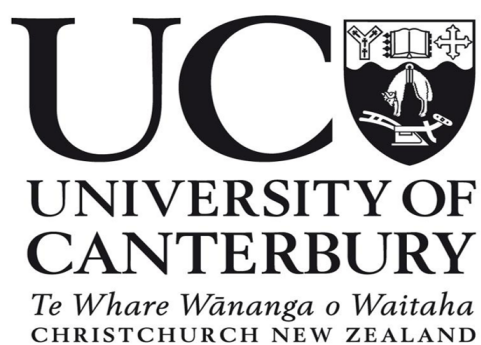


Real-Time Model-Based Fluid Therapy in the Intensive Care Unit

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Abstract

Fluid therapy is a vital clinical procedure used to treat circulatory shock. Approximately 30% of patients in the ICU undergo fluid therapy at some point during their stay, rising to 50-80% in some specialised units. It affects ≈ 1 million patients per year in the EU, with similar proportions in the developed world. Fluid therapy aims to maintain, or increase, cardiac output by increasing the total volume in cardiovascular system, thereby maintaining sufficient organ perfusion.

Currently, it is estimated only 50% of patients receiving fluid therapy experience an increase in cardiac output. Furthermore, patients who receive unnecessary fluids are prone to fluid overload, which has been linked to increased requirement of mechanical ventilation, increased length of hospital stay, and increased mortality. Thus, to maximise benefit and minimise unintended harm, it is crucial to have a firm understanding of a patient's fluid responsiveness prior to administering fluids.

A patient is considered fluid responsive if they have a low preload, defined as the stretch in the cardiac wall before cardiac contraction occurs. However, since direct measurements of preload are not possible due to their highly invasive and risky nature, indices indicative of low preload are used instead. These indices are categorised into two separate types, static and dynamic.

Static indices have been found to be poor predictors of fluid responsiveness. Despite their poor performance, they are still widely used to guide fluid therapies in many hospitals globally, primarily due to their simplicity. Dynamic indices are defined based on cardiopulmonary interactions experienced during mechanical ventilation. They have been shown to be a better indicator of fluid responsiveness than static indices. However, they are highly limited in many different clinical scenarios, such as spontaneous breathing, open thorax or arrhythmias, and harder to obtain readily.

Mechanical ventilation is a critical support for many patients in ICU, and virtually all patients with cardiac shock or needing fluid therapy are ventilated. However, it is well known for having detrimental effects on cardiovascular system performance, particularly when using high positive end-expiratory pressure. High positive end-

expiratory pressure levels cause a decrease in stroke volume, which, under normal conditions, usually brings about a decrease in stressed blood volume and perfusion. The result is two necessary therapies, mechanical ventilation and fluid therapy, act in a contrasting or antagonistic fashion.

Stressed blood volume (SBV) is defined as the total pressure-generating blood volume in the circulation and describes the volume contributing to tissue perfusion. It has recently been validated as a potential index of fluid responsiveness by multiple studies. However, clinically determining the stressed blood volume of a patient is a highly complex and dangerous procedure, involving multiple cardiac arrests and fluid infusions, and is clearly not a clinically viable diagnostic or monitoring procedure. Therefore, accurate model-based or other surrogates are required if SBV is to be used as an index of fluid responsiveness in regular monitoring.

Model-based tools are being increasingly explored for bedside diagnostics. There is currently a large movement towards the so-called “digital twin”, a digital version of a patient which can be used to simulate treatment therapies and provide predictions for patient outcome. Being able to predict a patient’s response to treatment therapies has the potential to greatly reduce cost, length of stay, and ultimately mortality.

Generally, respiratory and haemodynamic care are provided independently of one another. However, since positive end-expiratory pressure alters both stroke volume and stressed blood volume suggests both the pulmonary and cardiovascular state should be conjointly optimised and used to guide positive end-expiratory pressure. However, the complex and patient-specific nature of the cardiopulmonary interactions which occur during mechanical ventilation presents a challenge for accurate modelling of respiratory and cardiovascular interactions required to better optimise care.

Furthermore, for model-based methods to be implemented in the ICU, they require access to a patient’s clinically available data. The currently used bedside care systems are bedside monitoring devices, which provide real-time visual information to bedside nurses and clinicians. While providing a crucial service to bedside care, these proprietary devices act as a large obstruction to advancements in model

based care, as they do not provide access to real-time patient information and keep information locked away behind large cost barriers.

This work explores multiple cardiovascular and combined cardio-pulmonary models, to evaluate their ability to reliably identify haemodynamics parameters, and crucially, stressed blood volume. A newly created data capture system is designed to obtain haemodynamic measurements in a clinical setting. The device is used for a trial at University of Liege hospital (CHU de Liege) to capture haemodynamic measurements from patients undergoing fluid therapy. The data obtained from the trial is then used in a real-time simulation for identification of stressed blood volume. Finally, a validation of the real-time identified stressed blood volume as an index of fluid responsiveness is performed.

All of the 3 models, the 3 chamber model and two cardiopulmonary models, were simulated using experimental porcine data obtained from experiments performed at the University of Liege. The 3 chamber model ultimately proved to be more reliable than the cardiopulmonary models, particularly during higher PEEP. A clinically feasible 3 chamber model was validated on the same porcine data, using an arterial transfer function to identify aortic pressure from femoral pressure. The clinically feasible model was able to reliably identify SBV from a clinically available measurement set.

The data capture system was trialled successfully at CHU de Liege, and captured arterial and venous pressure, as well as fluid infusion rates from 3 patients during a fluid infusion. This data was then used to perform a real-time simulation, where the retrospective data was streamed over serial in real-time to a MATLAB application which split the data into beats and was able to identify SBV on a beat-to-beat basis in real-time. Finally, the real-time SBV was validated as an indicator of fluid responsiveness, ultimately performing the first ever validation of real-time identified SBV from a clinically obtained dataset.

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Acronyms and Abbreviations

Γ	Reflection coefficient
p_{SBP_2}	Peripheral secondary systolic shoulder
ARDS	Acute respiratory distress syndrome
AV	Atrioventricular
BPM	Beats per minute
CO	Cardiac output
CVP	Central venous pressure
CVS	Cardiovascular system
DAQ	Data acquisition device
DN	Dicrotic notch
E_{ao}	Aortic elastance
E_{es}	End-systolic elastance
E_{lung}	Lung elastance
E_{lv}	Left ventricle elastance
E_{rs}	Respiratory system elastance
E_{vc}	Vena cava elastance
E_{wall}	Chest wall elastance

ECG	Electrocardiogram
ESPVR	End systolic pressure volume relationship
HR	Heart rate
ICU	Intensive care unit
LV	Left ventricle
MAE	Mean absolute error
MV	Mechanical ventilation
P_{ao}	Aortic pressure
P_{aw}	Airway pressure
P_{DN}	Dicrotic notch pressure
P_f	Forward travelling wave
P_{lung}	Lung pressure
P_{lv}	Left ventricle pressure
P_r	Reflected wave
P_{th}	Intrathoracic pressure
P_{vc}	Vena cava pressure
PEEP	Positive end-expiratory pressure
PPV	Pulse pressure variation
PP	Pulse pressure
PRM	Recruitment manoeuvre
PSD	Power spectral density

PTT	Pulse transfer time
PVR	Pulmonary vascular resistance
Q_{aw}	Airway flow
Q_{in}	Ventricular input blood flow
Q_{out}	Ventricular output blood flow
Q_{sys}	Systemic blood flow
R_{aw}	Airway resistance
R_{in}	Ventricular input resistance
R_{out}	Ventricular output resistance
R_{sys}	Systemic resistance
RMS	Root mean squared
RV	Right ventricle
SBP_1	Primary systolic shoulder
SBP_2	Secondary systolic shoulder
SBV	Stressed blood volume
SVV	Stroke volume variation
SV	Stroke volume
TC	Thoracic cavity
TF	Transfer function
TL	Tube load
V_{ed}	End diastolic volume

V_{es}	End systolic volume
V_{lung}	Lung volume
$V_{\text{s,ao}}$	Aortic stressed volume
$V_{\text{s,lv}}$	Left ventricle stressed volume
$V_{\text{s,vc}}$	Vena cava stressed volume
Z_{c}	Characteristic impedance
Z_{in}	Input impedance

Chapter I

Introduction

1.1 Motivation

As technology advances, the medical world is ever searching for new ways to improve and reduce the cost of patient care. In the USA alone, sepsis is one of the leading causes of patient intensive care unit (ICU) admission and in-hospital deaths, accounting for as much as 10% of all admissions and resulting in an estimated 215,000 deaths per year at a cost of \$16.7 billion [1]. A recent study estimates sepsis may account for up to 11 million deaths globally each year [2].

Mechanical ventilation (MV) is a critical support for many patients in ICU. Positive-end expiratory pressure (PEEP) is used to maximise alveoli recruitment for increased blood oxygenation. However, excessive PEEP is dangerous and can cause lung damage, increasing length of stay, mortality and cost [3–8]. Elevated levels of PEEP also cause an increase of pressure in the thoracic chamber, where the heart and vena cava are located. This rise in intrathoracic pressure (P_{th}) is known to decrease cardiac preload, and thus, decrease venous return, ultimately reducing both the stroke volume (SV) and stressed blood volume (SBV) of the system [9–11].

SBV is defined as the total pressure-generating blood volume in the circulation and describes the volume contributing to tissue perfusion. Recently, SBV has been shown to be a potential index of fluid responsiveness as it is a major determinant of the mean systemic filling pressure (MSFP) and thus, venous return, making

it a potentially important diagnostic tool [12]. However, clinically determining the SBV of a patient is a highly complex and dangerous procedure, involving multiple cardiac arrests and fluid infusions, and is clearly not a clinically viable, nor continuous, diagnostic procedure [13]. Therefore, accurate model based or other surrogates are required if SBV is to be used as an index of fluid responsiveness in regular monitoring.

Several lumped parameter models have been presented, most commonly the 6- and 3- chamber models [1, 14–17], as reviewed in [18]. While simple, identifiable models have proven successful at capturing the fundamental system dynamics of the CVS and estimation of total SBV.

However, they do not typically include the pulmonary system or the impact of ventilation. Instead, they rely on the effects of the pulmonary system to be contained in the left ventricle and vena cava pressure waveforms. Given the complex relationship mechanical ventilation has on the CVS, the ability to directly account for its effects could prove important in reliable patient state estimation, and in using SBV as an index of fluid resuscitation in care.

PEEP alters both SV and SBV, suggesting both the pulmonary and cardiovascular state should be conjointly optimised and used to guide both PEEP and fluid therapy. Clinically optimising these systems in isolation may benefit one system, but have highly detrimental effects on the other [19, 20]. A combined cardiopulmonary model has the potential to provide a better understanding of patient specific respiratory and cardiovascular state, as well as resulting cardiopulmonary interactions. It would also enable simultaneous optimisation of all cardiovascular and pulmonary parameters.

De Bournonville *et al* [21] presented a lumped parameter cardiopulmonary model combining 2 separate, clinically validated models of the cardiovascular and respiratory systems. The model reproduced the effects of mechanical ventilation on the CVS. However, while the study demonstrated the impact of PEEP on haemodynamic parameters, it did not demonstrate whether the added model complexity significantly improved the simulation of cardiovascular measurements.

In particular, the parameter estimation process and identifiability were not addressed, so there is no assessment of the impact of the combined model on the value and trends of haemodynamic parameters as PEEP and other MV settings change. Equally, the identifiability of the combined model was not addressed as a result. Thus, its identifiability and clinical utility are unknown, particularly in contrast to the simpler original, uncoupled, but clinically validated, 3-chamber cardiovascular model.

If model-based therapies are to be achieved within the ICU, data accessibility is crucial. Currently, haemodynamic measurements in the ICU are recorded using bedside monitoring devices. Most commonly, a Philips (TM) or equivalent bedside monitoring device is used, a centralised monitoring system capable of displaying a wide range of information pertaining to different bodily systems [22–24].

While providing a centralised interface for displaying crucial patient data, these bedside monitoring devices are proprietary systems. They thus can also act as a barrier for advancements in model-based care by limiting data access without added cost. Furthermore, monitoring devices alone have not been associated with decreased mortality in critically ill patients unless used in conjunction with effective treatment strategies [25–28], though this effect is difficult to quantify [29].

While some bedside devices allow for retrospective data export [24, 30], many bedside units do not have this added functionality. Thus, the data is often not available for use in real-time, when it is actually needed for diagnostic purposes. Philips has developed a solution called the Research Data Explorer (RDE) for automated acquisition of waveform data. However, this system is also proprietary with a cost barrier involved. The system also does not acquire data at the native sampling rate of the signals and limits the number of waveforms which can be exported. All these limitations act as barriers between patient care and advanced monitoring and care protocols.

Clearly, current technology within the ICU lacks the ability to provide access to high-resolution, raw waveform data. Access to this type of data is crucial for achieving model-based care, which has the potential to provide far greater insights into a patients condition than is currently possible. Particularly, without this data,

identification of SBV in real-time is not possible.

1.2 Goals

This thesis aims to create a new model-based haemodynamic management protocol for patients in ICU. This goal requires both a reliable cardiovascular system model, able to identify SBV from clinically available measurements, as well as a system which can record and provide access to clinically available measurements in real-time. The goals of this thesis are thus specified:

- Investigate multiple cardiovascular models, including the 3 chamber cardiovascular model, as well as two cardiopulmonary models, to assess their candidacy as potential bedside fluid therapy guidance tools.
- Develop a novel data capture system that can be used in the ICU to record and provide access to haemodynamic measurements as well as fluid infusion data in real-time
- Perform a clinical validation of real-time identified SBV from clinically available measurements as an index of fluid responsiveness

To use a potential cardiovascular model as a bedside guidance tool, its ability to perform in real-time must be validated. Hence, this work ultimately aims to perform the first validation of real-time identified SBV, and provide a potential system to be used in future trials.

1.3 Overview

The first chapters introduce all relevant knowledge required and data used for this thesis. **Chapter 2** provides a literature review containing all the relevant background knowledge pertaining to the physiological, medical and mathematical

aspects of this work. **Chapter 3** provides an overview of the experimental data used in this work, obtained from experimental trials performed at the University of Liege.

The next chapters present the cardiovascular, respiratory and combined cardiopulmonary models assessed for potential use as bedside guidance tools. **Chapter 4** introduces the clinically validated 3 chamber model, as well as methods for identifying left ventricular volume and pressure measurements from the aortic pressure waveform. **Chapters 5** and **Chapter 6** introduce a previously validated cardiopulmonary model and a novel implementation of the cardiopulmonary model respectively.

Chapter 7 describes a newly created data capture system designed to obtain haemodynamic measurements in a clinical setting. The system is able to measure 2 pressure lines, 1 venous and arterial line, as well as fluid infusion rates. The chapter also details clinical trial where the system was successfully used to capture haemodynamic measurements from patients receiving a fluid infusion in the ICU.

Chapter 8 details an investigation into an important cardiovascular concept, the secondary systolic shoulder, which is used as an input to the arterial transfer function introduced in **Chapter 9**. **Chapter 9** also presents a clinically feasible implementation of the 3 chamber model using the arterial transfer function to identify central pressure from peripheral pressure measurements.

Chapter 10 details a real-time simulation of the clinically feasible 3 chamber model, using data obtained from the clinical trials performed at the University of Liege hospital. **Chapter 11** then uses the SBV obtained from the real-time simulation to validate real-time identified SBV as an indicator of fluid responsiveness, a first ever validation of real-time identified SBV.

Finally, **Chapter 12** presents the conclusions drawn from this work, and **Chapter 13** details ideas for potential future work to be explored.

Chapter II

Literature Review

2.1 *The Cardiovascular System*

The cardiovascular system (CVS) is responsible for the transportation of oxygen, nutrients and waste products to and from organs, ensuring that all organs of the body continue functioning appropriately.

The CVS consists of a heart and several different types of blood vessels, namely arteries, veins and capillaries. The CVS is split into two different circulations, the pulmonary circulation and systemic circulation. The pulmonary circulation is responsible for transporting de-oxygenated blood from the heart to the lungs via the pulmonary artery, where it is re-oxygenated and then sent back to the heart via the pulmonary vein. The systemic circulation is then responsible for sending oxygenated blood from the heart to the rest of the body via the aorta where the oxygen is distributed to all organs and tissues of the body through the capillaries. De-oxygenated blood is then returned to the heart via the vena cava.

2.1.1 The Heart

The heart is the core of the CVS, responsible for pumping blood around the entire body. The heart is divided into two major sections, the left and right side. The right side of the heart collects de-oxygenated blood from the systemic circulation

and sends it to the pulmonary circulation, where accumulated carbon dioxide is replaced with oxygen in the lungs. The left side collects oxygenated blood from the pulmonary circulation and sends it to the systemic circulation, where oxygen is transported to all the organs of the body.

Each side is composed of two contractile chambers; an atrium and a ventricle. Blood flows into the left and right atria via the pulmonary vein and vena cava respectively. Blood then flows from the left and right atria into their respective ventricles. Two valves are located up and downstream of each ventricle. These valves ensure that blood only flows in one direction through the CVS. The pulmonary and aortic valve lie downstream of the right and left ventricle, they prevent blood from the pulmonary artery and aorta from flowing back into the ventricles. The tricuspid and mitral valves, also known as atrio-ventricular valves, lie upstream of the right and left ventricles respectively. They prevent backward flow of blood from ventricle to atrium. A depiction of the heart and all it's valves and vessels is shown in Figure 2.1.

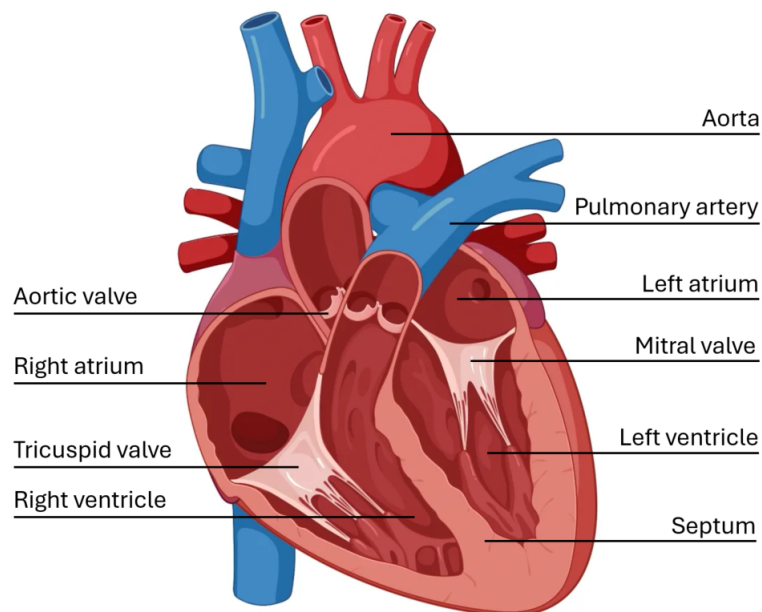


Figure 2.1: Cross section of the human heart

2.1.1.1 *The Cardiac Cycle*

The heart beats in a periodic fashion. The heart contracts to eject blood and relaxes to allow for filling before it contracts again. The cycle is divided into four distinct phases. Since the cycle is periodic, the starting point will be chosen as the end of the ejection phase, marked by the closing of the aortic and pulmonary valves.

Isovolumic Relaxation Isovolumic relaxation occurs after the end of ejection. During this phase, the heart begins to relax with all valves closed. Since all valves are closed, there is no change in volume in either of the ventricles, which causes a decrease in pressure in both ventricles.

Filling Once the pressure of the the ventricles falls below that of the atria, the atrial-ventricular valves open, allowing for blood to flow rapidly from atria to ventricles, marking the early filling phase. As the ventricles fill, their pressure increases until their pressure equals that of the atria and blood flow ceases. At this point, the atria contract, ejecting an extra amount of blood from the atria into the ventricles. During the entirety of this phase, the aortic and pulmonary valves remain closed to prevent back flow from these arteries into the heart.

Isovolumic Contraction Shortly after atrial contraction, the ventricles begin to contract. As the contraction begins, ventricular pressure quickly rises above that of the atria, causing the atrial-ventricular valves to shut. Ventricular contraction continues with all valves closed and therefore retaining a constant volume, causing a large increase in ventricular pressure.

Ejection When ventricular pressure exceeds aortic and pulmonary arterial pressure, the aortic and pulmonary artery valves open and blood is ejected from the ventricles into the pulmonary and systemic circulation. The ejection continues until ventricular pressure drops below aortic and pulmonary arterial pressure, causing

the valves to close, marking the end of ejection and the beginning of isovolumic relaxation, where the cycle begins again.

2.1.1.2 Automatic Rhythmicity of the Heart

The heart is responsible for its own contraction via specialised tissue capable of self-excitation. This specialised cardiac fibre is known as the sinus node, or sinoatrial node. The sinus node is surrounded by an extracellular fluid rich in sodium ions. Sodium ions are positively charged and the sinus node has a resting potential of about -55mV , also known as the hyperpolarised state. The high concentration of sodium ions in the surrounding extracellular fluid, as well as the moderate number of sodium channels which remain open at the sinus node's resting potential, causes a slow leakage of sodium ions into the sinus node, causing a slow rise its potential. This rise increases until it reaches a threshold potential of around -40mV . Once above this threshold, the sodium-calcium channels of the sinus node open, allowing for a rapid inflow of positively charged calcium ions, triggering the action potential of the sinus node where the voltage rapidly increases to about 20mV , depolarising the membrane. Thereafter, potassium channels of the sinus node open, causing a rapid outflow of positively charged potassium ions from the sinus node, until it again reaches its resting potential of -55mV . The potassium channels close, preventing further outflow of potassium ions, and the cycle begins again. The cycle is shown in Figure 2.2

The ends of the sinus node fibres are directly connected to the surrounding atrial muscle fibres. This allows the action potential from the sinus node to travel directly into the atrial muscle fibres. The conduction speed of most atrial muscle is around 0.3m/s . However, several small bands of atrial muscle conduct much faster, around 1m/s . These small bands of muscle allow the action potential to travel rapidly into the left atrium so that the atria contract simultaneously. The action potential travels down the muscle fibres of the atria toward the atrio-ventricular (AV) node. The conduction through the AV node is much slower than the muscle fibres of the atria. The action potential takes roughly 0.03s to travel through the atria to the AV node. Thereafter, it takes roughly 0.13 seconds to travel from the AV

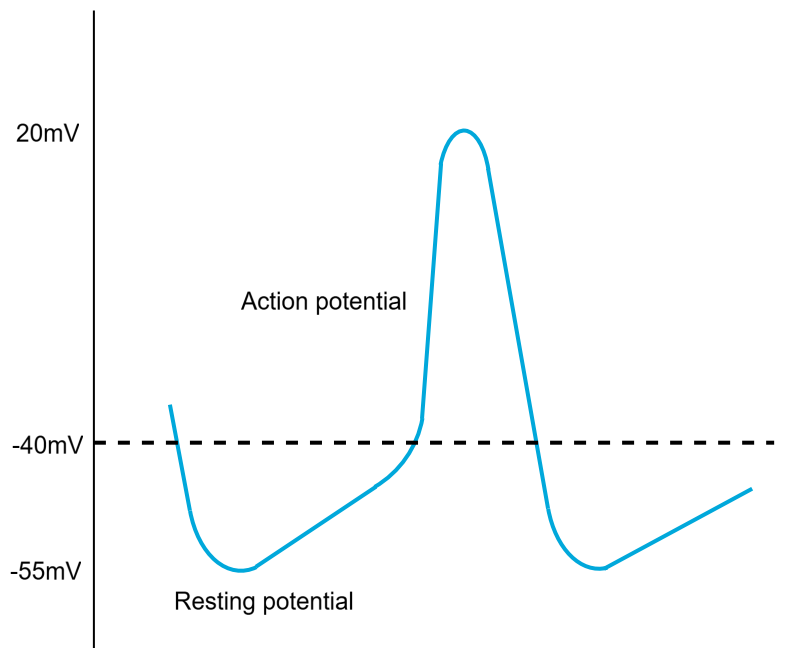


Figure 2.2: Rhythmical discharge of the sinus node.

node to the ventricles. This delay allows time for blood to travel from the atria to the ventricles before the ventricles contract to eject blood into their downstream arteries.

Once the action potential has travelled through the AV node, it reaches the contracting muscles of the ventricle. The ventricles contain specialised bands of conducting tissue called Purkinje fibres, which spread from the AV node throughout the ventricle walls. They are much larger than the ventricular muscle fibres, and allow for rapid conduction of the action potential, up to 4m/s. This allows for the rapid spread of the action potential into the entire ventricular muscle mass, allowing for strong, even contraction of the ventricles.

2.1.1.3 Pressure and Volume Waveforms

The cardiovascular system is dependent on the evolution of pressures and volumes caused by the beating of the heart. The graphs of these waveforms give further

insight into the functioning and underlying principles of the CVS. The waveforms are depicted in Figure 2.3.

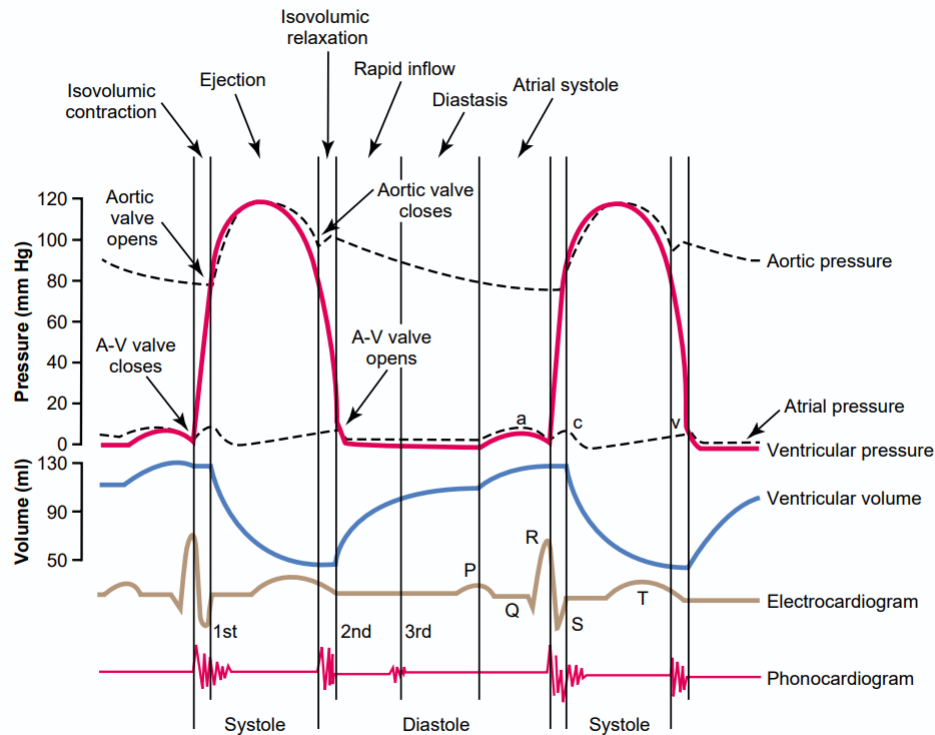


Figure 2.3: Pressure and volume waveforms of the cardiac cycle [14]

During ejection, the ventricular pressure rises above aortic pressure. At the same instant, left ventricular volume decreases rapidly as blood is ejected. The end of ejection is then marked by the notch in the aortic pressure waveform, known as the dicrotic notch. This notch occurs because of a small backflow of blood that occurs before the aortic valve fully closes [9].

Left ventricular pressure then rapidly decreases during relaxation until it falls below atrial pressure, causing the mitral valve to open and blood to flow to the ventricle. At this point, ventricular volume increases, causing ventricular pressure to slowly rise toward atrial pressure. At this point, the atrium contracts, shown as peak *a* on the left atrial pressure wave, causing a supplementary burst of blood into the ventricle. After atrial contraction, the ventricles begin to contract, causing

the mitral valve to close and ventricular pressure to rapidly increase until it rises above aortic pressure, thus re-entering the ejection phase.

As depicted in Figure 2.3, the relaxation and filling phase make up the diastole phase of the cardiac cycle and the ejection and contraction phase make up the systole phase of the cardiac cycle. Diastole is characterised by low ventricular pressure and systole is characterised by a high ventricular pressure.

2.1.1.4 Electrocardiogram

An electrocardiogram (ECG) uses electrodes placed on a patient's skin to measure the electrical impulse generated by the sinus node of the heart. The ECG wave is shown in Figure 2.3. The ECG is used to monitor the heart's electrical activity, as well as to determine a patient's heart rate. The ECG signal is generally composed of a P wave, the QRS complex and finally the T wave. The P wave represents the depolarisation (a switch from negative to positive voltage of the muscle membrane) of the atria, the QRS complex represents the depolarisation of the ventricles, and finally the T wave represents the repolarisation of the ventricles.

2.1.1.5 Determinants of Cardiac Output

Cardiac output, CO, is the average blood flow from the heart, defined as:

$$CO = SV \times HR \quad (2.1)$$

Where SV is the stroke volume and HR is the heart rate. The following are factors that directly influence SV, thus influencing the cardiac output of the CVS:

Preload The preload is defined as the stretch in the cardiac wall before contraction occurs. The higher the amount of blood returned to the heart during filling, the more the cardiac wall is stretched, resulting in a higher preload. A higher preload results in a stronger contraction and thus a higher stroke volume [9]. This

important relationship is depicted by the Frank-Starling curve shown in Figure 2.4. The curve shows the relationship between SV and preload.

Contractility Contractility is the ability of the heart to generate force. The larger the contractility, the larger the contraction force generated. The effect of contractility is shown on the Frank-Starling curve in Figure 2.5.

Afterload The afterload is defined as the resistance the ventricle has to overcome to pump blood. This can be attributed to the resistance from downstream valves and vessels. A greater afterload results in a lower SV, as the heart has to work harder to overcome a higher resistance. The effect of afterload is shown on the Frank-Starling curve in Figure 2.6.

2.1.2 The Circulation

The circulation is divided into two major systems, the systemic circulation, which carries oxygenated blood from the heart to all tissues of the body, and the pulmonary circulation, which carries de-oxygenated blood from the heart to the lungs, where it is re-oxygenated and returned to the heart.

2.1.2.1 Functional Parts of the Circulation

The circulation is made up of several fundamental functional components, and before understanding the details of circulatory functioning, it is important to understand the function of each of the individual components.

Arteries Arteries have to transport blood under high pressure and at high velocity. As arteries are close to the heart, blood flow through them is generally pulsatile in nature. Arteries therefore have thick, strong walls which can withstand the high pressured and pulsatile blood flow through them.

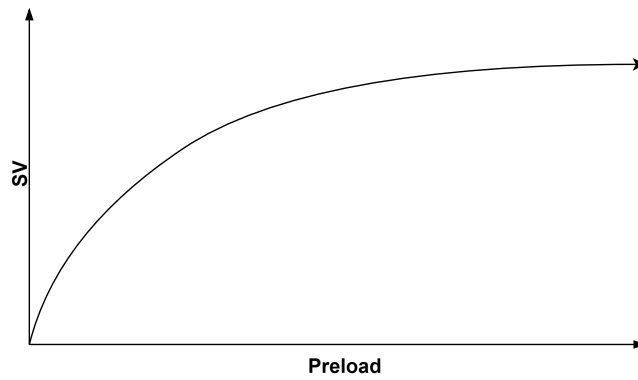


Figure 2.4: Frank-Starling curve

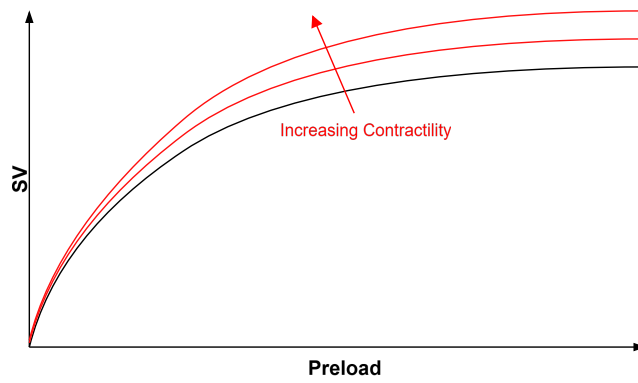


Figure 2.5: Effect of contractility on Frank-Starling curve

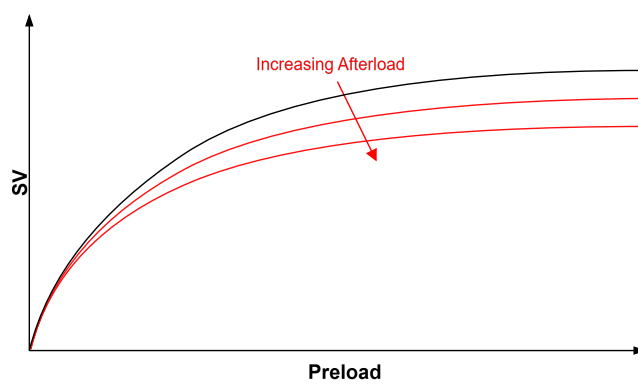


Figure 2.6: Effect of afterload on Frank-Starling curve

Arterioles Arterioles are the final branches of the arterial system. They control the amount of blood which flows to capillaries. The arterioles have strong muscular walls which can completely close the arteriole by contraction, or dilate it severalfold by relaxation. They thus have the capability to greatly alter blood flow in response to specific bodily needs.

Capillaries Capillaries are the smallest of blood vessels in the body, with internal diameters ranging between 5 to 10 micrometers. However, the capillaries comprise the largest total cross sectional area of all vessels in the body, around 2500cm^2 . They also have arguably the most important function, exchanging fluid, nutrients, electrolytes, hormones, and other substances between the blood and the interstitial fluid. This is possible due to the thin, porous walls of the capillary, which are permeable to water and other molecules, allowing for this diffusion of substances between the blood and tissues.

Veins Veins have thin walls, and generally operate under very low pressure. They also contain about 65% of the total blood in the CVS. They are mainly responsible for transporting blood from capillaries back to the heart. However, they also serve as a large reservoir for extra blood. Vein walls are muscular enough to contract, or expand, and by doing so, they can pump or store extra blood to or from the CVS as required.

2.1.2.2 Elasticity of Vascular Tissue

Vascular tissue is mainly made up of collagen, smooth muscle, and elastin. Elastin fibres are highly extensible and are characterised by an almost constant Young's modulus. Conversely, collagen fibres are very stiff, and their elasticity is roughly 1000 times greater than that of elastin. At small strains, collagen fibres remain unstressed and bear no load, and elastin and smooth muscle determine wall elasticity. At larger strains, collagen begins to bear more load resulting in an increase to wall elastance.

Vascular tissue is also viscoelastic, meaning that it has both elastic properties and viscous, or fluid-like properties [31]. The viscous effects cause a lag in strain when there is an applied stress. The resulting strain vs stress plot yields a hysteresis loop, as shown in Figure 2.7.

