1 Modelling physiological systems

4.1.1 Why model physiological systems

A model can be defined as an abstraction of reality which accounts for those properties of a phenomenon that are pertinent to the purpose of the model [Beneken and van Oostrom, 1998]. Several goals can be achieved with developing a model of which two are important for this research.

The first goal is the estimation of parameter values that are difficult or impossible to measure in the real world. When the internal structure of the developed model resembles the internal structure of the system, the model contains parameters that also have a meaning in the real world. By tuning the model's output to match the system's output for identical input signals, parameter values that are difficult to measure in the real world can be estimated in the model. For this research, examples of such parameters are ventricular preloads, a patient's total blood volume, or ventricular contractibility. This can be valuable, because the current patient's hemodynamical status can be evaluated by estimating values of the relevant model parameters. One remark should be made here. Correct parameter estimation is only applicable when the model produces unique results, which means that an output signal can only be produced by one unique set of parameter values and input signals. If this is not the case, imprecise parameter values can be estimated because a different set of parameter values can result in the same output signal.
The second goal is prediction of future states of the system. When the model parameters are tuned to the real world parameters, the model can be used for predicting future system states by assuming that parameter values will not change in the (near) future. This can be valuable because if the model is tuned to the patient, the model can be used to predict the patient’s response to fluid loading. This can be achieved by evaluating the model’s response to administered fluid, assuming that the patient’s response will resemble the model’s response.

4.1.2 Considerations regarding model complexity

As explained before, a model is defined as an abstraction of reality. This implies that a model never describes reality (i.e. the underlying process) exactly. Instead, the complexity of the model determines the accuracy of the model. When developing a model, choices have to be made that determine the complexity of a model because of several reasons:

- The model’s objectives. No general model of a process exists. The model’s objectives determine which parts of the process are important, and thus modelled, and which parts are not.
- The required accuracy. The more accuracy is required, the more parameters are necessary in general to describe the process, and the more complex the model will be.
- The knowledge about the process. Models are developed based on the author’s knowledge about the underlying process. This implies that the author’s knowledge also determines the complexity that is put into the model.

Also in this research, choices have to be made that influence the model complexity. The developed model should accurately describe the respiratory induced variations in intrathoracic blood flows during mechanical ventilation. However, because a number of unknown model parameters have to be estimated based on a fixed amount of data (recorded data during the time that the patient is stable and during which we may assume that model parameters do not change), the number of unknown model parameters has to be minimal. This results in a tradeoff between accuracy and the required amount of data. Therefore, several assumptions have to be made during the model development that are from a physiologically point of view not exactly correct, but still lead to reasonably accurate results.

4.1.3 How to model fluid transport systems

In this research, modelling the cardiovascular and respiratory system involves modelling fluid transport systems. For the cardiovascular system the transport of blood has to be modelled and for the respiratory system the transport of gas has to be modelled. Modelling fluid transport systems can be roughly subdivided into the finite element (FE) approach and the pressure-volume (PV) approach. The FE approach breaks the system down in small segments and uses finite element calculations to simulate the system. The PV approach divides the fluid transport system into larger segments and groups parameters in order to simplify the model as much as possible while still describing the essential dynamics. Because the number of unknown parameters should be minimal in the end-application, the PV approach is used to model both the cardiovascular and respiratory system. Moreover, this approach has nice properties which significantly simplify the calculations as will be explained.

Using the PV approach, a fluid transport system is subdivided into segments that consist of a rigid tube to model the fluid dynamics and a compliant chamber to model the pressure-volume relation. This is illustrated in Figure 4.1. When considering flow through a rigid tube, the flow rate equations can be derived from the Navier-Stokes relations of fluid transport:

\[
\frac{\partial u_x}{\partial t} + u_r \frac{\partial u_r}{\partial r} + u_\theta \frac{\partial u_r}{\partial \theta} + u_x \frac{\partial u_x}{\partial x} = -\frac{1}{\rho} \frac{\partial P}{\partial x} + \nu \left[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial u_x}{\partial r} \right) + \frac{1}{r^2} \frac{\partial^2 u_x}{\partial \theta^2} + \frac{\partial^2 u_x}{\partial x^2} \right]
\]

where \( u_x, u_r, u_\theta \) are the longitudinal, radial and angular velocities respectively, \( P \) the pressure in the tube, \( \rho \) the fluid density and \( \nu \) the fluid kinematic viscosity.
4.1. Modelling physiological systems

Figure 4.1: Fluid transport is modelled by dividing the system into segments which consist of a rigid tube to model the fluid dynamics and a compliant chamber to model the pressure-volume relation. The complexity of the model is determined by the number of used segments.

To simplify Equation (4.1), in order to reduce the number of parameters, several assumptions have to be made [Smith, 2003; Blom, 2004]:

- The fluid is incompressible.
- The fluid has a constant viscosity.
- The flow is laminar. Although this will not be true around the valves where some turbulence may occur, the overall effect of turbulence on the flow profiles can be assumed negligible.
- The tubes (vessels and airways) are rigid and have constant diameters.
- Velocity profiles are parabolic. This means that the effects of side branches, bifurcations and tube curvature are neglected because they distort the parabolic velocity profiles.
- The pressure is constant across the cross-section of the tube.

With these assumptions, Equation (4.1) can be reduced to:

\[
\rho \frac{\partial u(r, t)}{\partial t} = \frac{\partial P}{\partial x}(t) + \frac{\mu}{r} \frac{\partial}{\partial r} \left( r \frac{\partial u(r, t)}{\partial r} \right) \tag{4.2}
\]

where \(\mu\) is the fluid viscosity and \(u(r, t)\) the velocity along the tube as function of radius and time.

Because also constant resistance may be assumed in the cardiovascular system [Smith, 2003] as well as the respiratory system [Schott, 2005], Equation (4.2) can be further reduced to:

\[
\frac{pl}{\phi_0^2} \frac{\partial Q}{\partial t} = P_1 - P_2 + \frac{2\mu L}{\phi_0^2} \frac{\partial u}{\partial r}(r_0) \tag{4.3a}
\]
\[
Q(t) = \frac{\phi_0^4}{8\mu L} (P_1(t) - P_2(t)) \tag{4.3b}
\]

where Equation (4.3a) is used when inertial effects are included and Equation (4.3b) when not. For the complete derivation, the reader is referred to Smith [2003]. Equations (4.3a) and (4.3b) are very similar to the equations that describe the relation between voltage and current in electrical circuits. The relation between voltage and current of a resistor and inductor in series, and the relation across a single resistor are defined respectively as:

\[
L \frac{dl}{dt} = V_1 - V_2 + IR \tag{4.4a}
\]
\[
l(t) = \frac{1}{R}(V_1(t) - V_2(t)) \tag{4.4b}
\]

where \(V\) denotes voltage, \(l\) denotes current and \(L\) and \(R\) are the values of the inductance and the resistance respectively.
When Equations (4.3a) and (4.3b) are compared to Equations (4.4a) and (4.4b), the relation between the physiological domain and the electrical domain becomes clear. The equations of fluid transport in physiological systems are similar to the equations of electricity transport in electrical systems. Therefore equivalences can be found between both domains. These equivalences are listed in Table 4.1.

**Table 4.1: Equivalences between the physiological and electrical domain.**

<table>
<thead>
<tr>
<th>Physiological domain</th>
<th>Electrical domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure (mm Hg)</td>
<td>Voltage (V)</td>
</tr>
<tr>
<td>Flow (ml/s)</td>
<td>Current (A)</td>
</tr>
<tr>
<td>Volume (ml)</td>
<td>Charge (C)</td>
</tr>
</tbody>
</table>

The transition of quantities from the physiological into the electrical domain is extremely valuable with respect to the modelling of fluid transport systems. Much knowledge about modelling electrical circuits is available. Known electrical laws like Kirchhoff's law and Ohm's law can be applied directly in the physiological domain and so significantly simplify the calculations.

### 4.2 Modelling the cardiovascular system

Several studies focused on modelling the cardiovascular system by the PV approach [Smith, 2003; Olansen et al., 2000; Liu, 2005; Kentgens, 2001]. However, none of these studies focused on the combination of modelling the respiratory influences on the cardiovascular system during mechanical ventilation and the minimal modelling approach (i.e. the development of a model that describes the essential dynamics accurately enough with a minimal number of parameters). Modelling the respiratory influences is essential to investigate the variations in intrathoracic blood flows during mechanical ventilation. The respiratory influences are usually neglected because the cardiovascular system is the subject of interest. The minimal modelling approach is important because the model parameters have to be estimated in order to fit the model parameters to recorded patient data. The larger the number of unknown model parameters, the more patient data is required to estimate all parameters.

The cardiovascular model proposed by Smith [2003] is based on the minimal modelling approach. Moreover, Smith [2003] also showed that his model accurately captures the major hemodynamic trends and correctly simulates several disease states. Therefore, our model is based on the model of Smith [2003]. However, in order to further decrease the number of parameters, some unnecessary complexity of Smith's model will be left out which implies that the model has to be built up again. Next sections describe first the individual compartments of the model and finally combine these compartments which results in the closed-loop cardiovascular model.

#### 4.2.1 Modelling a passive compliant chamber

First of all, a model of a passive compliant chamber is developed. A passive compliant chamber is defined as a chamber which can store blood volume but does not add energy (e.g. a vessel). When a passive compliant chamber contains some blood volume, this volume will induce transmural pressure. Transmural pressure is defined as the pressure between the inside and the outside of a structure. A capacitance is used to model the storage of blood volume and the relation between the transmural pressure and the stored volume. Using a capacitance the pressure-volume relation is defined as:

\[ P(t) = \frac{V(t)}{C} \]

where \( P(t) \) is the transmural pressure, \( V(t) \) the stored blood volume and \( C \) the capacitance. According to Equation (4.5), the pressure-volume relation of a passive compliant chamber is assumed to be linear,
which indeed may be assumed for the normal operating range [Blom, 2004].

However, like filling a balloon with water, no transmural pressure is present for small volumes. The volume at which the transmural pressure starts to increase is called the unstressed volume. To account for this unstressed volume, a pressure source is added to the model. This pressure source ensures that the increase of transmural pressure starts from the unstressed volume. The addition of the pressure source results in:

\[ P(t) = \frac{V(t)}{C} - P_0 = \frac{V(t)}{C} - \frac{V_0}{C} = \frac{V(t) - V_0}{C} \]

(4.6)

where \( V_0 \) is the unstressed volume defined by the value \( (P_0 \cdot C) \).

From a physiological point of view one problem remains: the possibility of negative transmural pressures in the model. When the transmural pressure becomes zero, the chamber will collapse and no further pressure drop can occur. Although this situation will probably not occur in the model during normal conditions, incorrect initial conditions can lead to situations outside the normal operating range. Therefore, this situation has to be treated correctly. To avoid negative transmural pressures, a switch is added to the model whose state is determined by the transmural pressure. When the transmural pressure becomes negative, the switch will be connected to ground resulting in a transmural pressure of zero. Addition of the switch results in the following relation for \( P(t) \):

\[ P(t) = \begin{cases} 0 & \frac{V(t) - V_0}{C} < 0; \\ \frac{V(t) - V_0}{C} & \text{elsewhere.} \end{cases} \]

(4.7)

The resulting model of the passive compliant chamber is shown in Figure 4.2. The capacitor \( C \) models the linear relation between transmural pressure and stored blood volume. The pressure source \( P_0 \) accounts for the unstressed blood volume from where the transmural pressure starts increasing. The time-varying switch \( S(t) \) is used to account for the correct pressure-volume relation of stored blood volumes outside the normal operating range. Within the normal operating range \( (S = 1) \), the chamber's transmural pressure is the sum of the pressure across the capacitor \( C \) and the pressure of the pressure source \( P_0 \). For too low blood volumes \( (S = 2) \), the transmural pressure becomes zero.

Figure 4.2: Model of a passive compliant chamber. Capacitor \( C \) models the linear relation between transmural pressure and stored blood volume. The pressure source \( P_0 \) accounts for the chamber’s unstressed blood volume. Switch \( S(t) \) accounts for the correct pressure-volume relation for blood volumes within the normal operating range (1), and too low blood volumes (2).

Before the transmural pressure can be calculated, the chamber’s blood volume has to be calculated. The chamber’s blood volume continuously changes because of the varying inflow and outflow of blood. The following equation is used to calculate these volume changes:

\[ \frac{dV}{dt} = Q_{in}(t) - Q_{out}(t) \]

(4.8)

where \( Q_{in} \) and \( Q_{out} \) are the inflow and outflow of blood, respectively.
4.2.2 Modelling an active compliant chamber

The heart cannot be seen as a passive compliant chamber because the heart does not passively store blood. Instead, the heart actively adds energy to the cardiovascular system. When the heart contracts, blood is forced out of the heart into the circulation. Therefore, the heart must be seen as an active compliant chamber. Like the passive compliant chamber, an active compliant chamber has the capability to store blood volume, but contrary to the passive compliant chamber it can also add energy.

As described in Section 2.2, the ventricles are the major determinants of the heart’s pumping function and the atria only increase ventricular efficiency. In consideration of the overall cardiovascular system, atrial contraction is therefore not important at normal heart rates [Shim et al., 2004]. For this reason, both sides of the heart are modelled as one pump that represents the ventricle. The atria are neglected, decreasing the number of parameters in the model without reducing its accuracy.

Modelling a ventricle can be done in three ways: as a time-varying pressure source, a time-varying flow source or a time-varying compliance [Mohamed, 2006]. From a physiological point of view, a ventricle does not generate new blood volume but only pumps the blood through the circulation. Therefore, modelling a ventricle as a flow or pressure source could introduce problems in closed-loop models because one has to make sure that no additional blood enters or leaves the model. When modelling a ventricle as a time-varying compliance, i.e. modelling the time-varying ventricular pressure-volume relation, this problem will be avoided. By varying the value of the compliance, the ventricular pressure can change with constant volume, which is in accordance with the isovolumetrically changing ventricular pressure during ventricular contraction and relaxation. Therefore, a ventricle is modelled by a time-varying compliance.

A common way to simulate the time-varying compliance, is by using a time-varying capacitance [Smith, 2003]. By taking also the unstressed volume of the ventricles into account, the pressure-volume relation can be described as:

\[ P(t) = \frac{V(t) - V_0}{C(t)} \]  

(4.9)

where \( V(t) \) is the ventricular volume, \( V_0 \) is the unstressed volume and \( C(t) \) the time-varying capacitance. By varying the capacitance in time, the heart’s pumping function can be simulated.

