Measuring vital signs and simulating hemodynamic patterns during closure of the patent ductus arteriosus

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Measuring vital signs and simulating hemodynamic patterns during closure of the patent ductus arteriosus

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Abstract

Complications arising from preterm birth account for one million deaths each year, with preterm birth being a risk factor in over 50% of all neonatal deaths. From fetal to neonatal life complications can arise that undermine maturation of neonates. A common condition within this transition process is the patent ductus arteriosus (PDA). Ductal steal of oxygen rich blood from the aorta leads to abnormal cerebral perfusion and hypoperfusion of the gut circulation, which causes life threatening conditions. Ductal tracking using a patient’s vital signs will enable the continuous monitoring of ductal patency in order to adequately treat the patient before these clinical deterioration take place. Within this thesis vital signs are analyzed for possible patterns related to a PDA which can be used to track ductal patency within preterm patients. Additionally hemodynamic simulations are preformed to study possible blood pressure trends during ductal closure.

To characterize vital signs patterns associated with closure of the ductus, vital signs were analyzed during a 6-day window surrounding ductal treatment. Vital sign features were calculated every half hour, and at six hourly intervals the mean trends of these features were determined. A 28 weeks gestational age and 1000 gram birth weight preterm hemodynamic model, with ductal flow segment, was created to simulate blood pressure trends during ductal closure. Ductal patency within this model was varied to simulate closure of the ductal flow segment. Blood pressure trends are given with respect to ductal flow, which makes it possible to compare measured and simulated blood pressure trends during ductal closure.

Measured vital signs trends during ductal closure showed patterns which can be linked to the ductal closure occurring within PDA patients. The effect of ductal closure is most pronounced in the systolic pressure increase after successful pharmaceutical treatment of the PDA. Results from the hemodynamic simulations showed that the model was able to correctly stimulate closure of the ductal flow segment. Measured and simulated systolic pressure showed to be within the same range, however measured diastolic pressures were higher than the simulated diastolic pressures during ductal closure. The simulation results showed to have blood pressure trends during ductal closure which are comparable with blood pressure trends reported in literature. Measured and simulated blood pressure were given with respect to an estimated ductal flow, but they did not show the same patterns during ductal closure.

This thesis shows that there are possible patterns that can be detected during ductal closure. Tracking ductal patency using these general patterns within individual patients will remain challenging.
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Chapter 1

Introduction

In 2010, worldwide an estimated 11.1% of all live births were born preterm (15 million babies born before 37 weeks of gestation), ranging from about 5% in several European countries to 18% in some African countries [1]. The distribution of gestational age subgroups shows that the proportion of births at less than 28 weeks’ gestation was 5% (extremely preterm), while the rate of birth less than 32 weeks’ gestation was 10% (very preterm) and rate between 32 and 37 weeks’ gestation was 85% (moderate or late preterm infant) [2].

Direct complications of preterm birth account for one million deaths each year, and preterm birth is a risk factor in over 50% of all neonatal deaths. Moreover, preterm birth can result in a range of long-term complications in survivors, with the frequency and severity of adverse outcomes rising with decreasing gestational age and decreasing quality of care.

The survival rate of preterms is strongly associated with gestational age. In a recent population-based study in Sweden which has comparable neonatal care as the Netherlands, the 1-year survival of infants born alive at 22 to 26 weeks of gestation is 70% and ranged from 9.8% at 22 weeks to 85% at 26 weeks [3].

The low survival rate is explained by the fact that the very preterm infant is underdeveloped in organ structure and functioning, and needs specialized care in order to survive. This specialized care is given in a neonatal intensive care unit (NICU).

Among ten Dutch NICU centers, Máxima Medical Center provides the neonatal intensive care for the south-eastern part of Noord-Brabant. Approximately 400 preterm infants are admitted annually to this NICU.

In Figure 1.1 an example of a specialized neonatal care room is shown. The figure shows a single-infant NICU room set-up with incubator, ventilator, bedside patient monitor and several infusion pumps. Neonatal innovations like early surfactant replacement for the immature lung and the use of non-invasive respiratory support have successfully improved neonatal outcomes.

Monitoring within a specialized neonatal care environment

In the NICU, health care providers can continuously monitor the clinical state of critically ill patients, detecting critical deterioration signaling the need for medical support or intervention. Continuous patient monitoring is achieved using a variety of important vital signs. These vital signs reflect the condition of the most important body functions. Heart activity, for example, is measured using the skin-adhesive ECG leads. These leads measure the electrical depolarization waveform over the heart. Arterial blood pressure is measured to monitor the pressures within the
cardiovascular system of a patient. The other vital signs monitored are temperature, respiratory rate and blood oxygenation. These signals monitor the functioning of a patient’s temperature regulation system and lungs. These vital signs are shown on a bedside monitor system in figure 1.2. Bedside monitoring systems are used to directly show the vital signs to health care providers.

Despite vigilant clinical assessment of infants in NICU, the diagnosis of life threatening conditions (sepsis, shock, necrotizing enterocolitis) often does not occur until an infant is clinically deteriorating. Hence, the clinical assessment of deterioration may be relatively late in the course of illness, until the time of (nearly) complete decompensation. A sepsis (blood stream infection) for instance can relatively easily be treated with antibiotics but if administered too late the infection can prove fatal.
A step forward would be to predict clinical deteriorations before they result in critically life-threatening conditions, to support the health care providers in preventing pathological conditions. Predictive monitoring involves analysis of vital signs and other clinical data to identify infants at highest risk and to detect early-stage illness, leading to timelier treatment and improved outcomes.

Despite several clinical applications of predictive monitoring, a lot has to be done to make predictive monitoring safe for the clinical situation. Therefore several research groups are now trying to create predictive monitoring systems for the future and validate these for clinical use [4, 5].

**Transition from fetal to neonatal cardiovascular physiology**

A condition that is very common among preterm patients concerns the transition of the cardiovascular system from fetal to neonatal life. The ductus arteriosus is an important vascular connection between the main pulmonary artery and the aorta. During fetal life, the ductus arteriosus diverts blood from the pulmonary artery into the aorta, thereby bypassing the lungs. After birth, the ductus arteriosus undergoes active constriction and eventual obliteration. In term babies closure occurs within 24 hours after birth, while in preterm infants the ductus arteriosus may fail to close, a condition which is called patent ductus arteriosus (PDA). PDA occurs commonly in premature infants, especially in those with respiratory distress syndrome (surfactant deficiency). In very low birth weight infants (birth weight below 1500 g) the incidence of PDA is approximately 30 percent [6].

The diagnosis of PDA is usually based upon its characteristic clinical findings and confirmed by echocardiography. Clinical findings seen in the majority of preterm infants with a hemodynamically significant PDA include heart murmur, hypotension and signs of respiratory distress.

The condition of a persistent PDA may disturb the normal circulation resulting in abnormal flow to lungs, brain and gut. The shunting of blood through a PDA in premature infants is essentially all left-to-right. As a result, there is excessive flow through the pulmonary circulation and hypoperfusion of the systemic circulation. The hemodynamic significance of a PDA is related to the shunt across the ductus. PDA leads to volume overload in the lungs and results in respiratory distress. Abnormal cerebral blood perfusion may result in hemorrhage of the vulnerable germinal matrix vasculature. Hypoperfusion of the circulation to the gut is a risk factor of necrotizing enterocolitis. Therefore, hemodynamically significant PDA has a clear treatment necessity, which means that adequate and early detection is crucial.

Gold standard for patent ductus arteriosus detection consists of cardiac echo images to assess ductal flow and diameter. The method is accurate in detecting the presence of a PDA, but unsuitable to provide a continuous assessment of ductal patency. A limitation is the fact that echocardiography is normally performed after the notice of typical clinical indicators. This means that reopening of the ductus after treatment could be clinically missed. Or a echocardiographic assessment could be preformed too late for a optimal ductal patency treatment.

Research question: Is it feasible to retrieve information of ductal patency from clinical measurements of blood pressure, heart rate and blood saturation?

Within this thesis I hypothesize that continuous monitoring of blood pressure, heart rate and blood saturation in preterm infants who are treated for PDA, show characteristic and distinctive profiles of successfully closure (responder to treatment) or non closure (non-responder).
CHAPTER 1. INTRODUCTION

Research goal
The purpose of this Master thesis is to develop a multi-parameteric data analysis technique for monitoring (treatment effect of a) PDA using vital signs that are routinely measured in preterm infants. Vital signs of blood pressure, heart rate and oxygen saturation at low sample rate were analyzed before, during and after pharmacutical treatment of a patent ductus arteriosus. With these vitals the aim was to extract multi-parameter features able to track ductal patency and to predict closure.

Furthermore a physiological model was developed to simulate the blood pressure patterns present during the closure of the ductus. This model uses realistic hemodynamic elements to simulate the entire cardiovascular system in terms of pressure and flows throughout the entire cardiac cycle. By comparing the simulated blood pressure patterns with blood pressure values measured in the clinic this thesis investigates the underlying relationships. Increasing the understanding of the measured blood pressure signals and their relation to the closing ductus.

Thesis outline
Before describing the development of the analysis set-up: physiology, predictive monitoring techniques and previous hemodynamic models will be described in more detail in Chapter 2. Within the materials and method section in Chapter 4 and 5 the research methodology will explained. The results will be presented and discussed within chapter 6. Conclusions from these results are given within chapter 7 together with a future outlook for additional research.
Chapter 2

Neonatal physiology and monitoring

This chapter discusses neonatal physiology and the field of predictive monitoring. It starts with a literature review of neonatal physiology in which the cardiovascular system and its regulation mechanism is introduced. Within the neonatal physiology section, structural abnormalities of the heart are explained. Along with an extensive description about the patent ductus arteriosus, the main focus of this study. This is followed by a description about the current golden standard for patent ductus arteriosus detection, and promising biomedical signal analysis methods for monitoring ductal patency.

2.1 Physiology

In this section neonatal physiology is explained, starting with a discussion on cardiovascular circulation. Next the central nervous system and the baroreceptor reflex are introduced. The baroreceptor reflex is one of the body’s homeostatic mechanisms that helps to maintain blood pressure at physiological levels. Finally, this thesis explains the structure of the heart at birth and the transition of the fetal heart in order to adapt to the new neonatal environment.

2.1.1 The cardiovascular system

The fetal circulation is different from the adult circulation [7]. In the fetus, gas exchange does not occur in the lungs but in the placenta. The placenta receives deoxygenated blood from the fetal systemic organs and return its oxygen rich venous drainage to the fetal systemic arterial circulation. In addition, the fetal cardiovascular system is designed in such a way that the most highly oxygenated blood is delivered to the myocardium and brain. These circulatory adaptations are achieved in the fetus by both the preferential streaming of oxygenated blood (tissue flap within the right atrium) and the presence of intracardiac (open foramen ovale; shunt between left and right atrium) and extracardiac (ductus arteriosus) shunt.

As the fetus begins its transition to postnatal life, several cardiopulmonary adaptations occur. First, gas exchange must be transferred from the placenta to the lungs. Secondly, the fetal circulatory shunts (ductus) close and the left ventricular output increases. Thirdly, increased cardiac output (stroke volume times heart rate) is required to provide for the increases in basal metabolism, work of breathing, and thermogenesis. In the term fetus, due to the shunt the combined ventricular output is approximately 450 ml/kg/min, with the right ventricular output accounting for 65% of the cardiac output and the left ventricle ejecting 35% of the cardiac output. Soon after birth, the
circulation changes from "parallel" to "series", where the right ventricular output equals the left ventricular output. The cardiac output nearly doubles after birth to about 300-400 ml/kg/min (for the right and the left ventricle) with a stroke volume of 1-2 ml/kg and heart rate between 120 – 160 beats per minute.

The postnatal cardiovascular system is schematically represented in figure 2.1 on the left. Within this system, pressure differences are generated in order to provide a stable and continuous blood flow. The heart is the main driving force for pressure build-up within the cardiovascular circulation. Vascular changes can occur to modulate pressures within the circulatory system. In term neonates the blood flows from the right heart ventricle to the lungs, then to the left ventricle which pumps out to the aorta. From the aorta blood flows to the organs. The circulation is divided in two main loops; the pulmonary circulation which passes the lungs with the function to saturate the blood with oxygen, and the systemic circulation which provides oxygenated blood to the main organs and limbs.

Valves within the cardiovascular circulation prevent backward flow throughout the venous system during short pressure drops in between heart contractions.

The circulation cycle in figure 2.1 on the left can be further simplified to the circulation on the right. In this figure all organs are represented by a single periphery. During each cardiac cycle blood passes past the cardiovascular loop to provide sufficient blood flow to all major organs systems to enable the normal activity of vital processes.

The aorta is the main artery in the body which runs from the outlet of the left ventricle towards the entire systemic circulation branch. The aorta is branched into smaller arteries that end up in peripheral arterioles and capillary circulation. If blood pressure is too low (e.g. hypotension) blood flow to the organs will be insufficient (resulting in shock), while too high blood pressure (hypertension) may permanently damage end-organs (renal insufficiency; heart failure). The heart can vary stroke volume and thereby change the resulting ventricular ejection pressure. Furthermore, the blood pressure is influenced by the peripheral resistance.
Figure 2.2 shows a neonatal blood pressure waveform. The figure introduces blood pressure nomenclature and presents typical values. First we see a pressure increase due to ejection of the heart till the maximum pressure is reached. The maximum pressure within the blood pressure curve is called the systolic pressure. After the pressure wave from the heart has passed, the pressure decreases slowly due to the flow of blood out of the blood vessel. The minimum pressure that is reached throughout this cycle is called the diastolic pressure. The difference between systolic and diastolic pressure is called the pulse pressure. The length of the cardiac cycle is determined by measuring the beats per minute (BPM) these are typically around 120-160, resulting in a cycle length of half a second. The mean blood pressure is the average blood pressure over the entire blood pressure curve. Typical systolic pressure values are between 50 and 70 mmHg and typical diastolic pressures are between 25 and 40 mmHg [9].