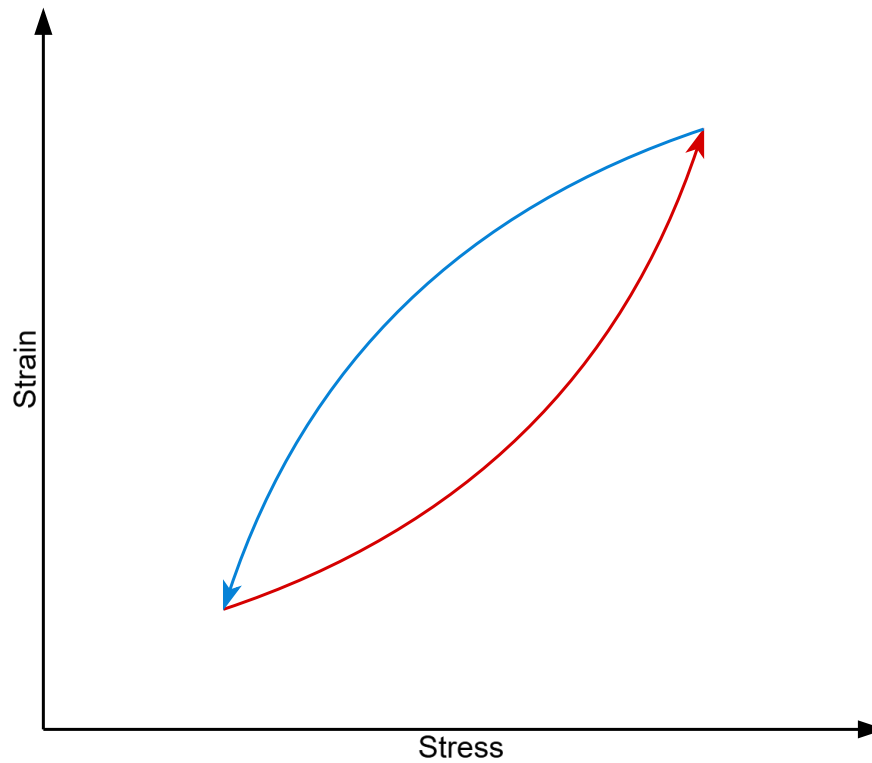


Figure 2.7: Strain vs stress hysteresis loop of viscoelastic materials.

The end result of the non-linearities of vascular tissue is the elastance of the tissue increases exponentially as volume is increased. Figure 2.8 shows the relationship between pressure and volume of vascular tissue.

2.1.2.3 Basic Principles of the Circulation

Although the circulation is highly complex, involving countless amounts of different control systems, there are several basic principles which govern the general functioning of the circulatory systems.

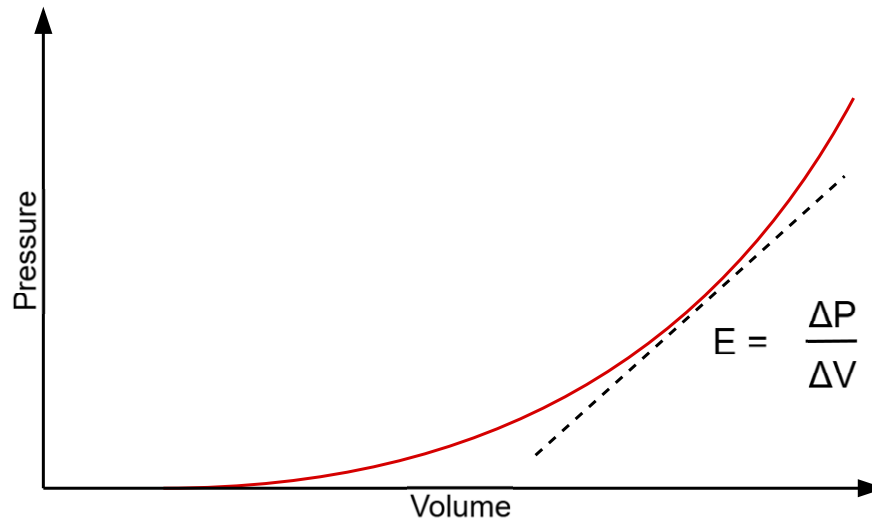


Figure 2.8: Pressure volume relationship (elastance) of vascular tissue.

Tissue Blood Flow Blood flow to different body tissues can vary greatly depending on the state of the tissue. Active tissues may require up to 30 times resting blood flow levels. The heart can only increase cardiac output by 4 - 7 times, meaning that on its own, it cannot accommodate the increased demands of active tissues. Instead, tissue needs are continuously monitored and local blood vessels are dilated or constricted to meet the exact blood flow requirements of the tissue.

Cardiac Output Cardiac output of the heart is controlled by the sum of all tissue flow. The heart can only pump out blood that it receives. The amount of blood the heart pumps out is therefore dependent on the amount of blood returned by tissues. Active tissues use more blood, and therefore return more blood to the heart. The heart thus automatically responds to increased tissue demand.

Arterial Pressures Arterial blood pressure is controlled independently of local tissue flow or cardiac output. The arterial blood pressure is controlled by autonomic responses which respond to changes in pressure. If arterial blood pressure

drops, nervous responses will act to raise the pressure back to normal levels. This could be through increased heart pumping, contraction of venous reservoirs or constriction of arterioles, to ensure that blood can accumulate in the arteries to increase the pressure.

2.1.2.4 Pressure Gradients of the Circulation

Blood begins its journey through the circulation as a high pressure pulse generated by the heart, which flows directly into the aorta and pulmonary artery. In the systemic circulation, the aorta carries this high pressure pulse into smaller arteries. As the pulse wave travels through the aorta and into smaller arteries, it will experience damping caused by the resistance and compliance of the vessels it travels through. By the time blood enters the capillaries, pulses are almost entirely damped, becoming almost indistinguishable, and blood moves as a smooth flow through capillaries into the veins. As blood flows through the circulation, the damping also reduces the mean pressure.

The mean pressure averages roughly 100mmHg in the Aorta and decreases slightly in smaller arteries. By the time it reaches the capillaries, it will have dropped to around 30mmHg at the arteriole ends, and 10mmHg at the venous ends. The pressure continues to drop in veins until it is almost at 0mmHg before it empties into the right atrium of the heart. The pressure changes in the pulmonary circulation are similar to those in the systemic circulation, except they are substantially lower. Mean pressure in the pulmonary artery starts off at around 25mmHg, dropping to around 7mmHg at the capillaries, and finally 0mmHg at the pulmonary vein before emptying into the left atrium.

2.2 Arterial Blood Flow

Major arteries of the CVS are made up of thick, highly elastic walls, allowing them to accommodate the high pressure blood pulse ejected from the heart. The high elasticity of the arteries also allow them to store large amounts of blood from the

initial systolic pulse, which allow them to continue to expel blood during diastole phase, ensuring blood continues to flow.

Since the blood flow through arteries is pulsatile, the complexity of analysis and modelling of pressure and flow increases greatly. Many standard techniques and equations used for analysis of steady state liquid flow, such as Poiseuille's equation, no longer accurately represent blood flow through the system. Furthermore, the pulsatile flow also results in wave reflections in the arterial system at impedance mismatch sites. The resulting pressure wave, seen when measured by pressure catheters, is an amalgamation of many forward and backward travelling waves which have been reflected, and re-reflected at terminal ends of the arterial tree [32]. The combination of pulsatile flow and wave reflections makes the analysis and modelling of arterial blood flow a highly complex and involved topic.

2.2.1 Pulsatile Blood Flow

Like steady blood flow, pulsatile blood flow is caused by pressure gradients. However, the factors involved in moving blood by oscillatory pressure are far more complex than those required for steady flow. At the end of the cardiac cycle, fluid is almost at rest. At the beginning of systole, the systolic pulse generated by the ventricle acts as a driving force, accelerating the blood. Initially, the inertia of the blood acts to resist the pressure force. The blood will continue to accelerate as the pressure gradient increases. As the pressure pulse continues to move downstream, the pressure gradient reverses. The reversal of the pressure gradient causes a rapid deceleration of blood flow. In some arteries, the blood flow may even reverse if the negative pressure gradient persists after flow ceases. This is typically seen in the femoral artery [32]. The aortic valve prevents flow reversal in the aorta when there is a negative gradient. However, there is a brief period of time at the end of systole, where the pressure gradient reverses and the valve has not yet closed, resulting in the small dicrotic notch on the aortic waveform. An example of pressure gradients and flow using simulated waveforms is shown in Figure 2.9.

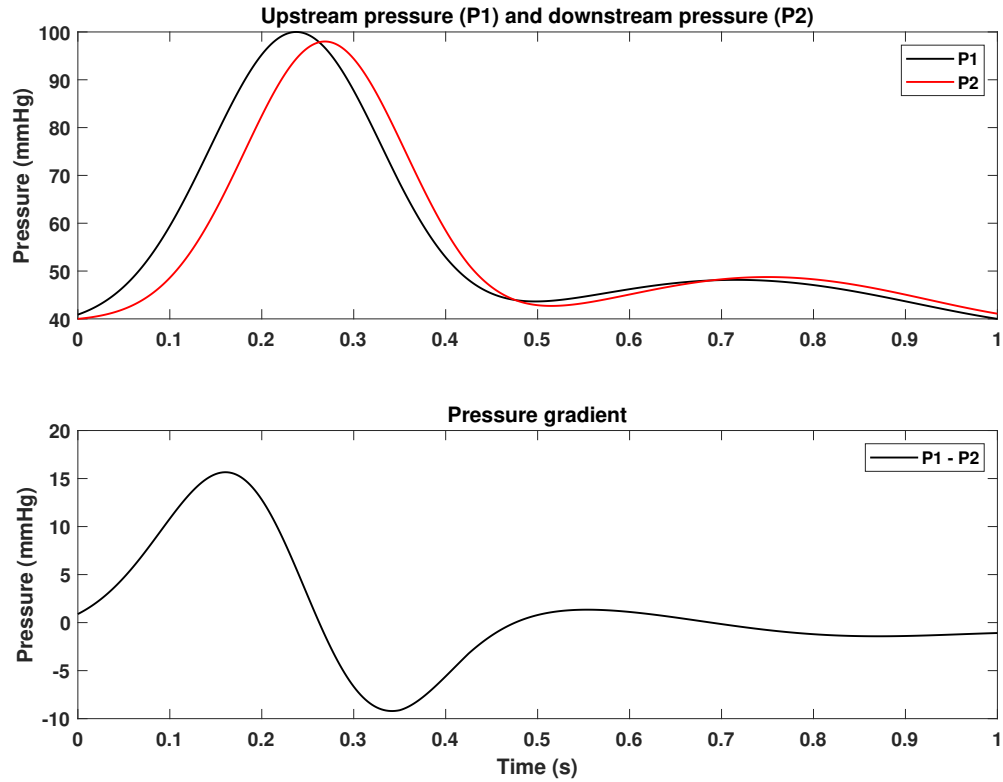


Figure 2.9: Pressure gradient of a travelling pressure wave. The first plot shows a simulated arterial pressure wave at two sites in the same artery, P1 is the upstream pressure and P2 is the downstream pressure. The second plot shows the pressure gradient between the upstream and downstream pressure.

2.2.2 Vascular Impedance

Impedance is the measure of opposition to flow in the circulatory system. Impedance within the cardiovascular system is difficult to determine, since impedance is frequency dependent, and not an instantaneously measurable quantity. In the vascular system, there are four types of impedance.

2.2.2.1 Longitudinal Impedance

Longitudinal impedance is the ratio of the pressure gradient to flow per unit length of a tube.

$$Z_L = \frac{P_1 - P_2}{LQ} \quad (2.2)$$

where P_1 and P_2 are the up and downstream respectively, L is the length of the tube segment and Q is the flow through the tube.

2.2.2.2 Input Impedance

Input impedance is the ratio of pulsatile pressure to pulsatile flow at a particular arterial site. It depends not only on the local properties of the vessel, but also on the properties of the downstream vascular bed. Input impedance is frequency dependent, and can be calculated as the ratio of harmonic terms of pressure and flow:

$$Z_{in}(j\omega) = \frac{P(j\omega)}{Q(j\omega)} \quad (2.3)$$

where $Z_{in}(j\omega)$ is the input impedance, and $P(j\omega)$ and $Q(j\omega)$ are the Fourier transforms of the pressure and flow waves respectively.

2.2.2.3 Characteristic Impedance

Characteristic impedance (Z_c) is the relationship between pulsatile pressure and flow in an artery when the waves are not influenced by wave reflection. There are virtually no circumstances where this occurs, since there are always reflected waves travelling through the vascular system. However, Z_c is an important concept, par-

ticularly used in wave separation techniques [32, 33]. It is possible to measure Z_c , however, this technique requires either a single flow measurement with 3 pressure measurements, or a single pressure measurement with 2 flow measurements.

Characteristic impedance is also frequency dependent, however, the modulus has shown very little fluctuations and its phase angle stays close to zero for all frequencies [32, 34]. Characteristic impedance is thus often assumed as constant, and can be calculated from pressure and flow in both the time and frequency domain.

Frequency Domain Calculation First, input impedance is calculated using Equation 2.3. Thereafter, Z_c is calculated by averaging the moduli of input impedance at higher frequencies.

At higher frequencies (15 - 25HZ), reflections are assumed to be negligible and the impedance moduli are assumed to be representative of Z_c [32, 35]. At lower frequencies (5 - 15Hz), the impedance moduli are expected to fluctuate around Z_c , and averaging should provide a good estimate [36].

Time Domain Calculation Since characteristic impedance is the relationship between pressure and flow, some works have used the initial upstroke of pressure and flow to calculate the characteristic impedance, with the assumption that early systole should not present any significant wave reflections [32, 35, 37]. Using the initial upstroke of pressure and flow, characteristic impedance is calculated as:

$$Z_c = \frac{\Delta P(t)}{\Delta Q(t)} \quad (2.4)$$

2.2.3 Terminal Impedance

Terminal impedance is the opposition to flow at the end of a vascular bed. This is caused by the very small arterioles found downstream of all arteries. The impedance of the arterioles is almost entirely resistive, as there is little effect from

blood inertia and vessel distensibility. Terminal impedance can thus be thought of as entirely resistive, and can be found from the ratio of mean pressure and flow [32].

2.2.4 Wave Reflection

As waves travel through the arterial system, they encounter impedance mismatches in the form of bifurcations, vessel tapering, changes in elastance and the high resistance arterioles [32, 38, 39]. When a wave encounters an impedance mismatch, it is reflected back through the arteries towards the heart. The magnitude of the reflected wave is dependent on the reflection coefficient, which is defined by the impedance mismatch:

$$\Gamma(j\omega) = \frac{Z(j\omega) - Z_c}{Z(j\omega) + Z_c} \quad (2.5)$$

where Z_c is the characteristic impedance of the artery, $Z(j\omega)$ is the frequency dependant impedance of the downstream load and $\Gamma(j\omega)$ is the reflection coefficient.

Reflected waves travel back up the arterial system where they interact with forward travelling waves. When a forward travelling wave encounters a reflected wave, there is constructive interference between the 2 pressure waves, resulting in an amplified overall pressure wave. This amplification is known as pulse pressure amplification (PPA).

The complex geometry of the arterial tree results in a large number of impedance mismatches, in turn resulting in a large number of reflected and even re-reflected waveforms. Due to the large number of reflected waves travelling in the arterial system, waves are generally clumped together as a single forward travelling wave, P_f , and a single reflected wave travelling from distal sites toward the heart, P_r .

An example of a forward and reflected pressure wave, and the combined pressure wave, are shown in Figure 2.10.

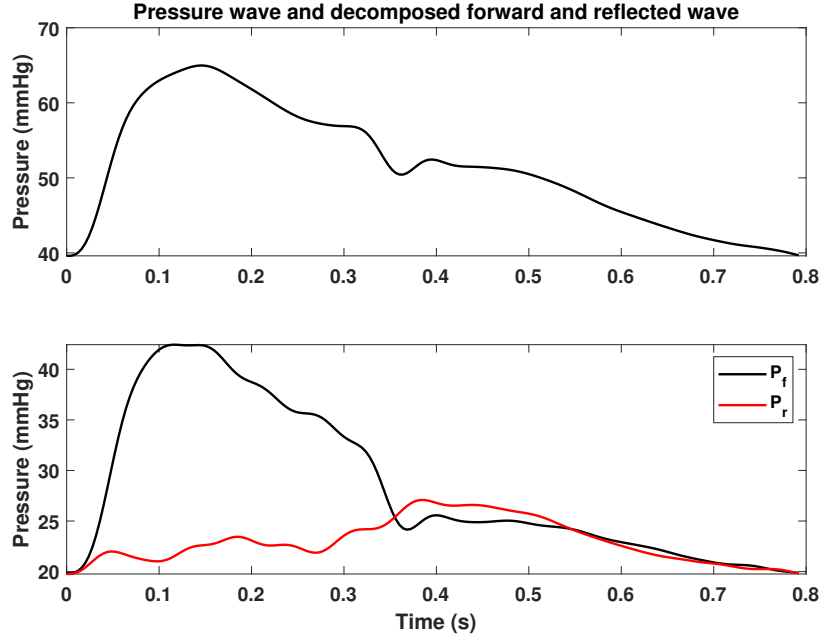


Figure 2.10: Pressure waveform decomposition. The first plot shows the pressure waveform, and the second plot shows the decomposed forward and reflected waves. The forward wave is shown in black and the reflected wave in red.

2.2.5 Waveform Decomposition

Given the flow and pressure within an artery, the pressure waveform can be decomposed into its forward and reflected constituents [32, 33, 40]. There are 2 main methods for waveform decomposition, one using the time domain, and the other in the frequency domain.

2.2.5.1 Frequency Domain Decomposition

To decompose flow and pressure into their forward and reflected constituents in the frequency domain, the reflection coefficient must be determined. First, input impedance is found using Equation 2.3, and characteristic impedance is found by averaging the moduli of higher frequency harmonics. Once the input and characteristic impedance are determined, the reflection coefficient is calculated:

$$\Gamma(j\omega) = \frac{Z_{in}(j\omega) - Z_c}{Z_{in}(j\omega) + Z_c} \quad (2.6)$$

The forward and backward waves are then calculated from the reflection coefficient:

$$P_f(j\omega) = \frac{P(j\omega)}{1 + \Gamma(j\omega)} \quad (2.7)$$

$$P_r(j\omega) = P_f(j\omega) \cdot \Gamma(j\omega) \quad (2.8)$$

Where $P_f(j\omega)$ and $P_r(j\omega)$ represent the frequency spectrum of the forward and reflected wave respectively. An inverse Fourier transform is used to convert the forward and reflected wave frequency spectra into the time domain.

2.2.5.2 Time Domain Decomposition

Characteristic impedance can be calculated in the time domain using Equation 2.4. The forward and reflected waves are then calculated:

$$P_f(t) = \frac{P(t) + Z_c Q(t)}{2} \quad (2.9)$$

$$P_r(t) = \frac{P(t) - Z_c Q(t)}{2} \quad (2.10)$$

2.3 The Respiratory System

The respiratory system is responsible for oxygenating and removing waste products such as carbon dioxide from the blood. This is done via all of the tiny alveoli within the lungs. The alveoli are responsible for the diffusion of oxygen and waste

products between blood and inspired air.

2.3.1 Mechanics of Ventilation

The lungs are usually expanded and contracted by downward and upward motions of the diaphragm, causing elongation and shortening of the chest cavity in which the lungs are situated. The lungs are not fixed to the chest cavity at any point, but rather float freely within. The walls of the lungs are coated in a fluid called pleural fluid that lubricates movement of the lungs within the cavity. This fluid is continuously absorbed by lymphatic channels, creating a suction force between the lungs and chest cavity which keeps the lungs firmly held to the cavity walls [9]. The pleural fluid thus acts as both a lubricant for the lungs and a mechanism with which to keep the lungs held to the walls of the chest cavity as it expands and contracts during inspiration and expiration, causing the lungs to inflate and deflate.

2.3.2 Pleural and Alveolar Pressure

Pleural pressure is the pressure of the pleural fluid between the lungs and chest wall. At rest, the pleural pressure is slightly negative, keeping the lungs “attached” to the chest wall. Roughly $-5\text{cmH}_2\text{O}$ pleural pressure is required to keep the lungs inflated at rest. During inspiration, the chest wall expands, pulling outwards on the lungs with greater force, creating a larger negative pleural pressure. During normal expiration, the chest wall relaxes, and elastic recoil of the lungs causes the pleural pressure to rise back up to its resting level.

The alveolar pressure is the pressure within the lungs, and at rest, it is equal to $0\text{cmH}_2\text{O}$ with respect to atmosphere. During inspiration, as the lungs expand, this creates a negative pressure inside of the lungs, causing air to flow into the lungs until lung pressure reaches atmospheric pressure again. During expiration, the elastic recoil of the lungs causes the lungs to shrink, increasing the alveolar pressure. Air flows out of the lungs until the pressure within the lungs once again

reaches atmospheric pressure.

The difference between the alveolar pressure and pleural pressure is called the transpulmonary pressure. It is a measure of the elastic forces in the lungs that cause the lungs to recoil during expiration. The changes in lung volume, alveolar pressure, pleural pressure and transpulmonary pressure over the course of a respiratory cycle are illustrated in Figure 2.11.

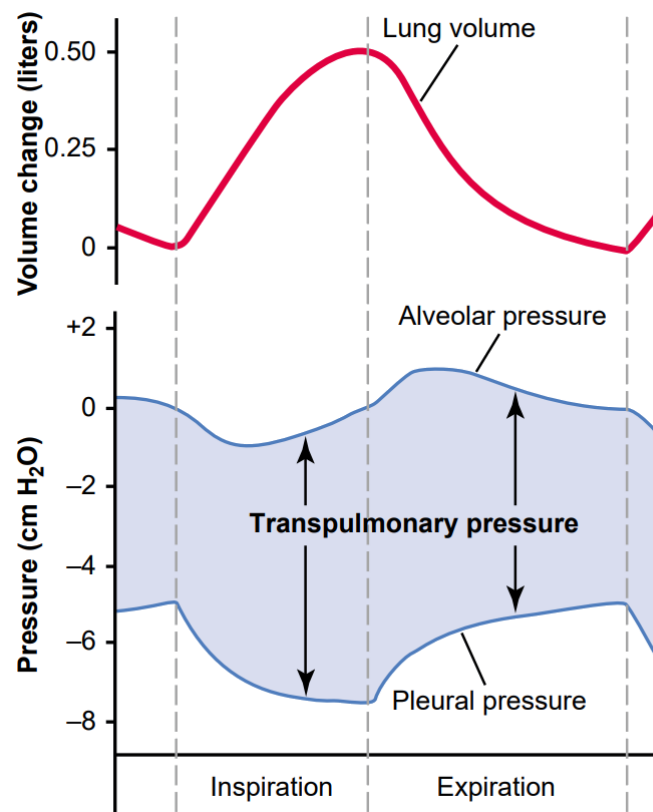


Figure 2.11: Changes in lung volume, alveolar pressure, pleural pressure and transpulmonary pressure over the course of a respiratory cycle. Figure taken from [9]

2.3.3 Compliance of the Lungs

The compliance of the lungs determines the extent to which they expand for a given transpulmonary pressure. The behaviour of lung compliance is shown in Figure 2.12. This is known as the compliance diagram of the lungs. The compliance diagram of the lungs is made up of 2 curves, the inspiratory and expiratory curve, and together, they illustrate the hysteresis behaviour of the lungs during respiration.

Lung compliance is dependent on 2 major factors: (1) *the elastic forces of the lung tissue itself* and (2) *elastic forces caused by surface tension of the fluid lining the walls of the alveoli*. The elastic forces of the lung tissue are determined mainly by elastic and collagen fibres interwoven within the lung tissue. The forces caused by surface tension are much more complex, and make up roughly two thirds of the total lung elasticity. The fluid surrounding the alveoli, made up mainly of water, forms a surface with the air. When water forms a surface with air, it causes the water molecules on the surface to have a strong attraction to one another. This causes an elastic contractile force on the alveoli, known as the surface tension elastic force of the lungs. The effect can be demonstrated by comparing the compliance of the lungs when filled with air, and when filled with liquid. This effect is shown in Figure 2.13.

2.3.3.1 Effect of Thoracic Cavity on Lung Expansibility

The thoracic cavity (TC) has its own elastic characteristics, similar to those of the lungs. The compliance of the lungs and the TC act in parallel, reducing the overall compliance of the system. The compliance of the combined lung-thorax system is roughly one half that of the lung alone. Furthermore, as the lungs are expanded, and the limitations of the chest become increasingly significant, the compliance of the combined lung-thorax system can reach as little as one fifth of the lungs alone.

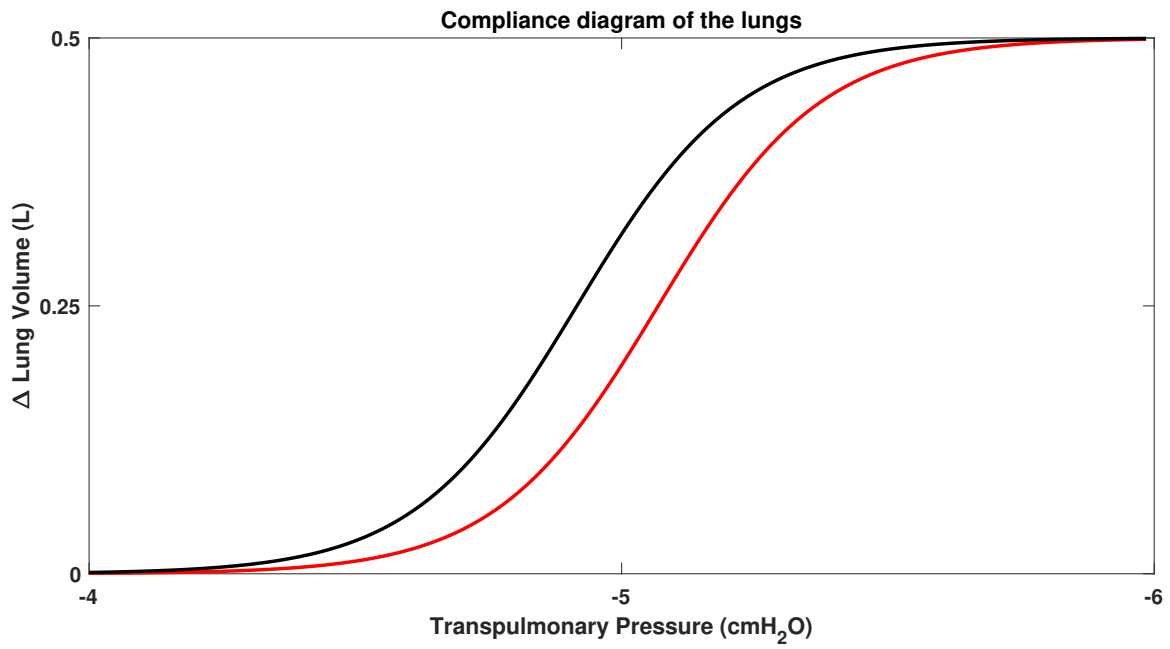


Figure 2.12: Compliance diagram of the lungs.

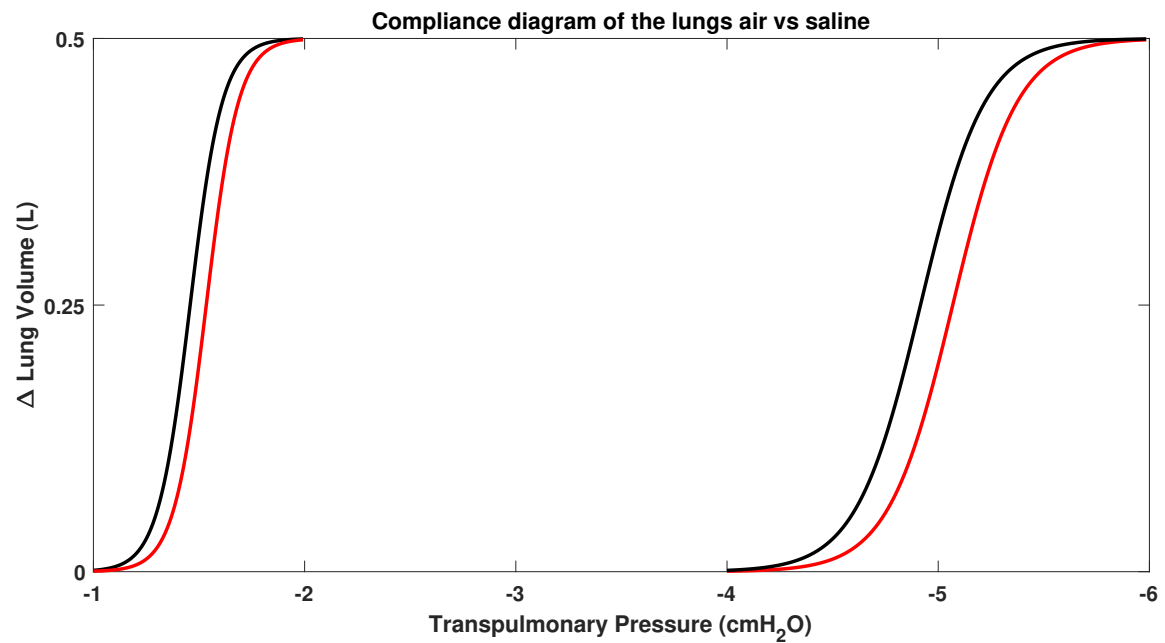


Figure 2.13: Compliance diagram of the lungs when filled with air vs when filled with saline solution.

2.3.4 Pulmonary Volumes and Capacities

Over the course of a respiratory cycle, the volume of air within the lungs can be divided into four distinct volumes, which when added together, make up the maximum volume to which the lungs expand.

1. *Tidal volume* is the volume of air expired during each normal breath, and is roughly equivalent to 500mL.
2. *Inspiratory reserve volume* is the extra volume of air that can be inspired above the normal tidal volume, when a person inspires such that the lungs are filled to their maximum volume. This is usually around 3000mL.
3. *Expiratory reserve volume* is the maximum amount of extra air that can be expired after normal tidal expiration, roughly 1100mL.
4. *Residual volume* is the remaining volume of air in the lungs after expiratory reserve volume has been expired, this volume averages around 1200mL.

When describing the pulmonary cycle, it is sometimes more useful to consider two or more volumes together. These combinations of pulmonary volumes are known as pulmonary capacities:

1. *Inspiratory capacity* is equal to the sum of the tidal volume and the inspiratory reserve volume, and describes the maximum amount of air a person can inspire from a normal expiratory level.
2. *Functional residual capacity* is equal to the sum of the expiratory reserve volume and the residual volume. This is the amount of air remaining in the lungs after usual expiration.
3. *Vital capacity* is the sum of inspiratory reserve volume, tidal volume and expiratory reserve volume. This describes the maximum amount of air a person can expel from their lungs after filling the lungs to their maximum volume.

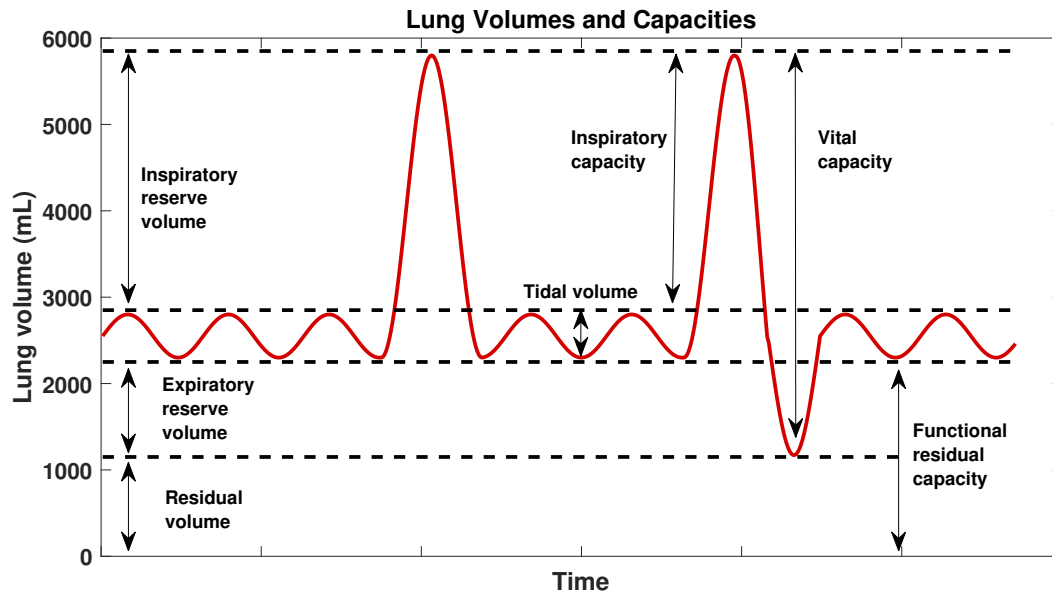


Figure 2.14: Lung volumes and capacities that make up the maximum volume of the lungs.

4. *Total lung capacity* is the maximum volume to which the lungs can be expanded and is equal to the sum of all the above mentioned lung volumes.

These pulmonary volumes and capacities are illustrated in Figure 2.14.

2.3.5 Mechanical Ventilation

In the intensive care unit (ICU), many patients are mechanically ventilated. Mechanical ventilation (MV) is used to aid recovery by reducing the work of breathing or taking over this work completely, if necessary. Each patient and their disease state are unique. Thus, the ventilator management needs to be individualised. As the patient's condition changes, the ventilator parameters need to be updated.

Mechanical ventilation has adverse effects on cardiac output of the heart. During mechanical ventilation, the usual mechanisms of breathing no longer occur, meaning that the chest cavity is no longer responsible for the expansion and contraction

of the lungs. The result of this is that the lungs now exert an increased amount of pressure on the thoracic cavity during inspiration when the lungs expand. The thoracic cavity also contains the heart and the blood vessels responsible for returning blood to the heart. The increased pressure exerted on the heart impedes on blood flow to the heart [9], essentially decreasing preload and thus reducing stroke volume and cardiac output. The opposite effect occurs during expiration, as the lungs deflate, the lungs exert less pressure on the heart, allowing the heart to fill and eject as usual.

2.3.6 Cardiopulmonary Interactions

It is well known MV usually brings about a decrease in SV [41–46]. However, the extent SV is affected, and the exact effects bringing about this decrease, are not clearly understood. Cardiovascular effects caused by mechanical ventilation are highly dependent on both the pulmonary and cardiovascular state of the patient, creating a large challenge for both clinicians and those attempting to model the CVS.

To optimise care and improve modelling, it is important to obtain a simultaneous understanding of the effects of MV on the CVS and patient-specific cardiopulmonary state. MV affects both the right and left circulation. However, since the right circulation lies entirely within the TC and much of the left circulation lies outside of the TC, the two circulations are affected very differently. While the effects on the 2 circulations are not independent, it is important to distinguish between them.