However, a more physiologically correct way to simulate the time-varying compliance is by using equations that describe the end-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (EDPVR) [Chung et al., 1997; Beyar et al., 1987; Smith, 2003]. The ESPVR gives a measure of cardiac contractility, which represents the strength of myocardial contraction. The EDPVR gives a measure of ventricular compliance, which defines the stiffness of the heart wall. When these two equations are weighted by a cardiac driver function that simulates ventricular contraction, the ventricular pressure-volume relation can be simulated more accurately. The most commonly used definitions of the ESPVR and EDPVR assume that the ESPVR is a linear function and the EDPVR is an exponential function of pressure and volume, defined as [Smith, 2003]:

\[ P_{es}(V) = E_{es}(V - V_d) \]  

\[ P_{ed}(V) = P_0(e^{\lambda(V-V_0)} - 1) \]  

(4.10a)

(4.10b)

where \( P_{es} \) represents the ESPVR and \( P_{ed} \) the EDPVR. The parameters \( E_{es}, V_d, P_0, \lambda \) and \( V_0 \) define the shape of both curves. By weighting both functions with the cardiac driver function, the ventricular pressure can be calculated according to:

\[ P(V, t) = e(t)P_{es}(V) + (1 - e(t))P_{ed}(V) \quad 0 \leq e(t) \leq 1 \]  

(4.11)

where \( e(t) \) is the cardiac driver function that is used to simulate ventricular contraction. The shape of this cardiac driver function determines the exact curvature of the ventricular pressure-volume loop.
Here, a series of Gaussian curves has been used according to [Chung, 1996]:

\[ e(t) = \sum_{i=1}^{N} A_i e^{-B_i(t-C_i)^2} \]  

(4.12)

where \( N \) is the number of Gaussian curves used and \( A_i, B_i \) and \( C_i \) are the parameters that influence the magnitude, width and delay of the individual Gaussian curves, respectively. Figure 4.3 shows the result of using a linear ESPVR and an exponential EDPVR together with a cardiac driver function in order to simulate the ventricular pressure-volume relation.

**Figure 4.3:** Simulation of the ventricular pressure-volume relation by weighing a linear ESPVR and an exponential EDPVR by a cardiac driver function according to Equation (4.11). Parameters \( V_0 \) and \( V_d \) determine at which volume both curves begin (adapted from Smith [2003]).

Note that the pressure-volume relation as defined by Equation (4.11) is non-linear because of the non-linear character of the function \( P_{ed} \). This implies that a time-varying (linear) capacitance cannot be used. Because no electrical component exists that can simulate this non-linear pressure-volume relation, a new electrical component is introduced: an elastic chamber. An elastic chamber is a capacitor-like component whose pressure \( P_{ec} \) is dependent on the cardiac driver function \( e(t) \) and on the stored blood volume \( V_{ec} \). The exact relation between pressure, volume and time is defined by Equation (4.11). Figure 4.4 shows the model of an elastic chamber.

**Figure 4.4:** Model of an elastic chamber. The pressure \( P_{ec} \) is dependent on the cardiac driver function \( e(t) \) and on the stored blood volume \( V_{ec} \) according to Equations (4.10a), (4.10b) and (4.11). The curvature of the cardiac driver function defines how the pressure changes with constant volume.

Because the heart is surrounded by the relatively rigid pericardium, the pericardium influences ventricular functioning. When the blood volume in the ventricles increases, the pericardium will act more and more as a filling constraint, thus increasing the pressure on the ventricular walls. Maniar et al. [2003] investigated the effects of the pericardium on the right atrial function of sheep after pericardiectomy. Pericardiectomy is a surgical procedure in which a part of the pericardium is removed. A substantial fall in both right atrial elastance (54%) and stiffness (39%) was measured after pericardiectomy, which can be explained by the removal of the constraint on the filling capabilities of the heart chambers.
Savitt et al. [1993] investigated the pericardial influences on the ventricles during cardiac tamponade. Cardiac tamponade is the compression of the heart caused by fluid accumulation in the space between the heart and the pericardium. A reduction in cardiac output of 37.8% was found, which can be explained by the increasing constraint on the filling capabilities of the heart chambers during cardiac tamponade. The results show that pericardial influences cannot be neglected and therefore need to be modelled. To account for the pericardial pressure, a pressure source is added to the model. The magnitude of this pressure source is dependent on the total blood volume of both ventricles according to [Chung et al., 1997]:

$$ P_{pcd}(V_{tot}) = P_0(e^{\lambda(V_{tot} - V_0)} - 1) $$  \hspace{1cm} (4.13)

where $\lambda$, $P_0$ and $V_0$ are constants to yield the pressure-volume relation of the pericardium, and $V_{tot}$ the total volume of both ventricles. This volume is calculated according to:

$$ V_{tot} = V_L + V_R $$  \hspace{1cm} (4.14)

where $V_L$ and $V_R$ are the blood volume of the left and right ventricle, respectively.

Besides the pericardium, the intraventricular septum influences ventricular functioning as well. When one heart chamber is filled with blood, the septum is pushed into the other heart chamber, reducing its filling capabilities. The more compliant the septum, the easier the septum is pushed into one of the heart chambers. Olansen et al. [2000] investigated the influences of the septum on the cardiovascular system. Although the ventricular end-diastolic volumes could change approximately 15%, the differences in systemic arterial pressure and cardiac output were in the range of only 2%. Therefore, the influences on the cardiovascular system induced by the septum may be neglected and are not included in our model.

It remains to model the heart valves. The heart valves prevent blood flow back from the heart into the venous sections and blood flow back from the arterial sections into the heart. Actually a very little back flow always occurs when a heart valve closes. However, this back flow is so small that it may be neglected. Therefore, ideal diodes are used to model the heart valves.

![Figure 4.5: Model of an active compliant chamber. An elastic chamber is used to model the time-varying nonlinear pressure-volume relation. The pericardial pressure, which is dependent on the total volume of both ventricles $V_{tot}$, is modelled by the pressure source $P_{pcd}$. The heart valves, which ensure unidirectional blood flow, are modelled by the diodes $D_{in}$ and $D_{out}$.](image)

Figure 4.5 shows the resulting model of an active compliant chamber. An elastic chamber is used to model the time-varying nonlinear pressure-volume relation. The pericardial pressure, which is dependent on the total volume of both ventricles $V_{tot}$, is modelled by the pressure source $P_{pcd}$. The two

$^1$Note that using ideal diodes to model the heart valves implies that the model is only applicable to patients with non-leaking heart valves. For patients that do have leaking heart valves where significant back flows occur, the model should be slightly adapted. This can, for example, be achieved by adding a resistor in parallel to the diode.

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diodes $D_{in}$ and $D_{out}$ are used to model the heart valves and ensure unidirectional blood flows.

### 4.2.3 Modelling the circulation

As indicated in Section 2.2, both the pulmonary and systemic circulation can roughly be subdivided into three sections: an arterial, venous and capillary section. Because these sections do not add energy, they can be modelled by passive compliant chambers. Dividing these sections into compliant chambers involves a tradeoff between complexity and accuracy. The larger the number of compliant chambers used to model a particular section, the more accurately this section can be modelled. However, the number of unknown parameters that has to be estimated also increases with the number of compliant chambers.

Based on the minimal modelling approach, both the pulmonary and systemic circulation are modelled by only two compliant chambers. One compliant chamber represents the arterial section and one compliant chamber represents the venous section. The capillary section is not modelled as a compliant chamber because the volume in the capillaries may be assumed negligible when compared to the other two sections [Guyton and Hall, 2000].

### 4.2.4 Closing the loop

Now that all parts of the cardiovascular system have been treated individually, they have to be combined in order to obtain a closed-loop model of the cardiovascular system. Combining these parts requires a method to handle the fluid dynamics. As blood flows through the cardiovascular system, the blood experiences resistance and inertial effects. Resistance effects are caused by frictional forces between the blood and the vessel walls. Inertial effects are caused by the fact that mass cannot be accelerated and decelerated instantaneously.

A resistor is used to model the frictional forces which result in a pressure drop along the vessel. Using a resistor, the blood flow between two compliant chambers can be calculated according to:

$$ Q = \frac{P_1 - P_2}{R} $$

where $P_1$ and $P_2$ are the pressures in the two compliant chambers and $R$ the resistance. So if the resistance increases (e.g. when a vessel gets compressed by an external applied pressure), the blood flow will decrease because it is more difficult for the blood to flow through the resistance.

An inductor is used to model the inertial effects. Accelerating and decelerating blood mainly occurs in the arterial side of the cardiovascular system where highly pulsatile blood flows occur. The venous sections act merely as a buffer receiving continuous blood flow from the organs. Therefore, less pulsatile blood flows occur in the venous sections and the inertial effects are much smaller. Smith [2003] investigated the inertial effects in the cardiovascular system and concluded that inertial effects are only significant at the arterial side. Therefore, the connection between the ventricles and the arterial sections does not consist of a single resistor, but instead it consists of an inductor and resistor in series. The corresponding relation between pressure and flow is defined as:

$$ \frac{dQ}{dt} = \frac{P_1 - P_2 + QR}{L} $$

where $Q$ is the blood flow, $P_1$ and $P_2$ are the pressures in the ventricle and arterial section respectively, $R$ the resistance and $L$ the inductance.

The complete closed-loop cardiovascular model can now be constructed by connecting the six compliant chambers. Figure 4.6 shows the resulting model.
Chapter 4. Modelling respiratory induced variations in blood flows

4.3 Modelling the respiratory system

Modelling the respiratory system involves modelling the airways, lungs and thorax. Several complex models have been proposed to model lung mechanics, however, a simple model can already give satisfactory results [Schott, 2005; Blom, 2004]. This simple model is shown in Figure 4.7.

During inspiration, when the air volume in the lung-thorax compartment is increasing, the pressure in the lung-thorax compartment is increasing as well. Although in reality the relation between pressure and volume in the lung-thorax compartment is not linear for the full range of pressures and volumes, this relation may be assumed linear in its normal operating range [Blom, 2004]. A capacitor is used to model this linear relation, analogously to Equation (4.5). Note that modelling the lungs by only one capacitor is only applicable when both lungs are assumed to behave in the same way. Otherwise two
4.3. Modelling the respiratory system

Capacitors and resistors have to be used in parallel, one branch for each lung.

As air flows through the airways, friction between air and the airway walls gives rise to frictional forces. These frictional forces are modelled by resistors. Because the resistance of the airways is different during inspiration and expiration, due to the contraction of smooth muscles in the bronchioles [Schott, 2005], two resistors are used. Diodes ensure that the flow experiences different resistances during inspiration and expiration. Inertial forces of accelerating and decelerating air may be neglected because of the small density of air and therefore are not modelled [Blom, 2004].

During mechanical ventilation, a patient is connected to a ventilator. Schott [2005] proposes a model of a patient which is connected to a ventilator. Although this model holds for fixed levels of the positive end-expiratory pressure (PEEP), in this research the level of PEEP changes when investigating the influence of the level of PEEP on the respiratory induced variations. Therefore, this model is slightly modified to account for varying levels of PEEP, resulting in the model as shown in Figure 4.8. The difference between both models, is that the bottom plate of capacitor $C_{it}$ is connected to the positive pole of the pressure source $P_{peep}$ in the model of Schott [2005]. This was done to model the initial pressure during inspiration (induced by the level of PEEP). However, this also implies that at the end of expiration, when the alveolar pressure equals the level of PEEP, no pressure drop across the capacitor exists and the lungs thus do not contain any air volume according to the model. Of course, this does not match with physiology. To solve this, the bottom plate of capacitor $C_{it}$ is connected to ground. The initial pressure at inspiration is modelled by the initial charge of this capacitor. The pressure induced by the ventilator is modelled by a time-varying pressure source $P_{v}(t)$. The resistances of the ventilator hoses during inspiration and expiration are modelled by the two resistors $R_{v,ins}$ and $R_{v,exp}$. The level of PEEP is modelled by a pressure source $P_{peep}$, and ensures a positive pressure in the lungs and airways in order to prevent collapse.

![Figure 4.8: Model of a ventilated patient. The ventilator pressure is modelled by the time-varying pressure source $P_{v}(t)$. The switch $S_{v}$ accounts for the different phases during ventilation: inspiration (1), the inspiratory pause (2) and expiration (3). The resistors $R_{v,ins}$ and $R_{v,exp}$ account for the frictional forces of air flowing through the ventilator hoses during inspiration and expiration respectively. Pressure source $P_{peep}$ is used to model the level of PEEP.](image)

A time-varying switch $S_{v}(t)$ is used to differentiate between the several phases of ventilation. During inspiration ($S_{v} = 1$), a positive pressure gradient between the ventilator pressure and alveolar pressure causes an inflow of air. The air flows through the ventilator hoses, via the airways into the lungs. The capacitor will be charged. During the inspiratory pause ($S_{v} = 2$), when the inspiratory and expiratory valves of the ventilator are closed, the air cannot leave the system and the pressure in the lungs remains
the same. This gives the diffusion process extra time to exchange oxygen and carbon dioxide between air and blood. During expiration ($S_v = 3$), the capacitor discharges. The air flows passively out of the lungs until the alveolar pressure has reached the level of PEEP.

As can be seen in Figure 4.7, the alveolar pressure can be measured as the pressure across the plates of the capacitor. Since the intrathoracic pressure is important, because this pressure influences the cardiovascular system, the intrathoracic pressure has to be estimated from the alveolar pressure. The intrathoracic pressure is built up of two components: the resting intrathoracic pressure and an additional pressure component transferred from the alveoli. The resting intrathoracic pressure is the pressure that is present in the thorax upon rest (approximately 4 mm Hg below atmosphere [Guyton and Hall, 2000]). The transferred pressure from the alveoli is the pressure in the thorax induced by the alveolar pressure (approximately 50% of the alveolar pressure [Blom, 2004; Aben, 2003]). The intrathoracic pressure $P_{it}$ can thus be estimated according to:

$$P_{it} = \frac{P_{alv}}{2} + P_{rest}$$  (4.17)

where $P_{alv}$ and $P_{rest}$ are the alveolar and resting pressure, respectively.

4.4 Modelling respiratory influences on the cardiovascular system

As indicated in Section 2.3, mechanical ventilation alters intrathoracic pressure. Because intrathoracic pressure is the surrounding pressure of all structures located in the thorax, the intrathoracic pressure influences the intrathoracic structures. These influences have to be modelled.

First of all, the intramural pressure of the intrathoracic structures changes because of the surrounding intrathoracic pressure changes. Intramural pressure is defined as the pressure inside the structure referenced to atmospheric pressure. The intramural pressure of the intrathoracic structures increases with the magnitude of the intrathoracic pressure. To model this pressure change, the magnitude of the intrathoracic pressure is superimposed on the intramural pressure of the passive and active compliant chambers located in the thorax.