Blood pressure characteristics are influenced by external factors, e.g. the breathing mechanism. Internal pressures are shifted by the external ambient pressure resulting in altered flow and pressure values throughout the cardiovascular system. Due to the negative pressure within the thorax, which is created to keep the lungs from collapsing, the intra-thoracic part naturally has a positive pressure difference compared to the extra-thoracic part of the circulation. The pulmonary circulation and a part of the systemic circulation are intra-thoracic. And the periphery, where most internal organs are located, is extra-thoracic. To model the cardiovascular circulation one therefore has to account for the external ambient pressures to achieve realistic flow parameters.

2.1.2 The nervous system & influences on blood pressure regulation

The nervous system is able to regulate almost every important body function including blood pressures. The nervous system consists of the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of the brain and the spinal cord while the PNS consists of nerves.

The nervous system is further divided into the autonomic nervous system that influences the involuntary part of the nervous system and the somatic nervous system, which controls all voluntary responses. The somatic nervous system controls voluntary actions like shaking someone's hand while the autonomic nervous system controls the involuntary actions like the response to stress or anxiety. The autonomic part also innervates all internal organs within the human body. This is done using two counteracting parts called the parasympathetic and sympathetic system. These two parts affect the same organs but have a different effect on them (stimulating/inhibiting). The heart rate for example will increase if it is stimulated by the sympathetic nervous system, inversely
it will decrease when stimulated by the parasympathetic system. A simple schematic representation of this interaction is given in figure 2.3.

![Schematic representation of heart rate and parasympathetic/sympathetic nervous system](source: OpenStax College)

**Figure 2.3:** Schematic representation of the interaction between heart rate and the para- and sympathetic nervous system. The figure additionally shows which nervous pathways are followed by each individual nervous system to affect the heart rate. (source: OpenStax College)

**Blood pressure regulation**

To provide an adequate feedback loop between the action of the central nervous system and blood pressures there are specialized sensors throughout the cardiovascular system called baroreceptors. Baroreceptors are specialized pressure sensors, with the most important ones located in the aortic arch. Measuring the blood pressures (with baroreceptors), processing this information and adapting organs to control the blood pressure is a feedback loop called the baroreflex (BR). The function of the baroreflex is to stabilize short-term disturbances on a person’s ideal blood pressure, while it can also play a role in long-term blood pressure regulation, though its exact role is unknown. Studies about the long-term regulation of blood pressures suggested that long-term pressures are regulated by an interplay between renal functioning and the central nervous system. Short and long term blood pressure should be low enough to prevent cardiovascular damage while maintaining sufficient perfusion throughout the body.

**2.1.3 Transition of the cardiovascular system from fetal to neonatal life**

**Patent ductus arteriosus**

The patent ductus arteriosus (PDA) is a vascular structure that connects the proximal descending aorta to the roof of the main pulmonary artery near the origin of the left branch pulmonary artery. A schematic picture of a PDA is displayed in figure 2.4.

![Schematic picture of a PDA](source: OpenStax College)

The ductal shunt structure is necessary in the intra-uterine vascular system to divert blood past non-functioning fluid filled lungs. In term babies, this ductal shunt usually closes within 24 hours after birth. However, the closure of this shunt after birth is problematic in many preterms. Within extremely preterm neonates, i.e. born with a gestational age 26 weeks, the chance of unsuccessful
Patent ductus arteriosus, shown in the heart on the right, is a shunt (opening) between the aorta and the pulmonary artery. A normal heart is shown on the left. (source: MAYO foundation)

ductal closure is fifty percent [10, 11]. The reasons for unsuccessful ductal closure are unknown but genetic and environmental factors may play a role.

Symptoms of unsuccessful closure of the ductal shunt

There is a long list of indicators related to unsuccessful closure of a patent ductus. Within this subsection I will discuss several that are widely used in the clinic. Knight et al. [17] reviewed randomized trials looking at PDA treatment. From this metastudy he composed a list of indicators that are used in clinics worldwide. He states there are three major effects a PDA has on the physiology of a newborn namely cardiovascular, respiratory and systemic effects:

1. A PDA obviously has a cardiovascular effect. A left-to-right ductal shunt results in a lower blood pressure within the systemic loop and elevated blood pressures within the pulmonary circulation. The pulse pressure, which is the difference between systolic and diastolic pressures, is shown to widen when ductal flow increases. Additionally a left-to-right flow means a flow from the high-pressured systolic system through the ductus into the relatively low-pressure pulmonary system, eventually leading to loading of the pulmonary vascular system. Loading of the pulmonary system will cause the left ventricular output to become elevated to compensate for the steal from the ductus [12]. This increased left ventricular output looks to be attributed to an increase in stroke volume of the heart and not by an increase of the heart rate [13].

2. The second major effect is seen in the patient’s respiratory system. There is a strong relation between the presence of ductal shunt and respiratory diseases [14, 15, 16]. Knight names two respiratory diseases, bronchi pulmonary dysplasia (BPD) and respiratory distress syndrome (RDS), which showed to be highly correlated with a PDA. The exact reason why a respiratory disease increases the chance for unsuccessful closure is unknown, but a poor lung function could delay the release of ductal closing hormones [17].

3. Thirdly, Knight pointed out that a PDA effects all major organ systems by affecting the overall systemic blood flow. The persistency of an open ductus creates increasing pulse
pressures with gestational age, which can lead to damage within the cardiovascular system. The shunt also gives rise to diastolic steal and retrograde diastolic flow. This effect decreases the normal cerebral perfusion and the flow of blood to the gut, resulting in a high prevalence of intraventricular hemorrhage (IVH), renal dysfunction and necrotizing enterocolitis (NEC) in patients with PDA.

**Patent ductus arteriosus treatment**

There are two main ways to treat a PDA: pharmaceutically and surgically. Because of the large impact cardiac surgery has on a newborn, the first step is always by means of pharmaceuticals. For closing the PDA, a pharmaceutical called Indomethacin is used in most hospitals [18]. More recently the use of Ibuprofen has shifted the treatment regimes. Ibuprofen and Indomethacin both are cyclooxygenase inhibitors. Ibuprofen has the same effect in terms of ductal closure rate but shows less kidney toxicity compared to Indomethacin [19, 20, 21]. Both pharmaceuticals are still used within hospitals worldwide.

In Máxima Medical Center (MMC) the Indomethacin protocol starts with administering one full course of three doses of Indomethacin after an echo showed there is a PDA present. The three Indomethacin doses are administered over the course of thirty-six hours, twelve hours between two consecutive doses. If the first three doses are unsuccessful, a new course is administered. This process can be prolonged to more courses or the patient can be signed up for surgical ligation.

The Ibuprofen protocol starts with administering one full course of three doses of Ibuprofen after an echo shows ductal patency. The doses are administered over the course of three full days. With twenty-four hours between consecutive doses. Additional courses can be administered if the first course is unsuccessful. A second course of Indomethacin can be given if the patient shows unresponsive to Ibuprofen treatment.

During surgical ligation, stitching the walls of the ductus together, mechanically shuts the ductal shunt. While surgical ligation does correct the physiological condition, patients seem to require longer durations of mechanical ventilatory support and higher oxygen levels during mechanical ventilation [22]. Surgical treatment is therefore used only if a preceding pharmaceutical treatment proves unsuccessful. In addition some studies show that pharmaceutical treatments are better in increasing lung compliance compared to a surgical treatment [23, 24, 25, 26].

**2.2 Current and future ductal monitoring techniques**

The current gold standard for detecting ductal patency is to assess ductal geometry and flow parameters using echocardiography. But additional research suggests that other physiological markers can be used to monitor ductal patency in the future.

With echocardiography the operator evaluates the patent ductus as being hemodynamically significant or non hemodynamically significant. This is based on a series of ductal and cardiac criteria shown in Table 2.1. Mainly focusing on trans ductal diameter, ductal flow, left heart volume loading and the diastolic flow in several important arteries. This is done taking into account for patient specific factors like patient gestational age and birth weight. Limitation of this method is that it only measures the ductal patency during one point in time making it impossible to give trend information about the closure process. Furthermore it gives limited information about treatment success probabilities. Furthermore Table 2.1 shows PDA grading protocol based on clinical criteria being used, the protocol is taken from the paper by McNamara et al. [27].
Table 2.1: Proposed staging system adapted from McNamara and Hellman for determining the magnitude of the hemodynamically significant ductus arteriosus (HSDA), which is based on clinical and echocardiographic criteria.

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Echocardiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1 No evidence of ductal flow on two-dimensional or Doppler interrogation</td>
<td>E1 No evidence of ductal flow on two-dimensional or Doppler interrogation</td>
</tr>
<tr>
<td>C2 Mild</td>
<td>E2 Small non-significant ductus arteriosus</td>
</tr>
<tr>
<td>Oxygenation difficulty (OI ≤6)</td>
<td>Transudal diameter &lt;1.5 mm</td>
</tr>
<tr>
<td>Occasional (&lt;6) episodes of oxygen desaturation and bradycardia or apnoea</td>
<td>Restrictive continuous transudal flow (DA Vmax &gt;2.0 m/s)</td>
</tr>
<tr>
<td>Need for respiratory support (nCPAP) or mechanical ventilation (MAP &lt;8)</td>
<td>No-sig of left heart volume loading (eg, mitral regurgitant jet &gt;2.0 m/s or LA:Ao ratio &gt;1:5:1)</td>
</tr>
<tr>
<td>Feeding intolerance (&gt;20% gastric aspirates)</td>
<td>No signs of left heart pressure loading (eg, E/A ratio &gt;1:0 or IVRT &gt;50)</td>
</tr>
<tr>
<td>Radiologic evidence of increased pulmonary vascularity</td>
<td>Normal end-organ (eg, superior mesenteric, middle cerebral) arterial diastolic flow</td>
</tr>
<tr>
<td>C3 Moderate</td>
<td>E3 Moderate HSDA</td>
</tr>
<tr>
<td>Oxygenation difficulty (OI 7 - 14)</td>
<td>Transudal diameter 1.5 - 3.0 mm</td>
</tr>
<tr>
<td>Frequent (hourly) episodes of oxygen desaturation and bradycardia or apnoea</td>
<td>Unrestrictive pulsatile transudal flow (DA Vmax &lt;2.0 m/s)</td>
</tr>
<tr>
<td>Increasing ventilation requirements (MAP 9 - 12)</td>
<td>Mild-moderate left heart volume loading (eg, LA:Ao ratio 1.5 to 2:1)</td>
</tr>
<tr>
<td>Inability to feed due to marked abdominal distension or emesis</td>
<td>Mild-moderate left heart pressure loading (eg, E/A ratio &gt;1:0 or IVRT &gt;50)</td>
</tr>
<tr>
<td>Oliguria with mild elevation in plasma creatinine</td>
<td>Decreased or absent diastolic flow in superior mesenteric artery</td>
</tr>
<tr>
<td>Systemic hypotension (low mean or diastolic BP) requiring</td>
<td>Middle cerebral artery or renal artery</td>
</tr>
<tr>
<td>a single cardiotropic agent</td>
<td></td>
</tr>
<tr>
<td>Radiologic evidence of cardiacomyalgia or pulmonary oedema</td>
<td></td>
</tr>
<tr>
<td>Mild metabolic acidosis ([pH 7.1 - 7.25 and/or base deficit &gt;7 - 12])</td>
<td></td>
</tr>
<tr>
<td>C4 Severe</td>
<td>E4 Large HSDA</td>
</tr>
<tr>
<td>Oxygenation difficulty (OI &gt;15)</td>
<td>Transudal diameter &gt;3.0 mm</td>
</tr>
<tr>
<td>High ventilation requirements (MAP &gt;12) or need for high-frequency modes of ventilation</td>
<td>Unrestrictive pulsatile transudal flow</td>
</tr>
<tr>
<td>Profound or recurrent pulmonary haemorrhage</td>
<td>Severe left heart volume loading (eg, LA:Ao ratio &gt;2:1, mitral regurgitant jet &gt;2.0 m/s)</td>
</tr>
<tr>
<td>&quot;NEC-like&quot; abdominal distension with tenderness or erythema</td>
<td>Severe left heart pressure loading (eg, E/A ratio &gt;1:5 or IVRT &gt;60)</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Reversal of end-diastolic flow in superior mesenteric artery, middle cerebral artery or renal artery</td>
</tr>
<tr>
<td>Haemodynamic instability requiring &gt;1 cardiotropic agent</td>
<td></td>
</tr>
<tr>
<td>Moderate-severe metabolic acidosis ([pH&lt;7.1] or base deficit &gt;12)</td>
<td></td>
</tr>
</tbody>
</table>

BP, blood pressure; DA Vmax, ductus arteriosus peak velocity; E/A, early to late atrial contraction phase of transudal filling ratio; IVRT, isochronic relaxation time; LA:Ao, ratio, left atrium to aortic ratio; MAP, mean arterial pressure; nCPAP, nasal continuous positive airway pressure; NEC, necrotising encephalitic; OI, oxygenation index.

Patients should be assigned both a clinical and echocardiography stage (eg, neonate with severe oxygenation failure, pulmonary haemorrhage and a 3.2 mm unrestrictive left-to-right shunt will be C4-E4 class HSDA).

Several studies focused on the selection of physiological markers to detect a PDA and the possibilities for an individualized assessment, tailored to different gestation ages, respiratory conditions and ductal shunt sizes. Using such a method, an early detection might become possible, before an echo assessment is performed. It might also help as a quantitative way of predicting PDA treatment success, perhaps even identifying a subgroup that will not benefit from treatment at all. The subsections below discuss several studies focusing on finding new PDA detection protocols, using physiological signals readily available within a neonatal care setting.

### 2.2.1 Patent ductus arteriosus and the central nervous system

A new approach focuses on the relationship between the hemodynamic disorder caused by a patent ductus and the central nervous system. This is possible by using the characteristic time behavior of the two parts of the central nervous system. The parasympathetic system affects the heart by the vagal nerve. This nerve has a relatively high communication speed between the brain and heart muscles. On the other hand the sympathetic system affects the heart using the sympathetic cardiac nerve. This nerve has a relative low communication speed between brain and heart. This difference in nervous speeds means that rapid heart rate changes can only be attributed to the parasympathetic nervous system. The slow changes on the other hand can be caused by both the para- and sympathetic system. This time signature is used to quantify the balance or imbalance between both parts of the central nervous system.