2.3.6.1 Effect of MV on the right circulation

Since the the right circulation is located exclusively within the TC, P_{th} should act largely equally on all parts of the circuit, and thus, does not alter pressure gradients of the system [44, 45, 47]. However, The volume of blood within a vessel is dependent on the transmural pressure of the vessel [44, 48]. As P_{th} increases, the

external pressure acting on the vessels of the right circulation increases, causing a decrease in transmural pressure, thus decreasing vessel volume. What is known is when P_{th} increases, there is a decrease in vessel volume leading to an initial increase of flow to the left ventricle, thereby displacing blood volume from the right to left circulation [44, 49].

Increasing positive end-expiratory pressure (PEEP) causes the lungs to expand, recruiting previously collapsed alveoli and further distending those already recruited. As alveoli are recruited, lung volume increases, and previously hypoxic vasoconstricted vessels are supplied with oxygenated blood and resume normal function, decreasing vessel resistance and potentially reducing total pulmonary vascular resistance (PVR) [47, 50]. Conversely, as the alveoli expand and lung volume increases, alveolar capillaries are compressed and stressed, increasing their resistance and elastance.

Thus, the resultant effect on PVR due to lung expansion is difficult to predict. Patients with lung disease may experience an overall decrease in pulmonary resistance, as the decrease in resistance caused by providing oxygenated blood to hypoxic vasoconstricted vessels outweighs the increase due to vessel compression. Patients operating in a normal range will generally experience an increase in PVR. However, the extent of these net effects is highly unpredictable [50].

The expansion of the lungs due to PEEP also augments P_{th} , thereby increasing external pressure acting on intrathoracic vessels. Blood flow through vessels is dependent on the pressure gradient across them, the resistance and elastance of the vessel, and, importantly, the external pressure of the vessel [44, 48, 49]. An increased external pressure on a vessel causes it to become stiffer, increasing its resistance and elastance respectively. If external pressure remains lower than internal pressure, the vessel remains fully open and the effect on resistance is negligible. However, if the external pressure exceeds the internal pressure of the vessel, vessel walls may partly collapse and resistance to flow increases significantly [48]. Furthermore, if the external pressure increases until it exceeds vessel output pressure, but not vessel input pressure, the pressure gradient governing flow through the vessel now becomes the gradient of input pressure and vessel external pressure,

reducing the pressure gradient, thereby decreasing flow through the vessel [44].

The change in both vessel resistance and vessel flow from increasing PEEP is thus highly dependent not only on P_{th} , but the P_{th} relative to the vessel pressure, which is both patient and condition specific, and can evolve as a patient's condition evolves. Furthermore, P_{th} changes due to increasing PEEP are proportional to lung compliance [6, 41, 49–51]. Consequently, stiffer lungs result in lower P_{th} while more compliant lungs result in a higher P_{th} for a given PEEP, resulting in very different changes in end expiratory lung volume based on lung recruitability [51, 52]. The change in vessel resistance and flow is thus also dependent on lung compliance and overall pulmonary state.

Furthermore, the vena cava is also located within the TC, and like the vessels of the pulmonary circulation, the P_{th} exerted on the vena cava causes an increase in both its resistance and elastance, potentially reducing blood flow from the vena cava to the right atrium, thus reducing venous return. If P_{th} exceeds vena cava pressure, it would cause the walls of the vena cava to collapse [44, 48], further increasing resistance to flow and reducing return to the right atrium. The reduced flow to the right atrium decreases the preload of the right ventricle, further impacting its SV and return to the left heart. The extent to which resistance to venous return is affected thus depends on whether P_{th} exceeds vena cava pressure or not.

2.3.6.2 Effect of P_{th} on the left circulation

Unlike the right circulation, only part of the left circulation lies in the TC and thus P_{th} effects the pressure gradients of the circuit. The left ventricle lies within the TC, while most of the aorta and downstream arteries lie outside. The increase in P_{th} decreases the transmural pressure of the left ventricle, thereby increasing the pressure gradient between the left ventricle and the downstream extrathoracic aorta, resulting in a lower left ventricle afterload [46, 47, 49, 50]. Furthermore, as discussed previously, the initial effects of P_{th} displaces blood from the pulmonary to systemic circulation, resulting in an initially increased blood flow to the left ventricle. The increased flow and decreased afterload result in an initial increase

in left ventricle stroke volume.

However, as venous return to the right ventricle diminishes, and its afterload increases due to increasing PVR, the venous return to the left ventricle is also reduced, causing a reduction in preload, ultimately leading to a decrease in SV. The reduced filling volume results in a reduced preload, which results in a reduction of both SV and end systolic pressure. This in turn causes a decrease in the mean and pulse pressure of the aorta and all downstream arteries. Conversely, patients suffering from certain left ventricular disorders, such as hypervolemic or congestive heart failure, may actually experience a lasting increase in SV from the decreased afterload [47, 49]. However, this effect is limited by the diminishing return from the RV. The resultant effect on SV in such patients is harder to predict as there is no way of knowing at which point decreasing return begins offsetting the augmented ejection.

It is important to note all the above mentioned effects are patient specific and depend on a patient having both healthy circulatory and respiratory systems operating within standard parameter ranges. Patients with disease or weakened cardiovascular systems may experience more severe reactions to P_{th} caused by positive pressure ventilation. Patients with right ventricular dysfunction, commonly encountered in acute respiratory distress syndrome (ARDS), are at potential risk of right ventricular failure due to the increased strain caused from the increased afterload [53, 54]. Right ventricular dysfunction is also reported to be one of the major determinants of mortality in ARDS [54]. Furthermore, the above-mentioned effects of P_{th} do not take into account the complexities of the autonomic nervous system responsible for ensuring proper circulatory function. While the effects of P_{th} on a fixed system are somewhat easy to comprehend, the difficulty of task is greatly magnified when considering the many compensatory mechanisms present within the CVS, which themselves are also patient specific and highly dependent on the health of the patient [46].

2.4 Fluid Resuscitation

Fluid resuscitation, also known as vascular filling, is the process by which fluid is administered intravenously to a patient's CVS with the goal of increasing cardiac output. It is one of the most common procedures used in ICU and is the main therapy used in treating circulatory shock [55, 56].

Despite its widespread use, fluid resuscitation has shown to be effective in as little as 50% of all cases and in many cases has even caused patient condition to worsen [56–59]. Fluid resuscitation is dependent on many factors, including the type and volume of fluid infused, the intervals of infusion, and crucially, the patients cardiovascular state at the time of infusion.

Fluid resuscitation was initially based on the Frank-Starling curve, seen in Figure 2.4. Since CO can be increased with a higher preload, fluid administration is used to increase preload and thus increase CO. However, the curve begins to flatten out after a certain point, indicating that preload no longer has an effect on CO and has even been shown to decrease CO if increased even further [60].

2.4.1 Fluid Overload

Fluid overload occurs when a patient presents with a fluid accumulation of more than 10% relative to their admission bodyweight [61, 62]. Fluid overload can occur as a result of unguided fluid therapy, and has been linked to increased mortality, requirement of mechanical ventilation and length of hospital stay [57, 62–68]. One study found for every 10ml/kg increase in fluid overload, the risk of mortality increased by 4% [69]. It is thus crucial to determine indicators of a patients fluid responsiveness to guide fluid resuscitation.

2.4.2 Indices of Fluid Responsiveness

Indices of fluid responsiveness are used to determine a patient's cardiovascular state and hence determine how a patient would respond to fluid resuscitation. There are two main types of indices, static and dynamic.

2.4.3 Static Indices

Static indices are static values of direct measurements used to guide fluid therapy. Since preload is associated with CO, initial indices were used as indicators of a low preload, since a low preload implies that an increase in preload would result in a large increase in stroke volume. An intuitive index would thus be the end-diastolic volumes of the right and left ventricle, as these volumes are directly related to preload. However, these volumes are not easy to measure and more readily available substitutes are often used instead, such as:

- Central venous pressure (CVP) [60]
- Right atrial pressure [70]
- Global end diastolic volume [71]

These indices have been found to be poor predictors of fluid responsiveness and hence considered to be inefficient [70, 72–74]. Despite its low performance, CVP was found to be the most frequently used index of fluid responsiveness in a study performed over 46 countries [55]. This is likely due to its high availability in ICUs.

2.4.4 Dynamic Indices

Dynamic indices have been defined based on cardiopulmonary interactions during mechanical ventilation. As mentioned previously, the stroke volume varies with

inspiration and expiration during mechanical ventilation. This variation in stroke volume also causes a similar variation in arterial pressure.

As shown in Figure 2.15, depending on a patients cardiovascular state at the time of preload, mechanical ventilation can have varying effects on stroke volume. If the patients preload was already high at the time of mechanical ventilation, there will not be a large change in stroke volume as a result of the mechanical ventilation. Conversely, patients with a low preload would experience a much larger variation in stroke volume caused by the mechanical ventilation.

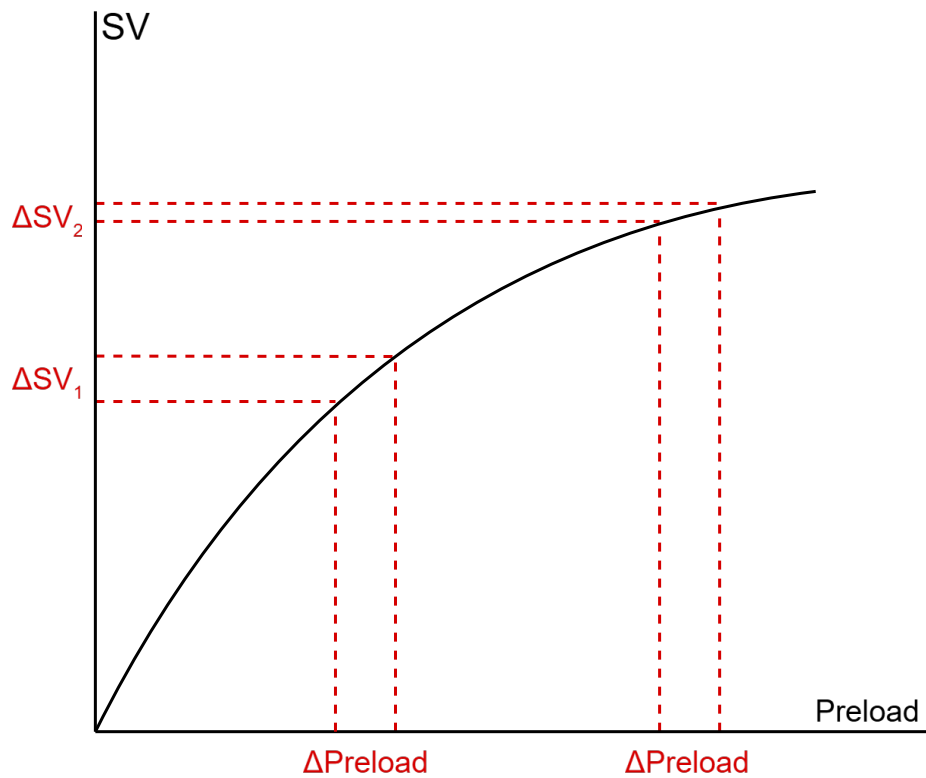


Figure 2.15: Different stroke volume variations for the same change in preload caused by mechanical ventilation

2.4.4.1 Stroke volume variation

Stroke volume variation (SVV) quantifies the magnitude of the variation due to mechanical ventilation [70]. It is defined:

$$SVV = 2 \frac{SV_{max} - SV_{min}}{SV_{max} + SV_{min}} \quad (2.11)$$

2.4.4.2 Pulse Pressure Variation

Since SV is often not accessible beat-by-beat in an ICU setting, it is difficult or sometimes not possible to determine SVV. Pulse pressure is the vessel reflection of stroke volume and is often used instead of stroke volume since pressures are often measured in real time in the ICU. Pulse pressure variation (PPV) is defined as follows:

$$PPV = 2 \frac{PP_{max} - PP_{min}}{PP_{max} + PP_{min}} \quad (2.12)$$

Despite the fact that dynamic indices have been found to be better indicators of fluid responsiveness in multiple studies [13, 60, 70, 75, 76], there are numerous scenarios in which dynamic indices are highly limited or cannot be used as a reliable predictor:

- Spontaneous breathing
- Open thorax
- Arrhythmias

The first point being of high importance, as current trend in ICUs is to let patients breathe spontaneously as early as possible. Furthermore, dynamic indices

are affected by a very complex combination of multiple physiological variables, including:

- Tidal volume [73, 77]
- Lung compliance [73]
- Chest wall compliance [77]
- Cardiac contractility [73, 77]

These influences make it very difficult to compare indices of different patients or even for the same patient in changing conditions.

2.4.5 Stressed Blood Volume

Stressed blood volume (SBV) is the blood responsible for pressure generation within the CVS [12]. Stressed blood volume has shown promising results as an index of fluid resuscitation [1, 12, 14, 16]. However, measuring SBV is a highly complex and dangerous procedure, involving regular cardiac arrests and fluid infusions. Since this is neither feasible nor ethical for implementation on patients, many investigative studies have examined the potential of a modelled equivalent of SBV [1, 14, 16]. Thus far, studies have only been conducted on retrospective animal data and have shown promising results. However, real time assessment of SBV and implementation for bedside assistance has not yet been achieved.

2.5 Modelling of the Cardiovascular System

2.5.1 Passive CVS Elements

The CVS is made up of multiple passive elements, such as vessels, chambers and valves. These are the building blocks of the CVS model. They are deemed passive

as, unlike the heart, they do not generate any pressure. The mathematical models for each of these elements is described here.

2.5.2 Vessels

Vessels are represented as simple resistances. The blood flow through a given vessel can be determined from its pressure gradient and resistance using Ohm's law:

$$Q(t) = \frac{P_{up}(t) - P_{down}(t)}{R} \quad (2.13)$$

Where P_{up} is the pressure upstream of the vessel, P_{down} is the pressure downstream of the vessel, Q is the blood flow through the vessel and R is the resistance of the vessel.

2.5.3 Valves

Valves are similar to vessels in that they have a resistance and the flow through them is also calculated using Ohm's law. However, the valves are also modelled as a diode, preventing flow if there is a negative pressure gradient across the valve. The blood flow through the valve is thus determined by a piecewise function:

$$Q(t) = \begin{cases} \frac{P_{up}(t) - P_{down}(t)}{R} & P_{up}(t) > P_{down}(t) \\ 0 & \text{else} \end{cases} \quad (2.14)$$

2.5.4 Passive Chambers

Large blood vessels, such as the aorta and vena cava, are modelled as passive elastic chambers because they store blood. The chambers act similarly to a capacitor, where pressure is analogous to voltage and the elasticity of the chamber

is analogous to capacitance.

The vena cava and aorta act as passive chambers, meaning they do not generate any pressure and the pressure of the chamber is therefore dependent solely on the volume inside of the chamber. The pressure of a passive chamber is represented as:

$$P(t) = E \int Q(t) dt \quad (2.15)$$

Where P is the pressure of the chamber, E is its elasticity and Q is blood flow. The integral of flow is equal to the stressed volume of the chamber and thus the equation can be rewritten:

$$P(t) = E \cdot V_s(t) \quad (2.16)$$

However, as described in section 2.1.2.2, elastance of a vessel increases exponentially with volume increases. This means a vessel has no singular elastance value, like that used in 2.16. Commonly, a volume “working point” is chosen, and a linear approximation is used around this point [31], illustrated in Figure 2.16. As shown in the figure, the linearly approximated unstressed volume ($V_{u,approx}$) differs significantly to actual unstressed volume. This results in high errors when using approximations around this range. However, the approximation works well for normal patient operating ranges.

2.5.5 Active CVS Elements

The chambers of the heart, the ventricles, and the atria are active chambers as they generate pressure during contraction. They are analogous to the power supply of the system. There are multiple ways of describing the time varying nature of ventricular pressure, the most common being the time-varying elastance theory [78]. However, there are other models which aim to address drawbacks of the time

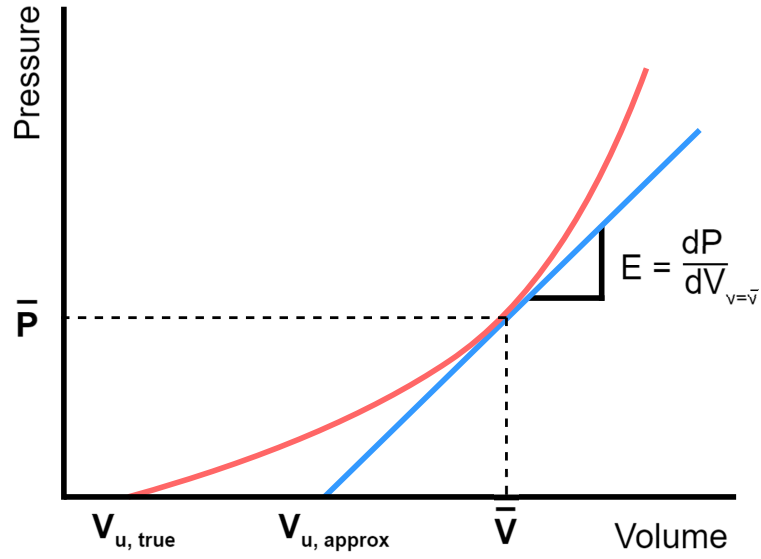


Figure 2.16: Linear approximation of elastance around working point, $\bar{V}$

varying elastance theory.

2.5.6 The Time Varying Elastance Theory

The time varying elastance theory was introduced by Suga *et al* [78]. The authors found the pressure-volume loops, obtained by plotting ventricle volume against ventricle pressure, shifted with afterload. They observed that the end systolic points (top left corner of the pressure loops) varied linearly with afterload. The gradient of the resulting line is the end-systolic elastance and is defined:

$$P = E_{es} \cdot V_s \quad (2.17)$$

The intercept of the line and the volume axis represents the unstressed volume of the chamber, V_u . The end systolic pressure volume relationship (ESPVR) is illustrated in Figure 2.17.

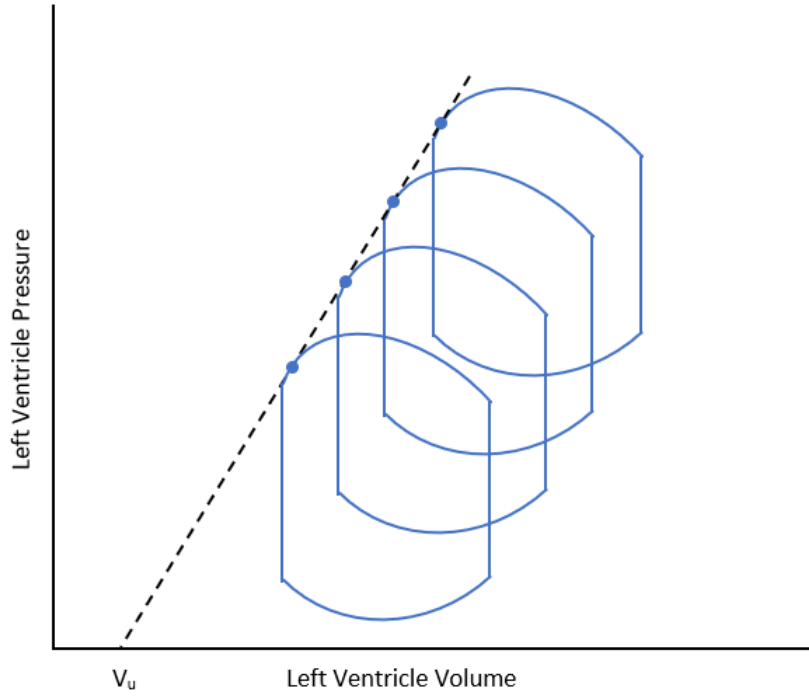


Figure 2.17: Illustration of the ESPVR experiment conducted by Suga *et al.* [78]

Suga *et al* repeated these experiments by altering both preload and contractility of the ventricle. Once again, they found that the end systolic points lay on linear line. Despite the gradient of the line having changed with both preload and contractility, there was no discernible change in unstressed volume, indicating that E_{es} represents a load independent index of ventricular contractility.

The pressure-volume relationship of the ventricle over the entire cardiac cycle was defined as:

$$E(t) = \frac{P(t)}{V(t) - V_u} \quad (2.18)$$

By normalising the function with respect to E_{es} , its maximum amplitude, the following is obtained:

$$e(t) = \frac{E(t)}{E_{es}} = \frac{P(t)}{E_{es}(V(t) - V_u)} \quad (2.19)$$

The resulting function is termed the driver or activation function, and is independent of preload, afterload and contractility.

2.5.6.1 Limitations

The time varying elastance theory provides a simple way to model ventricular contraction, and thus the driving force of the CVS model. However, there has been debate surrounding the linearity of the ESPVR. Several authors found the ESPVR to be curvilinear in nature [79–82]. These studies also found that linear estimations of the ESPVR resulted in a negative unstressed volume, which is physiologically impossible. Further studies demonstrated that the ESPVR may also be load dependent [79, 83, 84].

Despite the debates around the linearity and load dependence of the ESPVR, the time varying elastance theory has been widely adopted with great success. The activation function provides an accurate means for driving CVS models. The successful use of the driver function in CVS models has indirectly resulted in the validation of the time vary elastance theory, and has thus justified its use for such models [1, 16, 41].

2.6 Summary

This chapter provided an overview of the relevant literature pertaining to the cardiovascular and respiratory systems, as well as the modelling techniques used for such systems. An overview of the physiology of the cardiovascular system was presented, providing a brief descriptions of the heart, major and minor blood vessels, the cardiac cycle and arterial blood flow. The volumes and capacities of the respiratory system were summarised, and an extensive review on the understanding

of cardiopulmonary interactions was presented. Fluid therapy and the indices of fluid responsiveness were discussed, and finally, the mathematical means for modelling the cardiovascular system were presented.

Chapter III

Experimental Data

3.1 *Experimental Animal Clinical Trial Procedure*

The experimental protocol was approved by the Ethics Committee for the use of animals at the University of Liege, Belgium between September - November, 2015 (Reference Number 14-1726). Eight pure Pietrain pigs were anaesthetised and mechanically ventilated. Airway pressure and flow were provided from the ventilator at a sample rate of 250Hz. Septic shock was then induced in the subjects via a single infusion of endotoxin (lipopolysaccharide from *E. Coli*, 0.5 *mg/kg*, infused over 30 *min*). Pre-endotoxin infusion, a 500 *mL* saline solution was administered over 30 *min* simulating fluid resuscitation therapy.

Several PEEP driven preload recruitment manoeuvres (PRMs) were performed on each pig both pre- and post- endotoxin. Aortic, vena cava and femoral pressure in the subjects were continually measured via a catheter with a sampling rate of 250 Hz. Left ventricular pressure and volume were also continually measured at a rate of 250 *Hz* via an admittance pressure volume catheter inserted into the left ventricle via an apical stab. The full measurement set is summarised:

- Left ventricle pressure
- Aortic flow
- Left ventricle volume
- Femoral pressure
- Aortic pressure
- Vena cava pressure

- Airway pressure
- Airway flow

3.1.1 *Data Irregularities*

Though experiments were conducted on 8 pigs, not all of the pigs produced perfect, or fully usable data. Pig 1 did not record any negative flow for the airway flow measurements, as shown in Figure 3.1. This missing data is not a problem for the 3 chamber model, as it does not use respiratory data. However, using a potential cardiopulmonary model on this data would be highly challenging. Pig 1 also had issues with the aortic flow probe, where the initial upstroke and first half of the flow wave was entirely missing for many beats, as shown in Figure 3.2.

Furthermore, both Pigs 3 and 5 had issues with their left ventricle catheters, shown by Pig 3's left ventricular volume in Figure 3.3 and Pig 5's left ventricular pressure in Figure 3.4. Pig 3's left ventricle catheter was likely pressed up against the wall of the ventricle creating the large amount of interference observed, while the ventricle catheter for Pig 5 required repeated repositioning during the experiment, leaving only the final section of data usable. Finally, Pig 8 had a problem with measured aortic flow, showing clear offset errors resulting in a large part of the flow pulse being negative, where in reality the entirety of the pulse should be positive. Further, this offset was not consistent, and changed over time, depicted by 3 different flow pulses shown in Figure 3.5.

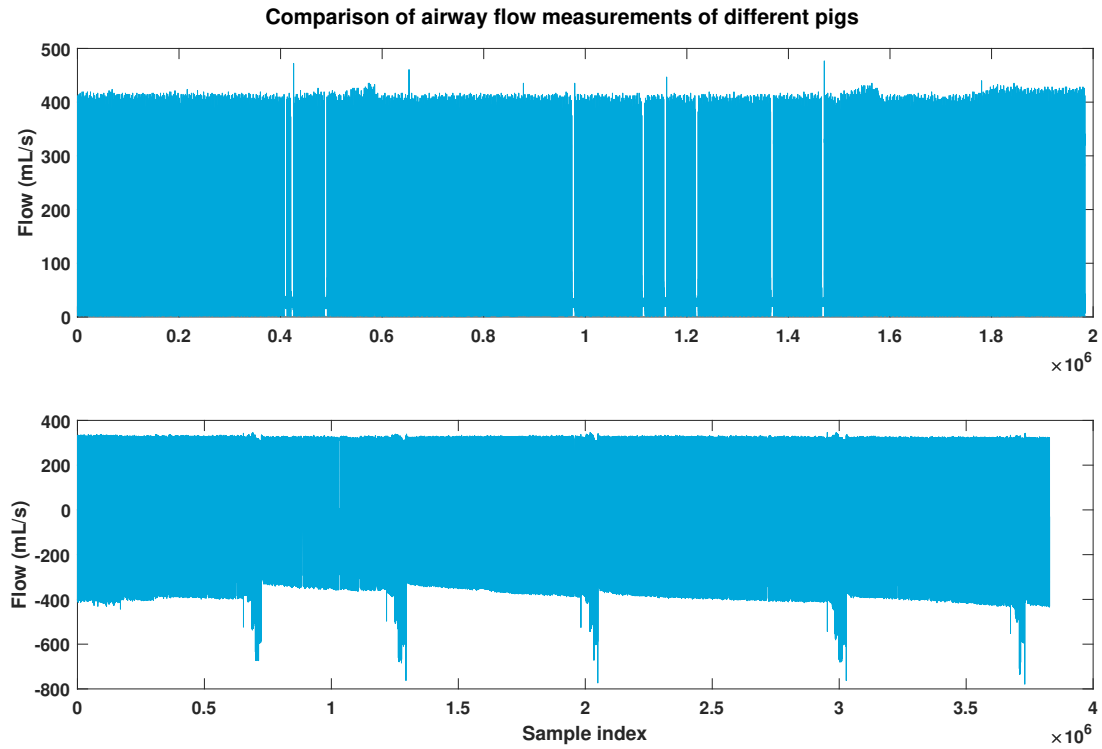


Figure 3.1: Airway flow of Pig1 (top) and Pig 2 (bottom). Pig 1 displays no negative flow readings.

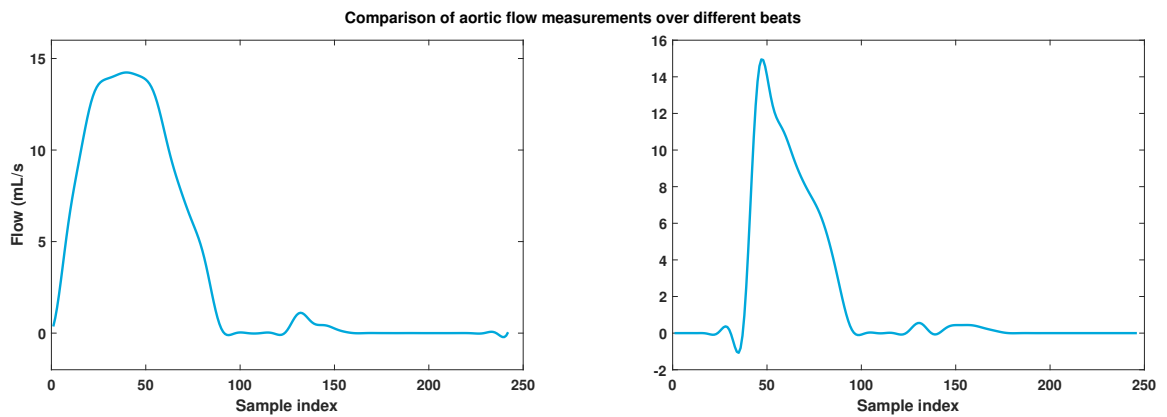


Figure 3.2: 2 different beats of aortic flow for Pig 1. The left side shows a correctly recorded flow wave, while the right hand side shows a flow wave where the initial upstroke and first half of the wave has not been recorded.

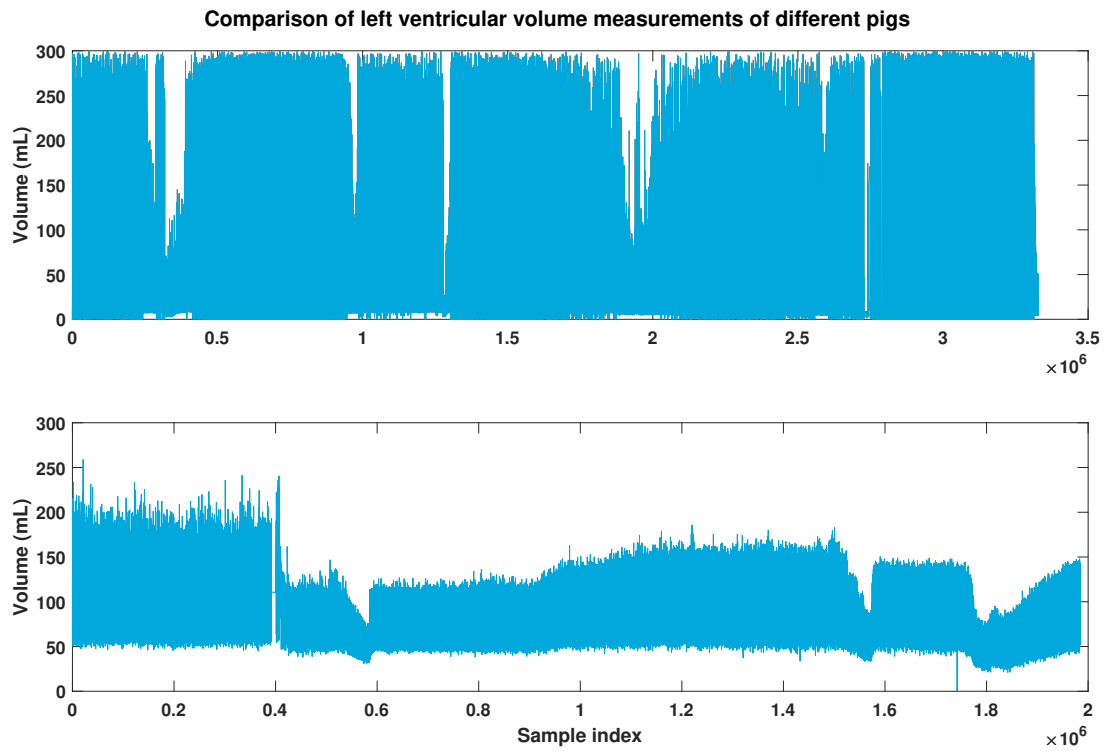


Figure 3.3: Left ventricular volume waveforms of Pig 3 (top) and Pig 1 (bottom). The amount of noise present in the volume waveform of Pig 3 left most sections of this data unusable.

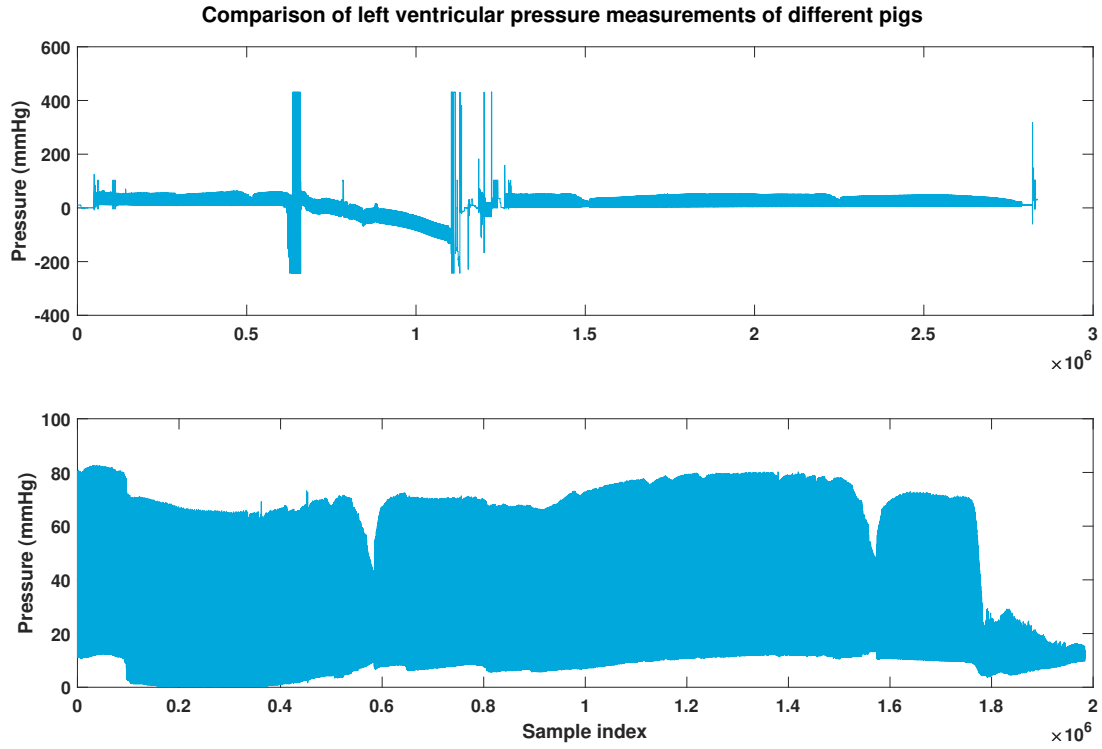


Figure 3.4: Left ventricular pressure waveforms of Pig 5 (top) and Pig 1 (bottom). At some points, the entire waveform is negative. The catheter was repositioned and the data is usable from sample index 1297500 onwards.