Secondly, the diameter of the compliant vessels which are located in the thorax is affected by the intrathoracic pressure. During inspiration, these vessels get compressed by the increasing intrathoracic pressure. This causes the squeezing effect of the pulmonary capillary vessels during inspiration [Michard, 2005]. Although the pulmonary arterial and venous sections are also located in the thorax, the intrathoracic pressure changes have the greatest effect on the pulmonary capillary vessels [Liu et al., 1998; Lu et al., 2001]. Therefore, only the pulmonary capillary resistance is adjusted with respect to the intrathoracic pressure and the influences on the arterial and venous resistances are neglected. The relation between the pulmonary capillary resistance and alveolar volume is defined as [Lu et al., 2001]:

$$R_{pc}(V_{alv}) = R_{pc,0} \left(\frac{V_{alv}}{V_{alv,max}}\right)^2$$  (4.18)

where $R_{pc}$ is the pulmonary capillary resistance, $V_{alv}$ the alveolar volume and $R_{pc,0}$ and $V_{alv,max}$ constants that represent the maximum pulmonary capillary resistance and maximum alveolar volume, respectively. As described in Section 4.3, the relation between intrathoracic pressure and alveolar pressure as well as the relation between alveolar pressure and alveolar volume are assumed to be linear. This results in a linear relation between alveolar volume and intrathoracic pressure according to:

$$V_{alv}(P_{it}) = 2C_{lt} \cdot (P_{it} - P_{rest})$$  (4.19)

where $C_{lt}$ is the lung-thorax compliance, $P_{rest}$ the intrathoracic resting pressure, and $P_{peep}$ the level of PEEP.
4.4. Modelling respiratory influences on the cardiovascular system

By inserting Equation (4.19) into (4.18), the following relation remains to change the value of the pulmonary capillary resistance:

\[
R_{pc}(P_{it}) = R_{pc,0} \left( \frac{2C_{lt} \cdot (P_{it} - P_{rest})}{V_{alv,max}} \right)^2. \tag{4.20}
\]

Now that the influences of the respiratory system on the cardiovascular system are modelled, the coupled model of the cardiovascular and respiratory system can be constructed. Figure 4.9 shows this coupled model containing the respiratory induced influences on the cardiovascular system.

Figure 4.9: The coupled model of the cardiovascular and respiratory system. The respiratory induced influences are modelled in two ways. First, the intrathoracic pressure is superimposed on the pressure of the passive and active compliant chambers that are located in the thorax. Secondly, the pulmonary capillary resistance is adjusted according to the intrathoracic pressure.
Chapter 5

Model implementation

Before the developed model can be used to perform the model simulations, the model has to be implemented on a personal computer. The software package used for the model implementation is LabVIEW 7.1 from National Instruments. LabVIEW is one of the standard software packages which facilitates the possibility to extend the model and model implementation afterwards by other users.

This chapter deals with the model implementation. First the numerical methods are discussed which are used for the model implementation. Next the implementation of both the cardiovascular and respiratory model is explained. Finally, this chapter ends with the implementation of the coupling between both models, in order to model the respiratory induced influences on the cardiovascular system.

5.1 Numerical methods for implementing the models

Implementing a model on a personal computer needs a numerical method to handle the continuous elements used in the model. The continuous variable $t$, used to indicate time, cannot be used anymore. Therefore, the continuous variable $t$ is replaced by the discrete variable $k$, used to indicate the iteration number since the start of the simulation. An iteration is defined as one step in which all the variables of the model are calculated.

Although most of the used equations can be transformed directly into the time-discrete domain, the used differential equations can not. Several methods exist to solve differential equations in the time-discrete domain [Strogatz, 2001]. In this research, the Forward-Euler method is used because of its excellent performance regarding speed issues while producing sufficient accurate results when small time steps are used. The time step determines the simulated time each iteration. The Forward-Euler method is based on a truncated Taylor expansion. By truncating the Taylor expansion after two terms, and thus neglecting the higher order terms, a simple equation remains only introducing a small error. Let's consider the following first-order differential equation:

$$\frac{dy}{dt} = f(y, t) \quad (5.1)$$

where $f(y, t)$ is a function of the variables $y$ and $t$. The Forward-Euler method approximates the derivative $\frac{dy}{dt}$ according to:

$$\frac{dy}{dt} \approx \frac{y(k+1) - y(k)}{\Delta t} \quad (5.2)$$

where $\Delta t$ is the used time step. Note that when using this approximation, it is assumed that the derivative $\frac{dy}{dt}$ is constant across the interval defined by the time step. Replacing the derivative $\frac{dy}{dt}$ in Equation (5.1) by its approximation results to:

$$y(k+1) \approx y(k) + \Delta t \cdot f(y, t). \quad (5.3)$$
Equation (5.3) is very similar to the discrete equation of a Taylor-expansion, which is defined as:

\[ y(k + 1) = y(k) + \Delta t \cdot f(y, k) + O(\Delta t^2) \]  

(5.4)

where \( O(\Delta t^2) \) is the induced error every time step. When Equations (5.3) and (5.4) are compared, the error introduced by using the Forward-Euler method can be evaluated. Every iteration an error of \( O(\Delta t^2) \) is made. Because the magnitude of \( O(\Delta t^2) \) increases when the time step is increased, the magnitude of the time step determines the error. The smaller the time step, the smaller the error and the more accurate the simulations will be. However, the required computing power to simulate some amount of time is also dependent on the time step. Small time steps imply that many iterations have to be performed in order to simulate some amount of time. As a result, the magnitude of the time step is a trade-off between accuracy and computing power. In this research, a time step of 0.005 seconds has been found empirically. Using a larger time step results in non-continuous pressures and flows which are not possible from a physiological point of view. Using a smaller time step results in increasing computing power without noticeably increasing the accuracy of the results.

5.2 Implementing the cardiovascular system

Passive compliant chamber

Implementing a passive compliant chamber involves implementing the time-discrete equivalent of the pressure-volume relation described by Equation (4.7). The time-discrete equivalent is described according to:

\[ P(k) = \begin{cases} 
0, & \frac{V(k) - V_0}{C} < 0; \\
\frac{V(k) - V_0}{C}, & \text{elsewhere.} 
\end{cases} \]  

(5.5)

where \( V(k) \) is the stored volume at iteration \( k \), \( C \) the chamber’s compliance, and \( V_0 \) the unstressed volume.

As each chamber has an inflow and outflow of blood, the chamber’s blood volume changes over time. The time-discrete equivalent of Equation (4.8), using the Forward-Euler method, for determining the chamber’s blood volume becomes:

\[ V(k) = V(k - 1) + \Delta t \cdot (Q_{in}(k - 1) - Q_{out}(k - 1)) \]  

(5.6)

where \( Q_{in} \) and \( Q_{out} \) are the inflow and outflow of blood respectively.

Active compliant chamber

The pressure in the active compliant chambers is not only dependent on the stored blood volume but also on the cardiac driver function and the pericardial pressure. Inserting Equations (4.10a) and (4.10b) into (4.11), results in the following relation for \( P(k) \):

\[ P(k) = e(k) \cdot E_\text{es}(V(k) - V_d) + (1 - e(k)) \cdot P_0(e^{V(k) - V_0} - 1) + P_{pcd}(k) \]  

(5.7)

where \( P_{pcd}(k) \) is calculated according to:

\[ P_{pcd}(k) = P_0(e^{V_{int}(k) - V_0} - 1). \]  

(5.8)

Implementing the time-discrete cardiac driver function \( e(k) \) involves implementing Equation (4.12). Equation (4.12) is transferred into the time-discrete domain according to:

\[ e(k) = \sum_{i=1}^{N} A_i e^{-B_i(k_{int} - C_i)^2} \]  

(5.9)
where \( k_{\text{circ}} \) is the relative place within the cardiac cycle. In order to simulate the periodic heart’s function, \( k_{\text{circ}} \) is made periodic according to:

\[
k_{\text{circ}}(k) = k \Delta t \mod \left( \frac{60}{HR} \right)
\]  

(5.10)

where \( HR \) is the heart rate defined in beats per minute. Figure 5.1 shows the time-varying elastance curve measured in-vitro by Senzaki et al. [1996], the implemented cardiac driver function and the resulting simulated time-varying elastance curve. The used parameter values for implementing the cardiac driver function are listed in Appendix A. As can be seen, the simulated time-varying elastance curve closely resembles the time-varying elastance curve measured in-vitro, which means that the heart’s pumping function is simulated correctly.

The volume of the active compliant chamber is calculated analogously to the calculation of the volume the passive compliant chamber, defined by Equation (5.6).

**Closing the loop**

It remains to calculate the blood flows between the passive and active compliant chambers. The blood flows are calculated by transforming Equations (4.15) and (4.16) into the time-discrete domain according to:

\[
Q(k) = \frac{P_1(k) - P_2(k)}{R},
\]

(5.11a)

\[
Q(k) = Q(k-1) + \Delta t \cdot \frac{P_1(k) - P_2(k) - R \cdot Q(k-1)}{L},
\]

(5.11b)

where Equation (5.11a) is used for the blood flow calculations between chambers when inertial effects are neglected and Equation (5.11b) is used when not.

**Initial conditions**

At the start of the simulations, the total blood volume has to be distributed among the several chambers. Although the model will eventually converge to a stable solution with any initial distribution, in order to decrease computing time it is important to start with accurate initial conditions. The closer the initial conditions are to the end-solution, the faster the model converges to the end-solution. Therefore, the total blood volume is initially distributed according to a physiological known distribution [Guyton and Hall, 2000], which is assumed to be close to the end-solution. Table 5.1 lists the initial distribution of the total blood volume.
Table 5.1: *Initial distribution of the total blood volume in the cardiovascular system. The percentages are based on normal percentages in the cardiovascular system according to Guyton and Hall [2000].*

<table>
<thead>
<tr>
<th>Chamber</th>
<th>Percentage of total volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle</td>
<td>4%</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>3%</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>4%</td>
</tr>
<tr>
<td>Pulmonary vein</td>
<td>5%</td>
</tr>
<tr>
<td>Aorta</td>
<td>13%</td>
</tr>
<tr>
<td>Vena cava</td>
<td>71%</td>
</tr>
</tbody>
</table>

5.3 Implementing the respiratory system

Implementing the respiratory system involves the implementation of the transfer function between ventilator settings and intrathoracic pressure. Each iteration the airway flow, lung-thorax volume and intrathoracic pressure have to be calculated.

The calculation of the airway flow can be split up in three phases. First of all, during inspiration a constant positive pressure gradient between ventilator pressure and alveolar pressure is imposed by the ventilator, resulting in a constant inflow of air into the lungs. This method of ventilation, which is often used in clinical practice, is called volume controlled ventilation. For simplicity reasons, however, the ventilator pressure is not changed in order to maintain a constant positive pressure gradient, but instead a constant flow is imposed. Secondly, during the inspiratory pause the valves in the ventilator hoses close, resulting in zero flow. Finally, during expiration the negative pressure gradient between ventilator pressure (i.e. the level of PEEP during expiration) and alveolar pressure results in an exponentially decreasing outflow. Combining these phases, the airway flow is calculated according to:

\[
Q_{aw}(k) = \begin{cases} 
Q_{insp}, & 0 \leq k_{resp} < T_{insp}, \\
0, & T_{insp} \leq k_{resp} < T_{insp} + T_{pause}, \\
\frac{P_{alv} - P_{peep}(k)}{R_{v,exp} + R_{aw,exp}}, & T_{insp} + T_{pause} \leq k_{resp} < T_{vent}.
\end{cases} 
\]  

(5.12)

where \( Q_{insp} \) is the constant imposed inflow during inspiration, \( P_{alv} \) the alveolar pressure, \( P_{peep} \) the level of PEEP, \( R_{v,exp} \) and \( R_{aw,exp} \) the expiratory ventilator and airway resistance respectively and \( n_{resp} \) the relative place in the ventilation period. In order create a periodic ventilator pressure, this relative place is made periodic according to:

\[
k_{resp}[n] = k \cdot \Delta t \mod (T_{vent})
\]  

(5.13)

where \( T_{vent} \) is the length of the ventilation period.

Now that the airway flow is calculated, the lung-thorax volume can be calculated according to:

\[
V_{lt}(k) = V_{lt}(k-1) + \Delta t \cdot Q_{aw}(k).
\]  

(5.14)

Note that during inspiration, the constant airway flow results in a linearly increasing lung-thorax volume. During the inspiratory pause, the lung-thorax volume remains the same because the airway flow is zero which implies that air cannot enter or leave the lungs. During expiration, the lung-thorax volume decreases exponentially because of the exponentially decreasing outflow.

\(^1\) Also other ventilation methods are used in clinical practice, resulting in other flow patterns. For more information about the different ventilation methods, the reader is referred to Oczenski et al. [1996]
Finally, the intrathoracic pressure is calculated from the lung-thorax volume. First the alveolar pressure is calculated according to:

\[ P_{alv}(k) = \frac{V_t(k)}{C_{it}}. \]  

(5.15)

Next the intrathoracic pressure is calculated from the alveolar pressure according to:

\[ P_{it}(k) = P_{alv}(k) + P_{rest} = \frac{V_t(k)}{2C_{it}} + P_{rest} \]  

(5.16)

where \( P_{rest} \) is the intrathoracic resting pressure. Note the linear relation between the lung-thorax volume and the intrathoracic pressure. Besides a offset due to the intrathoracic resting pressure and the level of PEEP, the shape of the intrathoracic pressure curve is therefore similar to the shape of the lung-thorax volume curve. Figure 5.2 shows the characteristic shapes of the airway flow, lung-thorax volume and intrathoracic pressure of a patient during volume controlled ventilation.

**Figure 5.2:** The characteristic shapes of the airway flow, lung-thorax volume and intrathoracic pressure of a patient during volume controlled ventilation. During inspiration (\( T_{insp} \)), a constant imposed positive airway flow results in a linearly increasing lung-thorax volume and intrathoracic pressure. During the inspiratory pause (\( T_{pause} \)), the airway flow is zero, so the lung-thorax volume and intrathoracic pressure remain the same. During expiration, the lungs empty passively, resulting in an exponentially decreasing airway outflow, lung-thorax volume and intrathoracic pressure.

### 5.4 Implementing the respiratory influences on the cardiovascular system

Implementing the respiratory influences on the cardiovascular system involves the implementation of the influences which are mentioned in Section 4.4.

First, the intrathoracic pressure has to be superimposed on the transmural pressure of the passive and active compliant chambers located in the thorax. This results into the calculation of the intramural pressure according to:

\[ P_{im}(k) = P_{tm}(k) + P_{it}(k) \]  

(5.17)
where $P_{tm}(k)$ is the transmural pressure defined by Equation (5.7) and $P_{it}(k)$ the intrathoracic pressure defined by Equation (5.16).

Secondly, the pulmonary capillary resistance has to be adjusted with respect to the intrathoracic pressure. This is done by transforming Equation (4.20) into the time-discrete domain according to:

$$R_{pc}(k) = R_{pc,0} \left( \frac{2C_{it} \cdot (P_{it}(k) - P_{rest})}{V_{alv,max}} \right)^2. \quad (5.18)$$
Chapter 6

Comparing model simulations with results from literature and patient data

In order to validate the developed model, model simulations have to be compared with results from literature and patient recordings. Therefore, a start is made with a qualitative model validation. This involves comparing the trends between the model simulations, results from literature and patient recordings during mechanical ventilation.

First, trends in the simulated ventricular preload patterns during mechanical ventilation, which are responsible for the variations in intrathoracic blood flows, are compared with trends found in literature. Secondly, trends in simulated intrathoracic blood flows are compared to results from literature and patient recordings for varying conditions. Also some remarks are made about the limiting factors that were present during the acquisition of patient data. The used parameter values for the simulations are listed in Appendix A.