One way of quantifying an imbalance within the two systems of the central nervous system is by looking at the Fourier transform of series of consecutive heart beat intervals. During each heart beat there is a depolarization peak which is called the R peak shown in the top of figure 2.5 on page 16. These R peaks seem to have a regular pattern (average heart rate). But when looking at the RR peak intervals more closely, a large amount of variations can be observed. These beat-to-beat
fluctuations are measured and shown as RR series. The Fourier transform of these series reveals that there are two main frequency bands within the RR intervals. One frequency band corresponds to the relatively slow variations in heart beat caused by the para- and sympathetic nervous system. The low frequency (LF) band has a range between 0.04 Hz and 0.15 Hz. The second band on the other hand can only be caused by the fast acting parasympathetic nervous system, since the latency within the sympathetic cardiac nerves is too big to react to changes in the high frequency band ($HF = 0.7 − 0.95 Hz$). The power in each frequency band is used to quantify the total activity in each frequency band. The ratio, i.e. LF/HF, of these two powers gives a value of the imbalance between both nervous systems over time. Goudjil et al. [28] showed that within the frequency domain the LF/HF ratio was lower in the group of PDA patients compared to controls, showing that a patent ductus causes a predominant stimulation of the parasympathetic nervous system. It is thus possible to measure disturbed function of the central nervous system within the frequency domain with respect to a pathology like the patent ductus arteriosus.

A second way to quantify the imbalance of the central nervous system is by using the asymmetry of RR-interval distribution within the time domain. By looking at changes in the distribution of the RR series described in the previous paragraph, one can show predominant para- or sympathetic stimulation. An increased parasympathetic stimulation results in a decrease of the heart rate and longer RR periods. Increased sympathetic simulation cause an opposite effect, leading to an increase in heart rate and subsequently shorter RR periods. Prietsch et al. [29] showed that you can quantify this asymmetry with a parameter called the long term heart variability (or calledNormalized-trend variability). They showed an elevated long-term heart variability within patients with a patent ductus, which signals a predominant stimulation of the parasympathetic nervous system. These frequency- and time domain studies show that it is possible to detect changes within the central nervous system due to patent ductus arteriosus.

2.2.2 Blood pressure characteristics associated with a patent ductus arteriosus

Development of the cardiovascular structures following birth, from an open ductus towards a closed pathway has an effect on blood pressures. There are several studies that show a relation between blood pressure patterns and a PDA treatment. Research shows a different effect of ductal closure in the term and preterm hemodynamics. These differences are discussed in the remainder of this section.

In a term neonate the effect of a PDA have been well studied, showing that a patent ductus causes a decreased diastolic pressure and a widened pulse pressure [30, 31]. For preterms Han et al. showed that the mean systolic and diastolic blood pressures were lower in the PDA group compared to the controls [32], and no significant change in the pulse pressure before and after closure. This is supported by the study of Evans et al. [33] who showed that the mean systolic and diastolic pressures increase during successful PDA treatment. Systolic and diastolic blood pressures increase by similar amounts resulting in an unchanged pulse pressure. Both studies showed that there where no changes in the group that was non responsive to pharmaceutical treatment. Furthermore these studies show a different hemodynamic closing effect between term and preterm patients treated for a patent ductus.

Beside the blood pressure trend data, the raw waveform data holds additional information about a PDA. This effect is most pronounced at the dicrotic notch, figure 2.5, in the blood pressure waveform. The dicrotic notch is a small downward deflection in the waveform following the closure of the semilunar valves in the heart. This point is believed to be the end ejection period of the heart. Lundell et al. showed that pulsatile ratio is lower in preterm and term before ductal closure [34]. The pulsatile ratio is the quotient between the amplitude of the dicrotic notch and the amplitude of the systolic peak. This is shown in figure 2.5 as the quotient between peaks A
and B. The dicrotic notch is interesting because it is the point at which the aortic valve closes. The fluid dynamics at this point in the cardiac cycle are severely affected by the ductal opening which creates steal from the main aortic pathway.

Figure 2.5: Pulse wave with A being the amplitude at the systolic stage and B the amplitude of the dicrotic notch. The values given are the pulsatile ratio calculated at every beat. In the top the ECG signal is given as an indication of the triggering of the heart.

2.2.3 Patent ductus arteriosus and the blood saturation

Due to the mixing of oxygen rich and oxygen poor blood through the ductal shunt the blood saturation of a PDA patient potentially contains saturation patterns different from neonates without a patent ductus arteriosus. Pulse oximetry is used to determine the blood saturation of a patient and is measured on the fingertips or toes. Thangaratinam et al. preformed a large metadata study to look at the value of pulse oximetry screening for heart defects [35]. Thangaratinam et al. identified 13 eligible studies that contain data from almost 230 thousand newborns. They show that the pulse oximetry has a very high specificity but lacks the sensitivity to be used for universal screening. They also state that the false-positive rate for detection decreases if the pulse oximetry screening is done in the first twenty-four hours after birth.

Conclusion

Based on the available literature, as discussed above, this thesis therefore hypothesizes that the approach of a multi-parameter (blood pressure, ECG and blood saturations) methodology may support health care providers to assess the treatment effects of a PDA.
Chapter 3

Neonatal modeling

In this chapter the mathematical background for the pre-existing hemodynamic neonatal simulations are introduced. Furthermore the simulation set-up and parameter values used within the hemodynamic simulations are explained.

3.1 Hemodynamic modeling

Hemodynamic models of physiological systems like the cardiovascular system of a neonate can provide a better understanding of the underlying (patho-) physiological events. If the model enables the user to correctly simulate the cardiovascular functions of the patient it can also be used to get information about parameters that can’t be clinically measured. The aim of these models is to create realistic blood pressure patterns using a simplified circulatory system to show how changes in the hemodynamics of the model effects the patient. In this section a description of the cardiovascular system in terms of nodes and segments is given. This approach showed to produce a model that is able to simulate realistic blood pressure values in several other studies [8, 36]. The derived mathematical background of this approach can also be found within the syllabus: "Model based cardiovascular pathophysiology" of Bovendeerd et al. [37]. The model was adapted for this study to simulate the transformations from open to closed ductus, this is explained within Chapter5.

3.1.1 Modular building blocks for the cardiovascular system

The cardiovascular circulation can be simplified into discreet elements which model the flow behavior within specific parts of the circulation. These discreet elements are used to model the flow behavior of a underlying complex interacting network of cardiovascular arteries or veins. Systemic intra-thoracic arteries for example are a complex network of arteries which can be modeled by one elements because they are all located at an intra-thoracic ambient pressure, they all have a characteristics arterial diameter and are part of the systemic circulation which is supplied by the left ventricle. These collective parameters are used to create one systemic intra-thoracic artery element which models blood flow within this arterial network.

Flow behavior within these discreet elements is split into two to model the most important functions of cardiovascular networks, e.g. the storage of blood and enabling flow throughout the cardiovascular circulation. The behavior of stored blood within an element is governed using a node with a flow component called compliance or elastance. The mathematical background of modeling blood storage in a node is derived within sub section 3.1.2. Blood flow within an element is governed by a segment with a specific inerance and resistance, the behavior of these two components is given in sub section 3.1.3. A schematic representation of a cardiovascular element
and its characteristic components is shown in Figure 3.1.

![Figure 3.1: A schematic representation of a cardiovascular element. The blood storage within element i is governed by the compliance of node i. The in and out flow of blood through element i and into node i is governed by the inerance and resistance of segment i.](image)

3.1.2 Blood storage within the cardiovascular system: Nodes

Nodes are representations of points within the cardiovascular system that are able to store blood. Within a node there is a certain volume $V$ of blood stored under a certain pressure $p$. There are passive nodes which have a direct relation between the stored volume of blood and the resulting pressure. And contractile nodes which have a time-dependent relation between the stored volume $V$ and the resulting pressure $p$. First the passive nodes are discussed after which the contractile nodes are introduced.

**Passive nodes**

The relationship between the stored blood volume and resulting pressure is given by the compliance $C$. The compliance of a node is defined as:

$$C = \frac{dV}{dp} \quad (3.1)$$

relating the volume change $dV$ to the resulting pressure difference $dp$ within the node. The units of $C$ are $[m^3 \cdot Pa^{-1}]$ in SI-units but for historical reasons care providers use $[ml \cdot mmHg^{-1}]$.

When using a node to model the properties of a blood vessel the compliance $C$ can be given in terms of vessel properties [37], shown in equation (4.2).

$$C = \frac{dV}{dp} = \frac{2\pi a_0^3 l_0}{E h_0} \quad (3.2)$$

Giving the compliance $C$ as a function of the vessel radius $a_0$, vessel length $l_0$, wall thickness $h_0$ and Youngs modulus $E$. Equation (4.2) shows a strong dependency of the compliance on the vessel radius $a_0$. Larger wall thickness and wall stiffness in arteries compared to veins result in a lower arterial compliance which means that they can store more blood at a lower pressure.

If vessel parameters are unknown the nodal compliance can be determined using the vessel specific pressure-volume relation. The pressure-volume relation shows pressure changes within the vessel that result from the amount of stored blood. An example of one of these pressure-volume relationships is shown in figure 3.2.

To simplify the calculation of flows and pressures within the model, this relation is linearized around the physiological pressure point $p_{phys}$. This linear relation between pressure and volume determines a vessels unstressed volume and compliance. Compliance is determined using the
Figure 3.2: A schematic relation between pressure and volume within a vessel. The dotted line is a linearization of the pressure-volume relation around a physiological working pressure $p_{phys}$. The slope and intersect of this linearization yields a compliance $C$ and a unstressed volume $V_0$. Figures adapted from [37].

The inverse of the slope of this line and the point of intersection of this line yields the unstressed vessel volume. This linear relation between vessel pressure and stored vessel volume is given by:

$$p = \frac{V - V_0}{C}$$ (3.3)

**Contractile nodes**

Contractile nodes are nodes with a pump function within the cardiovascular system, e.g. ventricles and atrium. A simple model to describe the pumping of the left ventricle is the time-varying elastance model, which was introduced by Suga et al. [38]. They measured several pressure loops from experiments on a single canine heart at different mean arterial blood pressures. These pressure loops can be divided into four different cardiac phases that are displayed within the pressure-volume loop in figure 3.3a. Suga et al. showed that the end-ejection points of several canine left ventricular pressure volume loops were all located along a straight line as shown in figure 3.3b. The slope of this line gives a measure for the maximum elastance of the heart $E_{max}$, with the elastance being the inverse of the compliance $C$. We use a new parameter elastance to emphasize that these nodes are active and not passive in which case we use the variable compliance. $E_{max}$ can be used to quantify the contractility of cardiac chambers independent of hemodynamic loading conditions. This makes it possible to simulate several cardiac settings of the heart with one underlying model. The intersect of the line with slope $E_{max}$ with the volume axis gives the unstressed left ventricle volume $V_0$. Several pressure-volume loops at different mean arterial blood pressures and the derived cardiac parameters are shown in figure 3.3b.
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(a) Pressure-Volume left ventricle

(b) Pressure-volume loops

Figure 3.3: Left: Pressure-Volume loop of the left ventricle with different cardiac stages. Right: Several pressure-volume loops of the left ventricle at three different filling volumes. The end-ejection point of the different loops all coincide on the line with slope $E_{\text{max}}$ and volume axis intersect $V_0$. The diastolic part of the pressure-volume loops follow the slope of $E_{\text{pas}}$, the passive elastance of the left ventricle. The relation between left ventricle pressure and volume is given by a time-varying elastance $E(t)$. Figures adapted from [37].
CHAPTER 3. NEONATAL MODELING

From the pressure volume loops Suga et al. formulated the time dependent pressure-volume ratio $E(t)$ as:

$$E(t) = \frac{p_{lv}(t)}{(V(t) - V_0)}$$  \hspace{1cm} (3.4)

When $E(t)$ was normalized with respect to the maximum $E_{max}$ and the time to reach this maximum $t|_{E=E_{max}}$ all pressure volume loops have the same normalized pressure-volume ratio $E(t^*)$. The normalized pressure-volume ratio from Suga et al. is displayed in figure 3.4.

![Normalized elastance as a function of the normalized time $t^* = t/t_{E=E_{max}}$. Figure adapted from [37].](image)

With these observations Suga et al. created the time-varying elastance model for modeling the contraction of the left-ventricle, the model is formulated as:

$$p_{lv}(t) = E(t)(V_{lv}(t) - V_0)$$

$$E(t) = E_{pas} + a(t)(E_{max} - E_{pas})$$  \hspace{1cm} time-varying elastance model \hspace{1cm} (3.5)

$a(t)$ is a dimensionless normalized activation function. With a minimum of zero at the beginning and end point of a cardiac cycle, and a maximum of one at the normalized time point $t^* = 1$. $E_{pas}$ is the slope of the passive diastolic pressure-volume relation. The time-varying elastance model can be used to simulate blood pressure behavior in all cardiac chambers.

3.1.3 Blood flow within the cardiovascular system: Segments

The flow throughout the cardiovascular system is modeled using segments, in which the modeled flow should be governed by continuum mechanics theory. By combining conservation of mass, conservation of momentum along with the proper initial and boundary conditions one can calculate the entire spatial and temporal flow properties within a segment. In this thesis we are interested in capturing the viscous and inertial flow effects of blood within discrete segments throughout the cardiovascular system.