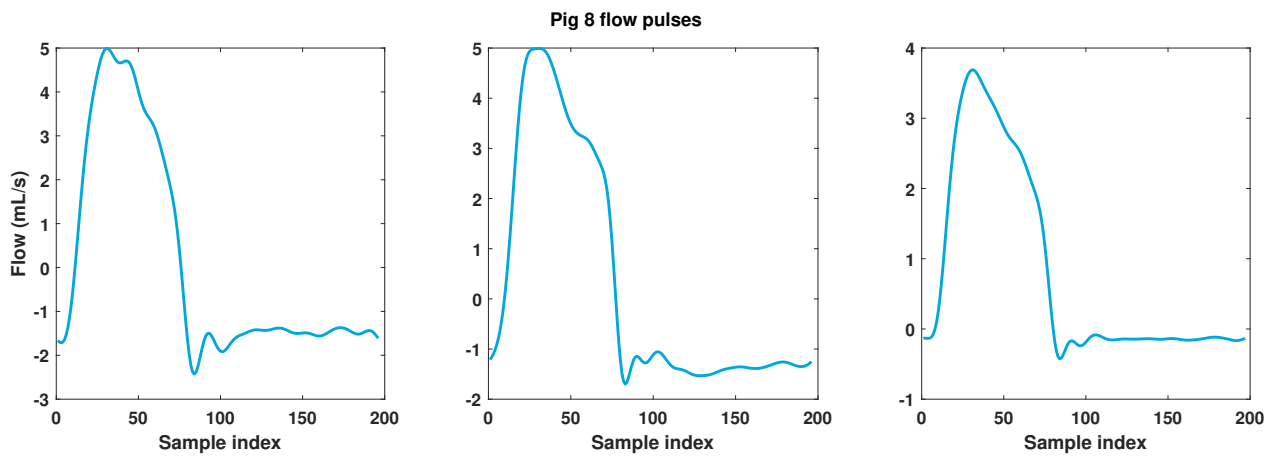


Figure 3.5: Different flow pulses from Pig 8 exhibiting different offsets.

Finally, Pig 6 experience an issue with the femoral pressure catheter, which throughout the experiment. Generally, peripheral pressures have lower mean pressures than central pressure, as the pressure pulse slowly decays as it travels down the arterial tree. Conversely, pulse pressure increases, as pulse pressure amplification is greater in peripheral locations due to earlier arriving reflected waves [9]. However, Pig 6 displays the opposite behaviour in measurements. Femoral pressure has a greater mean pressure, and a lower pulse pressure, than the aortic pressure, shown in Figure 3.6. The femoral pressure data for Pig 6 is thus unusable for this work.

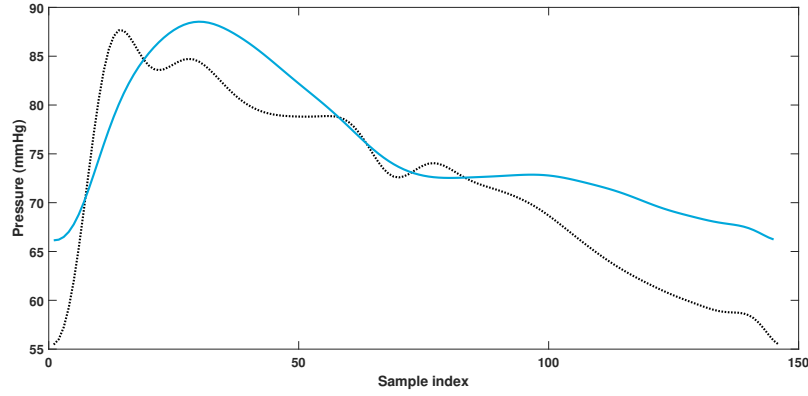


Figure 3.6: Femoral and aortic pressure for Pig 6. Femoral pressure is shown by the solid blue line while aortic pressure is shown by the dotted black line.

3.1.2 Data rectification

For many of the above mentioned problems, the data was not salvageable. However, for some of the pigs, there were solutions which provided usable data. The left ventricle volume measurement for Pig 3 was unusable. However, left ventricle volume is generally not available in the ICU anyway, and this work uses a modelled equivalent requiring only SV and ESV as inputs. However, SV and ESV were not reliably obtainable from the volume waveform. SV is easily obtained by integrating the aortic flow wave. However, ESV is not obtainable from flow, as it is a constant of integration. To obtain ESV for Pig 3, a linear regression model was

fit to SV and ESV data from all other pigs, and the model was used to calculate ESV for Pig 3 from SV.

The flow measurements from Pig 8 were also easily rectified, as there should be no diastolic flow (0 mean flow) since the aortic valve is closed during diastole. The flow wave can thus be corrected on a beat to beat bases by finding the mean flow during diastole of each beat, and subtracting it from the overall flow waveform, correcting the offset.

For the flow waves of Pig 1, many of the flow waves were measured correctly. In the case of incorrectly measured flow pulses, like the pulse seen on the left of Figure 3.2, the flow from the previous beat was used as a best estimate.

3.2 *Beat Separation*

Beat detection algorithms have many clinical applications [85], as most metrics used in the ICU are beat-to-beat metrics, such as mean and pulse pressures. Thus, beat detection is particularly important for cardiovascular modelling. In particular, data must usually first be separated into beats before it can be used as inputs into cardiovascular models.

In practice, beat separation is performed using ECG signals. Beat separation using ECG signals is a relatively simple, since the QRS complex of the ECG wave is highly pronounced, while the rest of the ECG signal is comparatively non-existent, making it very easy to identify by mathematical methods. However, the data used in this work did not contain ECG measurements. Thus, an algorithm for beat separation using pressure waves was required. Beat identification using pressure waves is more challenging than ECG signals. Pressure signals are far more complex than ECG signals, containing several highly individual specific features. This additional complexity results in pressure waveforms which can vary greatly, even between similar individuals.

There are many algorithms used for beat detection from pressure waves. Many

have been developed by medical device companies and are proprietary. However, many algorithms have also been presented in the literature [85–87]. The beat detection algorithm used in this work is a simplified version of the method used by Liu *et al.* [86].

3.2.1 Heart rate estimation

The first step in the beat separation process is estimating the heart rate from a pressure waveform. This estimate is made by finding the power spectral density (PSD) of the pressure waveform. The PSD of a signal shows how the power of a signal is distributed over its frequency range. Since pressure waveforms are periodic, they are made up of a fundamental frequency, and a summation of harmonics of the fundamental frequency [88]. The fundamental frequency of a pressure waveform is the heart rate, and this is usually the frequency with the maximum power. Thus, the heart rate is estimated by finding the frequency of the PSD with the highest power. Figure 3.7 shows an example pressure wave with 10 beats from the aortic pressure of Fig 2 and its PSD. The HR was correctly identified as 1.098HZ (shown in the data cursor), or 54BPM.

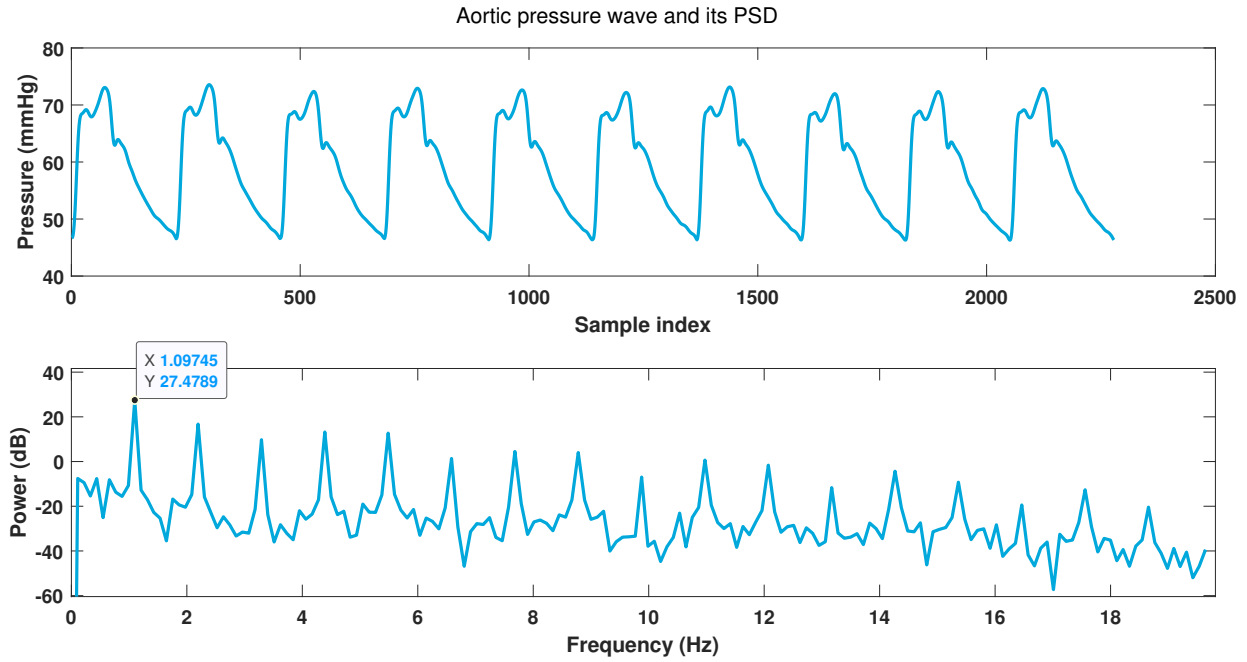


Figure 3.7: 10 beats of the aortic pressure of Fig 2 (top) and its PSD (bottom). The frequency of maximum power is shown by the data cursor on the PSD.

It is important to note this calculation only provides an estimate of HR and, equally, this method does not always correctly identify HR. Figure 3.8 shows 10 beats from Fig 8 and its PSD. The data cursor shows the maximum power of the signal is found at a frequency of 2.49Hz, which is approximately double the actual HR of the pig. This error is due to the large peak present during diastole caused by a late arriving reflected wave. This large diastolic peak gives the waveform a shape which more closely resembles a sinusoid oscillating at twice the fundamental frequency, resulting in higher power in the first harmonic. Usually, band pass filtering the signal is sufficient for eliminating harmonic frequencies. However, in this case, 2.49Hz, or 150BPM, is still a valid heart rate, and cannot be filtered out.

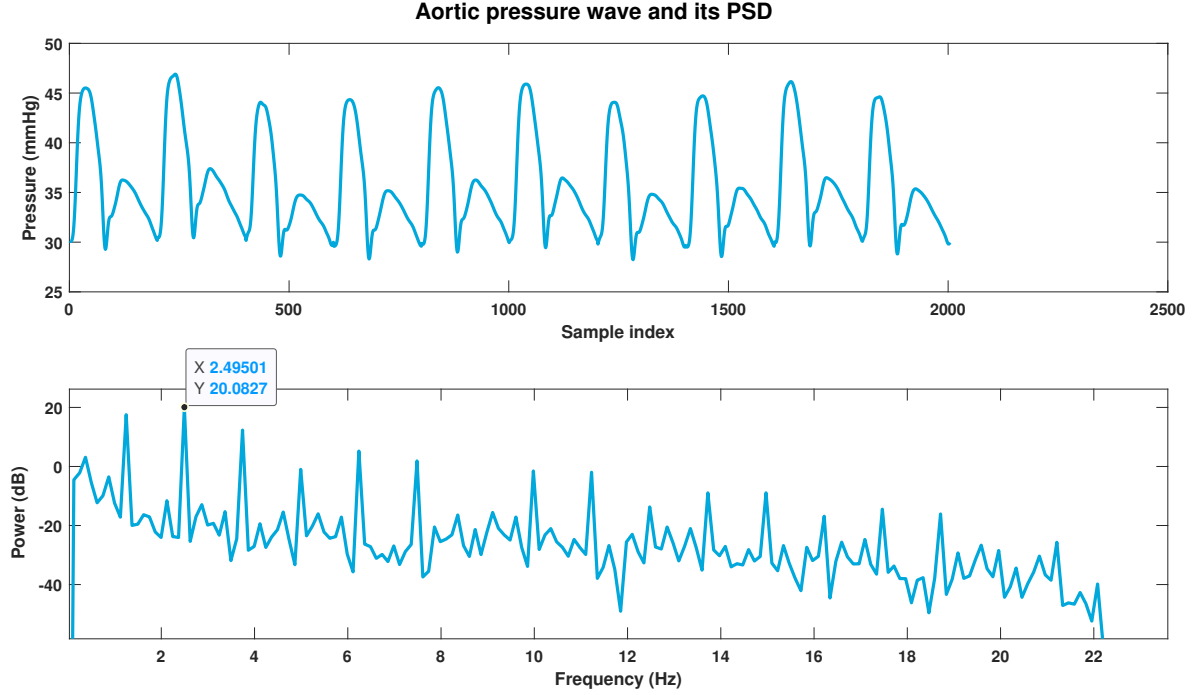


Figure 3.8: 10 beats of the aortic pressure of Fig 8 (top) and its PSD (bottom). The frequency of maximum power is shown by the data cursor on the PSD. The frequency of maximum power is incorrectly identified at roughly 2HR.

The identified frequency thus needs to be checked to verify whether it is the fundamental frequency, or a harmonic. To do this, the PSD is re-inspected, limited up to frequencies lower than the initially identified HR. The highest peak is located again, and if a significant peak is found at roughly half the frequency of the initially identified HR, then it can be confirmed as the fundamental frequency. The tolerance for a significant peak was set to at least half the magnitude of the initially identified HR.

$$|2 - (\frac{F_1}{F_2})| < 0.1 \quad (3.1)$$

The tolerance for frequency was set by Eq. 3.1, where F_1 is the frequency of

potential harmonic, and F_2 is the potential fundamental frequency. Note this method is limited in only checking if the first harmonic has been identified, and ignores higher harmonics. However, as most of the power of a pressure signal is contained within the fundamental frequency and first harmonic [89], it is highly unlikely higher harmonics will contain higher power than lower harmonics and the fundamental frequency.

In other cases, there are certain conditions resulting in a highly variable HR. Thus, this could highly skew the results of HR identification through spectral methods. This issue is particularly true of subjects who present atrial fibrillation, a condition which causes a fast and highly irregular heartbeat, where there is a very large amount of variation between beats [90, 91]. Using spectral methods for patients such as these for identification of HR is not impossible, however, only small segments of beats can be used at a time.

3.2.2 Window Sloped Sum

After finding the heart rate, the pressure waveform is fed through a window sloped sum function to enhance morphological features. In this case, the window sloped sum is used to enhance upstrokes of the waveform, while suppressing the remainder of the signal. The window sloped sum function is a piecewise function, defined:

$$z_i = \sum_{k=i-\omega}^i u_k, u_k = \begin{cases} \Delta y_k & \Delta y_k > 0 \\ 0 & \text{else} \end{cases} \quad (3.2)$$

where z_i is the output of the window sloped sum function at time i , ω is the length of the analysing window, and $\Delta y_k = y_k - y_{k-1}$, where y_k is the value of the low-pass filtered pressure signal at time k . The window size used for this work was 15.

Figure 3.9 shows an original aortic pressure waveform, and its window sloped output. The window sloped sum output heavily emphasize the upward strokes of

the waveform, while any overall downslopes are reduced to 0. The output of the window sloped sum function is thus highly simplified, and much easier to process than the original pressure wave.

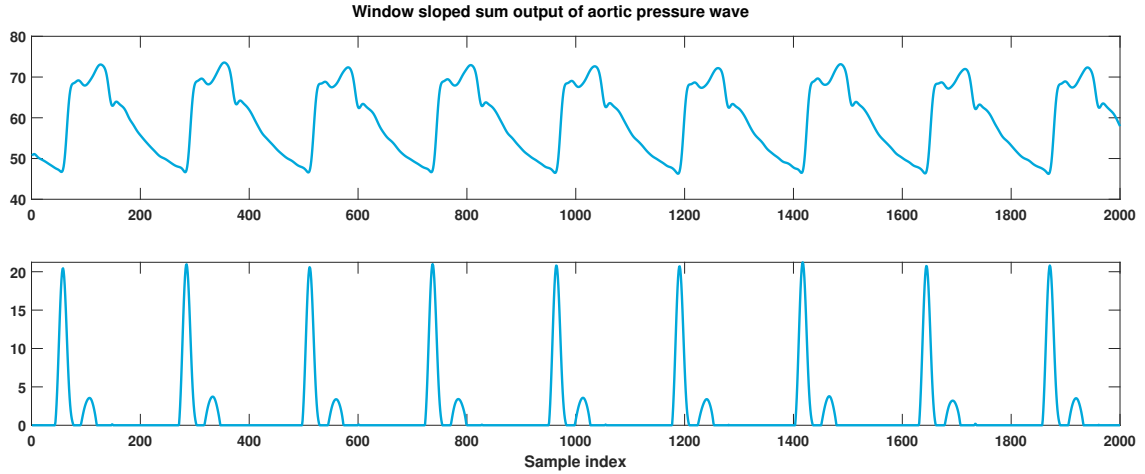


Figure 3.9: Aortic pressure wave of a pig (top) and the output of the window sloped sum function (bottom)

Thereafter, the prominent peaks of the window sloped sum waveform are found. The most prominent peak corresponds to the largest upstroke in the pressure waveform, present during early systole during ejection. Matlab's *findpeaks* function is used, setting the *MinPeakDistance* option to half of the approximate length of one beat, ensuring that only one peak per beat length is found. The approximate length of one beat is determined using the approximate HR previously found using the spectral estimation. The identified prominent peaks are shown in Figure 3.10.

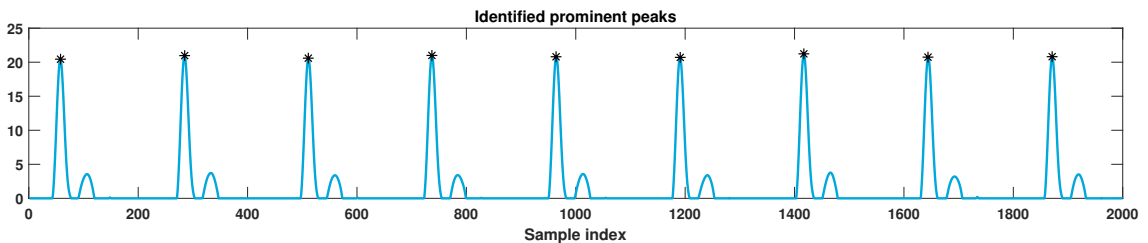


Figure 3.10: Identified prominent peaks (stars) of the window sloped sum function.

Following peak detection, the foot for each peak on the window sloped sum output is identified. A peak's foot is identified as the first 0 value before the peak. The window sloped sum wave's feet are then used to identify the feet of the pressure wave. The foot of the pressure wave will always occur after the foot of the window sloped sum function. Thus, the foot of a pressure wave is identified as a change from a negative to a positive slope. The foot of the pressure wave is thus identified as the first zero crossing from low to high of the gradient of the pressure wave following the foot of the window sloped sum function. Figure 3.11 shows the gradient of the pressure wave with identified zero crossings plotted alongside the window sloped sum function. The points of the zero crossing are also plotted on the original pressure waveform to illustrate identified feet.

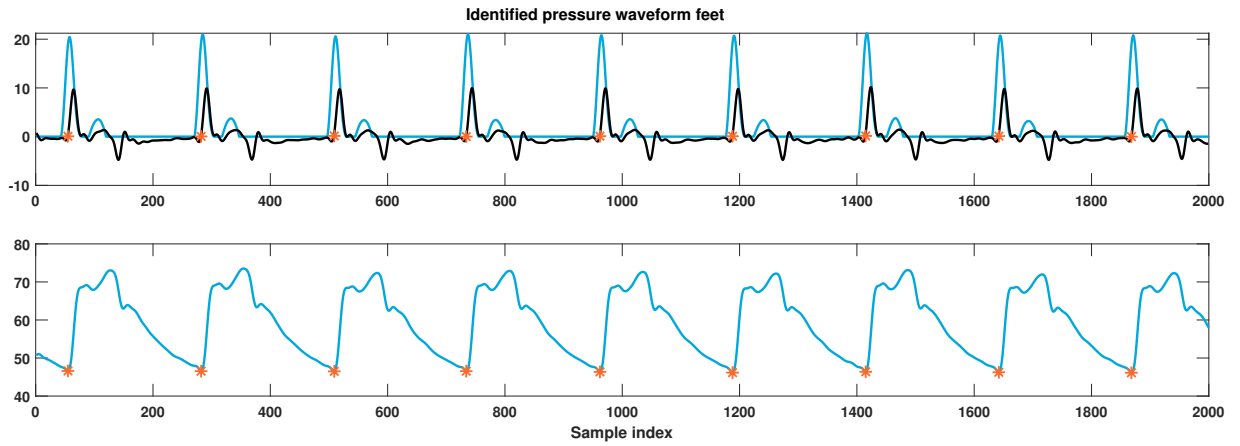


Figure 3.11: Identified zero crossings of the pressure gradient waveform. The top figure shows the window sloped sum wave (blue), the pressure gradient (black) amplified by a factor of 5 for improved visibility, and the identified zero crossings marked by orange stars. The bottom figure shows the same points marked on the original aortic waveform.

The waveform is then split into beats using the identified feet of the pressure waveform. Finally, outlier beats are eliminated if their length varies by over 20% from the median beat length. This threshold is empirically chosen for this data, but can be set for any specific value or data set.

3.3 Results

3.3.1 Data Rectification

The main pigs requiring data rectification were Pigs 3 and 8. Pig 3's left ventricular volume measurements were unusable. However, given the unavailability of left ventricle volume in the ICU, a modelled equivalent waveform would be used based on ESV and SV, as these are measurements generally available in the ICU. SV can be obtained by integrating the flow waveform over a single beat, however, it cannot provide ESV, as this is a constant of integration. Thus, a linear regression was used to predict ESV from SV. The linear model was fit from the ESV and SV data from the other 7 pigs and is shown in Figure 3.12

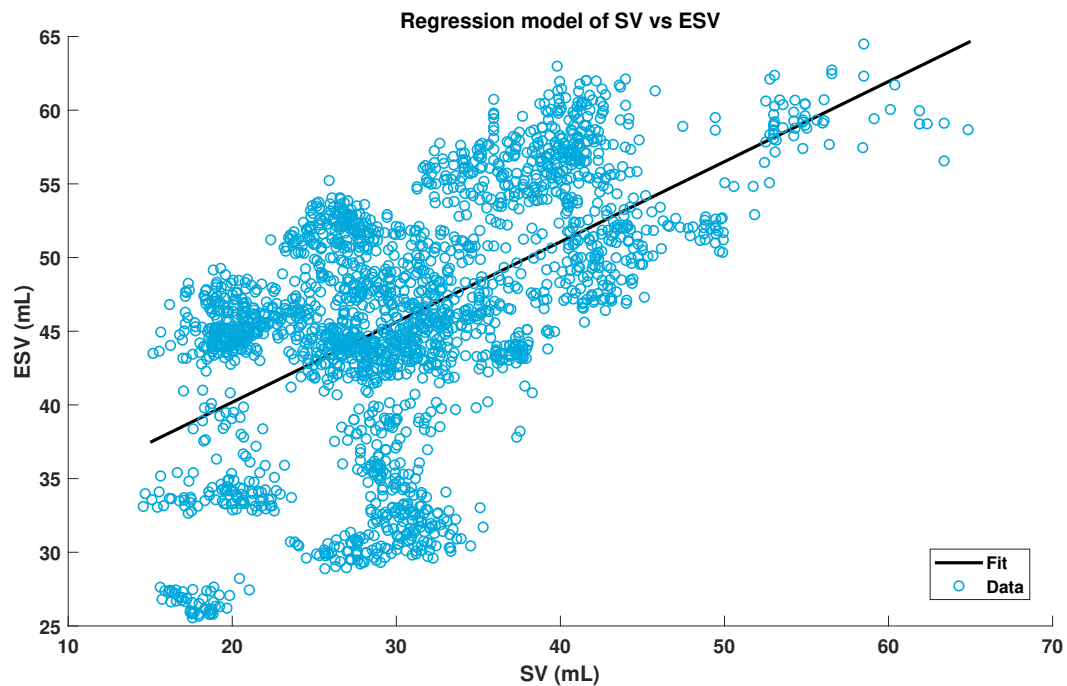


Figure 3.12: Linear regression of SV and ESV for all pigs over the RM.

Pig 8 had flow waveforms which often displayed offset errors. This issue was most

commonly observed as both the lower half of the flow pulse, and the diastolic section being negative. Usually, there is no flow during diastole due to the closing of the aortic valve. The offset is easily rectifiable by shifting the flow wave such that mean diastolic flow is 0. Figure 3.13 shows an original flow wave and corrected flow wave.

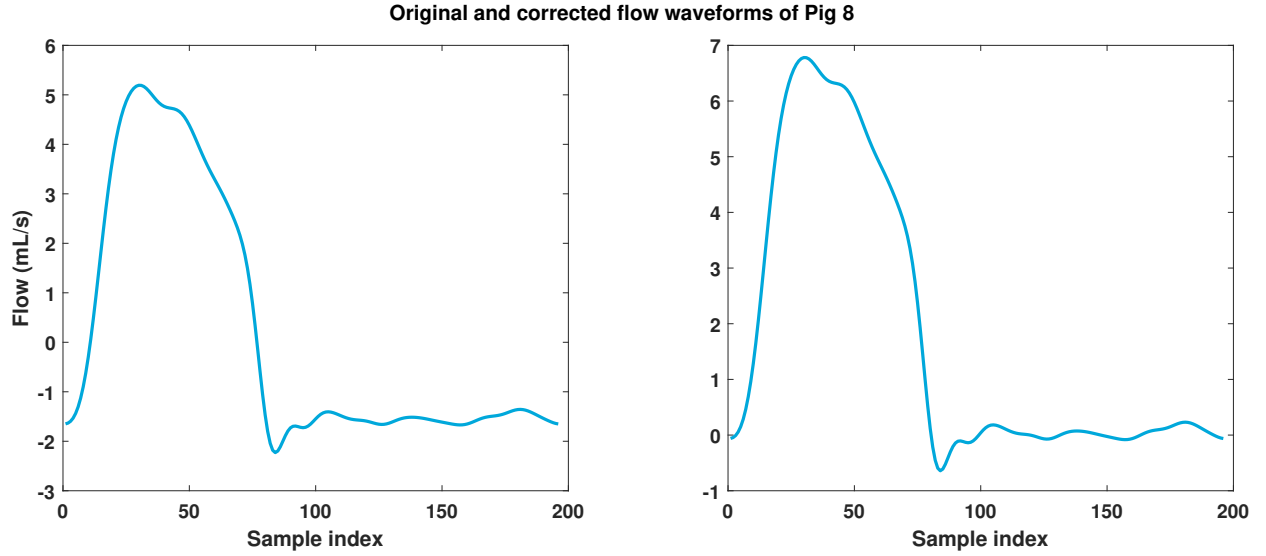


Figure 3.13: Original flow wave (left) and corrected flow wave (right) from Fig 8.

3.3.2 Beat Identification

The beat identification technique was validated through visual inspection, as well as through qualitative metrics such as sensitivity and positive predictive value (PPV). Figure 3.14 shows aortic pressure over the full PRM for each pig with identified beats. Table 3.1 shows total beats identified for each pig, incorrectly identified and missed beats, and the sensitivity and PPV of the beat detection algorithm.

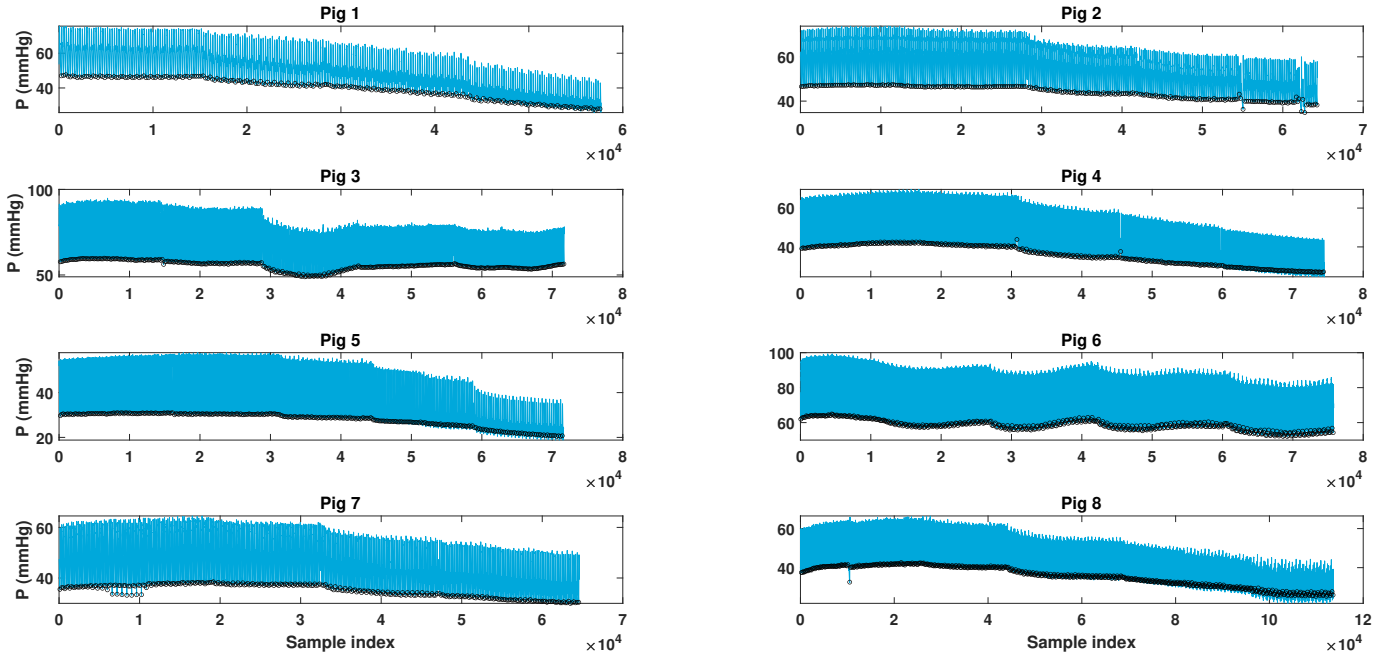


Figure 3.14: Aortic pressure for all pigs (blue) with identified beats (black).

Table 3.1: Identified beat metrics

Pig	Total beats	Misidentified beats	Missed beats	PPV (%)	Sensitivity (%)
1	234	0	0	100	100
2	285	0	0	100	100
3	368	0	0	100	100
4	384	0	1	100	99.74
5	331	0	0	100	100
6	499	1	0	99.8	100
7	316	0	0	100	100
8	574	1	0	99.83	100
	2995	2	1	99.93	99.97

The overall simplified beat detection algorithm presented was highly accurate in

its ability to accurately detect beats. The total number of beats identified for all pigs was 2995. Of those identified beats, only 2 were misidentified, and only 1 beat was missed, giving the simplified beat detection algorithm a PPV of 99.93% and a sensitivity of 99.97%. This algorithm is very lightweight, and can be used to identify beats in real time, as would be required for use in the ICU.

3.4 Summary

This chapter has presented the experimental data obtained by experiments performed at the University of Liege. The data obtained from the experiment provided left ventricle, aortic, femoral and vena cava pressure, aortic flow, left ventricle volume, and airway flow and pressure for 8 porcine subjects. Certain pigs presented erroneous measurements, but most of the data was still usable, or correctable.

A simplified beat identification algorithm was developed which can be used for rapid identification of beats from pressure waves in real time. The algorithm proved highly accurate and reliable, with a PPV and sensitivity of 99.93% and 99.97% respectively. Once sorted into beats, the data is ready to be used for cardiovascular modelling.

Chapter IV

Three Chamber Model

4.1 Introduction

The 3 chamber model is based on the work from Pironet et al [16]. It is a lumped parameter model consisting of three elastic chambers representing the left ventricle of the heart, the aorta, and the vena cava. Each of the chambers is linked by vessels, represented as resistances, and the heart valves are represented as diodes. The 3 chamber model is depicted in Figure 4.1.

This chapter presents all the components of the 3 chamber model, as well as the physiological assumptions used to derive them. To be clinically feasible, the model must be identifiable using typical clinically available measurements. Models created by Davidson *et al.* [92, 93] are used to approximate ventricular pressure and volume measurements from aortic pressure. Nominal parameter estimates were obtained from measurements where available. Where no measurements were available, parameter values from the literature were used. Parameter identification of the 3 chamber model is then performed by optimising an objective function.

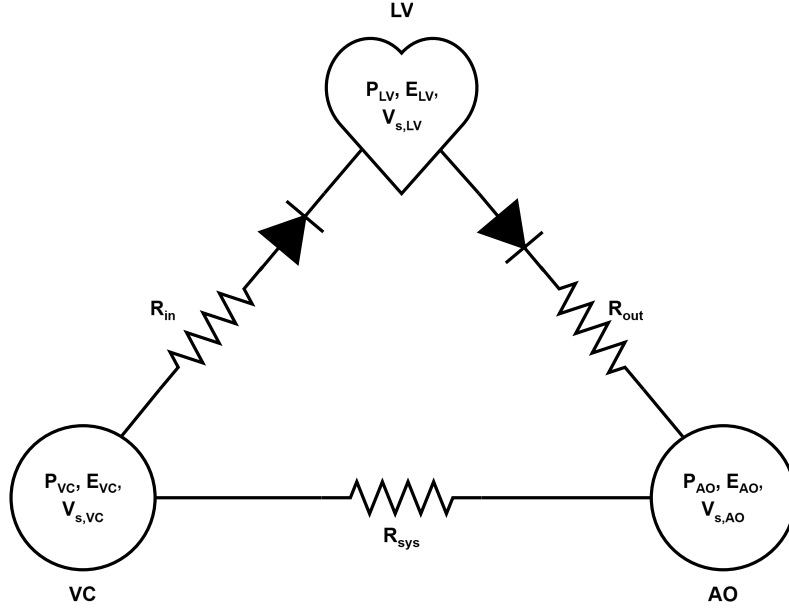


Figure 4.1: Three-Chamber CVS model. Each elastic chamber is represented by its pressure (P), elastance (E), and stressed volume (V_s). Vessels between the elastic chambers are represented as resistances (R), and the valves in and out of the heart are represented as diodes.

4.2 Model Derivations

4.2.1 Equations

The vena cava and aorta are passive chambers and are described:

$$P_{ao}(t) = E_{ao}V_{s,ao}(t) \quad (4.1)$$

$$P_{vc}(t) = E_{vc}V_{s,vc}(t) \quad (4.2)$$

Where P_{ao} and P_{vc} represent aortic and venous pressure, $V_{s,ao}$ and $V_{s,vc}$ represent the stressed volume of the aorta and vena cava, and E_{ao} and E_{vc} represent aortic

and venous elastance.

The left ventricle is an active chamber and is modelled with the time varying elastance theory. It is represented by:

$$P_{lv}(t) = e(t)E_{lv}V_{s,lv}(t) \quad (4.3)$$

Where $e(t)$ is the time varying elastance, P_{lv} represents ventricle pressure, $V_{s,lv}$ represents the stressed volume of the ventricle and E_{lv} represents end-systolic left ventricular elastance.

Systemic flow can be described using Ohm's law:

$$Q_{sys}(t) = \frac{P_{ao}(t) - P_{vc}(t)}{R_{sys}} \quad (4.4)$$

Where Q_{sys} denotes systemic flow and R_{sys} denotes systemic resistance.

Input and output flows to the heart are modelled with piecewise functions:

$$Q_{out}(t) = \begin{cases} \frac{P_{lv}(t) - P_{ao}(t)}{R_{out}} & P_{lv}(t) > P_{ao}(t) \\ 0 & \text{else} \end{cases} \quad (4.5)$$

$$Q_{in}(t) = \begin{cases} \frac{P_{vc}(t) - P_{lv}(t)}{R_{out}} & P_{vc}(t) > P_{lv}(t) \\ 0 & \text{else} \end{cases} \quad (4.6)$$

Where Q_{out} and Q_{in} denote the output and input flows, and R_{out} and R_{in} denote the output and input resistances.