6.1 Basic mechanism validation during mechanical ventilation

During mechanical ventilation, the changes in intrathoracic pressure cause variations in ventricular preload and afterload patterns which result in varying intrathoracic blood flows and pressures. The four key mechanisms that are responsible for these varying ventricular preload and afterload patterns, according to Michard [2005], are discussed in Section 2.3. In order to validate the coupling between the cardiovascular and respiratory model, these key mechanisms have to be simulated correctly. Therefore, each key mechanism has to be validated.

The first key mechanism is the decreasing right ventricular preload during inspiration. Because of the increasing intrathoracic pressure during inspiration, the right atrial pressure increases. This decreases the flow into the right heart because of the reduced pressure gradient for venous return (i.e. right atrial pressure minus mean venous pressure) and thus decreases the right ventricular preload. Figure 6.1 shows the simulated right ventricular pressure\(^1\) and right ventricular inflow during mechanical ventilation. As can be seen, during inspiration the right ventricular pressure increases and the right ventricular inflow decreases. The decrease of right ventricular inflow during inspiration is thus simulated correctly.

The second key mechanism is the increasing right ventricular afterload during inspiration. Because of the increasing pulmonary capillary resistance, the blood experiences more resistance to flow from the pulmonary arteries to the pulmonary veins. This results in accumulation of blood in the pulmonary

\(^1\)Note that in the model ventricular pressure also represents atrial pressure because the atria are neglected.
Chapter 6. Comparing model simulations with results from literature and patient data

Figure 6.1: Simulated right ventricular pressure, right ventricular inflow and intrathoracic pressure during one ventilation period. During inspiration (i.e. the time that the intrathoracic pressure increases), the right ventricular pressure is increasing. This decreases the right ventricular inflow because of the reduced pressure gradient for venous return.

Figure 6.2: Simulated pulmonary artery pressure, right ventricular outflow and intrathoracic pressure during one ventilation period. During inspiration, the pulmonary capillary resistance increases because of the increased intrathoracic pressure. This results in a reduced pulmonary blood flow from the pulmonary arteries to the pulmonary veins and hence in an elevated pulmonary artery pressure during inspiration.
6.1. Basic mechanism validation during mechanical ventilation

Figure 6.3: Simulated left ventricular volume and intrathoracic pressure during one ventilation period. During inspiration, the blood is squeezed from the pulmonary capillaries towards the left ventricle. This results in an initial increase of left ventricular preload.

Figure 6.4: Simulated left ventricular volume and intrathoracic pressure during one ventilation period, where the left ventricular preload is kept constant. During inspiration, the increasing intrathoracic pressure increases the pressure surrounding the heart, and thus assists left ventricular ejection.

arteries and hence in an elevated pulmonary artery pressure, which may be defined as the right ventricular afterload. Figure 6.2 shows the simulated pulmonary artery blood pressure and right ventricular outflow during mechanical ventilation. As can be seen, the pulmonary artery pressure increases during inspiration while the right ventricular outflow decreases, which indicates that the right ventricular afterload is increased. The increase of right ventricular afterload during inspiration is thus also simulated correctly.

The third key mechanism is the increasing left ventricular preload during inspiration. Because of the increasing intrathoracic pressure, the pulmonary capillaries get compressed, squeezing the blood contained in these capillaries towards the left side of the heart. Figure 6.3 shows the simulated left ventricular volume during one ventilation period. Ventricular preload volume is the top value of the volume curve each heartbeat. As can be seen, during inspiration the left ventricular preload rises and thus the increase in left ventricular preload during inspiration is simulated correctly. Note that the pulmonary capillaries are modelled as a resistance and therefore do not contain any blood volume in
the model. The squeezing effect is, however, still present because in the model blood is squeezed out of the pulmonary veins due to the increasing intrathoracic pressure.

The fourth key mechanism is the decreasing left ventricular afterload during inspiration. The increasing intrathoracic pressure increases the pressure surrounding the heart, and thus assists left ventricular ejection. This results in a reduced left ventricular afterload which means that the ventricular stroke volume is increased at the same ventricular preload. Because the left ventricular preload varies in the simulations, it is difficult to assess how the afterload is affected by the varying intrathoracic pressure. Therefore, simulations are performed where a constant left ventricular preload is forced at the end of diastole. Note that this introduces a small discontinuity in the volume curve. However, because we are only interested in the left ventricular stroke volume variations at a constant left ventricular preload, this discontinuity is not important. Figure 6.4 shows the left ventricular volume during one ventilation period. Ventricular afterload volume is the bottom value of the volume curve each heartbeat. As can be seen, the left ventricular afterload decreases during inspiration while the preload volume is kept constant. This indicates that left ventricular ejection is assisted, and thus the decreasing left ventricular afterload during inspiration is simulated correctly.

The trends in simulated ventricular preload and afterload patterns suggest that all four key mechanisms which are responsible for these varying patterns, according to Michard [2005], are simulated correctly by the developed model. Because the varying ventricular preload and afterload patterns are responsible for the variations in the intrathoracic blood flows, these variations are probably also simulated correctly. To verify this, trends in simulated intrathoracic blood flows during mechanical ventilation have to be compared to results from literature. Because atria are neglected in the model, the simulated venous flows do not contain the specific characteristics induced by the atria and therefore will differ from measured venous flows. Hence, only the arterial flows are compared to results from literature.

Feissel et al. [2001] measured aortic flows in 19 patients receiving mechanical ventilation and found the following cyclic variations. During inspiration, the aortic flow slightly increases. This increase is immediately followed by a large decrease during expiration. Finally, the aortic flow returns to the 'baseline' level that it had before inspiration. Figure 6.5 shows the simulated aortic flow during one ventilation period. As can be seen in the figure, the trends in the simulations resemble the trends found in literature.

![Figure 6.5: Simulated aortic flow and intrathoracic pressure during one ventilation period. A cyclic variation in aortic flow can be seen. During inspiration the aortic flow slightly increases, while during expiration it first decreases and then returns to the baseline level that it had before inspiration.](image-url)
6.2 Validation of the model's response to varying conditions

Vieillard-Baron et al. [1999] measured pulmonary artery flows in 10 patients receiving mechanical ventilation and also found cyclic variations. During inspiration, the pulmonary artery flow shows a large decrease. After a couple of heartbeats, when the intrathoracic pressure is decreased because of expiration, the pulmonary artery flow returns to the baseline level that it had before inspiration. Figure 6.6 shows the simulated pulmonary artery flow during one ventilation period. As can be seen in the figure, the trends in the simulations resemble the trends found in literature.

![Simulated pulmonary artery flow and intrathoracic pressure during one ventilation period.](image)

**Figure 6.6:** Simulated pulmonary artery flow and intrathoracic pressure during one ventilation period. A cyclic variation in pulmonary artery flow can be seen. During inspiration the pulmonary artery flow decreases, while during expiration it increases and returns to the baseline level that it had before inspiration.

Figure 6.5 and 6.6 indicate that the trends in the variations during mechanical ventilation are simulated correctly. Moreover, a closer look to both figures leads to another interesting observation. In both figures the simulations are made using the same parameter values. Still, the variations in pulmonary artery flow are much larger that the variations in aortic flow. This can be caused by the used parameter values, but it can also indicate that the pulmonary artery flow is more sensitive to intrathoracic pressure changes than the aortic flow is. However, no literature has been found that compares the variations in both flows, so this remains subject for future research.

Concluding, the trends in simulated ventricular preload and afterload patterns as well as the trends in simulated intrathoracic flows during mechanical ventilation resemble the trends found in literature. This suggests that the basic mechanisms during mechanical ventilation are simulated correctly, and that the coupling between the cardiovascular and respiratory system is thus modelled correctly.

6.2 Validation of the model's response to varying conditions

In order to qualitatively validate the model further, the model's response to varying conditions (i.e. varying ventilator settings and a changing total blood volume) has to be compared to results from literature and patient recordings. According to Michard [2005], conditions that affect the variations in blood flows are the tidal volume, the level of positive end-expiratory pressure (PEEP) and the total blood volume. Varying the tidal volume and the level of PEEP can be realized by varying the ventilator settings. Varying the total blood volume can be realized by fluid loading. Apart from the mentioned conditions, we also expect that the variations are affected by the I:E-ratio (i.e. the ratio of inspiratory time to expiratory time) and the respiratory rate, because these conditions determine the inspiratory

\(^2\)Actually, Michard [2005] mentions also the lung-thorax compliance. However, the lung-thorax compliance cannot easily be changed in patients and therefore is omitted.
Chapter 6. Comparing model simulations with results from literature and patient data

and expiratory time. Therefore, the model’s response to the I:E-ratio and respiratory rate is evaluated as well.

First, the expected response to the mentioned conditions is discussed. These expectations are based on physiological knowledge and observations of the simulated ventricular preload patterns as discussed in the previous section.

Secondly, model simulations are presented. This involves showing the variations in systolic peaks of both the aortic and pulmonary artery flow during mechanical ventilation for varying conditions. In order to reduce the fluctuations in the variations as mentioned in Section 2.3, the modulation approach proposed by Diepen [2006] is used. This means that instead of the individual systolic peaks during one ventilation period, a modulation envelope based on these peaks is constructed and shown. For more information about this modulation approach, the reader is referred to Diepen [2006].

Subsequently, results found in literature are presented. Since research about respiratory influences on the cardiovascular system during mechanical ventilation is mainly focused on the variations in arterial blood pressure, results from literature about the variations in intrathoracic blood flows are not available for all conditions. Therefore, for some conditions the results of variations in arterial blood pressure are presented. Because we may assume that the variations in arterial blood pressure are proportional to the variations in aortic blood flows [Michard, 2005], the trends between the variations in aortic flow and arterial blood pressure should match. The variations in pulmonary artery flow during mechanical ventilation for varying conditions have not been studied before. This means that no results from literature are available about the variations in these flows.

Next, results from patient recordings are presented. Because no patient data was present that contained information about the intrathoracic blood flows for varying conditions, patient recordings had to be acquired from the hospital. However, acquiring patient data was not trivial due to several problems:

- No systematic examination could be performed. If one wants to perform a systematic examination in which conditions are varied for research purposes, the patient or patient’s relatives have to give written consent. Moreover, the proposal to perform the examination has to be approved by the hospital’s medical-ethical committee. Because the time for writing and getting this approval was not available during the research period, a systematic examination could not be performed. This means that it was impossible to vary conditions in order to assess the influence of the varying conditions on the variations in intrathoracic blood flows. Instead, only some passive recordings could be made.

- The number of patients that could provide useful data was limited. During the model development several assumptions are made. As a result, the model is not applicable to all patients. First of all, patients have to be sedated and fully ventilated which implies that the patient recordings are limited to the operating room (OR) and intensive care unit (ICU). Secondly, patients can have abnormalities that are not modelled by the developed model. Examples of these abnormalities are atrial fibrillation, intra-cardiac shunts and very strong back flows.

- The available time for performing the recordings was very limited. Because in the hospital the patient’s well being is the primary concern, the clinicians did not always have the proper time available to perform the recordings.

- Not all desirable signals were digitally available. The developed system to record and store the intrathoracic blood flows processes the Doppler audio data from an ultrasound device. However, because the ultrasound device did not provide information about the airway pressure, the airway pressure was not digitally available. This implies that calculating the variations in intrathoracic blood flows could not be performed fully automatic, but required some manual intervention that indicated the beginning and end of each ventilation period.
Despite the mentioned problems, patient data from two patients was obtained in the OR. Both patients did not show any of the mentioned abnormalities, and both underwent a bypass operation. The recordings were performed at the beginning and end of the operation, during the time that the patient can be assumed hemodynamically stable for short periods. The variations in the intrathoracic blood flows are quantified as proposed by Feissel et al. [2001]. Each ventilation period the peak velocity variation (PVV) is calculated according to Equation (2.1). In order to reduce some fluctuations in the results, the mean value of five successive ventilation periods is calculated.

Finally, the trends between the simulations, results from literature and patient recordings are compared, and based on the results some conclusions are drawn.

6.2.1 Changing the tidal volume

**Expectation**

Due to the (assumed) linear relation between tidal volume and intrathoracic pressure, increasing the tidal volume results in an increasing intrathoracic pressure. As explained in Section 2.3, the magnitude of the intrathoracic pressure influences the right atrial pressure by increasing the right atrial pressure for increasing intrathoracic pressure. This results in a decreased pressure gradient for venous return, a decreased right ventricular preload, and finally in a decreased right ventricular stroke volume which induces a leftward shift on the Frank-Starling curve (i.e. towards the steep part of the curve). After a couple of heartbeats, this decreased right ventricular stroke volume is propagated to the left side of the heart and results in a decreased left ventricular preload. This will decrease the left ventricular stroke volume and also result in a leftward shift on the Frank-Starling curve. Since the variations in ventricular stroke volume due to ventricular preload changes are larger on the steep part of the Frank-Starling curve, the expected response to an increasing tidal volume is an increase in the variations of both the right and left ventricular stroke volume.

**Simulation**

Changing the tidal volume is simulated by increasing the inspiratory inflow while the inspiratory time is kept constant. This results in a faster increasing lung-thorax volume and in a larger tidal volume at the end of inspiration. The respiratory inflow is increased from 1 l/s to 4 l/s in steps of 1 l/s. The corresponding simulated systolic flow modulation envelopes of the aortic and pulmonary artery flow are shown in Figure 6.7(a) and 6.7(b), respectively. The envelopes indicate that, according to the simulations, increasing the tidal volume increases the variations in both the aortic and pulmonary artery flow. Moreover, we observe from the figures that the increase of the variations in pulmonary artery flow is larger than the increase of the variations in aortic flow. As mentioned in Section 6.1, this suggests that the pulmonary artery flow is more sensitive to intrathoracic pressure changes than the aortic flow is.

**Literature**

Reuter et al. [2003] investigated the influence of the tidal volume on the variations in left ventricular stroke volume (and thus on the accompanying aortic flow). In 20 mechanically ventilated patients they changed the tidal volume between 5, 10 and 15 ml/kg body weight, and found SVV-values of 7%, 15% and 21%, respectively. They concluded that the magnitude of the imposed tidal volume affects the resulting SVV-value by increasing the SVV-value when the tidal volume is increased. As mentioned before, no literature was found about the influence of the tidal volume on the variations in pulmonary artery flows.

**Recording**

Changing the tidal volume during mechanical ventilation is not trivial. In order to ensure that the patient is sufficiently ventilated, the air volume that is supplied to the lungs each minute has to be
Figure 6.7: Simulated systolic flow modulation envelopes for changing tidal volume of (a) aortic flow and (b) pulmonary artery flow. Changing the tidal volume is simulated by changing the respiratory inflow while the inspiratory time is kept constant. The respiratory inflow is changed from 1 l/s to 4 l/s in steps of 1 l/s.

kept constant. This air volume, called the respiratory minute volume (RMV), is calculated according to:

\[ RMV = f \cdot TV \]  

where \( f \) is the respiratory rate (i.e. the number of ventilation periods per minute) and \( TV \) the supplied tidal volume. In order to keep the RMV constant, changes in tidal volume require adjustments to the respiratory rate. This should be kept in mind when comparing the simulations to results from patient recordings.