Navier-Stokes

Flow throughout the cardiovascular system is governed by the conservation of mass and momentum. Modeling blood as an incompressible Newtonian fluid and inserting this within the momentum equation yields the Navier-Stokes equations. The Navier-Stokes equation for an incompressible fluid without gravitational effects and conservation of mass are given by:
\[ \rho \left( \frac{\partial \mathbf{u}}{\partial t} + (\mathbf{u} \cdot \nabla) \mathbf{u} \right) = -\nabla p + \eta \nabla^2 \mathbf{u} \]
\[ \frac{\partial \rho}{\partial t} + \rho (\nabla \cdot \mathbf{u}) = 0 \]

with the density \( \rho \), viscosity \( \eta \), velocity vector \( \mathbf{u} \) and pressure \( p \). To simplify equation (3.6) we assume rotational symmetry within the vessel. Switching to cylindrical coordinate system and assuming that the tangential velocity is small. Together with the assumption that there is no leakage through the vessel wall, i.e. no radial velocity components. These assumptions yield a velocity vector \( \mathbf{u} \) with only a z-component which is dependent on the \((r,z)\) location of the flow, \( \mathbf{u} \) is given by:

\[ \mathbf{u} = v(r,z) \hat{e}_z \quad (3.6) \]

With these assumptions the pressure \( p \) within the segment is only dependent on the axial coordinate. The axial component of the Navier-Stokes equation yields:

\[ \frac{\partial v}{\partial t} + v \frac{\partial v}{\partial z} = -\frac{1}{\rho} \frac{\partial p}{\partial z} + \frac{\eta}{\rho} \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial v}{\partial r} \right) \quad (3.7) \]

describing how the time dependent and convective acceleration of the fluid on the left side of the equation result from the pressure and viscous terms on the right side.

Navier-Stokes could be used to exactly model flow behavior throughout the cardiovascular circulation but an exact solution can only be found within certain flow regimes. Within these flow regimes the Navier-Stokes equation can be simplified to yield an exact solution governing the internal flow. The dimensionless Reynolds number can be used to calculate the important flow properties independent of the specific flow situation. The Reynolds number quantifies the relation between viscous and inertia forces and quantifies the resulting flow regime. The Reynolds number is given by:

\[ Re = \frac{v \cdot L}{\nu} \quad (3.8) \]

With \( v \) the characteristic flow speed, \( L \) the characteristic length scale and \( \nu \) de kinematic viscosity. Small Reynolds number show that viscous forces are dominant within the flow and results in a laminar flow. On the other hand big Reynolds number mean that inertial forces are dominant which results in a turbulent flow. While in practice the Reynolds number is insufficient to correctly quantify the flow regime, it serves as a first characterization. The Reynolds number in the aorta for example is high 4000 \[39\] compared to that of a laminar venous capillary 0.03 \[40\]. In the following subsection we will discuss both flow regimes and show how its behavior can be simulated within a hemodynamic patient model.

**Friction dominated flow (Re below \( \approx 2000 \))**

If we assume laminar flow an exact solution of the Navier-Stokes equation can be found in the form of a Poiseuille profile. Assuming a steady flow and a fully developed flow velocity field along the flow segment equation (3.7) can be simplified to:

\[ \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial v}{\partial r} \right) = \frac{1}{\eta} \frac{\partial p}{\partial z} \quad (3.9) \]

Using boundary conditions this yields a result for the parabolic flow profile of:

\[ v(r) = \frac{1}{4\eta} (a^2 - r^2) \frac{dp}{dz} \quad (3.10) \]
were $r$ is the radial position at which the velocity measured and $a$ the radius of the segment. Furthermore the no-slip boundary condition that is used in this derivation means that the flow is friction dominated and laminar along the entire flow path.

The total flow $q$ is obtained by integrating the velocity field over the entire cross-sectional area of the segment. The pressure gradient is given by:

$$\frac{dp}{dz} = -\frac{8\eta}{\pi a^4}q$$

(3.11)

If we have a segments of finite length $l$ with a certain pressure drop $\nabla p$ we can estimate the axial pressure gradient $\frac{dp}{dz}$ with $\nabla p$. Using this assumption we define the resistance $R$ of this segment as:

$$R = \frac{\nabla p}{q} = -\frac{8\eta l}{\pi a^4}$$

(3.12)

The estimated resistance $R$ of a finite length segment is strongly dependent on the inverse of the segment radius $a$. Meaning smaller circulatory segments have a higher resistance than bigger circulator segments, e.g. veins have a higher resistance compared to the larger arteries. Within a cardiovascular segment a resistance $R$ is used to model the friction dominated behavior of blood flowing through that segment. This gives realistic values of the resulting segment pressures and flow parameters if there is a laminar flow within that segment.

**Inertia dominated flow (Re above $\approx 2300$)**

Turbulent flow on the other hand can’t adequately be described using a laminar flow profile approach and should be modeled with the time-dependent inertia forces in equation (3.7). Inertia forces are considered to be the effect that fluid particles have on the other fluid particles within the flow. If these inertia forces dominate over viscous forces the flow has a high Reynolds number. In this flow regime the axisymmetric Navier-Stokes equation reduces to:

$$\frac{\partial v}{\partial t} = -\frac{1}{\rho} \frac{dp}{dz}$$

(3.13)

Fully developed turbulent velocity field has a very thin boundary layer and a flat velocity profile due to a high degree of turbulent mixing. Because the velocity $v$ is independent of the radial position $r$ the flow velocity integration simplifies to a multiplication of the cross-sectional area $\pi a^2$ with the flow velocity in (3.13):

$$\frac{dq}{dt} = -\frac{\pi a^2}{\rho} \frac{dp}{dz}$$

(3.14)

Again with the assumption that the pressure gradient can be simplified by a pressure drop $\nabla p$ over the segment length $l$ we find:

$$\nabla p = \frac{\rho l}{\pi a^2} \frac{dq}{dt}$$

(3.15)

Now we define the inertance $L$ of a segment as:

$$L = \frac{\nabla p}{(dq/dt)} = \frac{\rho l}{\pi a^2}$$

(3.16)

With the inertance $[L] = [Pa \cdot s^2 \cdot m^{-3}]$ a segment’s flow parameters can be modeled if there is a turbulent flow present within the segment. This means that a fast changing input flow velocity field will become damped within a segment with inertance $L$. 

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Using these components the exact flow behavior resulting from the Navier-Stokes equation can be approached to model vessel flow behavior within certain flow regimes. The circulation of blood is non-stationary varying within each heartbeat. This non-stationary behavior means that there is a possibility for laminar and turbulent flow moments within the cardiac flow cycle of one vessel. In this thesis these segments are modeled with a parallel resistance $R$ and inertance $L$. Segments with low flow speeds have laminar flow speeds during the full cardiac cycle and are modeled by a single flow resistance component $R$.

The adapted neonatal hemodynamic model by Sá Couto et al. is introduced in the following section.

### 3.2 Lumped parameter model of the cardiovascular system

A model that uses discreet elements with flow components to simulate blood pressure patterns is called a lumped parameter model. With a lumped parameter model important hemodynamic variables can be simulated without modeling the entire complex underlying cardiovascular structure. By adequate parameter estimation and a sufficient level of complexity a lumped parameter model is able to simulate the required time-dependent hemodynamic trends within this study.

A lumped parameter was selected for this study because of previous work by Sá Couto et al. [36] which created a realistic neonatal lumped parameter model, that was used as the basis for our ductal closing model. Besides the neonatal dimensions of the Sá Couto model the possibility to create a ductal flow is essential in the choice of this model. The model stimulates hemodynamic behavior of a healthy term neonate but redefinition of the input parameters enable scaling towards preterm dimensions.

#### 3.2.1 Term neonatal lumped parameter model

A schematic hydraulic analog of this term Sá Couto model is shown in Figure 3.5. The model uses 10 elements to model the entire cardiovascular circulation of a healthy term neonate. Each element is shown as a node and consecutive flow segment.

With the Sá Couto model it is possible to simulate time-dependent blood pressure and flow patterns during a stable cardiac cycle. Blood pressure and flow parameters during a full cardiac cycle are calculated for each individual element within the lumped parameter model. And are dependent on the fixed user defined input parameters of each element and of the hemodynamic state of all surrounding elements. Stability of the cardiac cycle is checked by reducing the deviation of the left and right stroke volume of two consecutive simulated beats below a certain set minimum value.

The hemodynamic state of the model is stored within the pressure vector $p$, volume vector $V$ and flow vector $q$. This hemodynamic state is time-dependent within one heart beat, but the temporal behavior is identical between two consecutive heart beats. The hemodynamic vectors are composed of the hemodynamic state of each individual model element.

The time-dependent pressure, volume and flow values of each individual element is determined by the hemodynamic state of surrounding elements and by the predefined flow parameters of the element of interest. First we will formulate how the pressure relationship was modeled within the model then we will explain the relationship for modeled flows and resulting volume changes. Finally we will discuss the necessity of directional flow paths or valves within the model and show how they were modeled.
Figure 3.5: Hydraulic analog of the simplified cardiovascular circulation within adults. The model was created by Sá Couto et al. [36]. The model shows the cardiovascular system can be broken down to segments and nodes to model blood flow and storage throughout the circulation. These elements govern the flow behavior within each element. This results in realistic pressure and flow patterns within the lumped parameter model.

Pressures within the lumped parameter model

Pressures of each individual element in the pressure vector $P$ are determined by a unique pressure relationship for each elemental node $i$. The pressure of node $i$ is given by:

$$p_i = P(V_i, t, \alpha_i) + p_{a,i} \quad (3.17)$$

here $V_i$ is the stored volume of blood in node $i$, at time $t$, and a set of fixed node properties $\alpha_i$. Shifted by a nodal ambient pressure of $p_{a,i}$.

There are two ambient pressures within the model: intra and extra-thoracic. Intra-thoracic pressure is lower than atmosphere pressure to prevent the lungs from collapsing. Extra-thoracic pressure is present within the periphery and is equal to atmospheric pressure.

The pressure function $P$ is node dependent and different between passive and contractile nodes.

Passive nodes don’t actively build up pressures by contraction, pressures within these nodes are only related to nodal volume changes. The pressure within a passive node is therefore given by:

$$p_i = \frac{V_i - V_0}{C_i} + p_{ambient,i} \quad (3.18)$$

With $V_0$ being the unstressed volume of node $i$ which is defined as model input parameter for each individual model node.

Active nodes on the other hand have a time-dependent pressure relationship which is given by the time-varying elastance model.
\[ p_{\text{ventricle},i} - p_{\text{ambient},i} = (E_{\text{pas},i} + a(t)(E_{\text{max},i} - E_{\text{pas},i}))(V_{\text{ventricle},i} - V_0,i) \]  

With predefined passive elastance \( E_{\text{pas},i} \) and maximum elastance \( E_{\text{max},i} \) model input parameters. \( a(t) \) is the dimensionless normalized activation function which is given by:

\[
a(t) = \begin{cases} 
\left( \sin(\pi \frac{t-t_{\text{delay}}}{t_{\text{act}}}) \right)^2 & \text{if } t < t_{\text{act}} + t_{\text{delay}} \\
0 & \text{else}
\end{cases}
\]

here \( t_{\text{act}} \) is the activation time of the left and right ventricle and \( t_{\text{delay}} \) is the delay between beginning of the ventricular and atrial contraction. The activation curve models the shape of the normalized pressure-volume ratio defined by Suga et al. in figure 3.4 on page 21. \( t_{\text{act}} \) and \( t_{\text{delay}} \) are related to the predefined heart rate of the neonatal model.

**Volume and flows within the lumped parameter model**

Pressure fluctuations discussed in the previous subsection will result in segmental blood flows, which will lead to changing nodal volumes. The state of these individual segments flows are stored within vector \( q \) and is determined by the specific flow relationship of segment \( k \) given by:

\[
q_k(t) = \frac{p_{\text{in}}(t) - p_{\text{out}}(t)}{R_i} + L_i \frac{dq_k(t)}{dt}
\]

with \( p_{\text{in}}(t) - p_{\text{out}}(t) \) the time-dependent pressure gradient over segment \( k \). If segment \( k \) runs from node \( i \) to node \( i + 1 \) the pressure gradient \( p_{\text{in}}(t) - p_{\text{out}}(t) \) is given by the pressure difference between node \( i \) and \( i + 1 \). \( \frac{dq_k(t)}{dt} \) is time derivative of flow within segment \( k \). And resistance \( R \) and inertance \( L \) predefined flow components. In most segments viscous forces throughout the cardiac cycle were modeled to be dominant over inertia forces, thus omitting a segmental inertance \( L \).

Imbalance between segmental in and out flow of each node will result in changes in the nodal volume. With blood being modeled as an incompressible fluid this relationship is given by the conservation of mass:

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

with \( q_{\text{in}}(t) - q_{\text{out}}(t) \) the flow gradient over node \( i \). This gradient is given by the difference between the nodal supplying segment \( k \) and nodal outflowing segment \( k + 1 \).

**Valves within the lumped parameter model**

Pressure build up due to cardiac contraction would lead to backward flow if there were no valves to direct flow within the cardiovascular circulation. This leakage would restrict the isovolumetric contraction which would lead to an insufficient rise of blood pressure within the heart. Two valves at the beginning and ending of a cardiac chamber first stop blood from flowing out of chamber during passive filling. Secondly they simultaneously close to enable an isovolumetric contraction and finally opening to allow outward flow from the high pressured chamber.

To prevent backward flow within the lumped parameter model valves are modeled as a directional flow resistance increase. A valve should ideally operate as a diode showing zero backward flow during a negative pressure. But within the model this diode behavior would mean an infinite resistance between two nodes making them uncoupled. Therefore, backward flow was restricted by creating an additional directional flow resistance during inverse pressure difference.

\[
q_{\text{valve}}(t) = \begin{cases} 
\frac{p_{\text{in}}(t) - p_{\text{out}}(t)}{R} & \text{if } p_{\text{in}}(t) \geq p_{\text{out}}(t) \\
\frac{100 \times p_{\text{in}}(t) - p_{\text{out}}(t)}{p_{\text{in}}(t) - p_{\text{out}}(t)} & \text{if } p_{\text{in}}(t) \leq p_{\text{out}}(t)
\end{cases}
\]
with \( p_{\text{in}}(t) \) and \( p_{\text{out}}(t) \) the boundary pressure conditions and \( R \) the predefined valve resistance. A resistance increase of 100 was study to be a realistic by Sá Couto et al.