The rate of change of stressed volume for each chamber is given by the difference of input and output flow:

$$\dot{V}_{s,ao}(t) = Q_{out}(t) - Q_{sys}(t) \quad (4.7)$$

$$\dot{V}_{s,vc}(t) = Q_{sys}(t) - Q_{in}(t) \quad (4.8)$$

$$\dot{V}_{s,lv}(t) = Q_{in}(t) - Q_{out}(t) \quad (4.9)$$

Summing the rate of change of stressed volumes for the system gives:

$$(Q_{out}(t) - Q_{sys}(t)) + (Q_{sys}(t) - Q_{in}(t)) + (Q_{in}(t) - Q_{out}(t)) = 0 \quad (4.10)$$

This implies the total stressed blood volume of the system remains constant, which can be shown by integrating the left hand side of the equation:

$$\int \dot{V}_{s,ao}(t) + \dot{V}_{s,vc}(t) + \dot{V}_{s,lv}(t) dt = V_{s,ao} + V_{s,lv} + V_{s,vc} = SBV \quad (4.11)$$

The parameters of the three-chamber model are summarised:

- E_{ao} - Aortic elastance
- E_{lv} - Ventricular end-systolic elastance
- E_{vc} - Venous elastance
- R_{sys} - Systemic resistance
- R_{in} - Input resistance
- R_{out} - Output resistance
- SBV - Total stressed blood volume

4.2.2 Driver Function Model

Using the time varying elastance from Equation 4.3, the driver function of the left ventricle can be defined:

$$e(t) = \frac{P_{lv}(t)}{V_{lv}(t) - V_u} \quad (4.12)$$

where V_u is the unstressed volume in the left ventricle.

The driver function is used to drive the 3 chamber model and contains crucial information pertaining to the cardiac cycle. However, measurements of left ventricle pressure and volume are not available in the ICU, as they are highly invasive. Thus, a modelled equivalent based on the work of Davidson *et al* [92] is employed. This model recreates the pressure and volume waveforms from other clinically available measurements and simple physiological assumptions.

To reconstruct the left ventricle pressure waveform, the aortic valve resistance is assumed to be negligible, implying $P_{lv} = P_{ao}$ during systole with some small amount of phase lag. During diastole, no information about P_{lv} can be extrapolated from P_{ao} . However, the left ventricle is largely passive during diastole. Thus, the relaxation and filling phases can be modelled as an exponential decay and rise respectively. The P_{lv} waveform can thus be reconstructed using the following piecewise function:

$$P_v(t) = \begin{cases} P_{ao}(t_1 + \delta < t < t_2 + \delta) & t_1 < t < t_2 \\ 6 + (P_{ao}(t_2) - 6)e^{-17.5(t-t_2)} & t_2 < t < t_3 \\ P_{lv}(t_3) + (P_{ao}(t_4) - P_{lv}(t_3))e^{37.5(t-t_4)} & t_3 < t < t_4 \end{cases} \quad (4.13)$$

where $\delta = 0.08s$ and:

$$t_1 = t \left(\frac{dP_{ao}}{dt}_{max} \right)_n \quad (4.14)$$

$$t_2 = t \left(\frac{dP_{ao}}{dt}_{min} \right)_n \quad (4.15)$$

$$t_3 = 0.62t_2 + 0.38t_4 \quad (4.16)$$

$$t_4 = t \left(\frac{dP_{ao}}{dt}_{max} \right)_{n+1} \quad (4.17)$$

where $t(\dots)_n$ denotes the current beat, and $t(\dots)_{n+1}$ denotes the next beat. These timing positions are illustrated in Figure 4.2.

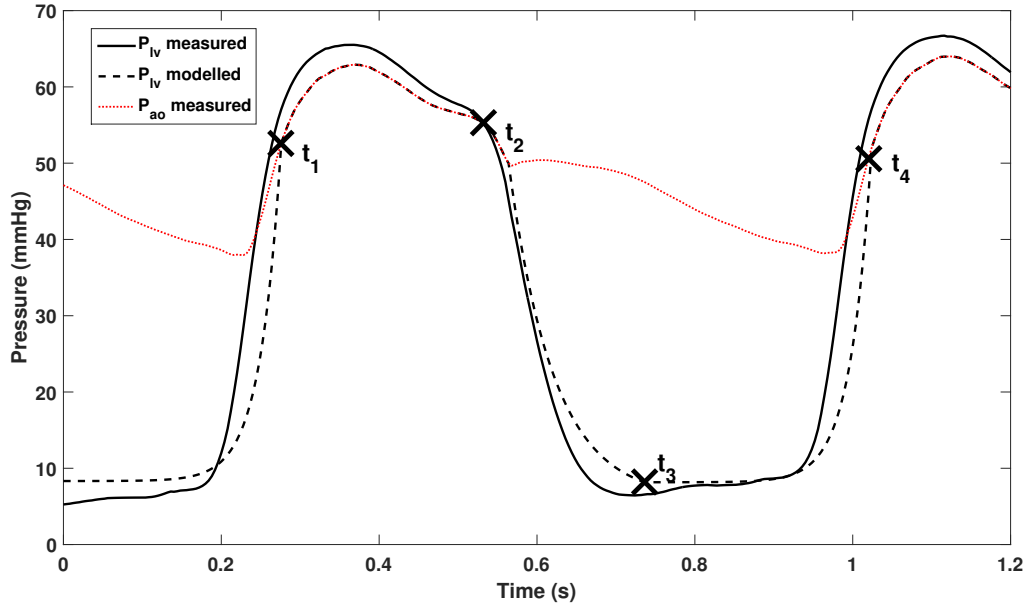


Figure 4.2: Estimated P_{lv} derived from P_{ao} timings.

The V_{lv} waveform is reconstructed using piecewise phase-shifted sine waveforms in conjunction with 3 timings from the aortic pressure wave, and four pieces of

volume information, V_{ES} , V_{ED} , SV and V_u . SV can be measured in the ICU through PiCCO, and V_{ES} can be measured intermittently in an ICU using an echocardiogram. V_u can be estimated as a fraction of V_{ES} [94]:

$$V_u = 0.48V_{ES} \quad (4.18)$$

Since readings of V_{ES} can only happen intermittently, baseline values are measured, and simple models are used to track V_{ES} until further readings are acquired. V_{ES} can be derived using the ESPVR:

$$P_{es} = E_{ES}(V_{ES} - V_0) \quad (4.19)$$

where V_0 is the ventricle volume at zero pressure. Since $V_0 \approx V_u$, and assuming that $P_{ao} = P_{lv}$ when the aortic valve closes, the following equation can be obtained from Equation 4.19:

$$P_{DN} = E_{ES}(V_{ES} - V_u) \quad (4.20)$$

where P_{DN} is the dicrotic notch pressure.

Davidson *et. al.* showed E_{ES} can be approximated as the product of an elastic coefficient, E_c , and a cubic heart rate term:

$$E_{ES} = E_c HR^3 \quad (4.21)$$

This elastic coefficient can be calculated once from baseline V_{ES} . First, E_{ES} is calculated using Eq. 4.20, and E_c is calculated from E_{ES} using Eq. 4.21. E_c is held constant, and the cubic HR term is used to track E_{ES} evolution between measurements. E_c is recalculated when a new V_{ES} measurement is obtained.

Subsequent estimations of V_{ES} are then made on a beat to beat basis:

$$V_{ES} = \frac{P_{DN}}{E_c \times HR^3} + V_u \quad (4.22)$$

Finally, V_{ED} can be calculated from V_{ES} and SV:

$$V_{ED} = V_{ES} + SV \quad (4.23)$$

These four pieces of volume information can then be used in conjunction with 3 aortic pressure timings to recreate the left ventricular volume waveform:

$$V_{lv} = \begin{cases} (V_{ED})_n + ((V_{ES})_n - (V_{ED})_n) \sin\left(\frac{\pi(t-t_1)}{2(t_2-t_1)}\right) & t_1 < t < t_2 \\ (V_{ES})_n + ((V_{ED})_{n+1} - (V_{ED})_n) \left(\frac{1}{2} \cos\left(\frac{\pi(t-t_2)}{(t_3-t_2)}\right) - \frac{1}{2}\right) & t_2 < t < t_3 \end{cases} \quad (4.24)$$

where:

$$t_1 = t(P_{ao_{min}})_n \quad (4.25)$$

$$t_2 = t(P_{DN})_n \quad (4.26)$$

$$t_3 = t(P_{ao_{min}})_{n+1} \quad (4.27)$$

The timing details of the V_{lv} waveform are shown in Figure 4.3.

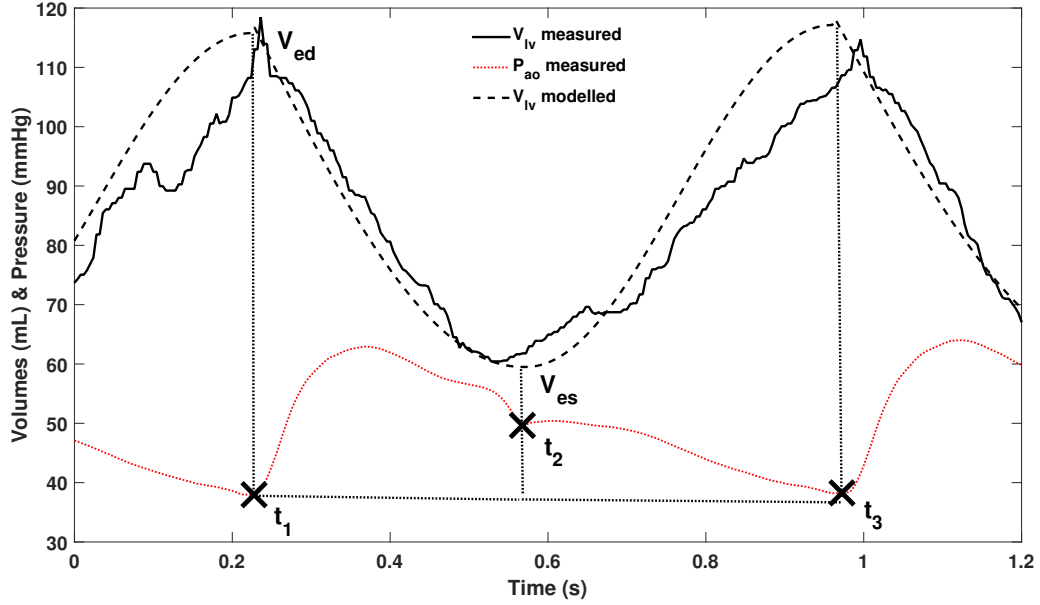


Figure 4.3: Estimated V_{lv} derived from P_{ao} timings.

4.3 Parameter Identification

Parameter identification is performed through iterative adjustment of parameter values from a set of initial conditions to minimise an objective function. The objective function is comprised of a set of error metrics derived from measurement data, with the ultimate goal of identifying a parameter set yielding model outputs that best fit measurement data.

4.3.1 Nominal Parameters

Optimisation problems can be highly sensitive to initial parameter estimates. Two different nominal parameter sets may produce two very different identified parameter sets due to the non-convexity and identifiability of the problem [95, 96]. To provide a best guess for an initial parameter set, nominal parameters are calculated from measurement data where possible, and in the case where measurement data is unavailable, literature values are used.

4.3.1.1 Systemic Resistance

Systemic resistance is the overall resistance of the systemic circulation. It is calculated using Eq. 4.4. However, flow waveforms are not available in a clinical setting. This can be solved by integrating both sides of the equation over a cardiac cycle:

$$\int_0^T Q_{sys}(t) dt = \frac{\int_0^T (P_{ao}(t) - P_{vc}(t)) dt}{R_{sys}} \quad (4.28)$$

The integral of systemic flow over one cardiac cycle is equal to SV, and the integral of a pressure wave over a single cardiac cycle is equal to the mean pressure multiplied by the period of the cardiac cycle, T . Systemic resistance can be solved:

$$R_{sys} = \frac{\bar{P}_{ao}(t) - \bar{P}_{vc}(t)}{SV} T \quad (4.29)$$

4.3.1.2 Input and Output Resistance

The input and output resistances can be found using a similar method to the finding of systemic resistance. However, input resistance can only be calculated over the filling period, since flow into the ventricle only occurs during filling. Similarly, output resistance can only be calculated during ejection, since flow out of the ventricle only occurs during ejection. Integrating over the respective filling and ejection periods yields:

$$\int_F Q_{in}(t) dt = \frac{\int_F (P_{vc}(t) - P_{lv}(t)) dt}{R_{in}} \quad (4.30)$$

$$\int_E Q_{out}(t) dt = \frac{\int_E (P_{lv}(t) - P_{ao}(t)) dt}{R_{out}} \quad (4.31)$$

where F and E represent the filling and ejection period respectively. The integral

of the flow into the ventricle during filling and out of the ventricle during ejection is equal to stroke volume. Input and output resistance can thus be solved:

$$R_{in} = \frac{\int_F (P_{vc}(t) - P_{lv}(t)) dt}{SV} \quad (4.32)$$

$$R_{out} = \frac{\int_E (P_{lv}(t) - P_{ao}(t)) dt}{SV} \quad (4.33)$$

4.3.1.3 Aortic Elastance

Aortic elastance can be found by fitting an exponential curve to the diastolic section of the aortic pressure wave. During diastole, there is no inflow to the aorta from the ventricle, and the rate of change of aortic volume is equal to the inverse of systemic flow, since flow into the systemic circulation is equal to flow leaving the aorta:

$$\dot{V}_{s,ao}(t) = - \left(\frac{P_{ao}(t) - P_{vc}(t)}{R_{sys}} \right) \quad (4.34)$$

Substituting in the P-V relationship for aortic pressure from Eq. 4.1, the aortic volumetric rate can be defined:

$$\dot{V}_{s,ao}(t) = - \frac{E_{ao}}{R_{sys}} V_{s,ao}(t) + \frac{P_{vc}(t)}{R_{sys}} \quad (4.35)$$

This is a simple differential equation, which when solved, yields:

$$V_{s,ao}(t) = V_{s,ao}(t_{BD}) e^{\left(-\frac{E_{ao}}{R_{sys}}(t-t_{BD})\right)} + \frac{P_{vc}(t)}{E_{ao}} \quad (4.36)$$

where t_{BD} marks the beginning of diastole. By multiplying both sides of the equa-

tion by aortic elastance, the equation can be written in terms of aortic pressure:

$$P_{ao}(t) = P_{ao}(t_{BD})e^{\left(-\frac{E_{ao}}{R_{sys}}(t-t_{BD})\right)} + P_{vc}(t) \quad (4.37)$$

where the vena cava pressure, P_{vc} , is the downstream pressure of aortic pressure according to the model. In reality, the downstream pressure would be mean circulatory pressure [97].

Fitting the exponential to aortic pressure yields the exponential coefficient $\frac{-E_{ao}}{R_{sys}}$, and using the previously found R_{sys} , E_{ao} can be identified. Figure 4.4 shows the fitting of an exponential to the diastolic section of the aortic pressure wave.

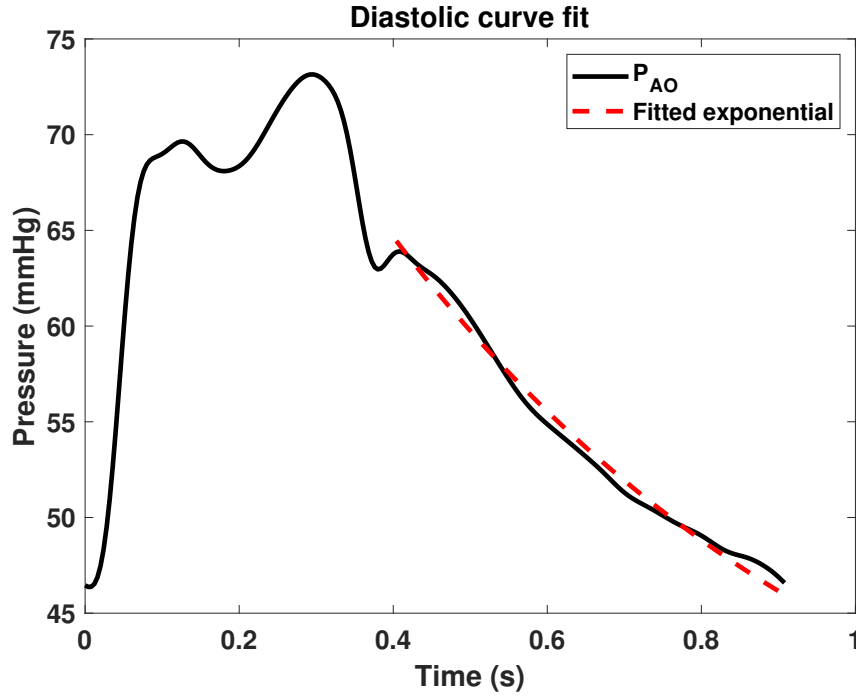


Figure 4.4: Exponential curve (red dashed) fitted to the diastolic section of the aortic pressure wave (black solid).

4.3.1.4 Left Ventricle End-Systolic Elastance

End-systolic left ventricular elastance (E_{LV}) is calculated directly from the left ventricle pressure and stressed volume as the maximum value of the P-V ratio over a cardiac cycle:

$$E_{lv} = \max \left(\frac{P_{lv}(t)}{V_{s,lv}(t)} \right) \quad (4.38)$$

4.3.1.5 Vena Cava Elastance

During systole, there is no flow from the vena cava into the left ventricle. The rate of change of vena cava volume is thus governed by systemic flow:

$$\dot{V}_{s,vc}(t) = Q_{sys}(t) \quad (4.39)$$

Flow into the vena cava from the systemic circulation is roughly constant, as the pressure pulse greatly diminishes when passing through small arterioles and capillaries. The volumetric rate can thus be assumed linear. Assuming systole takes roughly half the time of the cardiac period, the total inflow into the vena cava during systole is $SV/2$. Using $SV/2$ as the change in volume, and $T/2$ as the period, the volumetric rate is defined:

$$\dot{V}_{s,vc}(t) = \frac{SV}{T} \quad (4.40)$$

Multiplying both sides of the equation by vena cava elastance yields:

$$\dot{P}_{vc}(t) = E_{vc} \frac{SV}{T} \quad (4.41)$$

Integrating both sides of the equation over systole yields:

$$P_{vc}(t_{ES}) - P_{vc}(t_{BS}) = E_{vc} \frac{SV}{T} (t_{ES} - t_{BS}) \quad (4.42)$$

Where t_{ES} and t_{BS} are the end and beginning of systole respectively. Finally, assuming $P_{vc}(t_{ES}) - P_{vc}(t_{BS}) \approx \Delta P_{vc}(t)$ and $t_{ES} - t_{BS} = T/2$, vena cava elastance is obtained:

$$E_{vc} = \frac{2\Delta P_{vc}}{SV} \quad (4.43)$$

4.3.1.6 Total Stressed Blood Volume

Total SBV is taken as the summation of the approximate SBV of each individual chamber. For the ventricle, the stressed volume is taken as the mean of the stressed ventricular volume waveform. For the aortic and vena cava chamber, stressed volume is given by the mean pressure divided by the initial elastance estimate:

$$SBV = \bar{V}_{s,lv} + \frac{\bar{P}_{ao}}{E_{ao}} + \frac{\bar{P}_{vc}}{E_{vc}} \quad (4.44)$$

4.3.2 Output Vector

Model outputs were chosen as clinically relevant beat-to-beat metrics, rather than time dependent measurements. This choice is largely due to the fact the temporal evolution of all signals is not always available or exportable from bedside machines [14, 28]. As such, only beat-to-beat data, such as mean pressures and pulse pressures, are assumed to be available, where these values are also clinically used over the waveforms themselves.

Outputs were chosen to ensure structural identifiability [95, 96, 98, 99]. The work by Pironet lists the model outputs required to ensure structural identifiability of the CVS model [14, 16]. Means and ranges of available signals are used, as well as

the peak derivative of aortic pressure, which is an index of contractility [100] and has been linked to the identifiability of output resistance [101]. Thus, the output vector is defined:

$$X_{output} = [\bar{P}_{ao}(t), \Delta P_{ao}(t), \bar{P}_{vc}(t), \Delta P_{vc}(t), \bar{V}_{lv}(t), SV, \max(dP_{ao}(t)/dt)] \quad (4.45)$$

where $\bar{}$ denotes the mean of a signal, Δ denotes the range of a signal, $\max(dP_{ao}(t)/dt)$ is the maximum gradient of the aortic pressure during a single beat.

4.3.2.1 Objective Function

The objective function is a measure of accuracy for identified model outputs. It is defined as the error between the output vector of the model and the measurement data. If y^{ref} is a vector containing the N_y reference measurements and $y(p)$ is the output vector of parameter vector, p , each output's error is defined as the difference between the measurement and the output:

$$e_i(p) = y_i^{ref} - y_i(p), \quad i \in [1, N_y] \quad (4.46)$$

A percentage error is not used, since waveforms like vena cava pressure have much smaller values (2 - 10mmHg), and even small deviations from measurements result in large percentage changes. Since all outputs in the output vector are expected to have similar error ranges, simply using the difference between reference measurements and the output vector provides an approximately equal balance between all error metrics.

The error function is then defined using the RMS of all errors:

$$\psi(p) = \sqrt{\frac{\sum_{i=1}^{N_y} e_i(p)^2}{N_y}} \quad (4.47)$$

4.3.2.2 Practical Identifiability of Input Resistance

For many of the pigs, vena cava pressure was often lower than left ventricular pressure over the entire cardiac cycle. While this difference is physiologically possible, since the vena cava feeds into the right circulation of the CVS, and vena cava pressure only needs to be larger than right ventricular diastolic pressure not left ventricular diastolic pressure, it would prevent blood circulation from the vena cava to the left ventricle for the 3 chamber model. Consequently, this issue would cause the optimisation process to continually reduce R_{in} in an attempt to restore normal ventricular filling, breaking the model. Figure 4.5 shows two sets of waveforms, one where vena cava pressure exceeds left ventricular diastolic pressure, and one where it does not.

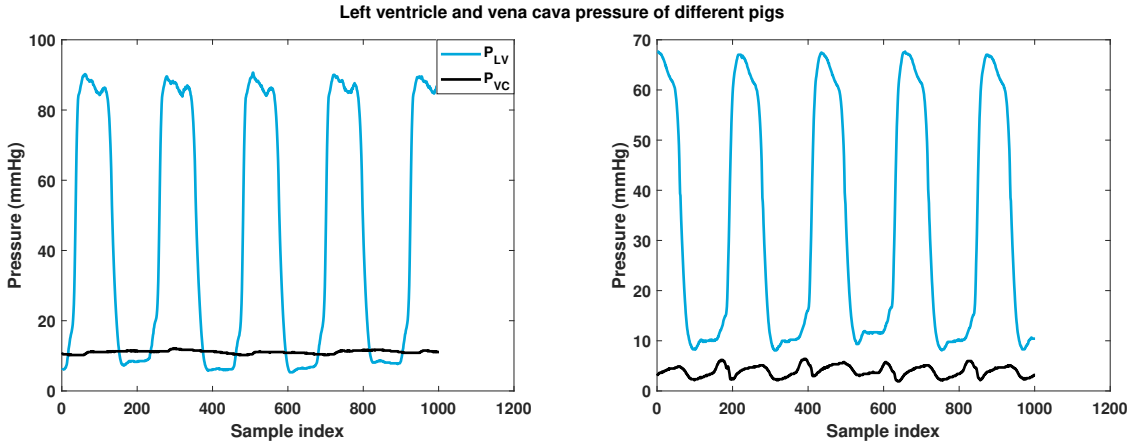


Figure 4.5: Left ventricular and vena cava pressure from different pigs. The figure on the left shows a case where vena cava pressure rises above left ventricular diastolic pressure, while the right shows an instance where vena cava fails to rise above left ventricular pressure at any point.

To alleviate this problem, the model driver function was normalised to have a minimum value of 0. A minimum value of 0 in the driver function results in

model output left ventricle pressure having a minimum value of 0mmHg. While physiologically inaccurate, it ensures vena cava pressure will always exceed left ventricular pressure during diastole, and normal ventricular filling can occur. The only effect this change has on identified parameters is a slight augmentation of R_{in} to compensate for the larger pressure delta which now exists between vena cava pressure and diastolic left ventricular pressure.

4.3.2.3 Parameter Identification

The parameter identification in this work was performed using MATLAB's (The Mathworks, Natick, MA, USA) *fmincon* function. The parameter set and error function were passed as parameters.

4.4 Results and Discussion

4.4.1 Driver function

The results of the modelled driver function are shown in Figures 4.6 - 4.8. Figure 4.6 shows the modelled and measured left ventricular volume, Figure 4.7 shows modelled and measured left ventricular pressure. Finally, Figure 4.8 shows modelled and measured driver functions.

Note, modelled left ventricular volume for Pig 3 is significantly different to measured volume. Pig 3's left ventricular volume measurements were erroneous, and the modelled volume did not use the end-systolic volume from the measured wave, but rather from the regression model of ESV and SV. The large difference between the volume waveforms also caused the modelled driver function of Pig 3 to be more significantly different from its measured counterpart relative to other pigs.

Modelled driver functions were normalised to have a 0 minimum value so the simulated left ventricular pressure from the 3 chamber model would always have a minimum value of 0, regardless of identified left ventricular end systolic elastance.

This ensured simulated vena cava pressure always rose above left ventricular diastolic pressure, ensuring input resistance remained identifiable.

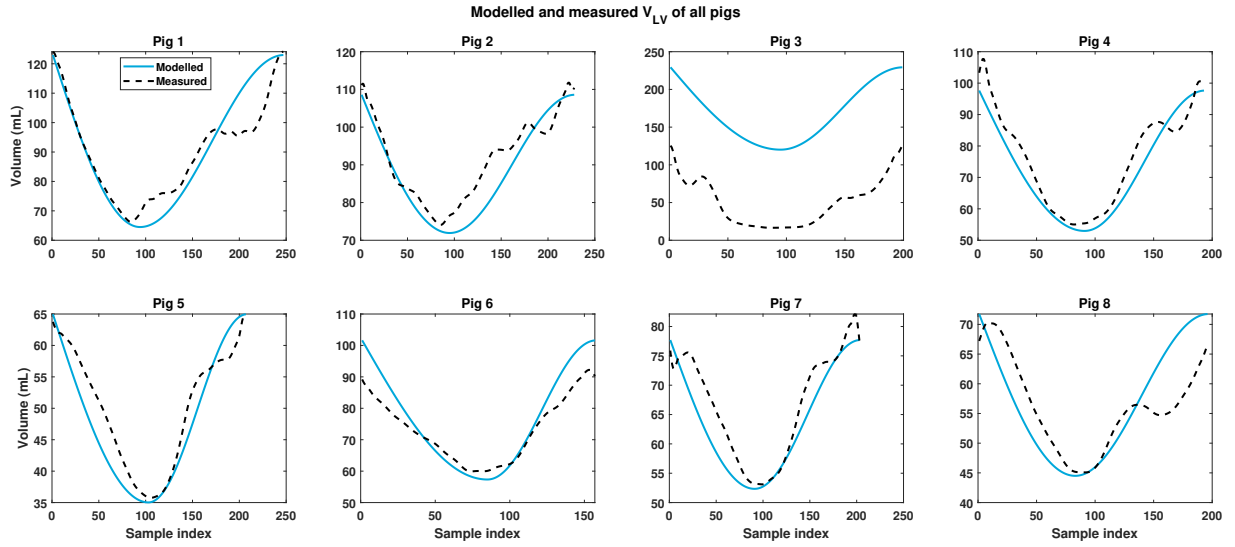


Figure 4.6: Modelled and measured equivalent left ventricular volume for all pigs. Modelled waves are shown in blue while measured waves are shown in black.

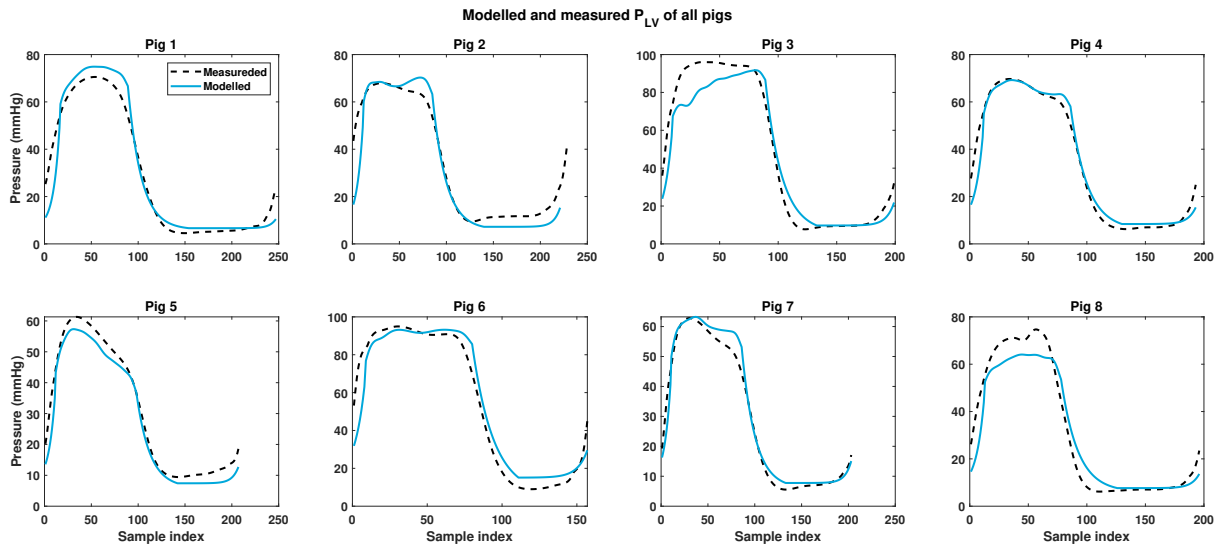


Figure 4.7: Modelled and measured equivalent left ventricular pressure for all pigs. Modelled waves are shown in blue while measured waves are shown in black.

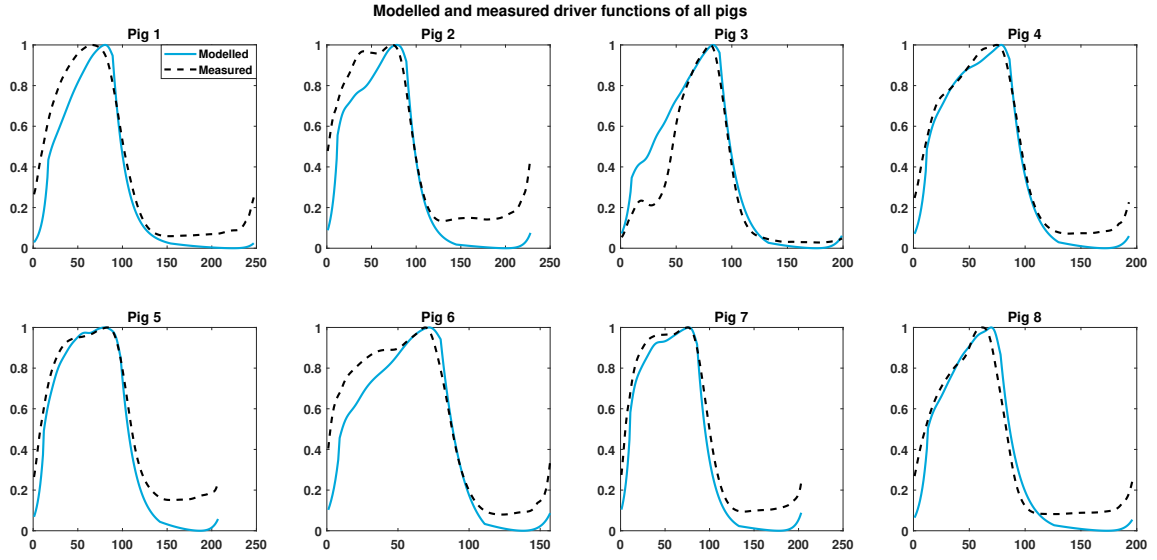


Figure 4.8: Modelled and measured equivalent driver functions for all pigs. Modelled driver functions are shown in blue while measured drivers are shown in black.

4.4.2 3 Chamber Model Outputs and Parameters

The 3 chamber model was used to identify haemodynamic parameters of all pigs. To validate the model, model outputs, errors and identified parameters were inspected. Figure's 4.9 and 4.10 show the aortic and left ventricular model outputs plotted alongside their respective measured waveforms for each pig. Dicrotic notches do not present in modelled aortic pressure because the model does not incorporate back flow into the valves. Furthermore, the modelled left ventricular diastolic pressure always reaches 0, unlike its measured counterpart. This difference occurs because the modelled driver function was normalised to have a minimum diastolic value of 0.

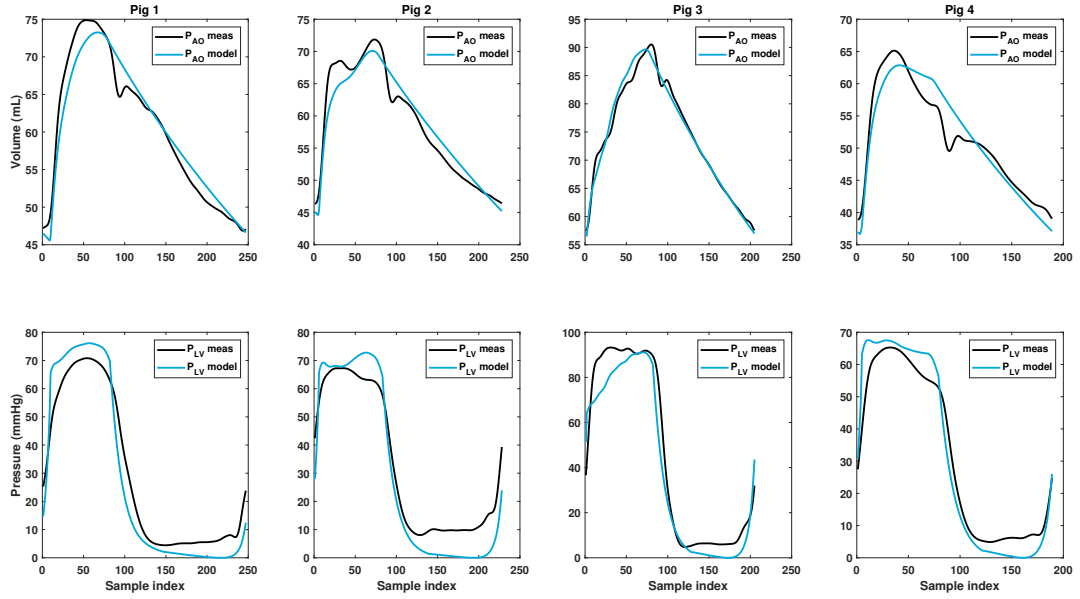


Figure 4.9: Measured and modelled aortic and left ventricle pressure waveform results from single beats for Pigs 1-4.