The calculated PVV-values and used ventilator settings are listed in Table 6.1. An increase in the PVV-value can be observed for both the aortic and pulmonary artery flow when increasing the tidal volume. This indicates that, for both patients, increasing the tidal volume also increases the variations in intrathoracic blood flows. As can be seen in the results of patient 2, the pulmonary artery flow seems more sensitive to the changing intrathoracic pressure than the aortic flow, like observed in the simulations. However, these results are not confirmed by the recordings of patient 1, whereas it should be noted that for this patient, the changing tidal volume was accompanied with an adjusted respiratory rate.

Conclusion

The trends in the simulated aortic flow resemble the trends found in literature and patient recordings. The response to an increasing tidal volume is an increase of the variations in aortic flow, which is in accordance with our expectations. The trends in the simulated pulmonary artery flows are only compared with patient recordings because no literature was available. The trends in the simulations resemble the trends in the patient recordings: when the tidal volume is increased, the variations increase as well. However, because data from only two patients is used and no literature was available that confirmed these findings, these results are only preliminary.

Another interesting observation is that, according to the simulations, the pulmonary artery flow seems more sensitive to intrathoracic pressure changes than the aortic flow. Although these findings are only preliminary, this may be very important because this indicates that the variations in pulmonary artery
6.2. Validation of the model's response to varying conditions

Table 6.1: Mean PVV-values of the aortic and pulmonary artery flow for five successive ventilation periods while changing the tidal volume (TV).

<table>
<thead>
<tr>
<th>Flow type</th>
<th>Time</th>
<th>TV (ml)</th>
<th>I:E</th>
<th>PEEP (cm H$_2$O)</th>
<th>Frequency (per minute)</th>
<th>PVV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>11:38:30</td>
<td>500</td>
<td>1:2</td>
<td>0</td>
<td>14</td>
<td>14.2</td>
</tr>
<tr>
<td>Aortic</td>
<td>11:44:10</td>
<td>700</td>
<td>1:2</td>
<td>0</td>
<td>10</td>
<td>20.1</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>11:33:20</td>
<td>500</td>
<td>1:2</td>
<td>0</td>
<td>14</td>
<td>19.1</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>11:36:30</td>
<td>700</td>
<td>1:2</td>
<td>0</td>
<td>10</td>
<td>22.7</td>
</tr>
<tr>
<td>Patient 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>12:11:50</td>
<td>575</td>
<td>1:2</td>
<td>0</td>
<td>10</td>
<td>7.1</td>
</tr>
<tr>
<td>Aortic</td>
<td>12:12:30</td>
<td>900</td>
<td>1:2</td>
<td>0</td>
<td>10</td>
<td>15.5</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>12:32:00</td>
<td>575</td>
<td>1:2</td>
<td>0</td>
<td>10</td>
<td>6.5</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>12:33:20</td>
<td>900</td>
<td>1:2</td>
<td>0</td>
<td>10</td>
<td>23.5</td>
</tr>
</tbody>
</table>

flow are more much valuable in predicting a patient’s response to fluid loading than currently used measurements such as aortic flow and pressure.

6.2.2 Changing the level of positive end-expiratory pressure

Expectation

Changing the level of the positive end-expiratory pressure (PEEP) changes the intrathoracic pressure. When the level of PEEP is increased, the intrathoracic pressure is increased as well. Like increasing the tidal volume, this results in an increased right atrial pressure and finally in a leftward shift on the Frank-Starling curve for both the right and left ventricle. Thus, the expected response to an increased level of PEEP is an increase in the variations of both the aortic and pulmonary artery flow.

Simulation

The level of PEEP is changed from 4 mm Hg to 24 mm Hg in steps of 4 mm Hg. The corresponding simulated systolic flow modulation envelopes of the aortic and pulmonary artery flow are shown in Figure 6.8(a) and 6.8(b), respectively. For the aortic flow, the variations increase when the level of PEEP is increased. For the pulmonary artery flow, the absolute variations decrease for increasing levels of PEEP, however, the relative variations around the mean value increase. It can be concluded that, according to the simulations, increasing the level of PEEP increases the variations in both the aortic and pulmonary artery flow.

Literature

No results in literature were found about the influence of PEEP on the variations in aortic or pulmonary artery flows during mechanical ventilation. However, Michard et al. [1999] investigated the influence of the level of PEEP on the magnitude of the pulse pressure variation (PPV). In 14 mechanically ventilated patients, they changed the level of PEEP from 0 cm H$_2$O to 10 cm H$_2$O and found mean PPV-values of 9% and 16%, respectively. They concluded that the level of PEEP affects the variations in arterial blood pressure by increasing the variations when the level of PEEP is increased.

Recording

The calculated PVV-values and used ventilator settings are listed in Table 6.2. The results show an increase in the PVV-values of both aortic and pulmonary artery flows when the level of PEEP is increased. This indicates that, for both patients, increasing the level of PEEP also increases the variations in the intrathoracic blood flows. Note that like the tidal volume recording, the pulmonary
Chapter 6. Comparing model simulations with results from literature and patient data

Figure 6.8: Simulated systolic flow modulation envelopes for changing level of PEEP of (a) aortic flow and (b) pulmonary artery flow.

artery flow seems most sensitive to intrathoracic pressure changes according to the recordings of patient 2. However, these results are not confirmed by the recordings of patient 1.

Table 6.2: Mean PVV-values of the aortic and pulmonary artery flow for five successive ventilation periods while changing the level of PEEP.

<table>
<thead>
<tr>
<th>Flow type</th>
<th>Time</th>
<th>TV (ml)</th>
<th>I:E</th>
<th>PEEP (cm H₂O)</th>
<th>Frequency (per minute)</th>
<th>PVV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>11:38:30</td>
<td>500</td>
<td>1:2</td>
<td>0</td>
<td>14</td>
<td>14.2</td>
</tr>
<tr>
<td>Aortic</td>
<td>11:39:20</td>
<td>500</td>
<td>1:2</td>
<td>10</td>
<td>14</td>
<td>20.7</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>11:33:20</td>
<td>500</td>
<td>1:2</td>
<td>0</td>
<td>14</td>
<td>19.1</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>11:35:20</td>
<td>500</td>
<td>1:2</td>
<td>10</td>
<td>14</td>
<td>21.8</td>
</tr>
<tr>
<td><strong>Patient 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic</td>
<td>12:16:20</td>
<td>575</td>
<td>1:2</td>
<td>0</td>
<td>10</td>
<td>9.0</td>
</tr>
<tr>
<td>Aortic</td>
<td>12:17:20</td>
<td>575</td>
<td>1:2</td>
<td>10</td>
<td>10</td>
<td>14.3</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>12:35:10</td>
<td>575</td>
<td>1:2</td>
<td>0</td>
<td>10</td>
<td>8.9</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>12:36:30</td>
<td>575</td>
<td>1:2</td>
<td>10</td>
<td>10</td>
<td>31.3</td>
</tr>
</tbody>
</table>

Conclusion

The trends in the simulated aortic flow resemble the trends found in literature and patient recordings. The response to an increasing level of PEEP is an increase of the variations in aortic flow. The trends in simulated pulmonary artery flows are only compared with results from patient recordings. Results from both the simulations and the patient recordings show an increase of the variations in the pulmonary artery flow when the level of PEEP is increased. However, because data from only two patients is used and no literature was available that confirms our findings, this remains subject for future research.
6.2.3 Changing the I:E-ratio

Expectation

Changing the I:E-ratio changes the ratio between the inspiratory and expiratory time. When using a constant ventilation period, this implies that the inspiratory time is changed. Because venous return is impeded during inspiration, due to the elevated intrathoracic pressure, changing the I:E-ratio also changes the time of impeded venous return. The expected response to an increasing I:E-ratio (i.e. an increasing inspiratory time) is thus an increase in the variations of the intrathoracic blood flows.

Simulation

Changing the I:E-ratio is simulated by changing the inspiratory time while keeping the inspiratory pause and ventilation period constant. The inspiratory time is changed from 1 second to 4 seconds in steps of 1 second. The corresponding simulated systolic flow modulation envelopes of the aortic and pulmonary artery flow are shown in Figure 6.9(a) and 6.9(b), respectively. The envelopes indicate that, according to the simulations, increasing the I:E-ratio results in an increase of the variations in aortic flow. However, contrary to our expectations, the variations in pulmonary artery flow decrease.

Figure 6.9: Simulated systolic flow modulation envelopes for changing I:E-ratios of (a) aortic flow and (b) pulmonary artery flow. Each curve corresponds to a different inspiratory period, as indicated in the legend. Because a constant ventilation period is used, changing the inspiratory period automatically changes the I:E-ratio.

Literature

No results in literature were found about the influence of the I:E-ratio on the variations in aortic or pulmonary artery flows during mechanical ventilation. However, Vedrinne et al. [1997] investigated the influence of the I:E-ratio on the variations in systolic pressure variation (SPV). In 9 mechanically ventilated patients, they changed the I:E-ratio from 1:3 to 1:1 using a constant ventilation period and found mean SPV-values of 6 mm Hg and 11 mm Hg, respectively. They concluded that the I:E-ratio affects the variations in arterial blood pressure by increasing the SPV-value when the I:E-ratio is increased.
Chapter 6. Comparing model simulations with results from literature and patient data

Recording

The calculated PVV-values and used ventilator settings are listed in Table 6.3. Because the I:E-ratio was not changed in the recordings of patient 1, only results of patient 2 are listed. Although the I:E-ratio was changed significantly, significant variations are observed in the calculated PVV-values of only the pulmonary artery flow. This indicates that, for patient 2, the variations in pulmonary artery flow are affected by the changing I:E-ratio, but the variations in aortic flow are not.

Table 6.3: Mean PVV-values of the aortic flow for five successive ventilation periods while changing the I:E-ratio.

<table>
<thead>
<tr>
<th>Flow type</th>
<th>Time</th>
<th>TV (ml)</th>
<th>I:E</th>
<th>PEEP (cm H₂O)</th>
<th>Frequency (per minute)</th>
<th>PVV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 2 Aortic</td>
<td>12:10:00</td>
<td>575</td>
<td>1:2</td>
<td>0</td>
<td>10</td>
<td>6.1</td>
</tr>
<tr>
<td>Aortic</td>
<td>12:11:00</td>
<td>575</td>
<td>2:1</td>
<td>0</td>
<td>10</td>
<td>7.3</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>12:29:10</td>
<td>575</td>
<td>1:2</td>
<td>0</td>
<td>10</td>
<td>6.4</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>12:30:10</td>
<td>575</td>
<td>2:1</td>
<td>0</td>
<td>10</td>
<td>17.4</td>
</tr>
</tbody>
</table>

Conclusion

The trends in the simulated aortic flow resemble the trends found in literature. The response to an increase in the I:E-ratio is an increase of the variations in aortic flow. This response is not confirmed by the patient recordings. However, because data from only one patient is used, this should be subject for further research. For the pulmonary artery flow, the simulations do not agree with the patient recordings. However, because no literature was found and data from only one patient is used, this should be subject for further research as well.

6.2.4 Changing the respiratory rate

Expectation

As can be seen in Figure 6.5 and 6.6, during expiration the systolic peaks of both the aortic and pulmonary artery flow return to the baseline level they had before inspiration. This is probably due to the fact that venous return is not impeded anymore during expiration, and restores to the level it had before inspiration. However, when the expiration period is set too short, the systolic peaks have not returned to this baseline level yet when a new ventilation period starts. For the left side of the heart, this implies that two effects will contribute to the increasing left ventricular preload during inspiration: the squeezing effect of the pulmonary capillaries, and the already increasing venous flow to the left atrium which started during the previous ventilation period. These effects result in an extra increased left ventricular preload during inspiration. For the right side of the heart, the effect of shortening the expiration period will be less because the systolic peaks have almost immediately returned to the baseline level after the large decrease during inspiration. Concluding, the expected response to changing the respiratory rate is a changing systolic flow modulation envelope. Furthermore, it is expected that this effect will be especially significant for the aortic flow.

Simulation

Changing the respiratory rate is simulated by changing the ventilation period while keeping the inspiratory time and inspiratory pause constant. The ventilation period is changed from 6 seconds to 12 seconds in steps of 2 seconds. The corresponding simulated systolic flow modulation envelopes of the aortic and pulmonary artery flow are shown in Figure 6.10(a) and 6.10(b), respectively. For the aortic flow it can be seen that, when using a short ventilation period, the systolic peaks have not returned to the baseline level before a new ventilation period starts. This results in a larger upward
6.2. Validation of the model's response to varying conditions

component during inspiration than when using a long ventilation period, and suggests that the systolic flow modulation envelope of aortic flow depends on the ventilation period. The same reasoning holds for the pulmonary artery flow, but to a smaller extent because the systolic peaks have almost returned to the baseline level for all ventilation periods.

![Figure 6.10](image)

Figure 6.10: Simulated systolic flow modulation envelopes for changing the respiratory rate of (a) aortic flow and (b) pulmonary artery flow.

Literature

No results in literature were found about the influence of the respiratory rate on the respiratory induced variations in blood pressures or flows. Therefore, the simulations cannot be compared to results from literature.

Recording

As explained before, changing the respiratory rate requires adjustments to the tidal volume. Therefore, the respiratory rate was not changed while the other conditions constant were kept constant. Because of this, no patient recordings were available for comparison with the simulation results.

Conclusion

Although the simulations suggest that the respiratory rate influences the systolic flow modulation envelopes of the intrathoracic blood flows, no results were found in literature that confirm these findings. Moreover, because no patient recordings were available in which the respiratory rate was changed while the other conditions were kept constant, the simulations could also not be compared to patient recordings. Therefore, the influence of the respiratory rate on the variations in intrathoracic blood flows remains subject for future research.

6.2.5 Changing the total blood volume

Expectation

As explained before, the relation between ventricular preload and ventricular stroke volume is described by the Frank-Starling curve. On the steep part of the curve, ventricular preload variations result in large stroke volume variations, while on the flat part of the curve, they have a much less marked effect on
Chapter 6. Comparing model simulations with results from literature and patient data

the stroke volume variations. Because, most likely, the ventricular preload increases for increasing total blood volume [Guyton and Hall, 2000], fluid loading induces a rightward shift on the Frank-Starling curve (i.e. towards the flat part of the curve). Therefore, the expected response to an increased total blood volume is a decrease of the variations in intrathoracic blood flows during mechanical ventilation.

Simulation

Changing the total blood volume is simulated by gradually administering blood to the vena cava. The total blood volume is changed from 4600 ml to 5500 ml in steps of 50 ml. After 50 ml of blood is administered, the model is simulated for one minute to ensure that the administered blood is distributed in the cardiovascular system and a new equilibrium has been reached. Next, the systolic flow modulation envelopes are calculated. The magnitudes of the variations in the systolic flow modulation envelopes are shown in Figure 6.11. The trends in the figures indicate that, according to the simulations, the variations in both the aortic and pulmonary artery flow decrease when the total blood volume is increased.