These mathematical flow relationships were used to model the behavior within cardiovascular elements and simulate resulting pressure and flow parameters. How input parameters were predefined for a neonatal hemodynamic model will be explained within the following section.

### 3.2.2 Redefined preterm lumped parameter model

Within this thesis we look at blood pressure patterns within preterm neonates this means that the original model suggested by Sá Couto has to be redefined to preterm dimensions. Redefinition of the model was done within the study of Dat et al. [8]. Creating a lumped parameter model able to realistically simulate the hemodynamic behavior of a spontaneous breathing preterm at 28 weeks gestational age and with a birth weight of 1000 gram. This model was adapted with a ductal segment to simulate blood pressure patterns within this study.

The new preterm model created by Dat et al. uses the same elements as the Sá Couto model but redefined input parameters which were verified with independent literature. First input values for elemental volumes, resistance and compliance were scaled by using hemodynamic characteristics of the term and preterm neonate. Secondly the atria of the redefined model were modeled as passive nodes by Dat et al.

Input parameters were redefined by scaling them with the systemic vascular resistance and total blood volume of a preterm neonate with respect to that of a term neonate. The systemic vascular resistance is clinically determined using the mean systemic pressure divided by the cardiac output, and is used to estimate the flow resistance of the systemic branch of the circulation. Dat et al. estimated the preterm systemic vacuum resistance using an independent literature study and showed it was 1.9 times the estimated systemic vacuum resistance of the term neonate. This factor was used by Dat et al. to redefine the segmental resistance values used by Sá Couto in a realistic preterm dimension.

Furthermore Dat et al. estimated that the total blood volume of a preterm was 110 ml/kg resulting in a modeled total blood volume of 110 ml. The modeled total term blood volume was estimated by Sá Couto to be 310 ml. Using the volume ratio of 0.35 unstressed volume parameters were redefined. Compliance and elastance both have a relationship in the model with respect to volume, with the volume ratio calculated by Dat et al. we can scale these input parameters to preterm dimensions. With compliances being directly proportional to the blood volume within a node, because elastance is the inverse of compliance this input parameters are proportional to \( 1/0.35 \).

The redefined preterm parameters that are used as the basis for our ductal closure model are shown within Table 3.1.

The redefined cardiac parameters are shown in Table 3.2.
Table 3.1: Values for the resistance, compliance, unstressed volumes and inertance used for each element within the model during simulations. Table is adapted from the thesis of Marco et al. [8].

<table>
<thead>
<tr>
<th>Element</th>
<th>Compliance [ml/mmHg]</th>
<th>Unstressed Volume [ml]</th>
<th>Resistance [mmHg·ms/ml]</th>
<th>Inertance [mmHg·ms²/ml]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathoracic systemic artery</td>
<td>0.025</td>
<td>3.1</td>
<td>34.5</td>
<td>1800</td>
</tr>
<tr>
<td>Extrathoracic systemic artery</td>
<td>0.058</td>
<td>8.2</td>
<td>2871</td>
<td>-</td>
</tr>
<tr>
<td>Systemic periphery</td>
<td>-</td>
<td>-</td>
<td>8039</td>
<td>-</td>
</tr>
<tr>
<td>Intrathoracic systemic vein</td>
<td>0.68</td>
<td>26</td>
<td>28.7</td>
<td>-</td>
</tr>
<tr>
<td>Extrathoracic systemic vein</td>
<td>1.35</td>
<td>22</td>
<td>402</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>0.031</td>
<td>1.1</td>
<td>34.5</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary periphery</td>
<td>-</td>
<td>-</td>
<td>1627</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary vein</td>
<td>0.71</td>
<td>7.8</td>
<td>28.7</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3.2: Parameter values of the preterm heart. Atria are passively modeled while ventricles have a time varying elastance model. Table is adapted from thesis Marco dat. [8].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Left ventricle</th>
<th>Right ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal elastance</td>
<td>[mmHg·ml]</td>
<td>7.7</td>
</tr>
<tr>
<td>Maximal elastance</td>
<td>[mmHg·ml]</td>
<td>156</td>
</tr>
<tr>
<td>Atrium elastance</td>
<td>[mmHg·ml]</td>
<td>10.6</td>
</tr>
<tr>
<td>Ventricle unstressed volume</td>
<td>[ml]</td>
<td>0.17</td>
</tr>
<tr>
<td>Atrium unstressed volume</td>
<td>[ml]</td>
<td>0.08</td>
</tr>
<tr>
<td>Valve resistance</td>
<td>[mmHg·ms/ml]</td>
<td>115</td>
</tr>
</tbody>
</table>
Chapter 4

Materials and methods

This chapter introduces the methodology by characterizing the patient population followed by a description on the acquisition of signals and ductal characteristics in two databases. At the end of this chapter the analyzed patent ductus arteriosus specific features are introduced.

4.1 Patient Population

The study population consisted of two databases which were collected during clinical studies in 2008 and 2015. The study inclusion criteria was a mean gestational age below 32 weeks and birth weight below 1500 gram. Only patient that had blood pressure measurements were included in both studies. 25 patients were retrospectively studied in three groups with 14 patent ductus arteriosus patients and nine controls. Of the 14 patients with a PDA, seven were treated with Indomaticin and seven with Iboprufen.

It is important to characterize the maturation of each patient because this has an effect on the measured vital sign patterns. Maturation effect arise from development of the subject during fetal and neonatal life. Maturation during the fetal life can be characterized by important birth parameters such as birth weight and gestational age. Maturation during neonatal life is best described by using the post menstrual age of a patient which is the gestational age plus the elapsed time from birth. Since patent ductus arteriosus treatment is given during the first week after birth the post menstrual age has limited extra maturational information compared to gestational age.

Ductal screening and treatment information from patient are used to define three relevant study groups within the study population. First group are controls, these patients didn’t show any clinical signs of a patent ductus arteriosus which means that natural closure probably took place within the first 24 hours after birth. The second group of patients did show clinical signs of a patent ductus arteriosus and showed ductal patency during a ductal screening by a skilled pediatric cardiologist. Hemodynamically significant shunts were treated by pharmaceuticals to stimulate ductal closure. Patients who responded to this first course of pharmaceutical treatment were labeled as responders in this study. Responsiveness to the pharmaceutical treatment was checked by a second follow-up echocardiograph screening which is routinely performed after the first pharmaceutical course is fully administered. The third group of patients still showed ductal patency during this follow-up screening and are labeled as non-responders.
CHAPTER 4. MATERIALS AND METHODS

Table 4.1: Mean gestational age (GA) and birth weight (BW) of the three study groups in the GE database. Characteristics of this database are described within section 4.3.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PDA Responders</th>
<th>PDA Non-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>infants &lt;32 weeks</td>
<td>(n = 4)</td>
<td>(n = 4)</td>
<td>(n = 3)</td>
</tr>
<tr>
<td>Mean GA (weeks)</td>
<td>30.0 ± 1.3</td>
<td>27.9 ± 0.7</td>
<td>26.9 ± 0.7</td>
</tr>
<tr>
<td>Mean BW(g)</td>
<td>1150 ± 96</td>
<td>973 ± 245</td>
<td>1153 ± 47</td>
</tr>
</tbody>
</table>

Table 4.2: Mean gestational age (GA) and birth weight (BW) of the three study groups in the Philips database. Characteristics of this database are described within section 4.3.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>PDA Responders</th>
<th>PDA Non-Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>infants &lt;32 weeks</td>
<td>(n = 5)</td>
<td>(n = 3)</td>
<td>(n = 4)</td>
</tr>
<tr>
<td>Mean GA (weeks)</td>
<td>29.5 ± 1.4</td>
<td>26.5 ± 0.7</td>
<td>25.6 ± 0.8</td>
</tr>
<tr>
<td>Mean BW(g)</td>
<td>1229 ± 400</td>
<td>817 ± 92</td>
<td>738 ± 68</td>
</tr>
</tbody>
</table>

4.2 Clinical Measurements

This section discusses the routinely employed methodology for ductal screening as well as the acquisition of the vital physiological signals.

4.2.1 Ductal screening

Patients who show clinical signs of a PDA undergo a ductal screening by a pediatric cardiologist to assess ductal patency. By a series of echocardiograph images, important ductal parameters are determined which tell the care provider if there is ductal patency and if it is hemodynamically significant. With this information, care providers determine if treatment should be given to stimulate ductal closure or to check whether the administered treatment had a sufficient effect.

Important ductal parameters, which are determined during a ductal screening are ductal diameter and maximum flow speeds within the ductus. Markers within the echocardiography image of the ductus are used to measure the ductal diameter. An echo image of the ductus is shown within Figure 4.1a. Doppler flow echo image of the ductus are used to measure a ductal flow waveform during several heart beats. From this a maximum flow speed within the ductus is determined. A doppler flow image of the ductus is shown within Figure 4.1b. With these parameter pediatric cardiologist are able to give an accurate assessment of the hemodynamic significance.

Quantifying ductal closure

Diameter and flow speeds of the ductal shunt are used to estimate ductal flow, which quantifies ductal steal. Ductal steal is an important parameter because it quantifies the hemodynamic significance of the ductal shunt. The estimation is made by assuming a cylindrical ductal flow segment with a diameter equal to the ductal diameter measured within the echocardiogram image of the ductus. The average flow speed within the ductus is set to the measured maximum flow speed within the ductus. This clearly is an overestimation but it is the only flow speed parameter that is measured during the doppler flow measurement. With these ductal parameters ductal flow was estimated by:

$$D_{flow} = \pi \left( \frac{D_{ductus}}{2} \right)^2 \cdot V_{ductus}$$ (4.1)
CHAPTER 4. MATERIALS AND METHODS

Ductal flow is the volume of blood that passes through the ductus within a certain time frame. Ductal steal is used to study the consequence of a ductal shunt on the blood flow within the aorta. Steal is the amount of flow that is diverted by the ductal shunt into the pulmonary artery. If this steal is large compared to the average flow within the aorta, it is a clear sign that systemic perfusion is at risk. Large ductal diameter or ductal flow speeds are not worrisome if the total ductal steal remains limited.

Because ductal diameter during closure decreases with respect to an increasing elapsed time, since the first pharmaceutical doses, a new closing parameter $C_p$ was defined. $C_p$ can be calculated using the measured ductal diameter during the echo directly before the first ductal closure treatment course and the follow-up echo which is performed immediately after the first ductal closure treatment course is finished. The closing parameter is calculated by:

$$C_p = 1 - \frac{D_{ductus}[T = t]}{D_{ductus}[T = 0]}$$

with $D_{ductus}[T = 0]$ the ductal diameter measured before pharmaceutical treatment and $D_{ductus}[T = t]$ after a full treatment course was administered.

4.2.2 Vital sign measurements

The most important vital signs within this ductal study are arterial blood pressure signals, the ECG signal and blood saturation signal. Possible patent ductus arteriosus patterns within these signals were introduced within Chapter 2. Vital signs are continuously measured and routinely exported from the central monitoring post to a research server. First a description is given how blood pressures are invasively measured. Secondly, it will be explained how heart rate values are determined from the ECG signal. Finally blood saturation measurements are explained.

Blood pressure values are measured invasively by a fluid filled catheter manometer system. A schematic overview of such a fluid filled catheter is displayed in figure 4.2. The system works by placing a small catheter in one of the arteries of the newborn. At the end of the fluid filled system a small pressure transducer converts pressure fluctuation within the blood into an electrical signal.
that is picked up by the patient monitoring system. The fluid filled catheter is effected by ambient room pressure drifts which means the system has to be frequently recalibrated.

![Image of a fluid filled catheter manometer system](image-url)

Figure 4.2: Schematic overview of a fluid filled catheter manometer system. In newborns the catheter is usually placed in the umbilical artery instead of the radial artery.

Heart activity was monitored using three thoracic ECG leads connected to a patient’s chest and abdomen. De- and repolarization of heart muscle during contraction is detected by the electrodes of these ECG leads. This distinct electric heart polarization process is measured along three different projection axes. The three projection axes are formed by measuring the voltage across lead 1 to lead 2, lead 1 to lead 3 and lead 2 to lead 3. Within each projection axes a characteristic QRS-complex is measured during each contraction of the heart. Detection of these QRS-complexes by an algorithm, gives the average heart beats per minute.

Blood saturation levels were non-invasively measured using a pulse oximetry device, which is clamped on a patient’s toe. These techniques use a difference in optical absorption properties between oxygenated and deoxygenated blood and gives a ratio between these two oxygenation states. This ratio can be used to determine the saturation level of a patient’s blood.

### 4.3 Database characteristics

Vital signs were collected during two clinical studies with two different monitoring systems. Important characteristics of both these databases are given in this section.

The first database was collected using a GE monitor system which was able to acquire high-resolution vital signs signals and had patent ductus arteriosus related annotations. The database holds vital signs of 11 preterm patients. The high-resolution vital sign signals were stored at 240 Hz for ECG, 120 Hz for ABP and 60 Hz for SpO2 and respiration. Additionally, vital signs averaged trends of these signals were generated the monitor and these parameter values were stored with a 2-s resolution for blood pressure, heart rate and saturation levels. PDA related annotations consisted of echo findings from pediatric cardiologists about the hemodynamic significance of a detected ductal shunt. Due to the retrospective use of this database, actual echocardiographic images were not available for these patients. Besides these echo findings time annotated pharmaceutical treatment points of the patent ductus arteriosus were available.
The second database was collected using the Philips monitor system which only stores low-resolution vital signs signals and had echocardiographically assessed ductal shunts with extensive treatment information. This database was recently collected and has 12 preterm patients. Resolution of the stored vital signs was 120 Hz, which makes this database unsuited for the analysis of heart rate variability [41]. Heart rate variability analysis is discussed more extensively within section 4.4. Parameter data from the Philips monitor was stored with a 1-min resolution. Echocardiographic images where used to determine important ductal parameters and quantify the degree of ductal closing during pharmaceutical treatment.