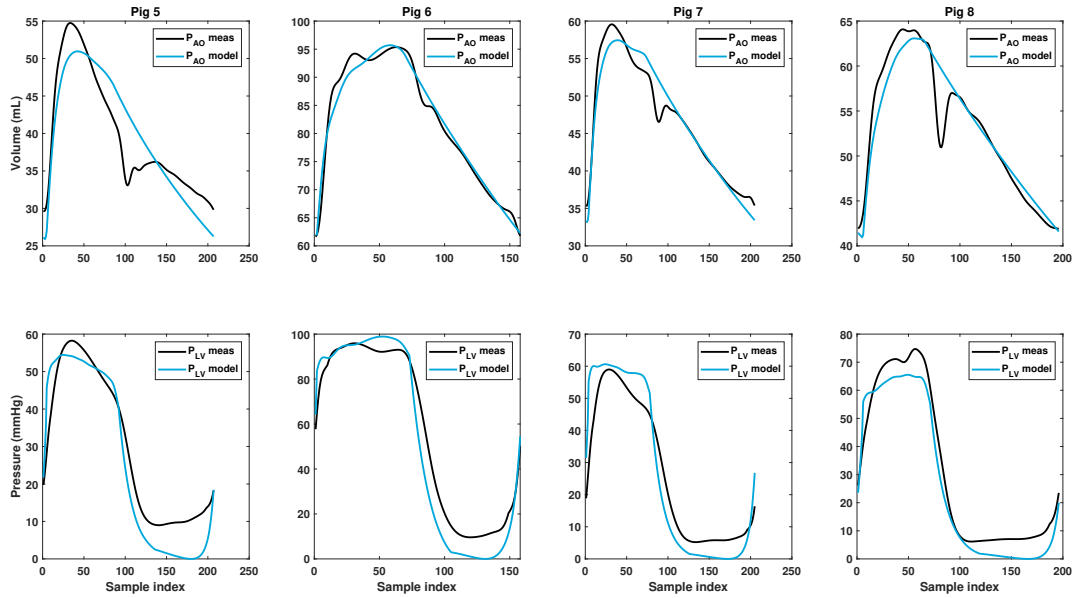


Figure 4.10: Measured and modelled aortic and left ventricle pressure waveform results from single beats for Pigs 5-8.

Figure 4.11 shows the measured and modelled left ventricular volume for all pigs from a single beat. Note, the volume measurements used are those derived from the driver function model, since full left ventricular volume waveform measurements are not available in the ICU. However, E_{SV} and SV are generally available in the ICU, where E_{SV} can be obtained intermittently through an echocardiogram and SV can be obtained continuously through PiCCO or intermittently via thermodilution.

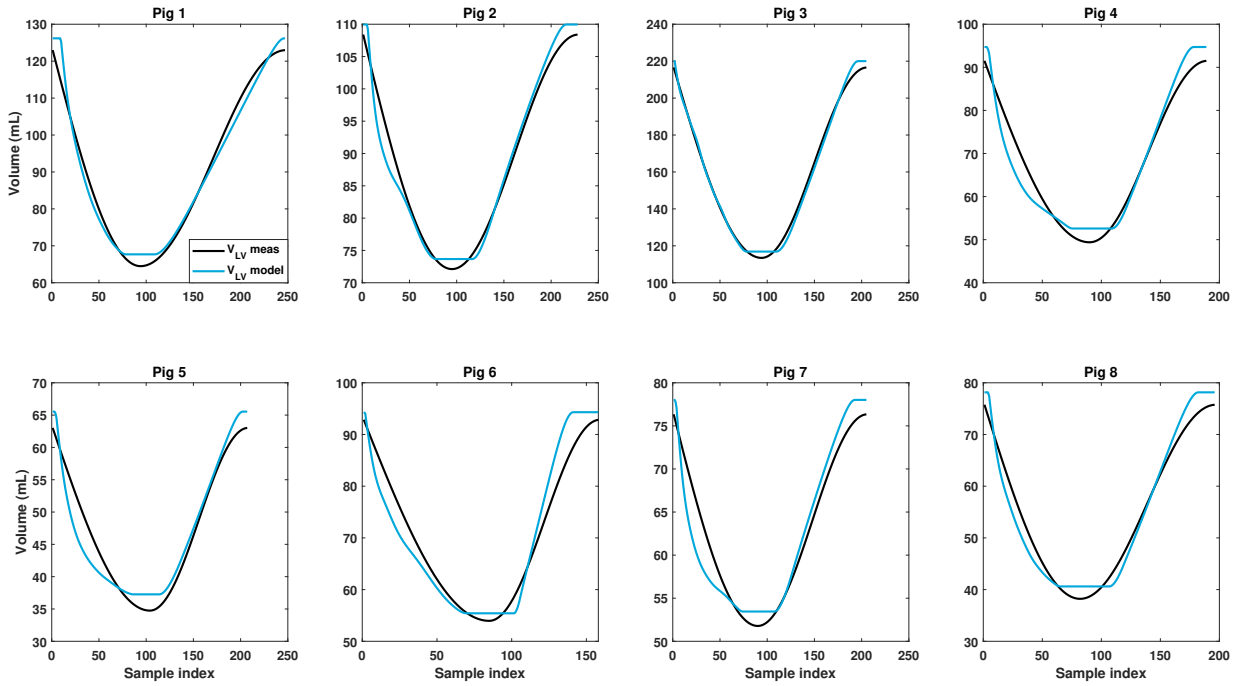


Figure 4.11: Waveform results from single beats. Modelled left ventricular volume (blue) is plotted alongside measured left ventricle volume (black) for all pigs.

The model outputs shown in Figure's 4.9 - 4.11 closely match their measured equivalents, illustrating the 3 chamber model's ability to accurately and reliably capture system dynamics. This is further emphasized by the left ventricle pressure shown in Figures 4.9 and 4.10. The left ventricle pressure is accurately recreated by the 3 chamber model, despite not being part of the objective function.

Since the 3 chamber model does not incorporate the respiratory system, it cannot

accurately capture the effects of cardiopulmonary interactions on the CVS. This is primarily evident in model outputs, as dynamic indices, such as PPV and SVV remain static over the PRM, where they would usually be shifting significantly. Figure 4.12 demonstrates a section of aortic pressure from Fig 8 where PEEP was set to $20\text{cmH}_2\text{O}$. The measured waveform shows large variations in aortic pressure, where the modelled output displays no variation, and fails to capture these dynamics.

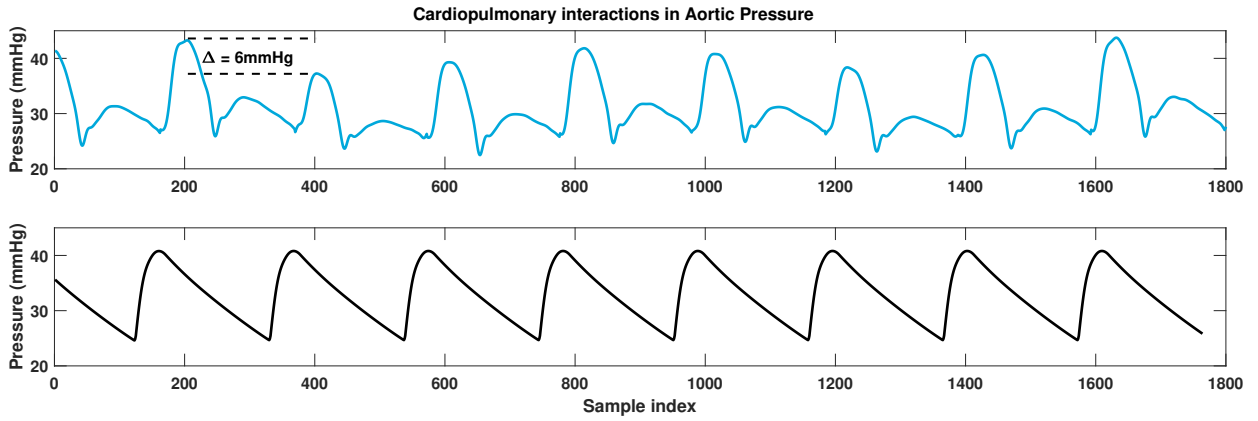


Figure 4.12: Measured (top) and modelled (bottom) aortic pressure from Fig 8 where PEEP was set to $20\text{cmH}_2\text{O}$. The delta of 6mmHg between peak values is shown between two black dashed lines.

The omission of cardiopulmonary interactions may limit the model's predictive ability, particularly in its ability to predict how increased PEEP in MV may affect overall system dynamics. However, the model was not designed to be used for its predictive ability, but rather to be used to identify SBV, and determine the fluid responsiveness of a patient.

Figure 4.13 shows the model errors over the course of the PRM. The error throughout the course of the PRM remains very low, with a highest observed error of 6×10^{-4} , emphasising the model's ability to accurately fit measurements and identify haemodynamic parameters. Furthermore, the error remains stable over the course of the PRM, where haemodynamic waveforms are shifting more rapidly than usual, further emphasising the model's reliability over a changing cardiovascular state.

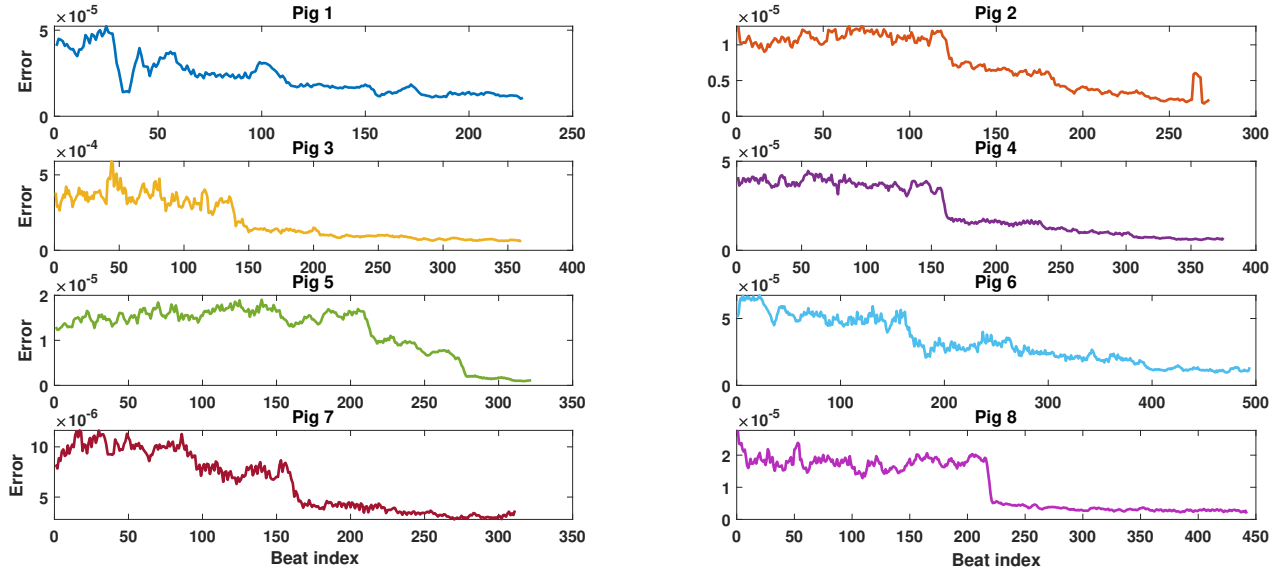


Figure 4.13: Model errors for all beats over the entire PRM for each pig.

Figures 4.14 - 4.16 show identified parameters over the PRM for all pigs. Figure 4.14 shows aortic elastance, left ventricular elastance and systemic resistance, Figure 4.15 shows vena cava elastance, input resistance and output resistance, and Figure 4.16 shows the identified SBV for all pigs.

The identified parameters display relatively smooth trends over the course of the PRM, with minimal beat-to-beat jumps between identified parameters. The mechanisms through which MV affects the cardiovascular system is highly patient specific and not clearly understood, thus trends for most parameters are not predictable or expectable. This lack of predictable trends is particularly evident when observing left ventricular and aortic elastance, and systemic resistance seen in Figure 4.14. For some pigs, the elastance and resistance remains stable over the PRM, whereas some decrease, and some increase. The change in state is highly dependent on a patient's current cardiovascular and respiratory state at the time of MV.

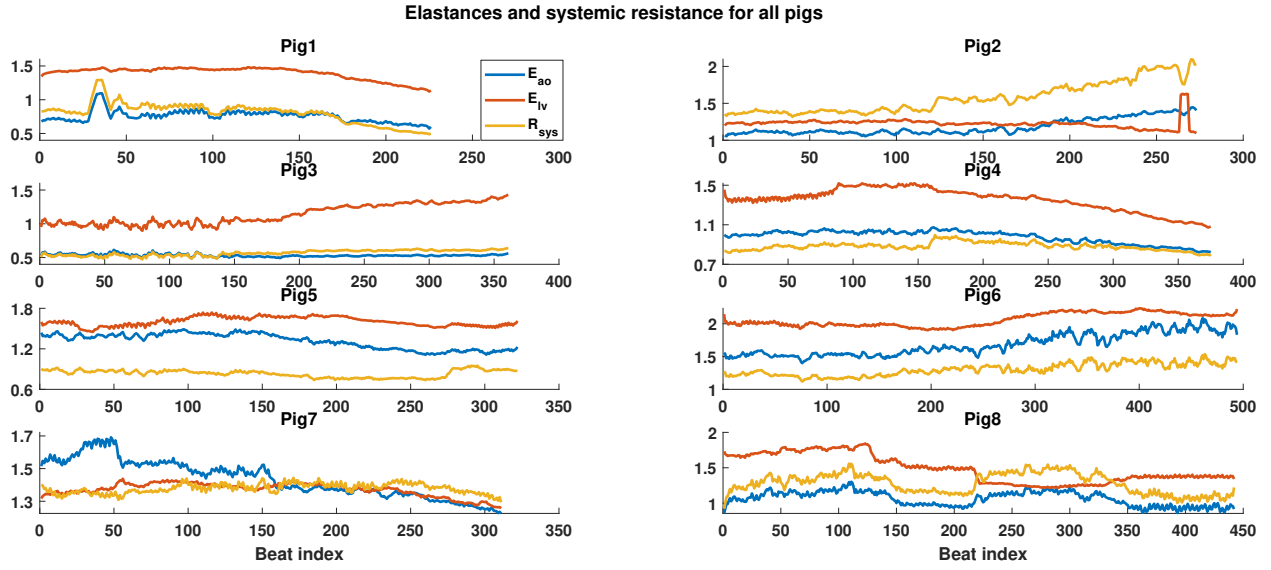


Figure 4.14: Identified aortic and left ventricular elastance, and systemic resistance for all pigs. Elastance is shown in mmHg/mL and resistance is shown in mmHg/(mL/s).

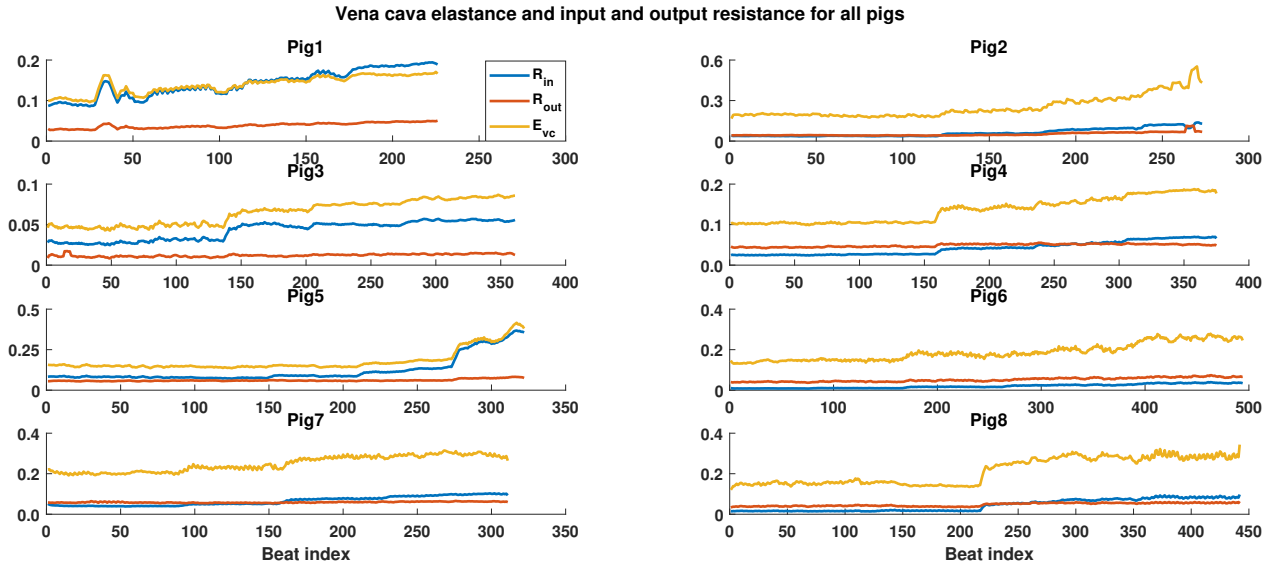


Figure 4.15: Identified input and outputs resistance, and vena cava elastance for all pigs. Elastance is shown in mmHg/mL and resistance is shown in mmHg/(mL/s).

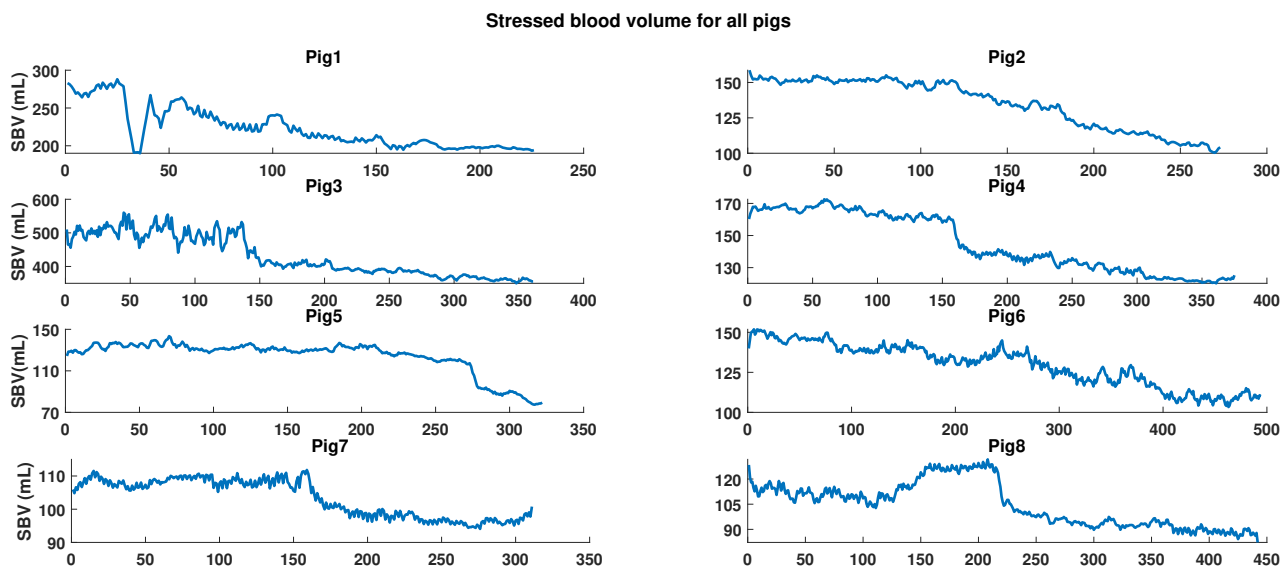


Figure 4.16: Identified stressed blood volume for all pigs.

However, other parameters displayed a more consistent trend across all pigs, with input and output resistance, and vena cava elastance gradually increasing over the course of the PRM for all Pigs, as shown in Figure 4.15. While these parameter trends may reflect the mechanisms by which SV is being diminished over the course of the PRM, the 3 chamber model does not incorporate cardiopulmonary interactions, and thus the interpretation of parameter trends may not be entirely meaningful, particularly as PEEP increases and cardiopulmonary interactions become increasingly present.

However, the 3 chamber model is a highly simplified lumped sum model, designed to capture overall system dynamics, and guide fluid therapy. While it is unlikely identified parameters are truly accurate without cardiopulmonary interactions, the model is still highly successful in its intended purpose of accurately capturing fundamental system dynamics. It thus remains a strong candidate for diagnostic purposes in the ICU.

Finally, as expected, SBV shows a marked decrease over the course of the PRM. Increasing PEEP is known to reduce SBV. Furthermore, SV is known to be highly

correlated with SBV [16, 102]. The model was able to accurately capture this relationship. Figure 4.17 shows linear regression fit to SV and SBV for each pig, illustrating the model's ability to capture this important system dynamic, which is often used in making care decisions, when available. The results of the linear regression fit are shown in Table 4.1.

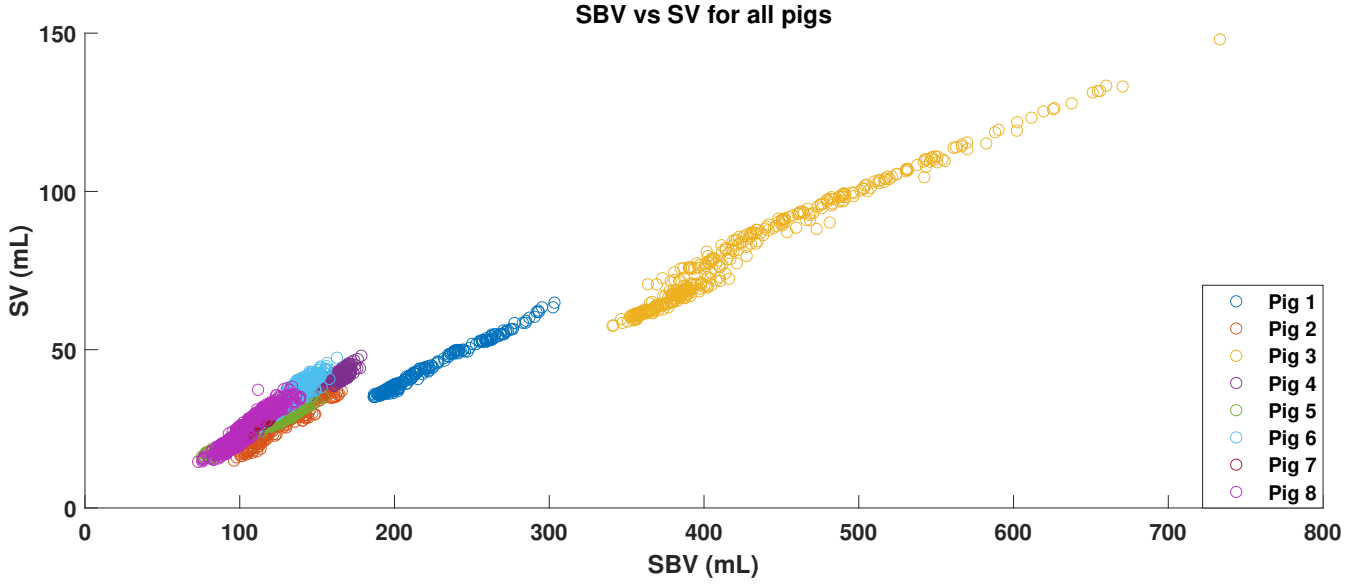


Figure 4.17: SBV vs SV for all pigs.

Table 4.1: Linear regression of SBV and SV

Pig	Gradient	Intercept	r^2
1	0.25	-11.45	0.991
2	0.36	-19.25	0.945
3	0.25	-26.92	0.970
4	0.35	-14.79	0.974
5	0.27	-6.08	0.959
6	0.40	-17.57	0.940
7	0.42	-19.62	0.884
8	0.39	-16.83	0.895

SBV is the most important parameter in the model, and the model has been repeatedly validated in its ability to identify this important parameter [14, 16, 102, 103]. However, the reliability over changing PEEP conditions has not yet been explored. Here, the model has proven its ability to reliably identify this important parameter over the course of a PRM, further emphasising the model's reliability in identifying parameters despite not incorporating cardiopulmonary parameters. Though the extent of the model's accuracy cannot be fully validated without comparison to a model which is able to accurately incorporate pulmonary dynamics.

4.5 Limitations

The 3 chamber model is a highly simplified lump sum model. Thus, it makes use of several simplifying assumptions which are not entirely physiologically accurate. Most notably, it excludes the entire right circulation of the CVS. The right circulation is responsible for carrying deoxygenated blood to the lungs and returning oxygenated blood back to the heart. However, the right circulation accounts for a very small portion of the CVS, only containing roughly an eighth of the amount of blood as the systemic circulation [9]. Furthermore, despite the omission of the pulmonary circulation, the 3 chamber model is still able to accurately and reliably capture overall CVS dynamics.

Furthermore, since the pulmonary circulation is omitted, the 3 chamber model uses vena cava pressure as the upstream pressure to left ventricular pressure, and thus, venous pressure governs filling into the left ventricle during diastole. For filling to occur, vena cava pressure would have to rise above left ventricular diastolic pressure. However, the actual upstream pressure of the left ventricle is pulmonary venous pressure. Thus, it is not necessarily true that venous pressure should rise above left ventricular diastolic pressure. This was easily rectified by using a normalised driver function, ensuring left ventricular diastolic pressure was always 0.

While it may seem more intuitive to use pulmonary venous pressure as the left

ventricle's upstream pressure, these measurements are not available in the ICU. Furthermore, according to the most widely adopted understanding of the CVS, the Guytonian view, venous pressure acts as the main driving force for the circulatory system [9, 104]. Thus, in using venous pressure as the upstream pressure of the left ventricle, the model is in fact more physiologically accurate in capturing the overall system dynamics despite not using the true upstream pressure for the left ventricle.

A further simplification of the model is it does not include the left atrium. At the end of filling, the atria contract, ejecting an extra portion of blood into the ventricles. Like the ventricles, the atria contract to eject blood, though the contraction is much smaller than ventricle contractions, and atrial contractions are only responsible for a small portion of filling [9]. Thus, filling can still be accurately represented as a passive process from the veins to the ventricles. Furthermore, unlike the ventricles, the time varying elastance theory has not been successfully applied to the atria [104]. Some studies have modelled the atria using more complicated multi-scale models [105]. However, the large number of additional parameters required would make such a model infeasible in an ICU setting.

The 3 chamber model also cannot account for cardiopulmonary interactions. The heart lies within the thoracic cavity, surrounded by the lungs. During respiration, the lungs physically press against the heart, as well as causing pressure changes within the thoracic cavity. This issue is especially present during PPV and PEEP, where the sustained positive pressure within the thoracic cavity causes a marked decrease in SV over time [45, 47, 106]. While the model was unable to replicate these interactions, shown in Figure 4.12, it was still able to reliably capture overall system dynamics, and importantly, to accurately identify SBV.

4.6 *Summary*

This chapter introduced the simple 3 chamber model for identifying haemodynamic parameters. The model consisted of a total of 7 parameters, left ventricle,

aortic and vena cava elastance, input, output and systemic resistance, and finally, stressed blood volume. The model was able to reliably identify haemodynamic parameters over the course of a preload reduction manoeuvre, consistently producing model outputs which closely matched the reference measurements. The 3 chamber model has been previously validated by multiple works [1, 16, 102, 103], and has proved a reliable model for identifying stressed blood volume in a clinical setting. The model is a good candidate for real time monitoring in the ICU. However, the model is unable to account for cardiopulmonary interactions, which can play heavily on haemodynamic parameters. A model which incorporates these dynamics may provide more physiologically accurate haemodynamic parameters, as well as allowing for simultaneous optimisation of both cardiovascular and pulmonary parameters.

Chapter V

Cardiopulmonary Model

5.1 Introduction

The respiratory system is known to cause cardiopulmonary interactions, occurring during the respiratory cycle. As the lungs inflate, they fill the thoracic cavity, pushing on the heart and intrathoracic blood vessels. Furthermore, positive pressure ventilation and PEEP result in a sustained positive P_{th} , exerting further forces on intrathoracic vessels. The resultant effects on the CVS are highly complex and unpredictable, due to their highly patient-specific nature and complex mechanical aetiology [45–47, 50, 106, 107]. The unpredictable and patient-specific nature of cardiopulmonary interactions presents a difficult challenge for model-based cardiovascular monitoring and decision support in the ICU.

The previous chapter introduced the simple 3 chamber cardiovascular model and how it could be used to identify haemodynamic parameters. This chapter presents the coupling between a simple, clinically validated single chamber respiratory model [3, 6, 43, 108–111] and the 3 chamber model to produce a new cardiopulmonary model. The cardiopulmonary model is validated on the experimental pig data obtained from trials performed at the University of Liege, and draws a comparison with the simpler, uncoupled 3 chamber cardiovascular model.

5.2 Model Equations

5.2.1 Respiratory System Model

Respiratory models have been developed to guide mechanical ventilation settings in order to maximise alveoli recruitment, and thus oxygen diffusion. The respiratory system model is a clinically validated lumped parameter model made up of a single chamber to represent the lungs connected to a mechanical ventilator [6, 43, 108–110, 112, 113]. It consists of a single compartment model linked to the mechanical ventilator via the airway. The respiratory system model is shown in Figure 5.1.

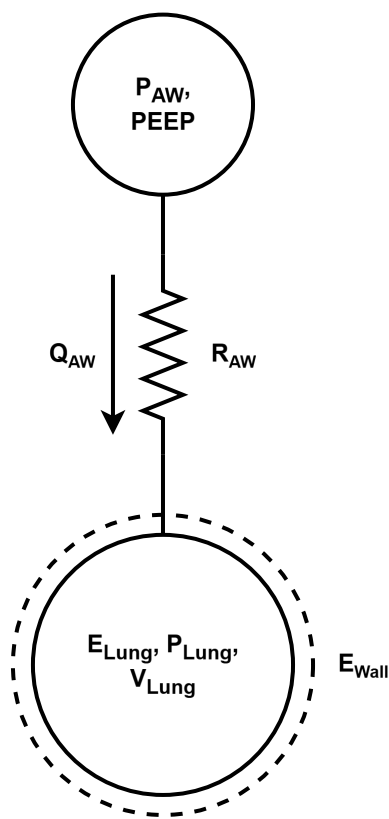


Figure 5.1: Respiratory System Model

Where $P_{aw}(t)$, $Q_{aw}(t)$ and R_{aw} are the airway pressure, flow and resistance respectively, PEEP is a mechanical ventilator setting which determines the airway

pressure at end expiration, $P_{lung}(t)$, $V_{lung}(t)$ and E_{lung} are the lung pressure, volume and elastance, and E_{wall} is the elastance of the chest wall.

5.2.1.1 Equations

The flow through the airway is defined using Ohm's law:

$$Q_{aw}(t) = \frac{P_{aw}(t) - P_{lung}(t)}{R_{aw}} \quad (5.1)$$

The lung is modelled as an elastic chamber and the lung pressure is thus defined as:

$$P_{lung}(t) = E_{rs} \dot{V}_{lung}(t) \quad (5.2)$$

Where E_{rs} is the total respiratory system elastance. The total respiratory system elastance is mainly comprised of the lung and chest wall elastance in series [21]:

$$E_{rs} = E_{wall} + E_{lung} \quad (5.3)$$

Lung volume can be defined as the integral of airway flow:

$$V_{lung}(t) = \int Q_{aw}(t) dt + \frac{PEEP}{E_{rs}} \quad (5.4)$$

Where $\frac{PEEP}{E_{rs}}$ is the integration constant.

By defining a periodic volume, $V_c(t) = \int Q_{aw}(t) dt$, and inserting Equations 5.4 and 5.2 into Equation 5.1, we can define airway pressure as:

$$P_{aw}(t) = R_{aw}Q_{aw}(t) + E_{rs}V_c(t) + PEEP \quad (5.5)$$

The parameters of the respiratory model are summarised:

- E_{rs} - Respiratory system elastance
- E_{wall} - Chest wall elastance
- R_{aw} - Airway resistance

5.2.2 Cardiopulmonary Model

The cardiopulmonary model is developed by coupling this simple, yet effective respiratory system model and cardiovascular system model together. This coupling is based on the work done by de Bournonville *et. al.* [21]. The coupling is achieved through intrathoracic pressure. Intrathoracic pressure is the pressure inside the thoracic cavity caused by expansion of the lungs, and is defined:

$$P_{th}(t) = E_{wall}V_{lung}(t) \quad (5.6)$$

By substituting Equation 5.4 into Equation 5.6, thoracic pressure can be defined:

$$P_{th}(t) = E_{wall}V_c(t) + PEEP \frac{E_{wall}}{E_{rs}} \quad (5.7)$$

The model assumes the venous and ventricular chambers are subjected to P_{th} , and thus Equations 4.2 and 4.3 can be modified as follows:

$$P_{vc}(t) = E_{vc}V_{s,vc}(t) + P_{th}(t) \quad (5.8)$$

$$P_{lv}(t) = e(t)E_{lv}V_{s,lv}(t) + P_{th}(t) \quad (5.9)$$

The parameters of the cardiopulmonary model are thus a combination of the three-chamber model and the single chamber respiratory model, and involves the combination of all their model equations and parameters as well as thoracic pressure which couples the two models. The full parameter set for the cardiopulmonary model is summarised:

- E_{ao} - Aortic elastance
- E_{lv} - Left ventricle elastance
- E_{vc} - Venous elastance
- R_{sys} - Systemic resistance
- R_{in} - Input resistance
- R_{out} - Output resistance
- SBV - Total stressed blood volume
- E_{rs} - Respiratory system elastance
- E_{wall} - Chest wall elastance
- R_{aw} - Airway resistance

5.3 *Parameter Identification*

The full cardiopulmonary model contains 10 parameters, 7 from the 3 chamber model, and 3 from the respiratory system model. The parameter identification process for the cardiopulmonary model remains largely unchanged from the 3 chamber model, with the exception of additional nominal parameter calculations and error metrics for the respiratory system parameters.

5.3.1 *Nominal Parameters*

The calculation of nominal parameters for the 3 chamber model remain unchanged from Section 4.3.1. However, nominal parameters must also be calculated for the 3 parameters of the respiratory system model, E_{rs} , E_{wall} , and R_{aw} .

5.3.1.1 Respiratory System Elastance and Airway Resistance

Given Equation 5.5, since all $P_{aw}(t)$, Q_{aw} , $V_c(t)$ and PEEP are measured or known, multiple linear regression is used to identify E_{rs} and R_{aw} from the equation.

5.3.1.2 Chest Wall Elastance

At normal lung volumes, E_{wall} is approximately equal to E_{lung} [9]. Since $E_{rs} = E_{wall} + E_{lung}$, and E_{rs} is known, E_{wall} can be approximated:

$$E_{wall} = \frac{E_{rs}}{2} \quad (5.10)$$

5.3.2 Output Vector

Since E_{rs} and R_{aw} are identified by multiple linear regression, the only parameter from the respiratory system model identified by optimisation is E_{wall} . Thus, only 1 additional error metric is required for the identification of the cardiopulmonary model.