![Figure 6.11: Magnitudes of the variations in the simulated systolic flow modulation envelopes during stepwise fluid loading of (a) aortic flow and (b) pulmonary artery flow. The total blood volume is changed from 4600 ml to 5500 ml in steps of 50 ml.](image)

Literature

Several authors investigated the patient's response to a changing total blood volume. Reuter et al. [2002a] performed fluid loading in 20 mechanically ventilated patients, and found a significant decrease in both SVV and SPV-values. Feissel et al. [2001] investigated the changes in PVV-values due to fluid loading in 19 mechanically ventilated patients and also found a significant decrease after fluid loading. The same results, for different patient populations and ventilator settings, were found by [Preisman et al., 2005; Slama et al., 2002; Monnet et al., 2005]. They all concluded that the variations in blood pressures and flows decrease after fluid loading.

Recording

A prerequisite to investigate a patient's response to fluid loading, is that the patient can be assumed hemodynamically stable during the time that the fluid is administered. In the operating room, however, the time that a patient can be assumed hemodynamically stable is very short. Moreover, because we
could only make passive recordings, it was not possible to keep the patient hemodynamically stable during the period of fluid loading (administering 500 ml of blood took about 30 minutes). Therefore, no patient recordings were made that can be used to evaluate the patient’s response to fluid loading.

Conclusion

No patient recordings were available for evaluating the patient’s response to fluid loading. However, numerous authors investigated the patient’s response to fluid loading. They all concluded that fluid loading decreases the variations in blood flows and pressures. The trends in the simulations agree with these conclusions. After gradually administering fluid, the variations in the systolic flow modulation envelopes of both the aortic and pulmonary artery flow decrease. It can be concluded that the model captures the trends during fluid loading that were found in literature.

6.3 Conclusions

Based on the comparisons between simulation data, results from literature and patient recordings, several conclusions can be drawn. First of all, the trends in the varying ventricular preload and afterload patterns during mechanical ventilation, which are responsible for the variations in intrathoracic blood flows, resemble the trends found in literature. Moreover, the trends in the cyclic variations of both the aortic and pulmonary artery flow resemble the trends found in literature. This suggests that the basic mechanisms during mechanical ventilation are simulated correctly, and thus the coupling between the cardiovascular and respiratory system is modelled correctly.

Secondly, the model’s response to varying conditions seems to resemble the patient’s response as found in literature and patient recordings. However, one should remark that these results are only preliminary because of two reasons. The first reason is that little literature was available which could be used for comparison because research about the variations during mechanical ventilation is mainly focused on the variations in arterial blood pressure. The second reason is that only a limited patient data was available because several factors limited the acquisition of patient data. However, despite the mentioned reasons, the simulation results are promising. For all conditions, the trends in the simulations were confirmed by the results from literature and patient recordings, which suggests that the respiratory influences during mechanical ventilation are modelled correctly.

Finally, two interesting observations were made from the simulations:

- The variations in pulmonary artery flow during mechanical ventilation have not been studied before. Both the simulations and patient recordings, however, show that during mechanical ventilation also cyclic variations in pulmonary artery flow occur. The simulations even show that the pulmonary artery flow is more sensitive to intrathoracic pressure changes than the aortic flow is. This suggests that measurements of the variations in pulmonary artery flow might be more valuable in predicting a patient’s response to fluid loading than currently used measurements such as aortic pressure and aortic flow.

- The simulations show that the respiratory rate influences the variations in intrathoracic blood flows. Such influences can especially be observed in the aortic flow. During expiration, the systolic peaks return to the baseline level that they had before inspiration. However, when the expiration period is set too short, the systolic peaks have not returned to this baseline level when a new ventilation period starts. This suggests that the respiratory rate should be taken into account when using the variations in intrathoracic blood flows as an indicator for a patient’s filling status.

Both observations have not been reported in literature, and should therefore be subject for future research.
Chapter 7

Estimating the unknown model parameters based on patient data

Although the developed model is promising in describing the variations in intrathoracic blood flows during mechanical ventilation, to make it useful, the model must be capable describing the hemodynamics of a specific patient. Therefore, the model must be tuned to a patient. This involves adjusting the patient specific model parameters until the model output matches with recorded patient data. Because of the complex interaction between the several parameters, it is impossible to adapt the parameters manually. Therefore, a method is required that automatically estimates the patient specific model parameters based on recorded patient data.

This chapter deals with the estimation of these model parameters. First the estimation problem and the used parameter estimation algorithm will be explained. Next, this algorithm is used to estimate the patient specific model parameters of the respiratory model. The implementation of the algorithm will be explained, and the results on simulation data will be presented. Subsequently, the implementation of the algorithm and the results on simulation data will be presented for estimation of the patient specific model parameters of the cardiovascular model. Finally, some conclusions will be presented, as well as some recommendations for further research.

7.1 Parameter estimation and the least-mean-square algorithm

Parameter estimation involves the process of estimating the unknown parameters of a system based on measured data of the system. This is accomplished by adjusting the unknown model parameters iteratively until the error (i.e. the difference between system and model output) is minimized.

A simplified block diagram of the parameter estimation process is shown in Figure 7.1. A known input \( x \) is applied to both the system and the model. The resulting system output \( y \) and model output \( \hat{y} \) are subtracted to form an error \( e = y - \hat{y} \), which is used as a basis for an optimization criterion in order to generate a new estimate of the unknown model parameters \( \phi \). This continues iteratively until the system response and model response match closely enough as specified by the optimization criterion.

Based on the error signal, several optimization criteria exist. In this thesis, the minimum mean-square error (MMSE) criterion is used. This criterion aims at minimizing the mean squared error (MSE). The MSE, of a data set that contains \( n \) samples, can be defined as:

\[
MSE = \frac{1}{n} \sum_{i=1}^{n} (e(i))^2.
\]  

(7.1)

Several algorithms exist to achieve the MMSE criterion. The least-mean-square (LMS) algorithm is the
Chapter 7. Estimating the unknown model parameters based on patient data

Figure 7.1: Simplified block diagram of the parameter estimation process (adapted from Raol et al. [2004]). Based on the error between the system output and model output, the parameters are adapted iteratively until the error satisfies the optimization criterion.

most widely used algorithm because it has several desirable properties [Nascimento, 2003]: the LMS algorithm is easily implemented, has a low computational cost, is robust to numerical errors, and has good tracking performance.

The LMS algorithm incorporates an iterative procedure that makes successive adaptations to the parameters in order to minimize the mean squared error. Every iteration, the LMS algorithm adapts the parameters based on the error signal according to:

$$\phi_i(k+1) = \phi_i(k) - \frac{1}{2} \mu \cdot \left[ \frac{\partial(e(k)^2)}{\partial \phi_i(k)} \right]$$  \hspace{1cm} (7.2)

where $\phi_i$ is the estimated value of the $i^{th}$ parameter, $k$ the iteration number, and $\mu$ the adaptation constant. The term within the square brackets defines the gradient of the squared-error with respect to the $i^{th}$ parameter. This gradient is a vector which points in the direction of the change in the parameter that will cause the greatest increase in the error signal. However, because the goal of MMSE is to minimize the mean squared error, Equation (7.2) updates the parameter value in the opposite direction of the gradient. The magnitude of the step that is made in the opposite direction of the gradient is determined by the adaptation constant $\mu$. A large value of $\mu$ results in large steps, which implies that the parameter values converge quickly. However, when using a large value of $\mu$, small errors (e.g. induced by noise) result in large fluctuations of the parameter values. A decrement of $\mu$ decreases these fluctuations, but instead the parameter values converge more slowly. Therefore, the choice of $\mu$ involves a tradeoff between speed and accuracy (i.e. immunity to noise) of adaptation.

Summarizing, the LMS algorithm adjusts each parameters every iteration in the opposite direction of the gradient of the squared error with respect to that parameter. Therefore, the squared error converges to a minimum\(^1\), and if the model's structure equals the system's structure, the parameter values converge to the system values as well.

\(^1\)Note that in nonlinear systems, this algorithm can also converge to a local minimum. This implies that initial parameter values become important. The closer the initial parameter values are to the system values, the more likely the parameter values will converge to these system values.
7.2 Estimating the respiratory system parameters

7.2.1 Implementing the LMS algorithm

In order to estimate the unknown model parameters of the respiratory system, a mathematical model has to be defined that describes the input-output relation of the developed respiratory model. For convenience, this respiratory model is depicted again in Figure 7.2.

![Figure 7.2: Model of the respiratory system, used for the estimation of the unknown model parameters of the respiratory system.](image)

The recorded patient data consists of the airway pressure and airway flow, both measured at the mouth of the patient. The corresponding relation between the airway pressure $P_{aw}$ and the airway flow $Q_{aw}$ can be described as:

$$P_{aw}(k) = R_{aw,ins}Q_{aw,ins}(k) + R_{aw,exp}Q_{aw,exp}(k) + \frac{V_{lt}(k)}{C_{lt}}$$ (7.3)

where $R_{aw,ins}$ and $R_{aw,exp}$ are the inspiratory and expiratory airway resistance, $C_{lt}$ the lung-thorax compliance, $Q_{aw,ins}$ and $Q_{aw,exp}$ the airway flow recorded at the patient's mouth during inspiration and expiration, and $V_{lt}$ the lung-thorax volume. Because the lung-thorax volume cannot be measured directly, it has to calculated from the flow recordings. The lung-thorax volume is calculated according to:

$$V_{lt}(k) = V_{lt}(0) + \Delta t \cdot \sum_{i=t}^{k} (Q_{aw}(i))$$ (7.4)

where $\Delta t$ is the sampling interval and $V_{lt}(0)$ the initial volume at the start of inspiration. Because this initial volume cannot be measured directly, it has to be estimated from the initial pressure, which is known (the level of PEEP). Therefore, the initial volume is defined as $(P_{peep} \cdot C_{lt})$, which results in the following relation for $P_{aw}(k)$:

$$P_{aw}(k) = R_{aw,ins}Q_{aw,ins}(k) + R_{aw,exp}Q_{aw,exp}(k) + \frac{\Delta t \cdot \sum_{i=1}^{k} (Q_{aw}(i)) + P_{peep}}{C_{lt}}.$$ (7.5)

Now that the respiratory model has been described mathematically, the error between the system output and the model output has to be calculated. This error is defined as:

$$e(k) = P_{aw}(k) - \tilde{R}_{aw,ins}(k)Q_{aw,ins}(k) - \tilde{R}_{aw,exp}(k)Q_{aw,exp}(k) - \frac{\Delta t \cdot \sum_{i=1}^{k} (Q_{aw}(i))}{C_{lt}(k)}.$$ (7.6)

where $\tilde{R}_{aw,ins}(k)$, $\tilde{R}_{aw,exp}(k)$, and $\tilde{C}_{lt}(k)$ are the estimated values of the parameters at iteration $k$. 

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**7.2. Estimating the respiratory system parameters**
Finally, the parameter values are adapted each iteration analogously to Equation (7.2). It can be shown that the equations for adapting the parameters are defined as:

\[
\begin{align*}
\hat{R}_{aw,ins}(k + 1) &= \hat{R}_{aw,ins}(k) - \mu \cdot e(k) \cdot (-Q_{aw,ins}(k)), \\
\hat{R}_{aw,exp}(k + 1) &= \hat{R}_{aw,exp}(k) - \mu \cdot e(k) \cdot (-Q_{aw,exp}(k)), \\
\hat{C}_t(k + 1) &= \hat{C}_t(k) - \mu \cdot e(k) \cdot \frac{\Delta t}{(\hat{C}_t(k))^2} \sum_{i=1}^{k} (Q_{aw}(i)).
\end{align*}
\]  

(7.7)  
(7.8)  
(7.9)

### 7.2.2 Results

Because the required patient data that contained information about the airway pressure and airway flow simultaneously was not available, the implemented LMS algorithm could only be tested on simulation data. This simulation data consists of simulated airway pressure and flow. In order to test if the algorithm is robust to noise in the recordings, simulation data disturbed with noise is also constructed. This noise consists of additive zero-mean Gaussian noise samples with a standard deviation (SD\_N) that is a certain percentage of the signal power.

Table 7.1 lists the original and estimated parameter values at the end of the simulation data, for different noise levels. The simulated airway flow and the accompanying simulated and estimated airway pressure are shown in Figure 7.3(a) and 7.3(b), respectively. The evolution of the error over time and the convergence characteristics of the parameter estimates are shown in Figure 7.4(a) and 7.4(b), respectively. Because the parameters are not within the same range, the parameter estimates are normalized to one in order to show the convergence of the parameters in a single graph.

**Table 7.1: Estimated parameter values of the respiratory system at the end of the simulation data for different noise levels.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original value (SD_N=0%)</th>
<th>Estimated value (SD_N=5%)</th>
<th>Estimated value (SD_N=10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_t</td>
<td>1.000 \cdot 10^{2}</td>
<td>1.000 \cdot 10^{2}</td>
<td>1.019 \cdot 10^{2}</td>
</tr>
<tr>
<td>R_aw,ins</td>
<td>1.000 \cdot 10^{-3}</td>
<td>1.002 \cdot 10^{-3}</td>
<td>0.934 \cdot 10^{-3}</td>
</tr>
<tr>
<td>R_aw,exp</td>
<td>1.000 \cdot 10^{-2}</td>
<td>1.000 \cdot 10^{-2}</td>
<td>0.978 \cdot 10^{-2}</td>
</tr>
</tbody>
</table>

Figure 7.3: Time course of the simulated airway flow (a), and the accompanying simulated and estimated airway pressure (b). Noise is absent.
7.3. Estimating the cardiovascular system parameters

7.3.1 Implementing the LMS algorithm

In order to estimate the unknown model parameters of the cardiovascular system, a mathematical model has to be defined that describes the input-output relation of the cardiovascular system. For this research, it is assumed that the measured patient data consists of the heart rate, the aortic and pulmonary artery flow, the minimum and maximum volumes of the left and right ventricles, and the aortic and pulmonary artery pressure. These patient data can be obtained non-invasively using echocardiography and ultrasound, or invasively via catheters that are often used in the OR and the ICU [Hann et al., 2006]. Moreover, the intrathoracic pressure, which can be estimated from the respiratory model, is assumed to be known.

Because the developed model is a closed-loop model, it is difficult to define an input-output relation. However, since heart valves allow blood flow during some phases of the cardiac cycle, and block blood flow during other, the cardiovascular system can be split up into several open-loop models during the different phases of the cardiac cycle. These include the left side of the heart, the right side of the heart, the pulmonary circulation, and the systemic circulation. Because the structure of the left and right side of the heart is the same, the implementation and results of the LMS algorithm will be discussed only for the left heart side. Based on the same reasoning, only the systemic circulation will be discussed.

The heart

During left ventricular ejection, the left ventricular outflow valve is open and the inflow valve is closed. As a result, blood flow can only leave the left ventricle. The (open-loop) model of the left ventricle, during left ventricular ejection, is depicted in Figure 7.5.