Table 4.3: Overview of patent ductus arteriosus database characteristics

<table>
<thead>
<tr>
<th>GE database</th>
<th>Philips database</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-frequency waveforms</td>
<td>Low-frequency waveforms</td>
</tr>
<tr>
<td>- 240 Hz ECG</td>
<td>- 120 Hz vital signs</td>
</tr>
<tr>
<td>- 120 Hz BP</td>
<td></td>
</tr>
<tr>
<td>- 60 Hz SpO2</td>
<td></td>
</tr>
</tbody>
</table>

Parameter data
- 2-second average trends
- 1-minute average trends

PDA annotations
- Time annotated treatment moments
- Echo findings

PDA annotations & images
- Time annotated treatment moments
- Echo findings
- Echo images
  - Ductal Diameter
  - Ductal systolic flow

### 4.4 Analyzing vital signs

Within this study we analyze ductal patency patterns around the controlled ductal closure point during the first pharmaceutical treatment doses of the first course of the patent ductus arteriosus. Naturally considerable variation is present between vital signs of patients and this method was designed to highlight variations that occur specifically during ductal closure.

Continuously collected vital sign patterns discussed within section 4.2 were analyzed for possible ductal specific patterns. The features created from these vital signs will be explained within this section.

**Trend data**

First parameter filtering was applied to correct for non-physiological artifacts within the parameter data series. During the acquisition of these signals, noise is created from sensor detachments or system calibration procedures. In our study this is filtered out by replacing blood pressure values below 10 mmHg and blood pressure values above 95 mmHg with NaN. Heart rate parameter values where filtered out if they exceeded 210 BPM or were lower than 50 BPM. Blood oxygenation parameter series were filtered by replacing values above 100 and below 55 procent saturation.

Secondly an analyzing protocol was set up to examine average trends within the physiological parameter data before and after ductual closure treatment. The window of interest was set 6 days surrounding the first treatment dose, starting 3 days before the first pharmaceutical treatment dose until 3 days after the first dose. Because a starting treatment point is absent within controls
we randomly selected a 6-day period from their NICU stay, with the beginning of this period being in the first week after birth.

Vital sign features were calculated for 30-min epochs and mean trends of these 30-min epochs were updated every 6-hours. These short timescale patterns are interesting because within this time window the patient can be considered free from long-term variations.

The 6-day window around the first pharmaceutical dose was taken because a full course of Indomethacin takes 1.5 days and Ibuprofen 3 days to be fully administered. A window of three days after the first doses of the first courses is able to show the vital sign patterns within the full first treatment course and has two echocardiographic assessments moments of ductal patency.

**Normalized-trend variability**

Normalized-trend variability normalizes absolute vital signs to a standardized score which corrects for natural drifts of the physiological signal. We determine the normalized-trend blood pressure variability within each half hour segment by:

$$NTV = \sqrt{\frac{\sum_{i}(x_i - \bar{x})^2}{n} \cdot \frac{1}{\bar{x}}}$$

(4.3)

with $x_i$ the raw monitor parameter data points within each half hour segment, $\bar{x}$ the average vital signs value within each analyzed half hour segment and $n$ the total amount of data point within each half hour segment. Vital signs normalized-trend variability is given within the same 6-day window surrounding the first ductal treatment doses.

Normalized-trend variability is used as a feature because it corrects for inter-patient variation during ductal closure.

**Heart rate variability**

Heart rate variability is a feature that is derived from a patient’s ECG signal to show the level of regularity in-between consecutive beats. This feature is used to quantify an imbalance of the nervous system, introduced within section 2.1.2. An imbalance which can be caused by the hemodynamic disorder of the patent ductus arteriosus and which changes during ductal closure.

Continuous ECG signals are used to study heart rate variability and because heart rate variability are subtle changes within cardiac contraction timing high-resolution ECG signals are necessary to make meaningful conclusions.

First the continuous ECG signal is preprocessed using a low and high pass Butterworth filter. The low-frequency Butterworth filter uses a cut-off frequency of 0.5 Hz to correct for baseline drifts within the raw ECG data over time. And the high-frequency Butterworth filter uses a cut-off frequency of 45 Hz to filter out high frequency noise and suppress the power grid.

Next the preprocessed ECG signals were analyzed using a R-peak detection algorithm created by Rooijakkers et al. [42]. This detection algorithm uses wavelet transformation to detect R-peaks with minimal complexity, which in turn reduces the computational power needed for a sufficient detection rate. This technique performs extremely well with even the most noisy neonatal signals. With the detected RR-series, inter-beat variations can be studied to quantify a possible imbalance of these intervals.

Quantification of this imbalance within our study is done in the time domain using the statistical parameters $pNN20$ and $pNN50$. $pNN20$ and $pNN50$ are features that quantify the increased imbalance in cardiac contraction resulting in a higher amount of de- or accelerations within the
RR-serie. This makes it possible to assess if there is an increase in sympathetic activation or parasympathetic activation. pNN20 and pNN50 are not determined by the RR-series but by the deviations of two consecutive heart RR-intervals within the RR-serie. pNN20 is the percentage of RR pairs in which the two consecutive intervals differ more than 20 ms. And with pNN50 being the percentage of pairs deviating more than 50 ms from one and other. Large deviations in the length of consecutive heart beats is believed to show an unstable and imbalanced nervous system.
Chapter 5

Materials and methods: Modeling ductal flow

5.1 Modeling closure of the patent ductus arteriosus

The model for ductal closure was created using the preterm model of Dat et al. that was introduced within chapter 3. This hemodynamic model of a preterm of 28 weeks GA and a body weight of 1000 gram was originally modeled with a close ductus. Within this study a PDA was created within the model to study changes in blood pressure patterns associated with ductal closure. The patency of the ductus arteriosus can be varied to change the hemodynamic significance.

The model was adapted by creating a ductal flow segment and by changing cardiac input parameters to compensate for ductal steal. The adapted version of the original model shown in figure 3.5 is presented in figure 5.1. The ductal flow segment runs from the intra-thoracic artery node to the pulmonary artery node. Flow within the ductal segment can be bi-directional and therefore no valves are placed within the segment. An extensive explanation about how ductal flow is modeled and how the significance of the ductus is controlled, is given within section 5.1.1. Cardiac compensation is modeled by adapting left ventricle input parameters to the hemodynamically open ductus state. This compensation mechanism is explained within section 5.1.2.

5.1.1 Modeling ductal flow

The ductal flow within this extra flow segment is governed by a resistance $R_{duc}$ and an inertance $L_{duc}$. With these parameters and pressure values in both nodes, the ductal flow is given by equation (3.21). The adapted model has a total of $n = 10$ nodes and $m = 11$ segments.

Ductal closure was modeled by increasing the segment’s resistance which results in a decrease in ductal flow. The ductal inertance remained unchanged during the closure of the ductus. Simulations have shown that ductal flow approaches a maximum value at a low ductal resistance in the order of $10^2$. Increasing the ductal resistance to the order of $10^7$ showed that ductal flow approaches a value of zero. A ductal segment without any flow is physiologically seen as a completely closed patent ductus arteriosus. Incrementally varying the ductal resistance and determining stable blood pressures within a full cardiac cycle at each step creates patency dependent blood pressure patterns.
5.1.2 Cardiac changes associated with a patent ductus arteriosus

If ductal steal is uncompensated by an increase in cardiac output, the systemic flow decreases which leads to insufficient perfusion of the systemic periphery. Within patients this compensation effect occurs naturally due to an increased venous return from the pulmonary circulation and by the Frank-Starling effect. Due to the presence of a ductal shunt blood volume from the aorta is diverted into the pulmonary circulation. This extra blood volume causes so called loading of the pulmonary circulation which results in a higher outflow of blood through the pulmonary vein into the left atrium. From the left atrium this excess blood leads to an increased filling of the left ventricle which results in a higher end-diastolic volume (EDV). The Frank-Starling mechanism triggers increased contractility of the heart due to this increased EDV. An increased contractility and higher EDV result in a larger left ventricle stroke volume which is the volume of blood that is pumped into the aorta by the left ventricle, at which point a new cycle starts.

Within the model, this compensation mechanism is simulated by changing the cardiac parameters to create a so called compensating heart. The three most important parameters for this compensation effect are the unstressed volume of the heart, the end diastolic volume and end systolic volume of the model heart. With these three points within the PV-diagram the minimum and maximum elastance can be determined. The unstressed volume of the heart is the geometric volume of the non-contracting heart. This parameter is unaffected by the presence of the ductal shunt. The minimum elastance is the slope between the unstressed volume and the end diastolic volume and maximum elastance the slope between the unstressed volume and the end systolic pressure.

First effect is the increased venous return which is caused by the loaded pulmonary circulation from blood supply by the ductal shunt. This increased venous return leads to an increased dias-
tolic filling of the left ventricle with increased end diastolic volume. This increased end diastolic volume together with a unchanged unstressed volume can be modeled by decreasing the minimum elastance of the left ventricle. With the minimum elastance defined as the slope between the unstressed volume and end diastolic volume.

Second effect is triggered by the Frank-Starling mechanism which states that an increased left-ventricle diastolic filling leads to an increased contractility of the ventricle. The contractivity of the modeled left-ventricle can be increased by increasing the maximum elastance of the left-ventricle. This leads to a decreasing end systolic volume if the unstressed volume remains constant.

The pressure-volume loops of a compensating and non-compensating heart for the left and right ventricle are shown within Figure 5.2.

![Pressure-Volume loop right ventricle](image)

![Pressure-Volume loop left ventricle](image)

**Figure 5.2:** Left: Simulated pressure-volume loops of the right ventricle with and without compensation for ductal steal. Right: Simulated pressure-volume loops of the left ventricle with and without ductal steal compensation. Compensation is visible in the left ventricle by a decreased slope between the left ventricle unstressed volume and the end diastolic volume point within the PV-curve. And by an increased slope between the unstressed volume and the PV end ejection point.

The amount of compensation by the heart is unknown during the dynamic closure of the ductal shunt. This makes it difficult to model blood pressure patterns with one single cardiac configuration. We therefore simulated blood pressure values within a range of possible cardiac compensation inputs. Simulating blood pressures ductal closure is modeled with a patent ductus arteriosus compensating heart and simulations in which there is no compensation of the heart for ductal steal. The degree of compensation was determined by scaling cardiac parameters of the open and closed ductal neonatal model created by Sá Couto et al. [36] to preterm dimensions. Cardiac parameters within the used preterm model for the compensating heart are shown in Table 5.1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV minimal elastance [mmHg*ml]</td>
<td>5.01</td>
</tr>
<tr>
<td>LV maximal elastance [mmHg*ml]</td>
<td>303.4</td>
</tr>
</tbody>
</table>

Table 5.1: Cardiac compensation parameters for simulations with open ductus.
CHAPTER 5. MATERIALS AND METHODS: MODELING DUCTAL FLOW

5.2 Sensitivity simulation method

A sensitivity test was done to study the importance of each estimated input parameter on the resulting simulated blood pressure values. This information is used to make the analysis as robust as possible by reducing the influence of parameters that had a large effect on the simulated blood pressure values.

The test was performed by a piece-wise change of the input parameters by plus and minus ten percent and determining the percentage change of the simulated blood pressure values. Two blood pressure characteristics were studied, the shift in blood pressure value and the blood pressures patterns during closure. Blood pressure shift was determined by looking at the shift in mean blood pressure during ductal closure. Blood pressure patterns were studied by comparing closure patterns of the adapted model with the original model with the correlation coefficient between both patterns. A correlation coefficient of one means that the two patterns are identical. Normalization of the two patterns made the correlation independent of possible blood pressure shifts.

The test showed that blood pressure values are sensitive for inaccurate input estimations while blood pressure patterns are insensitive to changes of the input parameters. The percentage change of simulated blood pressure with an absolute 10 percent changed input parameter are shown within Table 5.2 and 5.3. Results for the blood pressure patterns are not shown because they did not show sensitivity to the used input parameters.

Table 5.2: Absolute percentage changes in systemic blood pressures with respect to a 10 percent change of each individual vascular input parameter.

<table>
<thead>
<tr>
<th>Element</th>
<th>Compliance [%ΔP(10%ΔC)]</th>
<th>Unstressed Volume [%ΔP(10%ΔV₀)]</th>
<th>Resistance [%ΔP(10%ΔR)]</th>
<th>Inertance [%ΔP(10%ΔL)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrathoracic systemic artery</td>
<td>0.86</td>
<td>0.74</td>
<td>0.01</td>
<td>0</td>
</tr>
<tr>
<td>Extrathoracic systemic artery</td>
<td>0.26</td>
<td>1.96</td>
<td>1.19</td>
<td>3.76</td>
</tr>
<tr>
<td>Systemic periphery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrathoracic systemic vein</td>
<td>1.87</td>
<td>6.20</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Extrathoracic systemic vein</td>
<td>3.17</td>
<td>5.25</td>
<td>0.16</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>0.30</td>
<td>0.26</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Pulmonary periphery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary vein</td>
<td>2.86</td>
<td>1.86</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

Table 5.3: Absolute percentage changes in systemic blood pressures with respect to a 10 percent change of each individual cardiac input parameter.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Left ventricle [%ΔP(10%Δ)]</th>
<th>Right ventricle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal elastance</td>
<td>2.26</td>
<td>3.6</td>
</tr>
<tr>
<td>Maximal elastance</td>
<td>0.58</td>
<td>1.03</td>
</tr>
<tr>
<td>Atrium elastance</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Ventricle unstressed volume</td>
<td>0.04</td>
<td>0.03</td>
</tr>
<tr>
<td>Atrium unstressed volume</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Valve resistance</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Heart rate</td>
<td>5.19</td>
<td></td>
</tr>
<tr>
<td>Total blood volume</td>
<td>26.24</td>
<td></td>
</tr>
</tbody>
</table>

Strong dependency of simulated blood pressure values with respect to the total blood volume can be reduced by normalizing simulated blood pressures by the total blood volume or birth weight.
Birth weight can be used because there is a direct relationship between the birthweight of a patient and the total blood volume.