From Equation 5.7, P_{th} is directly proportional to E_{wall} . Cardiopulmonary interactions modulate the pressure and volume waveforms of the CVS [46, 47, 106]. As stated previously, cardiopulmonary interactions are highly complex and patient specific, and there are many factors influencing the degree of modulation applied to the waveforms of the CVS. However, the cardiopulmonary model assumes P_{th} is responsible for observed cardiopulmonary interactions. Thus, the modulation of the aortic peaks is assumed proportional to calculated P_{th} . Figure 5.2 shows an aortic pressure waveform with shifting peaks due to cardiopulmonary interactions.

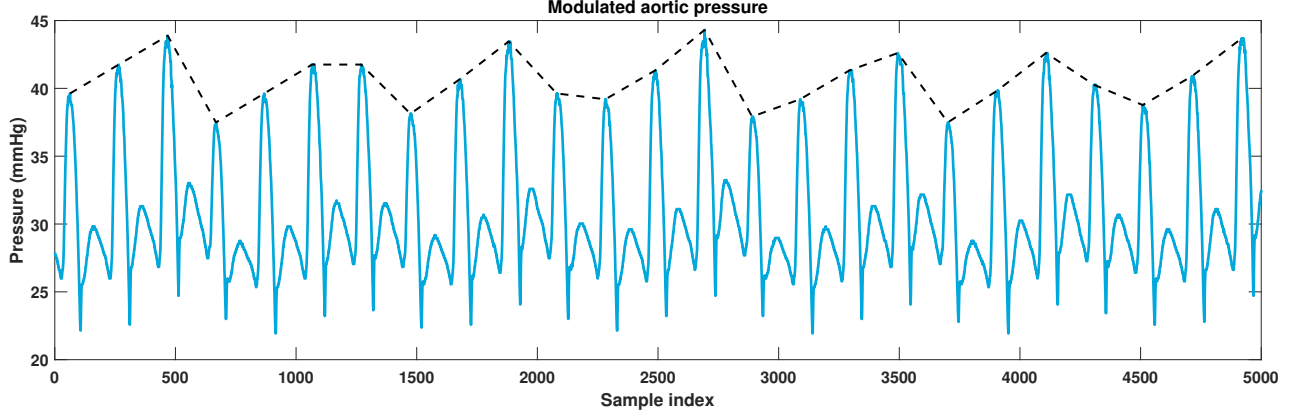


Figure 5.2: Aortic pressure waveform modulated by cardiopulmonary interactions

The error metric used to identify E_{wall} is thus the change in aortic peak pressure over the course of 1 full respiratory cycle, expressed $\Delta max(P_{ao})_T$, where T is the respiratory period. With the additional error metric, the full objective function is expressed:

$$X_{output} = [X_{3CH}, \Delta max(P_{ao})_T] \quad (5.11)$$

where X_{3CH} is the output vector used for the 3 chamber model, defined in Equation 4.45. The error vector is then calculated as in Equation 4.46, and the objective function output is calculated as the RMS of the error vector.

5.3.3 Exclusion of Pig 1

As previously mentioned in Section 3.1.1, Pig 1 experienced an issue with its flow measurements, where both aortic and airway flow did not record any negative measurements. While this issue is less important for aortic flow, as it is mostly positive due to the presence of the aortic valve, airway flow is negative during all of expiration. The missing expiration data results in approximately half the airway flow waveform missing over the course of a respiratory period. Without the

expiration data, the tidal volume waveform cannot be determined by integration of airway flow, and respiratory parameters are indeterminable. Thus, Fig 1 was excluded from the cardiopulmonary model analysis.

5.3.4 *Analyses*

Model dynamics and quality of fit were analysed by inspecting the mean absolute error (MAE) of identified parameters and by comparison of simulated and measured waveforms. Model outputs of the cardiopulmonary model were compared to outputs of the 3-chamber model to analyse the effects of the cardiopulmonary coupling on model outputs. The progression of all parameters over the PRM were then analysed and compared to expected physiological trends. The effect of thoracic pressure on parameter estimation was analysed by comparing parameter progressions of the two models.

5.4 *Results and Discussion*

5.4.1 *Cardiopulmonary Outputs and Parameters*

As was done for the 3 chamber model, the cardiopulmonary model was validated by inspecting model errors, outputs and identified parameters. Figures 5.3 and 5.4 show the model outputs at the highest level of PEEP for Figs 2 - 8. The figures show modelled and measured aortic, left ventricle and vena cava pressure. Figure 5.5 shows the cardiopulmonary errors over the course of the PR.

Model errors of the cardiopulmonary model are shown to be far more unstable than those of the 3 chamber model, and tend to increase with increasing PEEP. Figures 5.3 and 5.4 show the left ventricle diastolic pressure and vena cava pressure have risen substantially higher than measured counterparts. This error is due to the equations governing the cardiopulmonary coupling. Equation 5.8 can be rearranged to show that $P_{vc}(t) - P_{th}(t) = E_{vc}P_{vc}(t)$. The result is P_{vc} must be greater than or equal to P_{th} , or the product of elastance and pressure would be

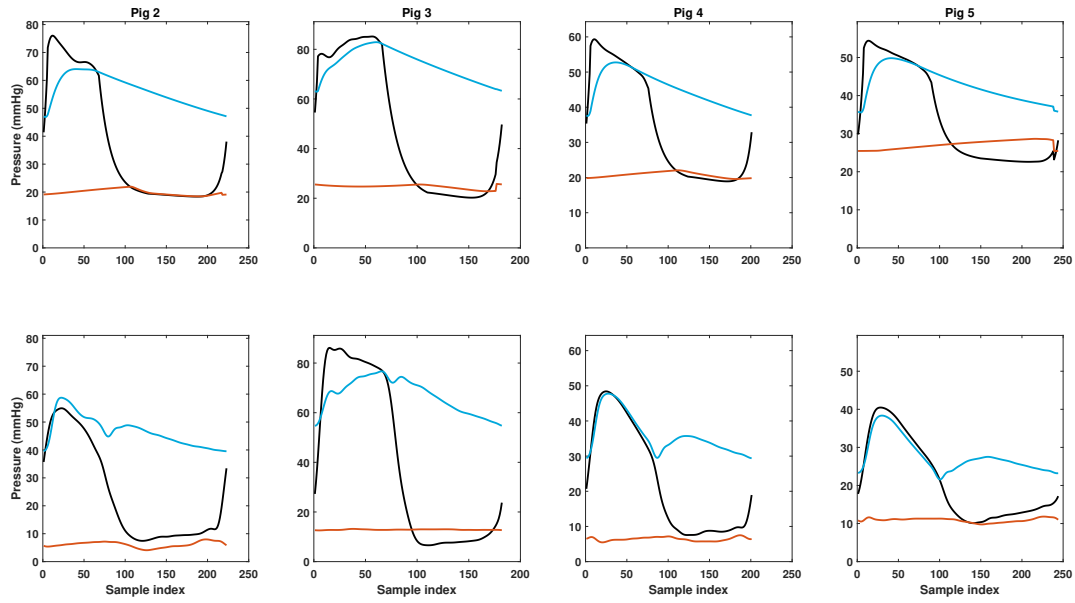


Figure 5.3: Modelled and measured waveforms for maximum PEEP. The top row shows the modelled outputs, and the bottom shows measured equivalents.

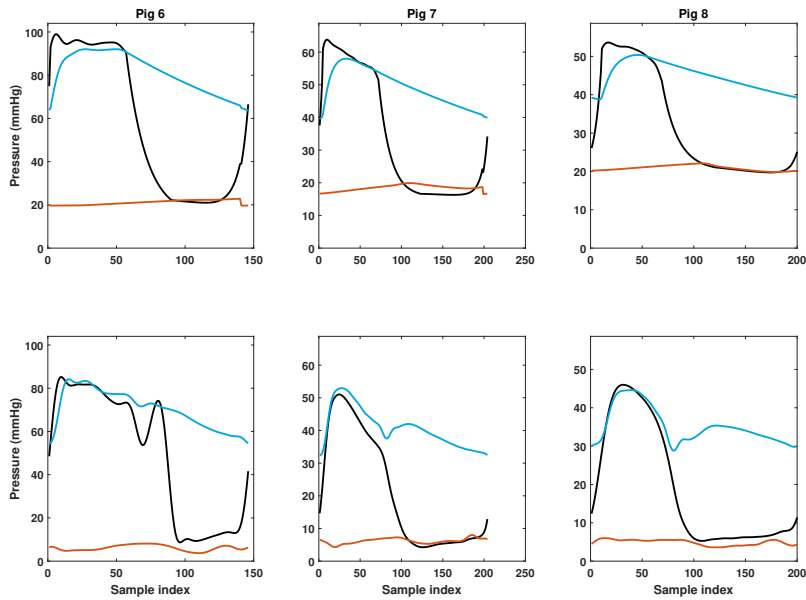


Figure 5.4: Modelled and measured waveforms for maximum PEEP. The top row shows the modelled outputs, and the bottom shows measured equivalents.

negative, resulting in the model identifying a negative elastance, which is not physiologically possible. The same applies to the left ventricle pressure in Equation 5.9.

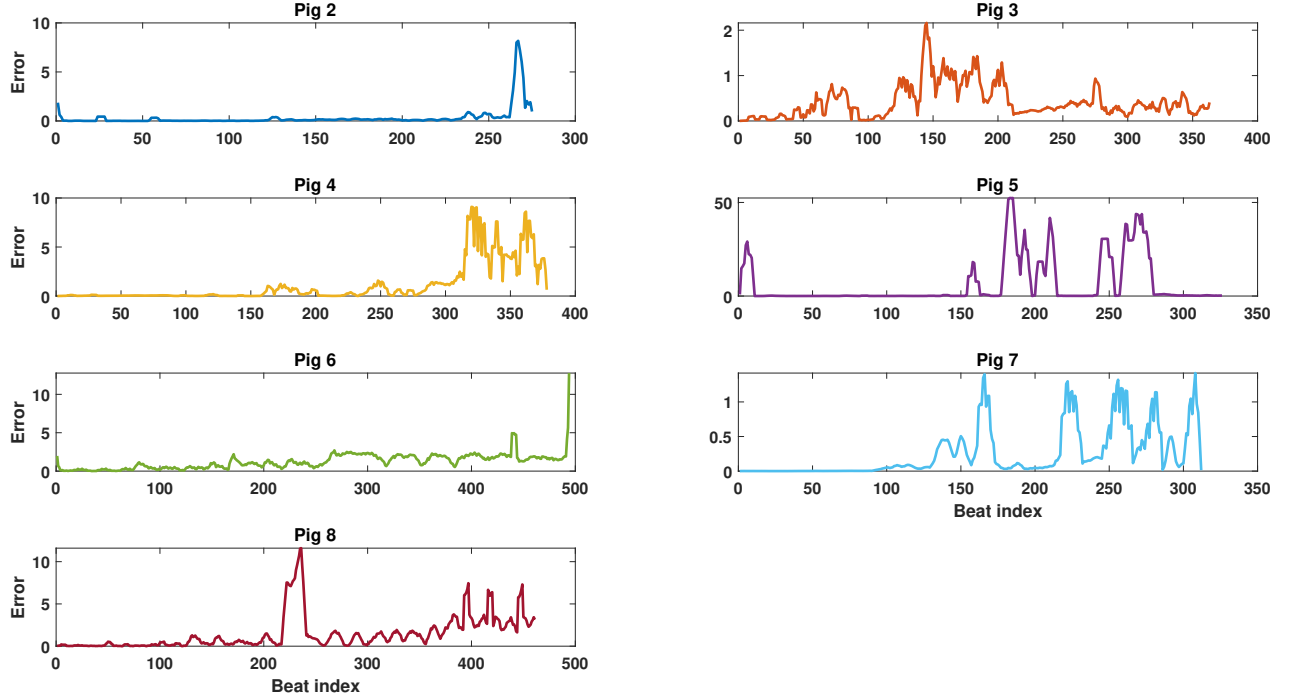


Figure 5.5: Cardiopulmonary model errors for all pigs.

The cardiopulmonary model is highly simplistic in its implementation of cardiopulmonary interactions. Thoracic pressure is applied directly as an external pressure to both the left ventricle and the entire vena cava. However, this approach is a physiologically incorrect assumption.

All cardiac chambers are contained within the pericardium. Thus, the external pressure acting on the left ventricle is the pericardial pressure, rather than thoracic pressure. The pericardium, depending on its elasticity, acts as a damper, and does not fully transmit thoracic pressure to the left ventricle. Thus, the effects of thoracic pressure are potentially exaggerated by this model approach, despite its being well-justified in fundamental literature [21, 114, 115].

Furthermore, the model subjects the entire venous blood supply to thoracic pressure. The venous system contains most of the blood of the CVS [9], much of which is extrathoracic. Thus, most of the blood within the venous system is not subjected to intrathoracic pressure. Consequently, the effects of thoracic pressure on the venous system are also exaggerated by the model.

Figures 5.6 and 5.7 show how model output venous pressure and left ventricle pressure are affected by calculated thoracic pressure. Since pressures of these chambers must always be greater than thoracic pressure for the model to be physically realisable, at higher PEEP levels, thoracic pressure becomes the dominating factor, resulting in greatly exaggerated modulation of venous and left ventricle diastolic pressure.

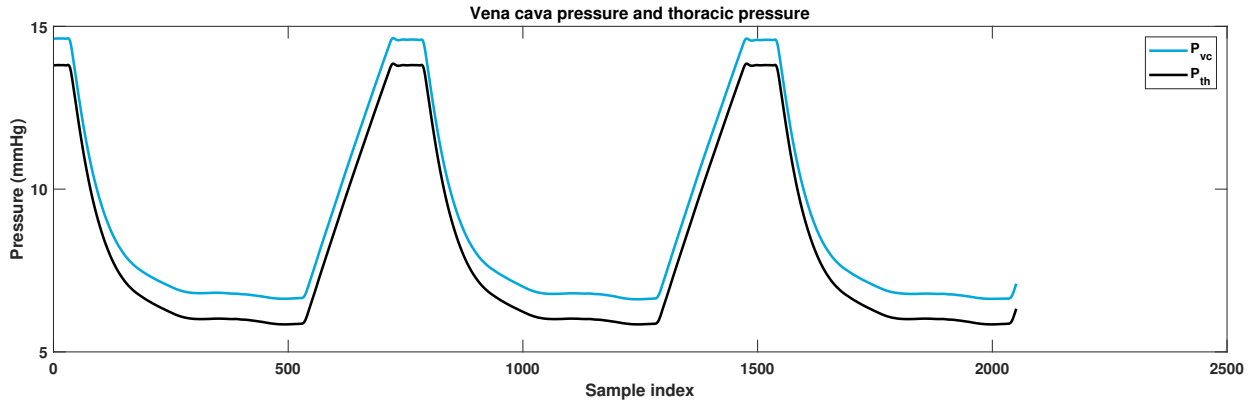


Figure 5.6: Effect of thoracic pressure on venous pressure.

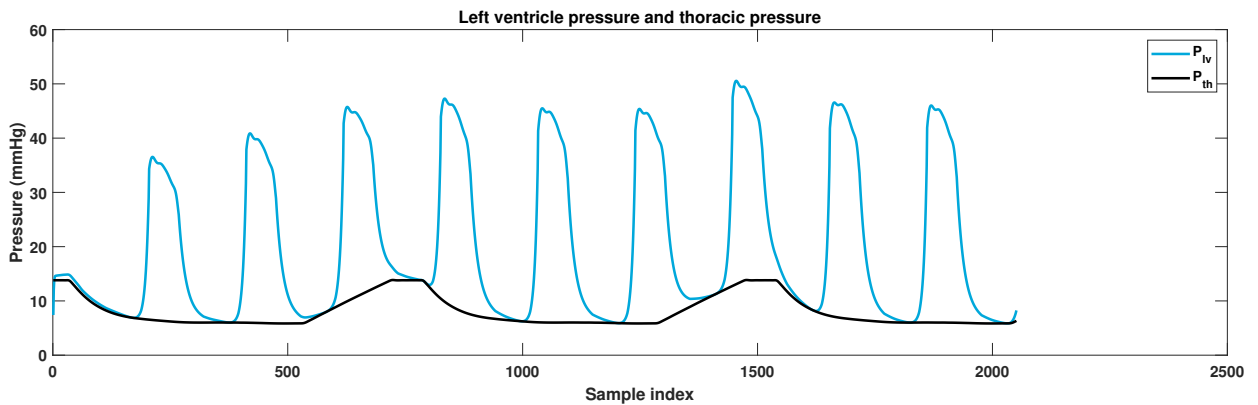


Figure 5.7: Effect of thoracic pressure on left ventricle pressure.

The objective function of the model is constantly fighting in an attempt to balance the errors between the aortic peak pressure variation and the mean and pulse venous pressure. As PEEP increases, and aortic peak pressure fluctuation grows. During the identification process, this forces the model to increase calculated thoracic pressure by increasing identified chest wall elastance. However, as shown in Figure 5.6, this increase in thoracic pressure causes an unrealistic augmentation of venous pressure, which causes a rise in the errors of both mean and pulse venous pressure. The error metrics of venous pressure and aortic peak pressure variation thus become directly conflicting at higher PEEP levels.

5.4.2 Comparison of Model Parameters

Identified SBV of both models is shown in Figure 5.8. The SBV identified by the 3 chamber model (SBV_{3CH}) is displayed with a dotted line, while the cardiopulmonary model SBV (SBV_{CP}) is displayed with a solid line. SBV_{CP} and SBV_{3CH} are almost identical at lower PEEP levels earlier in the PRM. However, as PEEP increases, SBV_{CP} becomes more erratic, and fluctuates between SBV_{3CH} and a highly exaggerated value. This error is the direct result of the model attempting to obtain the best trade off between peak aortic pressure variation and venous pressure error metrics. As the venous system contains the largest amount of blood in the CVS, the application of thoracic pressure to the entire venous blood supply has a highly impacting effect on identified SBV.

Figure 5.9 shows identified input resistance from both models. As expected, input resistance from the 3 chamber model ($R_{in,3CH}$) is very similar to input resistance of the cardiopulmonary model ($R_{in,CP}$) for low PEEP. However, as thoracic pressure increases, both vena cava pressure and left ventricular diastolic pressure are forced to rise above thoracic pressure. This causes the pressure gradient between the vena cava and left ventricle chambers to diminish during filling.

Consequently, the cardiopulmonary model constantly decreases $R_{in,CP}$ relative to $R_{in,3CH}$ to ensure that stroke volume is maintained. This compensatory mechanism of the cardiopulmonary model exhibits an inverse relationship to expected

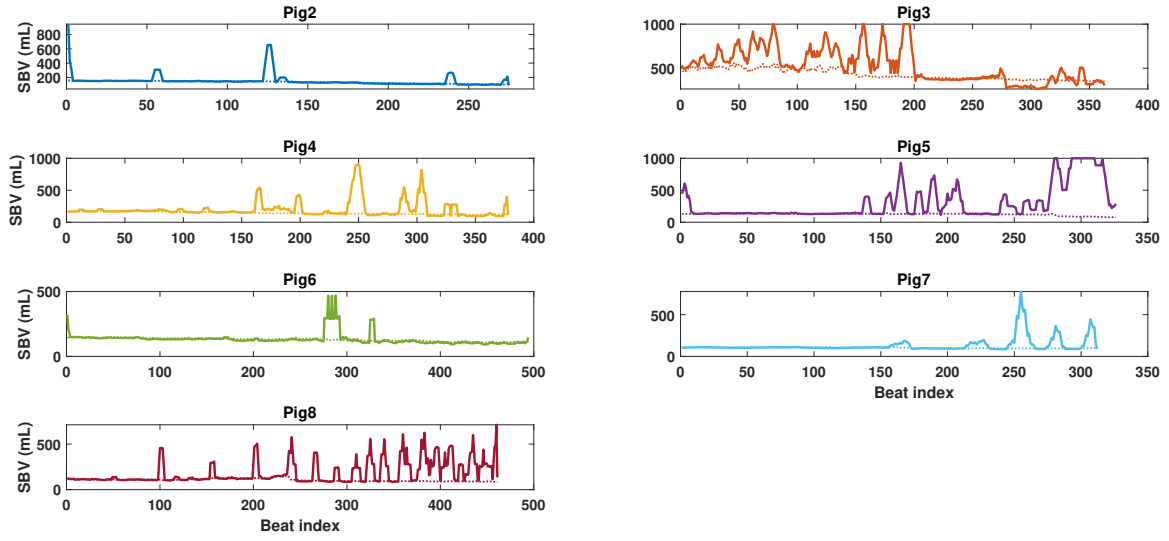


Figure 5.8: Identified SBV from both models. SBV from the 3 chamber model is displayed with the dotted line, while the cardiopulmonary model is displayed with a solid line.

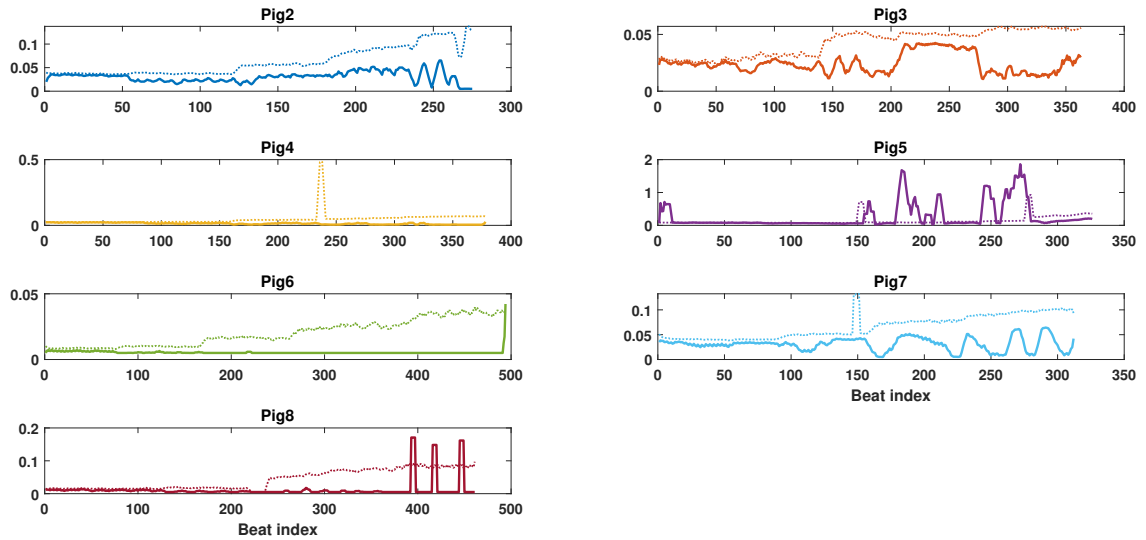


Figure 5.9: Identified input resistance from both models. Input resistance from the 3 chamber model is displayed with the dotted line, while the cardiopulmonary model is displayed with a solid line.

fluctuations of input resistance with increased PEEP. The applied external pressure causes vessels to narrow, or even collapse if thoracic pressure exceeds internal vessel pressure [44, 48]. The overall result is an increase in resistance of blood flow to the heart.

Figure 5.10 shows identified vena cava elastance from both models. Vena cava elastance from the 3 chamber model ($E_{vc,3CH}$) also closely matches vena cava elastance of the cardiopulmonary model ($E_{vc,CP}$) at low PEEP. However, as with input resistance, $E_{vc,CP}$ tends to decrease relative to $E_{vc,3CH}$ as PEEP increases. This relative decrease is contrary to the effect of an increased external pressure on an elastic vessel, as increased thoracic pressure results in an apparent stiffening of intrathoracic vessels [44, 46–48, 106], and thus an increase in elastance is expected as PEEP increases.

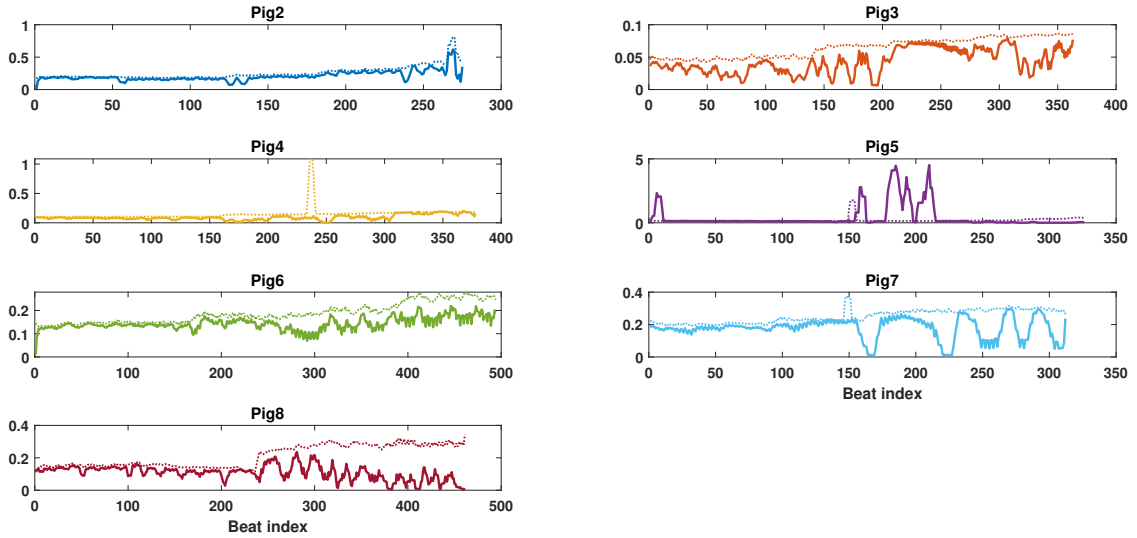


Figure 5.10: Identified vena cava elastance from both models. Elastance from the 3 chamber model is displayed with the dotted line, while the cardiopulmonary model is displayed with a solid line.

Despite the simplicity of the coupling of the cardiopulmonary model, the model struggles to correctly identify haemodynamic parameters at high PEEP levels, due

to the direct conflict between error metrics used to identify vena cava elastance and SBV, and those used to identify chest wall elastance. To remain physically realisable, the model is forced to compensate by altering identified parameters. This compensation results in higher model errors, as well as unreliable parameter identification. Consequently, the simple 3 chamber model produces parameters that more closely resemble expected parameter trends over the course of a PRM than the cardiopulmonary model.

5.5 Limitations

The cardiopulmonary model assumes thoracic pressure is directly applied to both the vena cava and the left ventricle. This simple assumption allows the model to recreate cardiopulmonary interactions. However, it is not physiologically accurate.

The left ventricle is encased within the pericardium, and thoracic pressure is only partially transmitted to the left ventricle. Furthermore, the model assumes the entire venous system is subjected to thoracic pressure. This assumption results in highly exaggerated effects of thoracic pressure on the venous system, as in reality, only a small portion of the venous system lies within the thoracic cavity.

The model also excludes the entire right circulation. While the 3 chamber model has been validated as a clinically feasible tool for identification of important cardiovascular parameters [95, 96], the omission of the right circulation makes modelling of cardiopulmonary interactions highly challenging, as the right circulation is arguably the most affected by PPV and PEEP, since it is entirely located within the thoracic cavity.

Furthermore, much of the vessels of the right circulation lie within the lungs, and are highly affected by the changing pressures and volumes of alveoli as PEEP is increased. These changes in alveolar pressure and volume during mechanical ventilation have highly complex effects on blood flow through the lungs, and are highly dependent on a patient's pulmonary state. The omission of the right circulation makes it impossible to model any of these events. However, measurements from

the right circulation are not clinically available, and a model including the right circulation would not be physically realisable in the ICU.

Finally, the goal of cardiovascular modelling in the ICU is to capture overall system dynamics, rather than producing highly complex and physiologically accurate models. Models which lump parameters together, such as the 3 chamber model, still have powerful diagnostic capabilities within the ICU. The fundamental question is whether these trade offs impact clinical utility.

5.6 Summary

This chapter introduced a simplistic cardiopulmonary model, which incorporated cardiopulmonary interactions by directly applying thoracic pressure to intrathoracic chambers, specifically the left ventricle and vena cava chamber. The simplistic assumption allowed the model to recreate cardiopulmonary interactions, which were quantified by aortic peak pressure variation. Thoracic pressure acts as an external pressure on intrathoracic chambers, thereby decreasing their transmural pressure. While this approach is accepted as an accurate means for modelling the effects of an external pressure applied to an elastic pressure chamber, it is not necessarily accurate. In particular, thoracic pressure is not directly applied to the left ventricle, and is only applied to a small portion of the venous system. At low PEEP levels, this difference was not a problem, as the model essentially behaved similarly to the 3 chamber. However, at higher PEEP levels, this difference results in highly exaggerated effects of thoracic pressure on the vena cava and left ventricle diastolic pressure, creating unrealistically modulated waveforms, increasing model error and reducing the accuracy and reliability of identified parameters. The 3 chamber model is thus a more likely candidate for as a diagnostic tool in a clinical setting.

Chapter VI

Modified Cardiopulmonary Model

6.1 Introduction

As previously shown, the cardiopulmonary model did not perform well under high PEEP conditions. This poor performance is largely due to the limitations of the simplistic coupling of the respiratory and cardiovascular system models [41, 116]. Since the CVS model only uses 1 chamber to represent the entire venous blood system, the entirety of the venous system is subjected to P_{th} . However, in reality, only the intrathoracic portion of the vena cava is subject to this pressure. Since the vena cava chamber contains a large majority of the blood volume of the 3 chamber model, this assumption has a highly exaggerated effect.

Furthermore, the cardiopulmonary model applied calculated thoracic pressure directly to the left ventricle as an external pressure, greatly reducing its transmural pressure. In reality, the left ventricle is contained within the pericardium, which only transmits a portion of thoracic pressure to the left ventricle.

These assumptions could be remedied by adjusting the means by which thoracic pressure is applied to intrathoracic chambers. A physiologically accurate approach would separate the single venous chamber into 2 chambers, an intrathoracic and extrathoracic chamber, as well as modelling the effects of venous collapsibility under high external pressure [48]. Further, pericardial pressure could be calculated and applied to the left ventricle as an external pressure.

While these techniques would be physiologically accurate, they would be infeasible in a clinical setting due to the lack of clinically available measurements. It would not be possible to determine the intrathoracic and extrathoracic blood volumes in the venous system. In particular, only one venous pressure measurement is available, and there would be insufficient measurements to identify 2 chambers. Finally, the calculation of pericardial pressure involves knowing the volume of all cardiac chambers at 0 pressure [115, 117], which is not clinically feasible. Thus, a simpler approach is required.

This chapter poses a novel, modified cardiopulmonary model. The model uses a new parameters, α , to regulate the percentage of P_{th} applied to left ventricle and vena cava, respectively, with the aim of improving the reliability of the cardiopulmonary model at high PEEP levels, as well as improving the model's ability to adapt to patient specific conditions. Model parameters are identified using the full experimental data set. Model dynamics and identified parameters are compared to those from the original cardiopulmonary model to evaluate its relative performance and reliability.

6.2 *Alpha model equations*

From Equation 5.8, P_{vc} must exceed P_{th} , or the equation yields a negative value for stressed blood volume, which is not physiologically possible. Thus, when identified P_{th} exceeds measured P_{vc} , the model is forced to augment P_{vc} to a level greater than P_{th} , leading to increased model errors.

Further, only a portion of P_{th} is applied to the left ventricle, since it is encased within the pericardium, where pericardial pressure is the external pressure applied to the left ventricle, rather than P_{th} . Thus, both left ventricle and vena cava pressures are subjected an exaggerated external pressure.

A simple solution for this problem is to diminish the amount of pressure applied to both of these chambers. Consequently, a new parameter was added to modulate the percentage of P_{th} applied to the intrathoracic chambers. This added parameter,

α , is applied to P_{th} from Equations 5.8 and 5.9, yielding:

$$P_{lv}(t) = e(t)E_{lv}V_{slv}(t) + \alpha P_{th}(t) \quad (6.1)$$

$$P_{vc} = E_{vc}V_{s vc}(t) + \alpha P_{th}(t) \quad (6.2)$$

where α represents the percentage of thoracic pressure applied to the intrathoracic chambers.

6.3 Parameter Identification

Both α and E_{wall} are not independently identifiable. Substituting Equation 5.6 into Equations 6.1 and 6.2, it can be shown α and E_{wall} are directly correlated:

$$P_{lv}(t) = e(t)E_{lv}V_{slv}(t) + \alpha E_{wall}V_{lung} \quad (6.3)$$

$$P_{vc} = E_{vc}V_{s vc}(t) + \alpha E_{wall}V_{lung} \quad (6.4)$$

Consequently, using optimisation to identify α would not work, as the model could equally scale α and E_{wall} in opposite directions and achieve the same result, presenting an impossible challenge for optimisation algorithms. However, while seemingly redundant, α allows the model to apply thoracic pressures much lower than would otherwise be identifiable by physiologically accurate values of E_{wall} .

Thus, to identify an optimal combination of α and E_{wall} , a grid search is used to identify α . The cardiopulmonary model identification process remains the same as in Section 5.3. However, the parameter identification process is repeated for values of $\alpha \in \{0, 0.1 \dots 1.0\}$, enabling a two part optimisation where the new second

step line searches for an optimum α value.

6.4 Analysis and Comparisons

Model dynamics and quality of fit were analysed by checking the mean absolute error (MAE) of parameter estimates and by comparison of simulated and measured waveforms. To investigate the effects of thoracic pressure of each model, vena cava and diastolic left ventricle pressure outputs are compared to measured equivalents. Finally, differences in errors and outputs between the two models are compared to assess the relative performance of the alpha model compared to its predecessor.

6.5 Results and Discussion

Figures 6.1 and 6.2 show the model outputs for a single beat from the novel cardiopulmonary model presented for the optimal α at the highest PEEP level. The optimal value of α was determined as the value which resulted in the lowest mean error over all beats from a section at a given PEEP level. The optimal α for each PEEP level of all pigs is shown in Figure 6.3.

When contrasted to the waveforms of the cardiopulmonary model, shown in Figures 5.3 and 5.4, both vena cava pressure and diastolic left ventricle output pressures from the optimum Alpha Model are much lower compared to those from the original cardiopulmonary model. This change is due to the reduced thoracic pressure applied to these chambers.