In order to estimate the unknown parameters of the left ventricle, a mathematical model has to be defined that describes the relation between the aortic pressure $P_{ao}$ and the aortic flow $Q_{ao}$. This relation can be defined as:

$$P_{ao}(t) = P_{ic}(t) + P_{pca}(V_{tor}) + P_{iv}(t) - L_{ao} \frac{dQ_{ao}}{dt} - R_{ao} Q_{ao}(t)$$  \hspace{1cm} (7.10)
Chapter 7. Estimating the unknown model parameters based on patient data

Figure 7.5: Model of the left ventricle during the ejection phase.

where $P_{it}$ is the intrathoracic pressure, $P_{pcd}$ the pericardial pressure, $P_{iv}$ the left ventricular pressure, and $L$ and $R$ are the inductance and resistance, respectively. Inserting Equations (4.11) and (5.8) into (7.10), and transforming Equation (7.10) into the discrete domain, results in the following relation for $P_{ao}(k)$:

$$P_{ao}(k) = P_{it}(k) + P_{0,pcd}(e^{\lambda_{pcd}(V_{tot}(k)-V_{pcd})}-1) + e_{iv}(k)E_{es}(V_{iv}(k)-V_d) +$$

$$(1 - e_{iv}(k))P_0(e^{\lambda_{iv}(V_{iv}(k)-V_d)} - 1) - L_{ao}Q_{ao}(k) - R_{ao}Q_{ao}(k - 1) - R_{ao}Q_{ao}(k). \quad (7.11)$$

Because the left ventricular volume $V_{iv}$ and the pericardial volume $V_{tot}$ cannot be measured directly, both have to be calculated from the flow recordings. The left ventricular volume can be calculated analogously to Equation (7.4), where the initial volume is the volume at the beginning of the ejection phase (i.e. the maximal volume). The pericardial volume can be calculated by calculating the right ventricular volume as well, and summing up the volumes of the left and right ventricle, analogously to Equation (4.14).

Now that the left ventricular model has been described mathematically, the error between the system output and model output can defined as:

$$e(k) = P_{ao}(k) - P_{it}(k) - P_{0,pcd}(e^{\lambda_{pcd}(V_{tot}(k)-V_{pcd})}-1) -$$

$$e_{iv}(k)E_{es}(k)(V_{iv}(k) - \bar{V}_d(k)) - (1 - e_{iv}(k))P_0(e^{\lambda_{iv}(V_{iv}(k)-\bar{V}_d(k)} - 1) +$$

$$L_{ao}Q_{ao}(k) - Q_{ao}(k - 1) + R_{ao}Q_{ao}(k) \quad (7.12)$$

where (\*) denotes that the parameter values are estimated values.

Finally, the parameters have to be adapted. Although any of the parameters in Equation (7.12) can be used for adaptation, selecting appropriate parameters is important. If too few parameters are chosen, the parameter estimation algorithm may not converge to a solution within the required accuracy. If too many parameters are chosen, this can result in unnecessary long computing times and non-unique solutions. For approximately the same ventricular model, Hann et al. [2006] argued that the parameters $P_{0,pcd}$, $\lambda_{pcd}$, $V_{0,pcd}$, $V_d$, $\lambda_{iv}$, and $V_0$ may be assumed generic. Using this assumption, the following parameters remain for adaptation: $E_{es}$, $L_{ao}$, $R_{ao}$, and $P_0$. Analogously to Equation (7.2), it can be shown that the equations for adapting these parameters are defined as:
7.3. Estimating the cardiovascular system parameters

\[ \dot{E}_{es}(k+1) = E_{es}(k) - \mu \cdot e(k) \cdot (-e_{lv}(k)(V_{lv}(k) - V_0)), \quad (7.13) \]

\[ \dot{I}_{ao}(k+1) = I_{ao}(k) - \mu \cdot e(k) \cdot \frac{Q_{ao}(k) - Q_{ao}(k-1)}{\Delta t}, \quad (7.14) \]

\[ \dot{P}_{ao}(k+1) = P_{ao}(k) - \mu \cdot e(k) \cdot (Q_{ao}(k)), \quad (7.15) \]

\[ \dot{P}_{0}(k+1) = P_{0}(k) - \mu \cdot e(k) \cdot (-1 - e_{lv}(k))(e_{lv}(V_{lv}(k) - V_0) - 1)). \quad (7.16) \]

The circulation

During the time that the right ventricular inflow valve is closed, no flow enters the right ventricle. As a result, blood flow can only enter the systemic circulation. The (open-loop) model of the systemic circulation, during the time that the right ventricular inflow valve is closed, is depicted in Figure 7.6.

Figure 7.6: Model of the systemic circulation during the time the right ventricular inflow valve is closed.

In order to estimate the unknown parameters, a mathematical model has to be defined that describes the relation between the aortic pressure \( P_{ao} \) and aortic flow \( Q_{ao} \). Combining the following equations:

\[ V_{ao}P_{ao} = C_{ao}Q_{ao}, \quad (7.17a) \]

\[ V_{vc}P_{ao} = C_{vc}Q_{ao} + P_{sys}Q_{ao}, \quad (7.17b) \]

\[ Q_{ao} = Q_1 + Q_2, \quad (7.17c) \]

and calculating the volumes \( V_{ao} \) and \( V_{vc} \) analogously to Equation (7.4), it can be shown that the relation between the aortic pressure and aortic flow is described as:

\[ P_{ao}(k) = \frac{R_{sys}Q_{ao}(k) + \frac{R_{sys}C_{vc}}{\Delta t}P_{ao}(k-1) + \frac{\Delta t}{C_{vc}} \sum_{i=1}^{k} (Q_{ao}(i)) - \frac{C_{ao}}{C_{vc}} P_{0,a0} - P_{0,vc}}{1 + \frac{C_{ao}}{C_{vc}} + \frac{R_{sys}C_{vc}}{\Delta t}}. \quad (7.18) \]

Now that the model of the systemic circulation has been described mathematically, the error between the system output and the model output has to be calculated. This error is defined as:

\[ e(k) = (1 + \frac{\bar{C}_{ao}(k)}{\bar{C}_{vc}(k)})P_{ao}(k) - \bar{R}_{sys}(k)Q_{ao}(k) + \bar{C}_{ao}(k)\bar{R}_{sys}(k)\frac{P_{ao}(k) - P_{ao}(k-1)}{\Delta t} - \frac{\Delta t}{\bar{C}_{vc}(k)} \sum_{i=1}^{k} (Q_{ao}(i)) + \frac{\bar{C}_{ao}(k)}{\bar{C}_{vc}(k)} \bar{P}_{0,a0}(k) + \bar{P}_{0,vc}(k) \quad (7.19) \]
where *( ) denotes that the parameter values are estimated values. Although Equation (7.19) can be used to estimate the unknown parameters, combining parameters reduces the interaction between the parameters during adaptation. This results in the following relation for e(k):

\[
e(k) = \left(1 + \frac{\tilde{\phi}_1(k)\tilde{\phi}_2(k)}{\tilde{\phi}_3(k)}\right)P_{ao}(k) - \tilde{\phi}_3(k)Q_{ao}(k) + \frac{\tilde{\phi}_2(k)P_{ao}(k) - P_{ao}(k - 1)}{\Delta t} \sum_{i=1}^{k}(Q_{ao}(i)) + \tilde{\phi}_4(k) \tag{7.20}
\]

where \( \tilde{\phi}_1 = \frac{1}{C_{ao}}, \tilde{\phi}_2 = \tilde{C}_{ao}R_{sys}, \tilde{\phi}_3 = R_{sys}, \) and \( \tilde{\phi}_4 = \frac{\tilde{C}_{ao}P_{0,ao} + \tilde{P}_{0,vc}}{\tilde{C}_{ao}}. \) Although the parameters \( P_{0,ao} \) and \( P_{0,vc} \) are not uniquely defined by \( \tilde{\phi}_4, \) using both Equation (7.17a) and the estimate \( \tilde{\phi}_4, P_{0,ao} \) and \( P_{0,vc} \) can be calculated separately.

Finally, each iteration the parameter values have to be adapted analogously to Equation (7.2). It can be shown that the equations for adapting the parameters are defined as:

\[
\begin{align*}
\tilde{\phi}_1(k + 1) &= \tilde{\phi}_1(k) - \mu \cdot e(k) \cdot \left(\frac{\tilde{\phi}_2(k)}{\tilde{\phi}_3(k)}\right)P_{ao}(k) - \Delta t \sum_{i=1}^{k}(Q_{ao}(i))), \tag{7.21} \\
\tilde{\phi}_2(k + 1) &= \tilde{\phi}_2(k) - \mu \cdot e(k) \cdot \left(\frac{\tilde{\phi}_1(k)}{\tilde{\phi}_3(k)}\right)P_{ao}(k) + \frac{P_{ao}(k) - P_{ao}(k - 1)}{\Delta t}, \tag{7.22} \\
\tilde{\phi}_3(k + 1) &= \tilde{\phi}_3(k) - \mu \cdot e(k) \cdot \left(-\frac{\tilde{\phi}_1(k)\tilde{\phi}_2(k)}{\tilde{\phi}_3(k)^2}P_{ao}(k) - Q_{ao}(k))\right), \tag{7.23} \\
\tilde{\phi}_4(k + 1) &= \tilde{\phi}_4(k) - \mu \cdot e(k) \cdot (1). \tag{7.24}
\end{align*}
\]

7.3.2 Results

Because no patient data was available that contained the required signals simultaneously, the implemented LMS algorithm could only be tested on simulation data. For both the ventricular and circulation model, this simulation data consist of simulated aortic pressures and flows. In order to test if the algorithm is robust to noise in the recordings, simulation data disturbed with noise is also constructed. This noise consists of additive zero-mean Gaussian noise samples with a preset standard deviation \( \text{SD}_N \) of the signal power.

The heart

Table 7.2 lists the original and estimated parameter values at the end of the simulation data, for different noise levels. One period of simulated aortic flow and the accompanying simulated and estimated aortic pressure is shown in Figure 7.7(a) and 7.7(b), respectively. Because the parameters did not converge in one period, several periods were concatenated until convergence was achieved. The evolution of the error over time and the convergence characteristics of the parameter estimates are shown in Figure 7.8(a) and 7.8(b), respectively. Note that because the parameters values are not within the same range, the parameter estimates are normalized to one in order to show the convergence of the parameter values in a single graph.

From the results it can be concluded that, if the model's structure is good, the parameter values of the left ventricle can be estimated rather accurately. However, it should be noted that the convergence time is quite long. More optimal tuning of the adaptation constant \( \mu \) is therefore desirable in order to minimize the convergence time. More optimal tuning of the adaptation constant could, for example, be achieved by using the normalized LMS algorithm, which uses a variable adaptation constant. More information about the normalized LMS algorithm can be found in [Slock. 1993].
Table 7.2: Estimated parameter values of the left ventricle at the end of the simulation data for different noise levels.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Original value (SDN=0%)</th>
<th>Estimated value (SDN=5%)</th>
<th>Estimated value (SDN=10%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{es}$</td>
<td>$4.543 \cdot 10^8$</td>
<td>$4.543 \cdot 10^8$</td>
<td>$4.551 \cdot 10^8$</td>
</tr>
<tr>
<td>$L_{ao}$</td>
<td>$3.000 \cdot 10^6$</td>
<td>$3.000 \cdot 10^6$</td>
<td>$2.995 \cdot 10^6$</td>
</tr>
<tr>
<td>$R_{ao}$</td>
<td>$2.750 \cdot 10^6$</td>
<td>$2.751 \cdot 10^6$</td>
<td>$2.724 \cdot 10^6$</td>
</tr>
<tr>
<td>$P_0$</td>
<td>$1.682 \cdot 10^2$</td>
<td>$1.702 \cdot 10^2$</td>
<td>$1.839 \cdot 10^2$</td>
</tr>
</tbody>
</table>

Figure 7.7: Time course of the simulated aortic flow (a), and the accompanying simulated and estimated aortic pressure (b). Noise is absent.

Figure 7.8: Evolution of the error over time (a), and the convergence characteristics of the normalized parameter estimates over time (b). Noise is absent.

The circulation

Table 7.3 lists the original and estimated parameter values of the systemic circulation at the end of the simulation data. The simulated aortic flow, and accompanying simulated and estimated aortic pressure, are shown in Figure 7.9(a) and 7.9(b), respectively. The evolution of the error over time and the convergence characteristics of the parameter estimates are shown in Figure 7.10(a) and 7.10(b), respectively. Again, the parameter estimates are normalized to one in order to show the convergence of the different parameters in a single graph.
Chapter 7. **Estimating the unknown model parameters based on patient data**

Although the results seem good, one remark should be made. The simulations showed that the accuracy of the results is dependent on the initial parameter values and on the level of noise. Another set of initial parameter values or addition of noise can lead to other solutions, or even to instable solutions. Therefore it can be concluded that, although the results are nice for clean signals and particular initial parameter values, further research is necessary to estimate the parameter values of the circulation when the recorded signals are heavily disturbed with noise (which will be the case in general).

**Table 7.3:** *Estimated parameter values of the systemic circulation at the end of the simulation data.*

<table>
<thead>
<tr>
<th>Parameter ( \phi_i )</th>
<th>Original value ( \phi_i )</th>
<th>Estimated value ( \phi_i )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \phi_1 )</td>
<td>( 6.891 \cdot 10^{-7} )</td>
<td>( 7.008 \cdot 10^{-7} )</td>
</tr>
<tr>
<td>( \phi_2 )</td>
<td>( 3.380 \cdot 10^9 )</td>
<td>( 3.380 \cdot 10^9 )</td>
</tr>
<tr>
<td>( \phi_3 )</td>
<td>( 3.200 \cdot 10^8 )</td>
<td>( 3.200 \cdot 10^8 )</td>
</tr>
<tr>
<td>( \phi_4 )</td>
<td>( 3.786 \cdot 10^2 )</td>
<td>( 3.741 \cdot 10^2 )</td>
</tr>
</tbody>
</table>

**Figure 7.9:** *Time course of the simulated aortic flow (a), and the accompanying simulated and estimated aortic pressure (b). Noise is absent.*

**Figure 7.10:** *Evolution of the error over time (a), and the convergence characteristics of the normalized parameter estimates over time (b). Noise is absent.*
7.4 Conclusions

Using simulation data, the parameters of the respiratory parameters are adapted within sufficient accuracy and time. Even when the airway pressure and flow is disturbed with different noise levels, the parameters can be estimated within an error of a few percent.

The estimation of the cardiovascular parameters is more complex because defining an input-output relation of a closed-loop model is more difficult. However, because the heart valves prevent blood flow during several phases of the cardiac cycle, the model is split up into several open-loop models: a ventricular model and a circulation model. The parameters of the ventricular model can be estimated rather accurately, even if the signals are disturbed with noise. The parameters of the systemic circulation can be estimated as well, but it was found that the solution was dependent on the set of initial parameter values and on the level of noise in the recordings. Because in practice the recordings are always disturbed with noise, further research is necessary to estimate the parameters of the circulation more reliably.