With these adaptations within the original model we are able to simulate realistic blood pressure values for a preterm of 28 weeks with a birth weight of 1000 gram undergoing ductal closure. We will use the model to compare it with blood pressure patterns of preterm undergoing a controlled ductal pharmaceutical closure. By assessing the similarity of simulated and observed blood pressure patterns we hope to find patterns which are specific to physiological closure of an open ductus.
Chapter 6

Results & discussion

In this chapter the results of the patent ductus arteriosus study are presented and discussed. First the measured hemodynamic patterns occurring during pharmaceutical treatment of the patent ductus are presented. Secondly simulated blood pressure patterns resulting from a modeled closure of the ductus will be shown. Thirdly I will present characteristics of ductal patency and corresponding hemodynamic trends during ductal treatment. Finally measured and simulated blood pressure patterns during ductal closure are compared.

6.1 Vital sign patterns during pharmaceutical treatment of the patent ductus arteriosus

6.1.1 Blood pressures

To characterize the blood pressure behavior upon ductal closure, blood pressure trends are analyzed in a window of ± 3 days surrounding the first pharmaceutical treatment point. Average blood pressure values are calculated each half hour. At six hourly intervals, the mean of the these half hour values is shown. Patients within the GE database were treated with Indomatacin administered 0.2 [first dose] - 0.1 [second dose] - 0.1 [third dose] kg/ml every 12 hour. Philips database patients received Ibuprofen 10 [first dose] - 5 [second dose] - 5 [third dose] mg every 24 hours. The first dose is administered at $T = 0$ within this analysis.

Analyzed mean systemic blood pressure trends of individual controls within the GE database are shown to illustrate the inter-group blood pressure variations. Controls that are ABP monitored have another indication besides ductal patency for ABP monitoring, which means that there might be other illnesses patterns within these measurements. GE control mean systemic blood pressures are shown within Figure 6.1. The error bars represent the standard error of the mean.

This figure shows two important characteristics of our analysis. First there is considerable variation in blood pressure between individual controls. Secondly, the drift within a patients systemic pressure during there neonatal intensive care can be substantial. Because the amount of patients that was analyzed was low individual outliers like $C1$ can cause drifts within group average trends. Despite these observations and the limit availability of true control patient data average systemic blood pressure trends were analyzed for possible collective behavior between each individual patient.

Average systemic blood pressure trends in controls, responders and non-responders are presented within Figure 6.2. Control one within the GE database is omitted within the analysis of the average GE control trends. The standard error of the mean of the individual blood pressures trends within each group is shown as error bars.
Figure 6.1: *Analyzed mean systemic blood pressures of GE controls. Blood pressures are analyzed in a window of ± 3 days surrounding treatment of the PDA. Error bars are given by the standard error of the mean.*

To investigate these blood pressure trends mean values pre- and post-treatment are calculated together with the so called "pre- and post-treatment" blood pressure difference. These values are given within Table 6.1. "Pre-treatment" blood pressure values were determined by averaging the data points between $-2.5 < T < -1.5$ and "post-treatment" blood pressures were determined by averaging the data points between $1.5 < T < 2.5$. Except within the controls in which "post-treatment" blood pressures are determined within $0.5 < T < 1.5$. 
Figure 6.2: Weighted average blood pressure trends during pharmaceutical ductal treatment. Error bars are given by the standard error of the mean.
CHAPTER 6. RESULTS & DISCUSSION

Table 6.1: Quantitive pre- and post ductal treatment blood pressure values within the systemic blood pressure measurements.

<table>
<thead>
<tr>
<th></th>
<th>Systolic</th>
<th>Mean</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Treat</td>
<td>Post-Treat</td>
<td>∆P</td>
</tr>
<tr>
<td>Philips (n=13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls (n=3)</td>
<td>50.3 ± 1.4</td>
<td>56.3 ± 1.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Responders (n=3)</td>
<td>43.4 ± 2.1</td>
<td>54.4 ± 0.6</td>
<td>11</td>
</tr>
<tr>
<td>Non-Responders (n=4)</td>
<td>44.3 ± 1.6</td>
<td>47.4 ± 0.9</td>
<td>3.1</td>
</tr>
<tr>
<td>GE (n=10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls (n=3)</td>
<td>50.4 ± 2.3</td>
<td>62.9 ± 1.3</td>
<td>12.5</td>
</tr>
<tr>
<td>Responders (n=4)</td>
<td>52.2 ± 2.3</td>
<td>59.8 ± 2.5</td>
<td>7.6</td>
</tr>
<tr>
<td>Non-Responders (n=3)</td>
<td>50.7 ± 1.2</td>
<td>52.9 ± 1.5</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Remark: For controls, ∆P is related to maturation. For PDA patients, ∆P is a combined effect of maturation and PDA closure due to treatment. The ∆P difference between controls and PDA patients is most pronounced within the systolic pressure.

Table 6.1 shows the "pre- and post-treatment" blood pressures between PDA patients and controls. Within controls an overall increase in systemic blood pressures is detected, this effect might be explained as an maturation effect. This maturation effect on absolute blood pressure increases shows to be bigger in systolic blood pressure compared to the diastolic blood pressure. A result that is supported by the maturation study performed by Kent et al. [9].

Pre- and post-treatment blood pressures from controls are compared with the pre- and post-treatment blood pressures measured within PDA patients. This analysis shows that together with the maturation effect there is an additional effect which seems to be caused by pharmaceutical closure of the ductus. This effect is best illustrated within the Philips systolic pressures where pre-treatment pressures between responders and non-responders are similar and post-treatment responders blood pressure values shifted more towards that of the control group. This effect is less pronounced within the GE database because of the limit number of controls within the 6 day analyze window.

There is a large variation between both databases. Besides the large inter-patient variability there are additional possible explanations for this variation between the GE and Philips database. First is the usage of two different types of pharmaceuticals for treating the patent ductus arteriosus patients. Second reason is the fact that these databases were collected seven years apart from each other. During this period a lot has changed within the treatment protocols of the MMC neonatal intensive care which has an effect on the measured blood pressures.

To study the variability within these measured blood pressure the normalized-trend variability (NTV) of these signals was studied during pharmaceutical treatment of a patent ductus. NTV of the systolic, mean and diastolic blood pressure measurements are shown within Figure 6.3a to 6.3f. The standard error of the mean are shown as error bars.
Figure 6.3: Results of the variability analyses of the diastolic, mean and systolic blood pressure trend measurements.
Though the number of patients is limited, normalized-trend variability seems to increase within responders and non-responders during pharmaceutical treatment of the patent ductus arteriosus. Furthermore controls seem to have a very slow increasing variability which could be a possible sign of maturation. After treatment the variability within responders and non-responders increases is larger than that of the controls, see Table 6.2.

Normalized-trend variability data between the GE and Philips database have a large absolute difference. This is caused by the dependency of normalized-trend variability on the number of data points that are analyzed within each epoch. Normalized-trend variability within the GE database is done within 900 data points per half hour compared to 30 data points within the Philips database. The amount of sample points within the Philips database was limited by the export protocol and not by the patient monitor itself.

### 6.1.2 Blood saturation

To investigate saturation patterns arising from the ductal shunt, blood saturation trends were studied during pharmaceutical closure. Average blood saturation levels within controls, responders and non-responders are presented within Figure 3a and 3b with the standard error of the mean as error bars.

![Figure 6.4: Blood saturations trends during pharmaceutical ductal treatment.](image)

The blood saturation measurements show that all subject groups have saturation levels within the target range of 90-95% and that non-responders have a lower mean saturation compared to the controls and responders. This finding supports the concept that successful closure of the ductus is determined by the oxygen environment of the patient [43]. Furthermore mean saturations levels within the Philips database are lower compared with the GE database. A clear reason for this is unknown but possibly changed care protocols (2008 vs 2015) could have an effect on the mean...
saturation levels.

Variability of these mean blood saturation trends are characterized using the normalized-trend variability parameter, these results are shown within Figure 6.5. Error bars were determined using the standard error of the mean.

![Figure 6.5: Variability analysis of the measured trends saturation patterns.](image)

The normalized-trend variability results show high degree of stability of the blood saturation levels within controls and patients. Showing that the variability within the blood saturation signal is significantly lower compared to that of the blood pressure measurements. With no visible effect within the blood saturation signal due to pharmaceutical treatment of the open ductus.

6.1.3 Heart rate and Heart rate variability

Average heart rate patterns were studied during pharmaceutical closure using ECG measurements. Results are shown within Figure 6.6.

![Figure 6.6: Average heart rate trends during pharmaceutical ductal treatment.](image)

Mean heart rate measurements do not show a clear pattern, following pharmaceutical treatment of the PDA, differences within mean heart rate can be explained by looking at the gestational age.
of each patient group. A comparison between mean group gestational age and mean heart rate is shown within Table 6.3.

Table 6.3: Mean heart rate and gestational age for each group within both databases. Table shows an increasing measured mean heart rate with respect to a decreasing mean gestational age of each study group.

<table>
<thead>
<tr>
<th></th>
<th>GE</th>
<th>Philips</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n GA</td>
<td>Mean HR</td>
<td>n GA</td>
<td>Mean HR</td>
</tr>
<tr>
<td>Controls</td>
<td>4 30.0 ± 1.3</td>
<td>148 ± 7</td>
<td>5 29.5 ± 1.4</td>
<td>150 ± 4</td>
</tr>
<tr>
<td>Responders</td>
<td>4 27.9 ± 0.7</td>
<td>149 ± 4</td>
<td>3 26.5 ± 0.7</td>
<td>146 ± 8</td>
</tr>
<tr>
<td>Non-Responders</td>
<td>3 26.9 ± 0.7</td>
<td>158 ± 6</td>
<td>4 25.6 ± 0.8</td>
<td>152 ± 6</td>
</tr>
</tbody>
</table>

Table 6.3 shows an increasing heart rate with respect to a decreasing gestational age.

Ductal closing effects on the heart rate variability are characterized using a statistical analysis of the continuous ECG waveforms during pharmaceutical treatment. Methodology how heart rate variability can be determined within the time domain is given within section 4.4. Within 6-days surrounding ductal closure the statistical parameters pNN20 and pNN50 are determined, this is shown within Figure 6.7. Analysis was only performed on the GE database because high-frequency ECG signals were unavailable within the Philips database.

Figure 6.7: Statistical characterized variability within continuous ECG waveform data, characterization was done with 6-days surrounding the first pharmaceutical treatment doses. Elevations of the pNN20 and pNN50 score show that there is a large amount of inter-beat variability in the underlying ECG waveform.

These figures show that average heart rate and heart rate variability are poor vital sign features to monitor ductal patency because they lack patent ductus specific patterns. Furthermore the pNN20 and pNN50 parameters show a high degree of sensitivity which results in spiky patterns during the 6-day analyze window.
6.2 Simulated hemodynamic patterns during ductal closure

Hemodynamic parameters such as pressure and flow were simulated during ductal closure. This section is structured by first introducing time-dependent simulated preterm blood pressures and flows during a full cardiac cycle. After which trends of these time-dependent hemodynamic patterns are given with respect to a changing ductal patency. At the end of this section the modeled ductal closure is analyzed to show the interpretation of systemic pressures with respect to ductal flow.

6.2.1 Time dependent hemodynamic patterns

Simulations of hemodynamic patterns during a full cardiac cycle were performed to characterize preterm blood pressures and flows. Blood flows and pressures within the main elements of the lumped-parameter model are shown within Figure 6.8. Simulations were performed with a ductal segment of resistance $R_{duc} = 1500 \text{ mmHg} \cdot \text{ms/ml}$ and inertance $L_{duc} = 1800 \text{ mmHg} \cdot \text{ms}^2/\text{ml}$. These ductal parameters were estimated by scaling ductal parameters from the term neonate ductal simulations performed by Sá Couto et al. [36]. The preterm model parameter from Table 3.1 were used together with the cardiac contraction parameters within Table 3.2.

![Figure 6.8](image)

Figure 6.8: This figure shows important flow and pressure values within the preterm hemodynamic model during two full consecutive heart cycles. First letter of the abbreviations used is p for pressure or q for flow. Last two letters of the abbreviations is used to indicate each individual node or segment. Noted by lv: left ventricle, la: left atrium, rv: right ventricle, ra: right atrium, pa: pulmonary artery, ao: aorta, sp: systemic periphery; pp: pulmonary periphery, tv: tricuspid valve, mv: mitral valve.

6.2.2 Ductal resistance dependent blood pressure patterns

To investigate trends of the simulated cardiac-cycle hemodynamic patterns with respect to a varying modeled ductal patency, stable cardiac cycle simulation were simulated with a varying ductal resistance $R$. The measured mean systemic pressure as a function of ductal resistance $R$ is shown within Figure 6.9. Mean systemic blood pressure patterns are given for two cardiac settings. One with a so called compensating heart to compensate for ductal flow and a second setting without cardiac compensation. The shaded area in-between these cardiac settings serves as a predictive
range for possible physiological blood pressure values during ductal closure. Within this shaded
area a line is shown as guide to the eye for how blood pressure changes due to the transition form
a compensation to a non-compensating heart.

![Graph showing blood pressure trend with respect to ductal resistance](image)

**Figure 6.9:** The systemic blood pressure trend with respect to a changing ductal resistance $R_{duc}$. Mean systemic pressure is given for a compensating and non-compensating heart with a shaded area in-between to indicate possible physiological ranges.

Within this figure the effects of both the ductal closure and the heart compensation mechanism are shown together with a qualitative analysis of the interaction between the two. First a clear increase in mean systemic pressure is seen with respect to an increasing ductal resistance to simulate ductal closure. Secondly, the compensation mechanism shows to have an additional effect on the simulated blood pressures, which is in the range of the blood pressure increase resulting from the ductal resistance increase. Within the preterm model the amount of compensation by the heart for a PDA was estimated by scaling the compensation mechanism of the term-model with ductal shunt. This scaling might be incorrect because the ability for the preterm heart to compensate for ductal steal can be different than the compensating within term neonates. The modeled blood pressure increase from the open ductus model with compensating heart towards the closed ductus model without compensating heart is $\approx 10$ mmHg which is in the same range as predicted by Evans et al. [33] for Indomethacin treatment.
6.2.3 Hemodynamic characteristics of ductal flow

A relationship between modeled ductal resistance and ductal flow is given within Figure 6.10. Clinically determining the ductal resistance is complicated because of its dependency on ductal diameter and ductal in- and out flow pressures. Ductal flows however can be estimated using the echocardiographic images of the ductal shunt. Blood pressure patterns are therefore given with respect to ductal flow to enable the comparison of the available simulated and measured blood pressure values. Within the previous subsection we presented blood pressure patterns with respect to the ductal resistance. This relationship between simulated blood pressures and ductal flow is created by fitting a relationship between ductal resistance and ductal flow. With this relationship the simulated blood pressure as a function of $\Omega_{ductus}$ can be reformulated with respect to ductal flow.