Because no patient data was available or could be obtained that contained all necessary signals simultaneously, the parameter estimation algorithm is only tested on simulation data. Further research is necessary to test the algorithm on patient data, and enable it to be eventually useful for making a quantitative model validation. This will also prove if the made assumptions (e.g. fixing several ventricular parameters at generic values) are justified. Therefore, it is recommended to extend the developed system that can record the intrathoracic blood flows by enabling it to record the patient’s heart rate and (intrathoracic) pressures simultaneously as well. Moreover, a method should be developed that can estimate the maximum and minimum ventricular blood volume during one heartbeat.
Chapter 8
Conclusions and recommendations

8.1 Conclusions

A new patient specific model has been developed that has potential to predict a patient's response to fluid loading. This model describes the essential dynamics of the cardiovascular system, and also includes the influences of the respiratory system during mechanical ventilation. Although several cardiovascular models exist in literature, none of these models focuses on the combination of describing the respiratory induced influences during mechanical ventilation and the minimal modelling approach (i.e. describe the essential dynamics with a minimum number of parameters). The former is important because these influences might reveal information about how a patient will respond to fluid loading, the latter is important because only limited patient data will be available to estimate the unknown model parameters.

In order to compare model simulations with patient recordings, a system has been developed to record and store intrathoracic blood flows. The system obtains Doppler audio data from an ultrasound device, available in the hospital. By processing this data, the velocity profile of the blood flow in the vessel of interest is constructed. Based on this velocity profile, the system automatically calculates the blood flow profiles, by assuming a constant cross-sectional vessel area and making an estimation of the mean blood velocity. The system has been shown to reproduce the velocity profiles as constructed by the ultrasound device. Because no in-vitro set-up was available for validation, the recorded blood flows could only be compared with manually obtained results, calculated by a trained clinician. The automatically calculated flows show good correlation with the manually calculated results, the error made is within 5%. This indicates that the developed system can be used for continuous assessment of the intrathoracic blood flows, as accurate as manual calculations would be.

A start has been made with a qualitative model validation. Trends in simulated ventricular preload patterns and intrathoracic blood flows during mechanical ventilation have been shown to match with results found in literature. Moreover, trends in simulated intrathoracic blood flows during mechanical ventilation have been compared to results found in literature and results from patient recordings for varying conditions (i.e. varying ventilator settings and changing total blood volume). This comparison is only preliminary due to two reasons: the available literature about the variations in intrathoracic blood flows was sparse and several factors limited patient data acquisition. However, the trends in the simulations are consistent with the trends found in literature and patient recordings, which suggests that the model is capable of simulating the variations in intrathoracic blood flows during mechanical ventilation reliably.

In order to perform a quantitative model validation, a parameter estimation routine has been developed that estimates the unknown model parameters based on recorded patient data. These patient data can be readily obtained non-invasively using echocardiography and Doppler ultrasound. The unknown
model parameters are adjusted until the error (i.e. the difference between recorded and simulated data) is minimized. Based on simulation data, the respiratory model parameters can be estimated accurately, even if the signals are disturbed with noise. Using assumptions found in literature, the major parameters of both ventricles can also be estimated accurately. The estimation of the parameters of the circulation did, however, impose some problems. It was found that the parameter estimates are dependent on both the initial conditions and on the level of noise. Therefore, reliable estimation of these parameters requires further research. Because the necessary patient data could not be recorded simultaneously, the performance of the parameter estimation routine has not been tested on patient data. Therefore, a quantitative model validation is not performed.

It can be concluded that the ability of the developed model to describe the variations in intrathoracic blood flows during mechanical ventilation indicates that it has potential to predict a patient's response to fluid loading and, eventually, assist clinicians with diagnosis and therapy selection for patients that suffer shock conditions. However, because a qualitative validation could not be finished and also a quantitative validation could not be performed, future research is necessary in order to give a general assertion of the model’s usability in predicting a patient’s response to fluid loading.

8.2 Recommendations

The developed model has been shown to simulate the major trends in intrathoracic blood flows during mechanical ventilation. However, several assumptions were made to minimize the number of model parameters at the expense of physiological accuracy. Further modifications to the model could enable it to be more physiologically accurate, and make it applicable to more patients. Examples of potential modifications include:

- The heart valves are modelled as ideal diodes. Although small back flows always occur when the heart valves close, these flows can be neglected in general. However, patients that suffer heart valve dysfunction might have significant back flows which cannot be neglected. More accurate modelling of the heart valve dynamics would enable the model to describe the hemodynamics of patients that suffer heart valve dysfunction as well.

- Although the heart rate can be adjusted in the model, the model assumes a roughly constant heart rate. However, several abnormalities (e.g. atrial fibrillation) can cause disturbances in the regular rhythm of the heartbeat. These disturbances are called arrhythmias. Addition of an algorithm that can handle these arrhythmias would enable the model to describe the hemodynamics of patients that suffer arrhythmias as well.

- Because it is assumed that both lungs behave roughly in the same way, the lung-thorax compartment is modelled as a single compliant chamber. However, several lung diseases can disprove this assumption (i.e. the compliance and resistance of the left and right lung are not similar). Modelling the lungs by two compliant chambers, one for each lung, would enable the model to capture lung dynamics of patients that suffer a lung disease as well.

- Because the atria are neglected, both heart sides are modelled by a single compliant chamber that represents the ventricle. This implies that the model does not contain atrioventricular valves and the accompanying atrioventricular flows. Therefore, the influences of the respiratory system on these flows could not be investigated. Addition of atria would enable the use of recorded atrioventricular flow data for investigation of the influences of the respiratory system on these flows.

Although these potential modifications can increase physiological accuracy, care should be taken to only make modifications if they make a significant and necessary contribution to the physiological accuracy, because every modification will probably increase the number of unknown model parameters that have to be estimated.
The qualitative model validation could not be finished due to the limited available patient data. Recordings from more patients should be used to validate the model further for numerous patients and for various circumstances. Moreover, these patient recordings should be made according to an extensive and approved measurement protocol. This provides better assessment of the influence of the several conditions, because a particular condition can be varied while the other conditions are kept constant. Another recommendation to extend the data set is performing animal experiments. This enables the measurement circumstances to be controlled and conduct experiments that are not possible on human subjects.

Although the developed parameter estimation routine shows promising results based on simulated data, the performance of the routine has not been tested on patient data because the necessary patient data could not be recorded simultaneously. Therefore, it is recommended to extend the developed system that records intrathoracic blood flows, by enabling it to also record aortic pressure, pulmonary arterial pressures, and the patient’s heart rate simultaneously. Moreover, the estimation of the parameters of the circulation did not show to be reliable, and should be subject for further research.

Based on the model simulations, two interesting observations were made which have not been reported in literature and should be subject for further research:

- The simulations suggest that pulmonary artery flow is more sensitive to intrathoracic pressure changes than aortic flow is. For varying conditions, the influence of the varying condition on the variations in pulmonary artery flow was much more evident than its influence on the variations in aortic flow. This indicates that measurements of the variations in pulmonary artery flow might be more valuable in predicting a patient’s response to fluid loading than currently used measurements such as aortic flow and aortic pressure.

- The simulations suggest that the respiratory rate influences the shape of the modulation envelopes. During expiration, the systolic peaks of the intrathoracic blood flows return to the baseline level that they had before inspiration. If the expiration period is set too short, these systolic peaks have not returned to the baseline level when a new ventilation period starts. According to the simulations, this results in different modulation envelopes. This indicates that the shape of the modulation envelope might also provide information about the patient’s filling status.

For both observations, it is recommended to perform a clinical study in order to investigate whether the observations are confirmed by patient recordings.
References


References


Hann CE, Chase JG and Shaw GM. Integral-based identification of patient specific parameters for a minimal cardiac model. Computer methods and programs in biomedicine, 2006.


References


Savage RM and Aronson S. Comprehensive textbook of intraoperative transesophageal echocardiography. Lippincott Williams & Wilkins, 2005.


Wesseling KH, de Wit B, Weber JAP and Smith NT. A simple device for the continuous measurement of cardiac output. Advanced Cardiovascular Physics, 5, 16–52, 1983.
Appendix A

Used model parameter values

Several parameters values have been used for the simulations of the cardiovascular and respiratory system. This appendix lists the used parameter values.

A.1 Parameter values used for the cardiovascular system

Passive compliant chambers

Passive compliant chambers have been used to simulate the structures that store blood volume, but do not add energy (e.g. a vessel). Table A.1 lists the parameters of the passive compliant chambers. These parameters determine the chamber’s elastance and unstressed volume.

Table A.1: Parameter values used for the passive compliant chambers.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$E_{es}$</th>
<th>$V_d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units</td>
<td>N/m$^5$</td>
<td>m$^3$</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>4.530 · 10$^7$</td>
<td>1.60 · 10$^-4$</td>
</tr>
<tr>
<td>Pulmonary vein</td>
<td>8.291 · 10$^5$</td>
<td>2.00 · 10$^-4$</td>
</tr>
<tr>
<td>Aorta</td>
<td>9.470 · 10$^7$</td>
<td>8.00 · 10$^-4$</td>
</tr>
<tr>
<td>Vena cava</td>
<td>1.450 · 10$^6$</td>
<td>2.83 · 10$^-3$</td>
</tr>
</tbody>
</table>

Active compliant chambers

Active compliant chambers have been used to simulate the structures that store blood volume and also add energy (e.g. a ventricle). Table A.2 lists the parameters of the active compliant chambers. These parameters determine the chamber’s pressure-volume relation.

Table A.2: Parameter values used for the active compliant chambers.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$E_{es}$</th>
<th>$V_d$</th>
<th>$V_0$</th>
<th>$\lambda$</th>
<th>$P_0$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Units</td>
<td>N/m$^5$</td>
<td>m$^3$</td>
<td>m$^3$</td>
<td>m$^{-3}$</td>
<td>N/m$^2$</td>
</tr>
<tr>
<td>Left ventricle</td>
<td>4.544 · 10$^8$</td>
<td>5.0 · 10$^-6$</td>
<td>5.0 · 10$^-6$</td>
<td>15.0 · 10$^3$</td>
<td>1.682 · 10$^2$</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>8.710 · 10$^7$</td>
<td>5.0 · 10$^-6$</td>
<td>5.0 · 10$^-6$</td>
<td>15.0 · 10$^3$</td>
<td>1.549 · 10$^2$</td>
</tr>
<tr>
<td>Pericardium</td>
<td>-</td>
<td>-</td>
<td>2.0 · 10$^-4$</td>
<td>30.0 · 10$^3$</td>
<td>6.670 · 10$^1$</td>
</tr>
</tbody>
</table>
Appendix A. Used model parameter values

In order to simulate the heart’s pumping function, a cardiac driver function is used. This cardiac driver function is described by Equation (4.12), and the exact curvature of this function is determined by the parameters listed in Table A.3.

Table A.3: Parameter values used to simulate the cardiac driver function.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( i = 1 )</th>
<th>( i = 2 )</th>
<th>( i = 3 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( A_i )</td>
<td>0.9556</td>
<td>0.6249</td>
<td>0.018</td>
</tr>
<tr>
<td>( B_i )</td>
<td>255.4</td>
<td>255.3</td>
<td>4225.0</td>
</tr>
<tr>
<td>( C_i )</td>
<td>0.3060</td>
<td>0.2026</td>
<td>0.2491</td>
</tr>
</tbody>
</table>

Closing the loop

In order to account for frictional and inertial forces in the cardiovascular system, resistors and inductors are used. The values of these resistors and inductors are listed in Table A.4. Note that inductors are only used at the connections between the heart and the arterial sides of the cardiovascular system, where very pulsatile flows occur.

Table A.4: Parameter values used for describing blood flow dynamics between the several active and passive chambers.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Resistance</th>
<th>Inertance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic valve</td>
<td>Ns/m^5</td>
<td>( 2.75 \cdot 10^6 )</td>
<td>( 1.00 \cdot 10^6 )</td>
</tr>
<tr>
<td>Pulmonary valve</td>
<td>Ns/m^5</td>
<td>( 1.00 \cdot 10^6 )</td>
<td>( 2.00 \cdot 10^4 )</td>
</tr>
<tr>
<td>Mitral valve</td>
<td>Ns/m^5</td>
<td>( 6.10 \cdot 10^6 )</td>
<td>-</td>
</tr>
<tr>
<td>Tricuspid valve</td>
<td>Ns/m^5</td>
<td>( 1.00 \cdot 10^6 )</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary circulation</td>
<td>Ns/m^5</td>
<td>( 9.40 \cdot 10^6 )</td>
<td>-</td>
</tr>
<tr>
<td>Systemic circulation</td>
<td>Ns/m^5</td>
<td>( 1.70 \cdot 10^8 )</td>
<td>-</td>
</tr>
</tbody>
</table>

Global parameters

Finally, three global parameters are listed in Table A.5. These parameters determine the patient’s heart rate, the patient’s total blood volume and the step size used for the simulations.

Table A.5: Global simulation parameters.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>Heart rate</td>
<td>91</td>
<td>beats/minute</td>
</tr>
<tr>
<td>TBV</td>
<td>Total blood volume</td>
<td>5500</td>
<td>ml</td>
</tr>
<tr>
<td>( \Delta t )</td>
<td>Step size</td>
<td>0.005</td>
<td>s</td>
</tr>
</tbody>
</table>
A.2 Parameter values used for the respiratory system

For the respiratory system, parameters are used to simulate the ventilator and simulate the patient's airways and lungs. The parameter values used to simulate the ventilator are listed in Table A.6. The parameter values used to simulate the patient's airways and lungs are listed in Table A.7.

Table A.6: Parameter values used to simulate the ventilator.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{insp}$</td>
<td>Inspiratory rise time</td>
<td>2</td>
<td>s</td>
</tr>
<tr>
<td>$T_{pause}$</td>
<td>Inspiratory pause time</td>
<td>1</td>
<td>s</td>
</tr>
<tr>
<td>$T_{vent}$</td>
<td>Ventilation period</td>
<td>12</td>
<td>s</td>
</tr>
<tr>
<td>$P_{peep}$</td>
<td>Level of PEEP</td>
<td>6</td>
<td>mm Hg</td>
</tr>
<tr>
<td>$R_{v,exp}$</td>
<td>Expiratory ventilator resistance</td>
<td>0.002</td>
<td>mm Hg s/ml</td>
</tr>
<tr>
<td>$R_{v,ins}$</td>
<td>Inspiratory ventilator resistance</td>
<td>0.002</td>
<td>mm Hg s/ml</td>
</tr>
</tbody>
</table>

Table A.7: Parameter values used to simulate the patient's airways and lungs.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_{aw,exp}$</td>
<td>Expiratory airway resistance</td>
<td>0.01</td>
<td>mm Hg s/ml</td>
</tr>
<tr>
<td>$R_{aw,ins}$</td>
<td>Inspiratory airway resistance</td>
<td>0.001</td>
<td>mm Hg s/ml</td>
</tr>
<tr>
<td>$C_l$</td>
<td>Lung-thorax compliance</td>
<td>100</td>
<td>ml/mm Hg</td>
</tr>
<tr>
<td>$P_{rest}$</td>
<td>Intrathoracic resting pressure</td>
<td>-4</td>
<td>mm Hg</td>
</tr>
</tbody>
</table>