Secondly, the simulated ductal flow is given for the compensating and non-compensating heart configuration against ductal resistance in Figure 6.10b. Because the transition from a compensating heart towards a non-compensating heart during ductal closure is unknown the mean ductal flow of both cardiac configuration is taken to fit a relationship between the ductal flow and ductal resistance. The mean simulated ductal flow is fitted with an exponential decay function with two time constant: Fit $y_2$.

![Figure 6.10](image)

(a) Ductal flow  (b) Fitted average ductal flow

Figure 6.10: Left: This figure shows the averaged ductal output during a cardiac cycle with respect to a changing ductal resistance. Ductal flow is shown for a compensating and non-compensating heart with a shaded area in-between to indicate the possible physiological range. Right: Mean simulated ductal flow with respect to ductal resistance. The exponential decay fit $y_2$ with two time constant was used for an exact relationship between ductal resistance and ductal flow.

Simulated ductal flow with respect to ductal resistance show that closure of the ductal segment can be modeled using an increasing ductal resistance. And that ductal closure occurs within both the compensating and non-compensating heart configuration at a single value for the ductal resistance.
With a relationship between ductal flow and resistance simulated systemic blood pressure patterns can be displayed as a function of ductal flow. This is shown within Figure 6.11. Because ductal flow decreases with respect to time the x-axis is switched.

Figure 6.11: The systemic blood pressures with respect to a decreasing ductal flow. Systemic pressures are given for a compensating and non-compensating heart with a shaded area in-between to indicate possible physiological ranges.

I use this figure to model blood pressure as a function of ductal flow. I checked the blood pressure values at zero ductal flow and a non-compensating heart, and they are in the same range as the original closed ductal model created by Dat et al. [8].

Comparing the systolic and diastolic pressures with respect to ductal flow and cardiac compensating an interesting dependency is observed. Blood pressures are affected by two main mechanisms: the closing of the ductus and the transition from a compensating heart towards the non-compensating heart.

The effect of ductal steal on simulated blood pressures can be quantified by the difference between blood pressure at a ductal flow of 200 ml/min and at 0 ml/min for any specific cardiac setting. This effect is shown by the parameter $\Delta(P_0 - P_{200})$.

The second effect can be quantified using the difference between compensating and non-compensating heart pressures at a certain fixed ductal flow. This effect is given by the parameter $\Delta(P_{\text{comp}} - P_{\text{non-comp}})$.

Figure 6.11 shows that for the systolic blood pressure $\Delta(P_{\text{comp}} - P_{\text{non-comp}})$ is high compared to the $\Delta(P_0 - P_{200})$. While in the diastolic pressures $\Delta(P_0 - P_{200})$ is relatively larger compared to $\Delta(P_{\text{comp}} - P_{\text{non-comp}})$. This means that simulated systolic blood pressures are more affected by cardiac compensation while simulated diastolic blood pressures are more affected by the ductal steal through the ductus.
6.3 Echocardiographic assessed patent ductus arteriosus

Echocardiograph findings from the skilled pediatric cardiologist were analyzed to characterize the ductal closing behavior of each patient within the Philips database. First ductal diameter was measured with respect to the elapsed time from the first treatment doses of the first course to study ductal changes during pharmaceutical treatment. This analysis is shown within Figure 6.12a.

Next estimations of ductal flow were made to characterize ductal significance during pharmaceutical ductal closure. Ductal flow is estimated by assuming a cylindrical flow tube with a constant flow speed with respect to the radial position. Echocardiographic measured maximum flow speeds within the ductus are taken as an estimate of the constant flow speed throughout the cross-section of the ductal shunt. The estimated ductal flows with respect to the elapsed time after the first pharmaceutical treatment dose of the first course are presented in Figure 6.12b.

![Figure 6.12: (a) Ductal diameter and (b) Ductal flow](image)

These two figures show that pharmaceutical treatment leads to closing of the ductus in the majority of patients. This closure effect by definition is larger for responders compared to non-responders, but most non-responders show a response to the medication as well. Interestingly, individual patterns are seen with NR3 who shows an increasing ductal diameter and flow despite receiving ductal closure medication. And patient NR2 who shows to have a small decrease in ductal diameter but an increase in ductal flow.

Assumption of an uniform flow speed within the ductal shunt equal to the measured maximum flow speed is a clear overestimation. But it is the only quantitative flow assessment that is performed during the echo-cardiac images. Furthermore the assumption that the ductal shunt is cylindrical simplifies possible complicated 3D phenomenon such as kinking of the ductal flow segment.
6.4 Comparison between measured and simulated blood pressure patterns during ductal closure

Measured and simulated blood pressures were compared to study if measured closure patterns can be verified using the hemodynamic ductal closing model. In chapter 5 a large dependency of absolute simulated blood pressures was shown with respect to the total blood volume. Because blood volume variability is large between individual patients and the model is large the simulated blood pressure are normalized after simulations with respect to the total blood volume for comparison. Total blood volumes in patients can be estimated using the birthweight of each patient and an average blood volume of 110 ml per kilogram birthweight [44]. Average birthweight of responding and non-responding patients respectively were 738 and 817 gram.

Figure 6.13: This figure shows the measured and simulated systemic blood pressures normalized to birthweight as a function of decreasing ductal flow. Simulated systemic pressures are given for a compensating and non-compensating heart with a shaded area in-between to indicate possible physiological ranges. Systemic blood pressures were measured over an entire day at the beginning and end of the first treatment course.
While the modeled and measured ductal flow could only be roughly estimated, Figure 6.13 shows that for systolic pressures, the model blood pressure range function well with the chosen parameters. For ductal diastolic however, the measured blood pressure values are above the simulation results. Because fitted model ductal flows were determined using the average ductal flow from the compensating and non-compensating heart, simulated ductal flows within a model with a transition from compensating to non-compensating would be higher than currently estimated. Meaning that the simulated blood pressure ranges would shift towards the left within the graph. Measured ductal flow on the other hand are over estimated which means that they would shift to the right in the graph.

Blood pressure trends show behavior which is opposite to that expected by the transition from the compensating to the non-compensating cardiac configuration. Possible explanation could be that the compensation mechanism within preterm is fundamentally different from that of neonates. Or maybe there are other effects such as the maturation. If this maturation effect is larger and opposite to the pressure effect arising from the transition of the heart from compensating to non-compensating this pattern can remain undetected. Maturation effects on the measured systemic blood pressure are presented within the study by Kent et al. [9] and show an increase over seven days after birth similar to the systolic pressure increases seen within figure 6.13.

From the systolic pressures one can state that there is limited cardiac compensation and that on top of ductal closure patterns a maturation effect is visible. Or that there is cardiac compensation within the patient but maturation effect results in a net increase of measured blood pressure during ductal closure. Without adequate characterization of the heart within PDA patients it is impossible to state which explanation is correct.
6.4.1 Blood pressure trends with assessed ductal patency

Assessed ductal patency parameters and measured blood pressures were used to study blood pressure patterns with respect to a quantified closing ductus. Systemic blood pressures were measured at $T = 0$ and $T = 3$ during the first and second check-up echocardiograph screening. And determined by looking at the average of four six hour blood pressure windows during the day of the echocardiograph screening. These results are shown within Figure 6.14 in which absolute and percentile blood pressure changes are displayed. Changes within systolic, mean and diastolic blood pressure are shown as a function of the closing parameter see equation 4.2 discussed in chapter 4.

Figure 6.14: Left: This figure shows measured systolic, mean and diastolic blood pressure trends during the first treatment course. Ductal diameter was measured at $T = 0$ and $T = 3$, with $T = 0$ being the moment of the first pharmaceutical treatment doses administration and $T = 3$ the moment at which a full treatment course was administered. Because ductal diameter decreases as a function of time a closing parameter is introduced which is calculated by $C_p = 1 - \frac{D_{duct}(T=3)}{D_{duct}(T=0)}$. Right: Ratio between the measured blood pressures at each echocardiograph screening within single patients normalized on the blood pressure at $C_p = 0$.

By comparing the relative systemic pressure increase with the trends seen within the maturation study performed by Kent et al. PDA patient blood pressure increases are lower than expected by maturation alone. For the systolic and mean pressures this can be explained by the compensation mechanism of the heart but for the diastolic pressure you would then expect an increasing effect due to cardiac compensation. But measurements show a relative small increase in diastolic pressures during ductal closure. Only characterization of the heart and the degree of compensation during ductal treatment can tell how maturation effect and compensation effects interact during ductal closure.
Chapter 7

Conclusion

The goal of this research was to develop a multi-parameter data analysis technique to monitor ductal patency related vital sign patterns and to simulate blood pressure patterns during ductal closure. PDA specific patterns were studied by analyzing vital signs during pharmaceutical treatment of the PDA.

Vital sign analysis showed that there are potential ductal patterns which can be used to monitor ductal patency. Of the three vital signs that were analyzed blood blood pressure showed to have the most significant ductal closing pattern. Average blood pressure values of responders and non-responders were lower compared to controls and the increase between pre- and post-treatment blood pressures of responders is more than that of controls and non-responders. Within both databases SpO2 values for non-responders were found to be lower compared to controls and responders, but well within the 90-95% target range. Measured mean heart rate and heart rate variability did not show to have any PDA specific patterns during ductal closure. Mean heart rate did however show to be linked to the mean gestational age of each patient group. While blood pressure showed to have patterns that can be linked to the presence of a PDA the detected patterns lack a PDA specificity to clinical track the patent ductus. Furthermore the small study group together with the large variations between both databases makes it hard to make statistical significant statements about the difference in vital signs between controls, responders and non-responders. These results therefore show possible patterns associated with a PDA but are to general to enable the tracking of individual patients.

Blood pressure simulations were performed using a preterm cardiovascular model with a ductal flow segment. With this model hemodynamic patterns were simulated within a full cardiac cycle. Ductal patency was varied to show trends of these hemodynamic parameters during ductal closure. Time-dependent pressure and flow simulations with a patent ductus showed to be comparable to patient hemodynamic patterns. Simulated ductal flow showed to decrease to zero with respect to an increasing ductal resistance, which means an effectively closing ductus. The increase of simulated mean systemic blood pressure during ductal closure was in the same range as in literature reported blood pressure increase during a full Indomatacin treatment course [33].

The simulated mean pressure increases during ductal closure Finally preterm simulations were compared to the measured blood pressure patterns during ductal closure. While estimated patient ductal flow and measured systolic pressures were within the simulated range, the dynamic behavior of these blood pressure patterns were incorrectly modeled. This is by possible because maturation effects which were not incorporated within the closing ductus model. Together with the unknown compensation mechanism of the heart. Measured diastolic pressure were significantly higher than the simulated blood pressure at a similar ductal flow. This could indicate that the used input parameters for the preterm model are inadequate to describe the cardiovascular structure of PDA patient during the entire ductal closure process.
Limitations: First limitation is the small number of patient data that was available for this study. Several factors influence blood pressure values a large study population is necessary to state if a vital sign pattern is statistical significant associated with respect to ductal closure. The treatment protocol within this study population should be standardized to exclude possible medication effects that are present between the GE and Philips database. While a bigger study population enables a clear statement about which patterns are PDA specific it will not help overcome the limited predictive power these general patterns have within individual patients.

Second limitation was the accuracy of ductal characterization that could be extracted from the ductal echo image. From these measurements only ductal diameter and maximum ductal flow speed could be used to give a rough estimation of the flow within the ductus. These parameters merely give a simplified estimation of the true three dimensional flow profile within the ductus. This three dimensional flow profile can only be determined using MRI imaging of the ductus.

Final limitation is the accuracy of the vital sign measurements and echo parameters, which are subjected to considerable measurement errors. Drifts within blood pressure measurements have to be corrected by frequent recalibration of the measuring device. If these recalibration are done incorrectly the measured blood pressure will drift from the real blood pressure value. Echocardiograph parameters are known to have considerable variations from the work done by Gill et al. [?].

General conclusion: This thesis shows that there are possible PDA specific patterns measurable within patients undergoing pharmaceutical treatment of the ductus. Furthermore, blood pressure trends during ductal closure can be simulated using a hemodynamic preterm model with a ductal flow segment. However, oversimplification of possible maturation effects and the PDA cardiac compensation mechanisms within the model results in an inconclusive relationship between the simulated and measured blood pressure trends during ductal closure.

Recommendations future work

To create a predictive monitoring system for clinical tracking of ductal patency and to enable patient specific PDA modeling a number of future challenges are shortly explained.

To prove that the PDA patterns, detected within this study, are directly caused by the closing of the ductus. Both the inter- and intra- patient variations should be investigated to enable a possible ductal tracking algorithm on these measured vital sign trend.

High resolution vital signs can be used to produce new features that have a higher specificity with respect to the PDA. Only by such features will an individual ductal patency tracking system become feasible within the future. Important about these new features is that they are insensitive to changes naturally occurring within the patient unrelated with the ductal closure. These natural changes included maturation and the development of blood regulation mechanism.

The preterm ductal closure model can be adopted with feedback mechanisms for cardiac compensation of the heart and by incorporating possible maturation effects. With these adaptations blood pressure patterns during ductal closure can be given within a narrower range than currently possible.

The ultimate goal would be to create an individual patient model which can be used to predict hemodynamic scenarios. This is complicated by the large amount of input parameters that have to be estimated and the limited amount of patient measurements available for estimating these parameters. Possible new measurements techniques could provide new information from which currently unknown parameters like pulmonary resistance can be estimated in the future.