Figure 6.3 shows optimum α values, the values of α resulting in the lowest average error per PEEP level for all pigs. The optimum α values do not display any form of predictable pattern. Given effects of intrathoracic pressure on intrathoracic chambers becomes increasingly exaggerated as PEEP increases, it would seem logical to assume as PEEP increased, optimum α would decrease, acting to reduce the overall effects of applied thoracic pressure on the intrathoracic chambers. However, Figure 6.3 clearly shows this behaviour and trend are not the case, and the

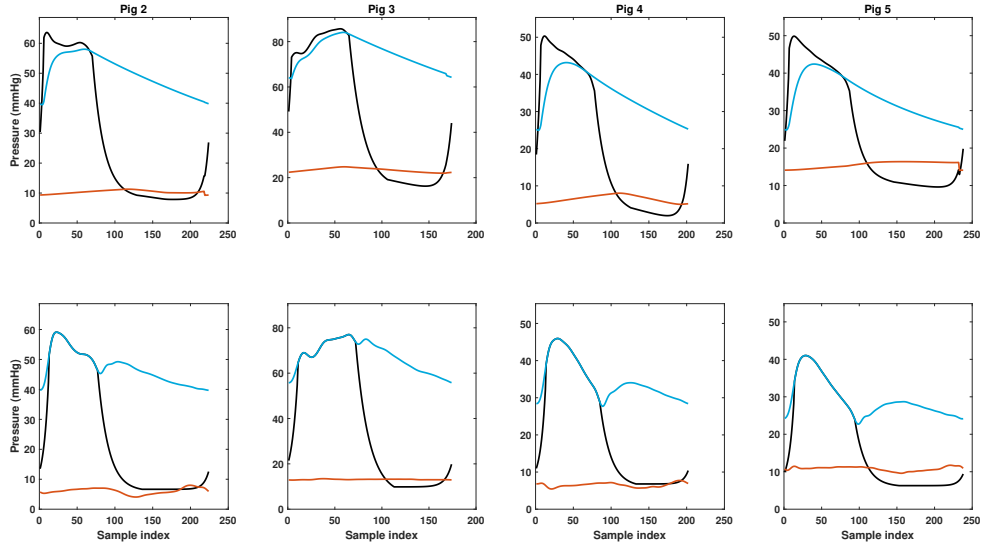


Figure 6.1: Modelled and measured waveforms for maximum PEEP and optimal alpha. The top row shows the modelled outputs, and the bottom shows measured equivalents.

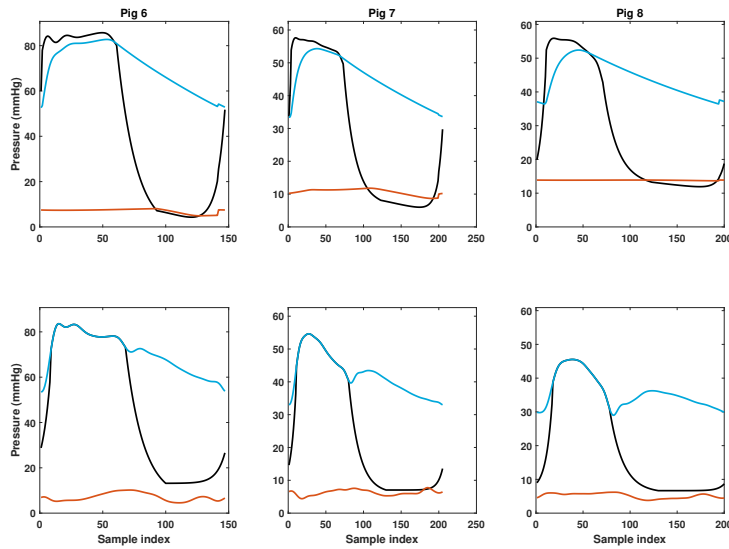


Figure 6.2: Modelled and measured waveforms for maximum PEEP and optimal alpha. The top row shows the modelled outputs, and the bottom shows measured equivalents.

optimum selection for α appears to be almost random.

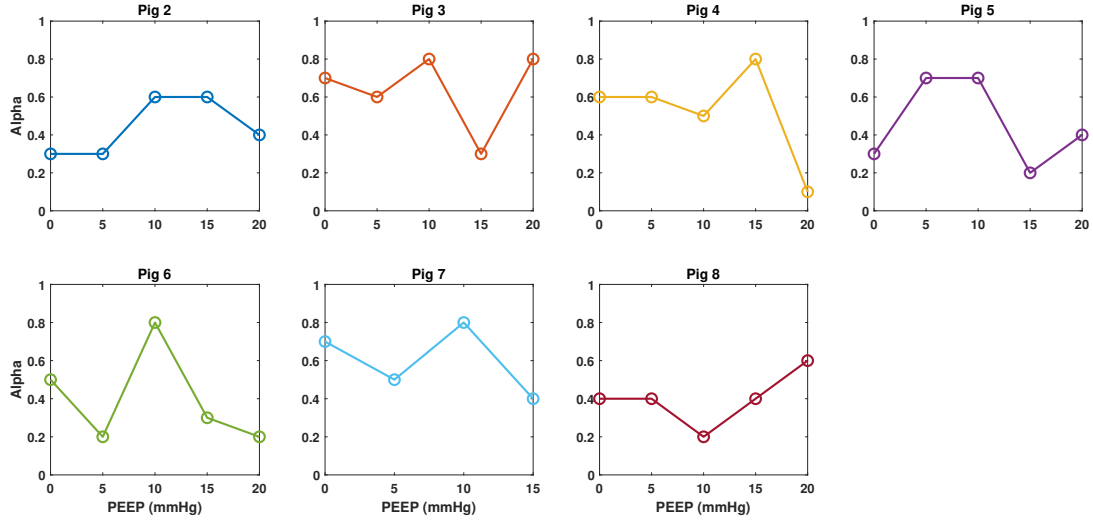


Figure 6.3: Optimum alpha for each level of PEEP for all pigs.

Tables 6.1 and 6.2 show the average error for each PEEP level for all pigs. The errors are also displayed as a bar chart in Figure 6.4 The optimum Alpha Model shows a lower average error for almost all PEEP levels for all pigs than the cardiopulmonary model. However, for most pigs and PEEP levels, the difference in error is small and not clinically significant.

Table 6.1: Optimum Alpha Model average errors per PEEP level

Pig	0mmHg	5mmHg	10mmHg	15mmHg	20mmHg
2	0.009	0.077	0.249	0.234	1.477
3	0.275	0.473	1.911	0.147	0.358
4	0.189	0.181	0.451	0.620	2.960
5	0.026	0.070	0.409	0.350	0.507
6	1.749	1.338	3.879	8.971	6.005
7	0.124	0.929	0.344	0.359	-
8	0.803	0.770	2.802	0.773	2.517

Table 6.2: Cardiopulmonary model average errors per PEEP level

Pig	0mmHg	5mmHg	10mmHg	15mmHg	20mmHg
2	0.012	0.163	0.363	0.266	1.568
3	0.310	0.497	1.930	0.202	0.463
4	0.198	0.182	0.461	0.650	7.115
5	0.893	0.431	0.410	0.455	1.072
6	1.150	1.351	5.431	7.308	4.463
7	0.325	0.652	0.352	0.392	-
8	1.111	1.007	4.962	0.774	2.525

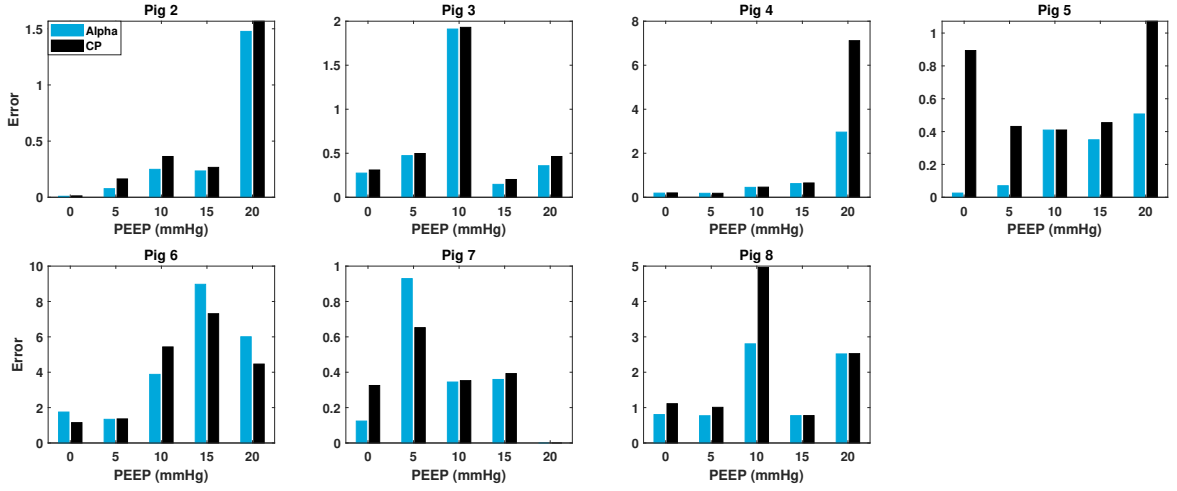


Figure 6.4: Bar chart showing average errors of each model per PEEP level for all pigs. Cardiopulmonary model errors are shown in black while alpha errors are shown in blue.

While the *alpha* parameter appears to have slightly improved the accuracy of the cardiopulmonary model, it comes at a large computational cost. Where the cardiopulmonary model only needs to perform the optimisation process once per beat, an already computationally heavy process, the Alpha Model must perform a grid search, performing the optimisation process for each step in the grid.

The α parameter was added in an attempt to provide a simple solution to improve the dynamics of the cardiopulmonary model. It aimed to reduce the exagger-

ated effects of thoracic pressure on intrathoracic chambers, which resulted in high model errors and inaccurate model outputs at high PEEP levels. While it was successful in reducing model errors and improving model output accuracy, it only produced slightly improved results than its predecessor. The differences were not clinically significant. Furthermore, the computational cost associated with finding an optimal value of α results in far longer computational times. Consequently, the added complexity associated with both the α and cardiopulmonary model has not proven sufficiently beneficial to justify their use over the 3 chamber model alone as a candidate for model based care in the ICU.

6.6 Limitations

The simple addition of the α parameter aimed to counteract the exaggerated effects of applied thoracic pressure to intrathoracic chambers. However, it was directly coupled to the already identified chest wall elastance, resulting in α not being identifiable by single step optimisation methods. While optimal α was found through grid search methods, the reliability of this parameter is still questionable given the strong correlation with chest wall elastance. Despite this issue, it still managed to produce more reliable results than the original cardiopulmonary model.

The reliance on a grid search for finding optimum α resulted in much longer computing times. To find the optimum value, the model was run 10 times for each beat for values of $\alpha \in [0.1, 1]$ in increments of 0.1. Given potential use of the application within the ICU, it is likely this method would simply take too long for it to be a useful candidate within the ICU, where diagnostic data is needed in real-, or at least semi-real-, time.

Finally, the same parameter was used to modulate the percentage of P_{th} applied to both the venous and ventricle chamber. However, the mechanisms affecting each of these chambers are highly different. The ventricle is only partially affected by thoracic pressure due to the presence of the pericardium, where the pericardium does not necessarily fully transmit thoracic pressure. Alternatively, the venous system is both intra- and extra- thoracic. Thus, only a portion of it is subjected

to thoracic pressure. Using one parameter to account for both of these systems is highly simplistic, and unlikely to produce an accurate estimation of either system. Equally, more complex models would likely not be identifiable in a clinical setting, and would thus not be considered as potential candidates for bedside use.

6.7 Summary

This chapter presented a simple, novel cardiopulmonary model. The chapter introduced a new parameter, α , which aimed to modulate the percentage of intrathoracic pressure applied to intrathoracic chambers. Although α was theoretically directly correlated to an already existing parameter, being applied as a linear scalar to the chest wall elastance, it was still able to improve overall model reliability and reduce model errors for an optimal α value. However, an optimum α is highly computationally intensive to find, having to grid search over multiple values, requiring the model to be run an exponentially higher number of times more than for the original 3 chamber and first cardiopulmonary models. Ultimately, the cardiopulmonary models, both original and modified, have proved to be less reliable, or at least no more reliable, than the original 3 chamber model, and it is clear the added cardiopulmonary coupling does not bring enough benefit to the model to warrant the additional complexity. The 3 chamber model will thus be used as a candidate model for future use as a bedside guidance tool.

Chapter VII

Data Acquisition Device

7.1 Introduction

Bedside monitoring is a crucial part of care in the ICU. Bedside monitoring provides crucial information to doctors and clinicians which aids in providing appropriate care. As highlighted previously, model-based care has the potential to provide doctors and clinicians with a wealth of patient-specific information that would otherwise be unavailable. While these bedside machines provide a crucial service to bedside care, these proprietary devices also act as a barrier for advancements in model based care. Without access to real time data, model based care would be infeasible in the ICU. In order to validate the model on human data, bedside data must be available for use both retrospectively and in real-time in the ICU. Thus, a device was created for the acquisition of real-time haemodynamic data in the ICU.

The acquisition system was based off of a previous system designed by Smith et al [28]. The system recorded data from a single pressure line and the fluid infusion rate using hanging scales. The system involved hydraulically tapping into an existing pressure line. This was done by connecting another pressure sensor in parallel to the existing pressure sensor already connected to the patient. Since the pressure sensors use the proprietary Philips IBP cables, and the data acquisition input used a RJ-45 cable, connecting the pressure sensor to the data acquisition device required cutting up the Philips and RJ-45 cables, soldering them together

and resealing them with heat shrink and insulation tape. Philips IBP cables are expensive, costing anywhere between \$60 and \$100 each, and cables connected with heat shrink and insulation tape are not a convincing solution for hospital bedside use. The addition of the extra pressure sensor is also not a straightforward system for bedside nurses and clinicians to set-up. The system could easily be installed incorrectly, invalidating any data that the device records.

This chapter presents a novel low cost data acquisition system for gathering pressure and fluid information from hospital bedside machines. The system allows for the measurement of 3 simultaneous pressure lines as well as the fluid infusion rate. Rather than hydraulically tapping an existing pressure line with an additional pressure sensor, the system intercepts the electrical connection between the bedside monitor and pressure sensor, removing the need for an additional pressure sensor and chopped up cables. This solution requires the development of a specific adaptor, which connects the pressure sensor to the bedside machine, and sends the pressure information from the pressure sensor to the data acquisition system.

7.2 Methodology

7.2.1 System Description

The hardware consists of 2 main pieces: 1) the main data acquisition device (DAQ); and 2) a custom designed adaptor enabling real time data capture from bedside machines. The DAQ consists of a custom printed circuit board (PCB), and an Arduino nano microcontroller. The PCB uses 4 RJ-45 ports as data input lines, 3 for pressure sensor inputs and 1 for a load cell input. Inputs are fed through INA821 instrumentation amplifiers before being sent to the analog to digital converter (ADC) inputs on the Arduino nano. The Arduino controller has a USB-C port, and the PCB is powered by the 5V supply of the Arduino, which is connected to a computer via the USB port. The data read by the ADCs is sent over serial connection to the computer, where data is collected and displayed using a Python based desktop application. The adaptor is used to create a T-branch between pressure sensors and the bedside machine. The adaptor keeps the connection between

bedside monitor and pressure sensor intact, but also allows the pressure signal to be sent downstream to the DAQ.

The device is based on a previously created device, a low cost circulatory pressure acquisition system designed by Smith *et al* [28]. Smith's device required the addition of extra pressure sensors to hydraulically tap into existing pressure sensors. While a good design in theory, this approach necessitated an extra pressure sensor, as well as the cutting of an RJ-45 and Philips IBP cable, and soldering them together, yielding a messy solution not suitable for hospital use. Furthermore, the addition of the extra pressure sensor presents a complex solution for bedside nurses. The adaptor presented here bypasses all of these issues, making a very easy to use system for bedside nurses, and removing the need for extra pressure sensors or chopped and re-soldered cables.

7.2.2 System Components

7.2.2.1 Casings

The full system required 3 casings; for the DAQ, the adaptor, and the hanging scale. Casings are made up of a base and lid. Most CAD files, with the exception of the hanging scale casing base and lid, were drawn using Solidworks. The casing for the hanging scale was created by Smith et al [28] using FreeCAD, and remained unaltered by this work. Both the DAQ and adaptor casings were designed using Solidworks.

7.2.2.2 Electronics

All PCB design was performed using KiCAD. In total, there are 2 PCB boards, 1 main board and 1 smaller board for the adaptor. The main board is used for the DAQ housing the Arduino. The adaptor board connects to the both female and male connectors, and houses an RJ-45 port to send data downstream to the DAQ unit. The schematic for the DAQ is shown in Figure 7.1, and the PCB design is

shown in Figure 7.2

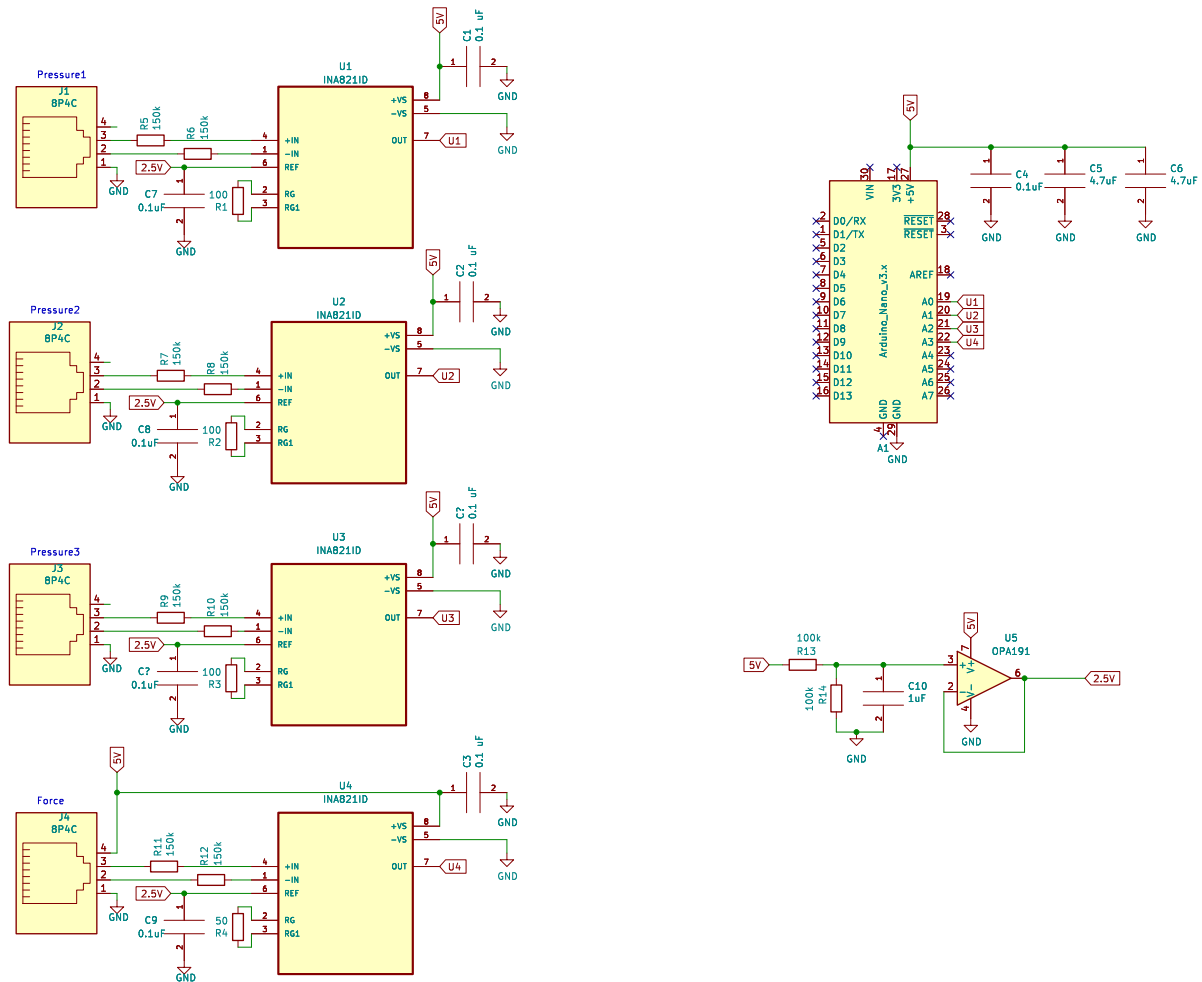


Figure 7.1: Schematic diagram for the DAQ.

7.2.2.3 Software and Firmware

There are 2 software components for this work. Embedded software which programs the Arduino, and a python application used for the main GUI. The Arduino is used to read data from 4 ADCs, and then send that data over a serial connection

leakage current of $50\mu\text{A}$ outlined in the standards prescribed for medical electrical equipment in IEC 60601.1:2015.

7.2.3 Device construction

The DAQ was constructed by populating the DAQ PCB with components, and 3D printing the housing for the DAQ. Once populated, the PCB was placed in the DAQ housing, which protects the device from any potential fluid leaks in the hospital. The adaptor, being a custom electro-mechanical design, necessitated a more complex construction. First, the adaptor PCB was populated, and all casing pieces were 3D printed. The adaptor is made up of a main housing, and female and male connectors that connect to the Philips IBP cable of both the pressure sensor and the bedside machine. The adaptor was constructed as shown in Figures 7.3 - 7.7. The final constructed adaptor is shown in Figure 7.7. Finally, the hanging scale assembly, used for measuring amount of fluids given to a patient, is constructed as shown in Figure 7.8.

7.3 System operation

An illustrative summary of data flow for the DAQ system is shown in Figure 7.9. To operate the system, first adaptors are connected to existing pressure sensors and the bedside machine. All adaptors and the hanging scale are then connected to the DAQ via RJ-45 cables, and the DAQ is connected to a laptop via USB-C. Once the DAQ is connected to the laptop, the python desktop application is started. Once running, the python application displays pressure and hanging scale measurements in real time, and is ready to record. The DAQ is shown in Figure 7.10 with all ports connected.

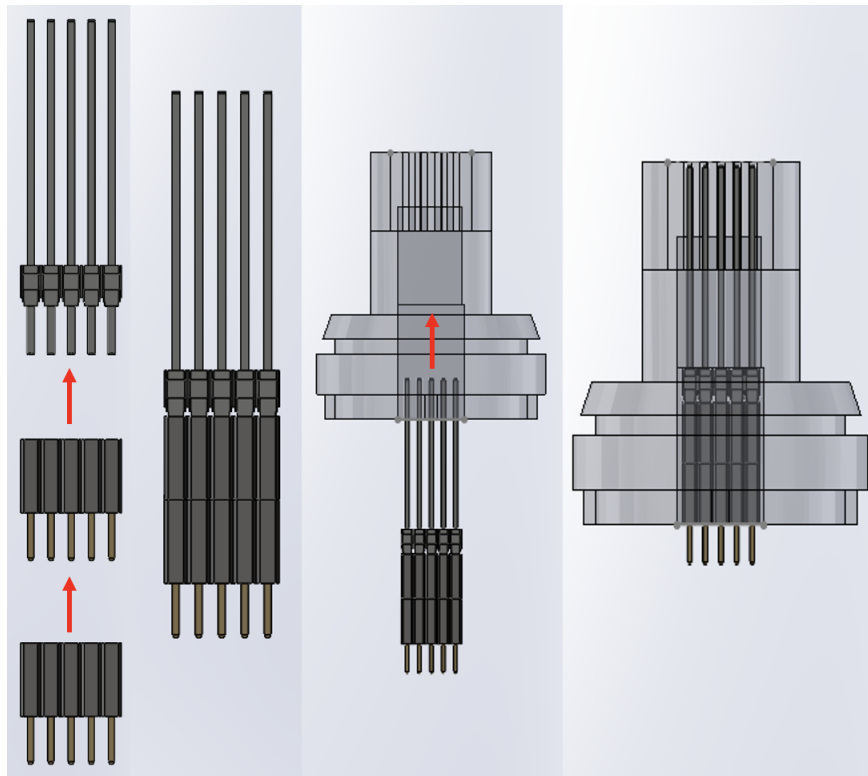


Figure 7.3: Diagram for construction of male connector. 1 male to male extended pin header is attached to 2 female to male pin headers. This assembly is then inserted into the small hole on the backside of the male connector such that the small elongated pins of the assembly slide easily through the small gaps on the male connector.

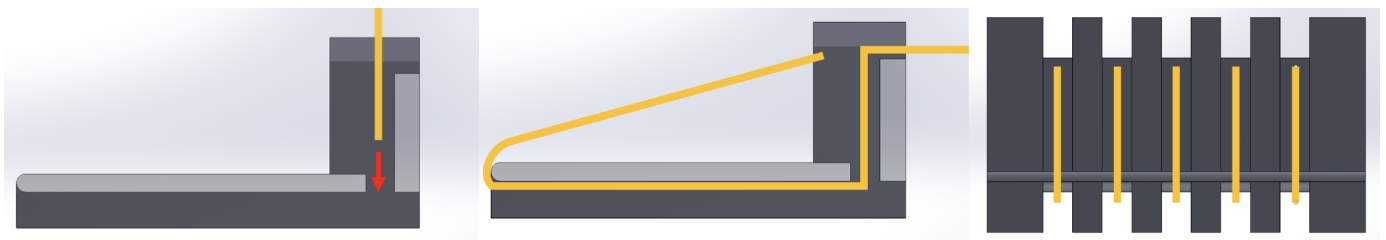


Figure 7.4: Diagram for inserting metal pins into female connectors pin holder. The left image shows how to insert the pin, the central image shows how to correctly shape the pin and the right image shows the front view once all pins have been inserted.

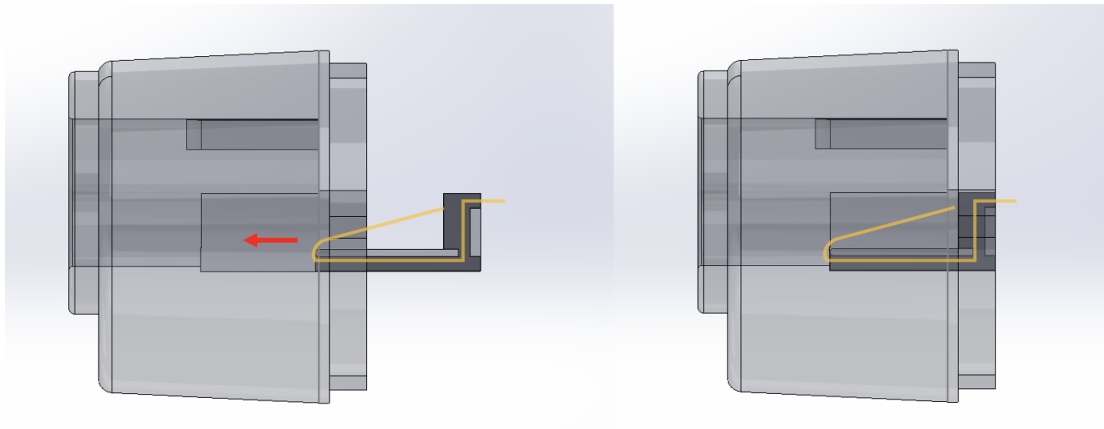


Figure 7.5: Diagram for construction of female connector. Pin holder is inserted into the hole on the rear side of the female adaptor as shown.

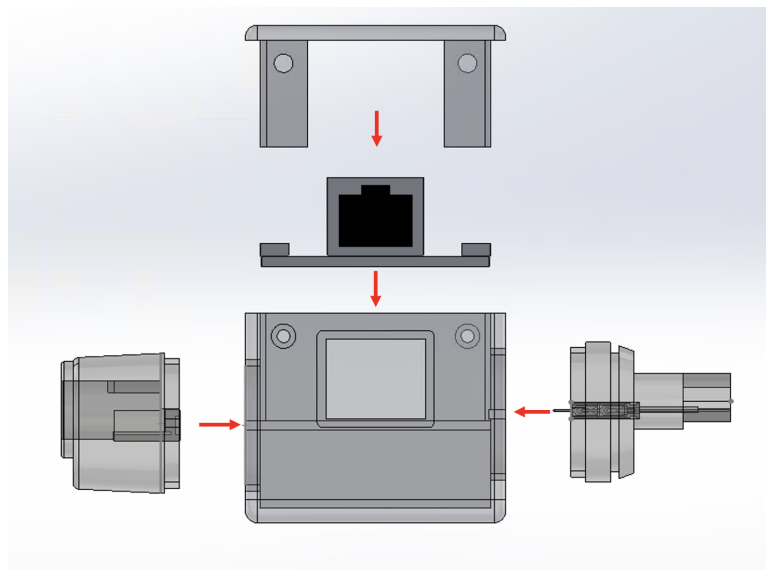


Figure 7.6: Pressure adaptor construction diagram. The PCB is inserted into the casing, and then the male and female connectors are attached to the PCB. Finally, the casing is closed with the enclosure lid.



Figure 7.7: Fully constructed pressure adaptor.

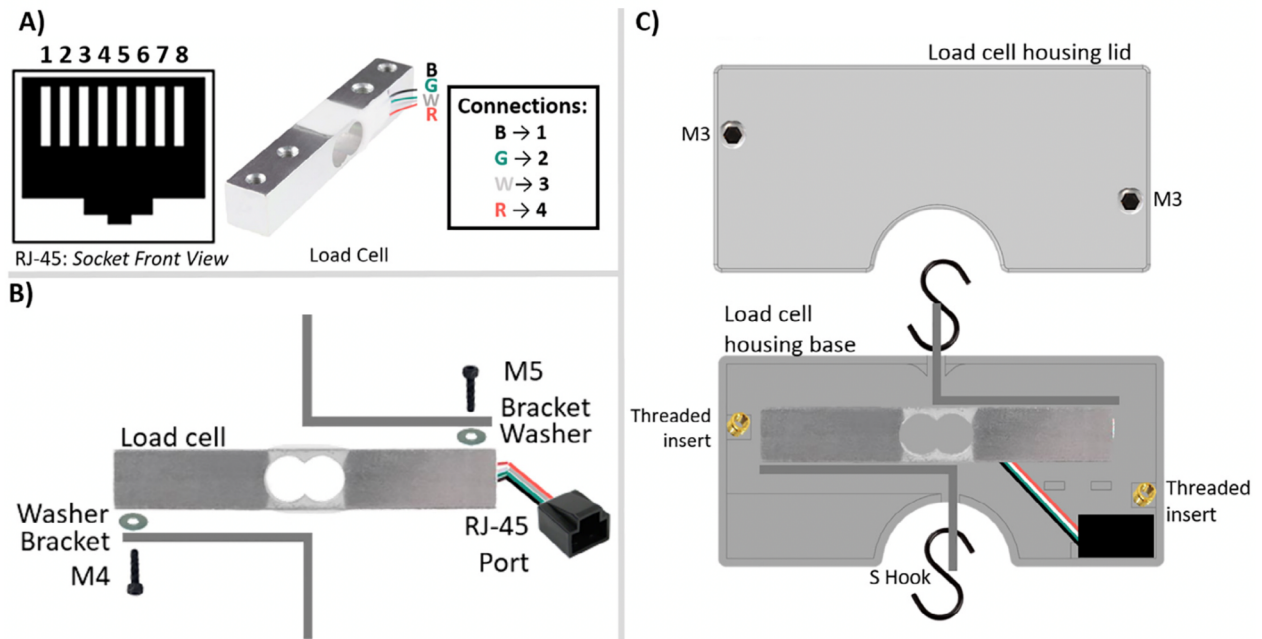


Figure 7.8: Hanging scale assembly. Image from [28]. The wires of the load cell are soldered to the RJ-45 port as per A. The load cell is then assembled as shown in B, and inserted into the casing as shown in C.

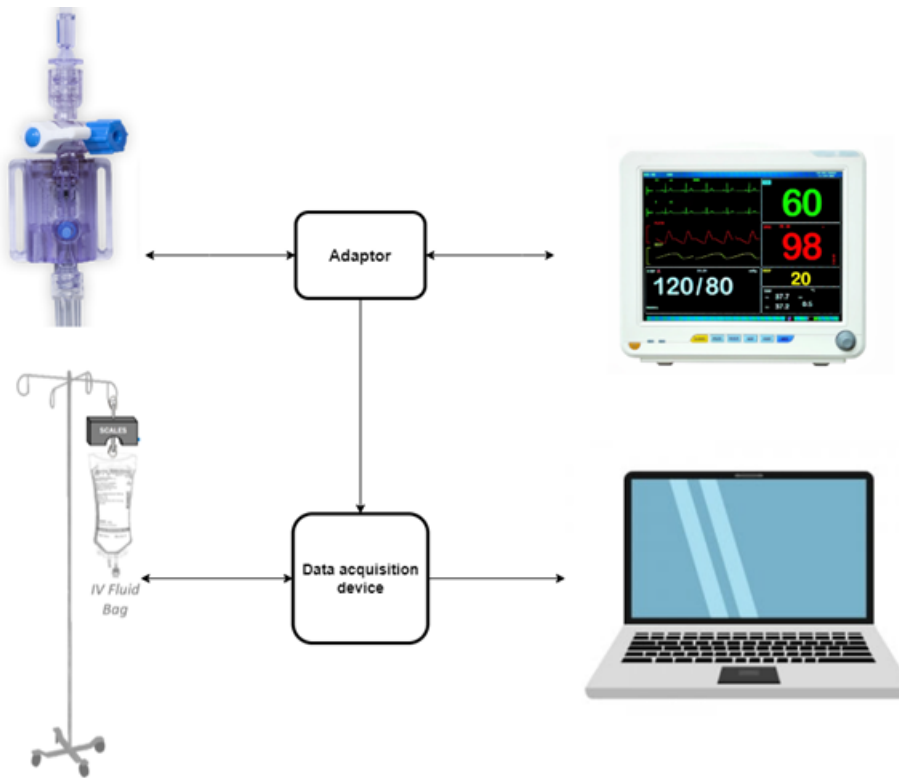


Figure 7.9: Data acquisition system.

7.3.1 Validation and Characterisation

The hanging scale was calibrated using known weights hung from the sensor and obtaining the calibration curve. The calibration curve is shown in Figure 7.11, and the linear calibration coefficients were found to be 7.1717 and -3742.4 for the gradient and offset respectively. Note the 5V amplifier used for amplification of the load cell signal amplifies both positive and negative voltages. Thus an input signal of 0V, resultant from a 0kg load, is output as 2.5V from the amplifier, which is roughly equivalent to an ADC value of 512. Thus, a 0kg load is read as 512 from the ADC.

The calibration for the pressure sensor was obtained by analysing data from both the Philips monitor and DAQ unit. A Philips monitor was made available for testing of the device. The Philips monitor used for testing had the capability to



Figure 7.10: DAQ unit with port numbers labelled. Ports 1 - 3 are for pressure sensor inputs, and port 4 is for the load cell input.

export data via a LAN cable to a computer (note this is not usually available on in-hospital units, and even when it is, it does not allow for real time data capture). For the test, the pressure sensor was connected to a syringe which acted as a pressure source. The syringe was used to create several pulses and the data from both the DAQ and the Philips monitor were collected. The Philips monitor records data at 125Hz, while the DAQ records at 500Hz.

The Matlab “interp” function was used to interpolate the Philips data to a 500Hz sample rate. Matlab’s cross correlation function “xcorr” was then used to find the sample offset between the two waveforms. Once the waveforms were aligned, the calibration coefficients for the pressure sensor were found by fitting the data from the DAQ to the data from the Philips monitor using simple linear regression. The calibrated DAQ data is shown with the monitor data in Figure 7.12. The calibration yielded the linear calibration coefficients of 0.3832 and -199.498 for the gradient and offset respectively.

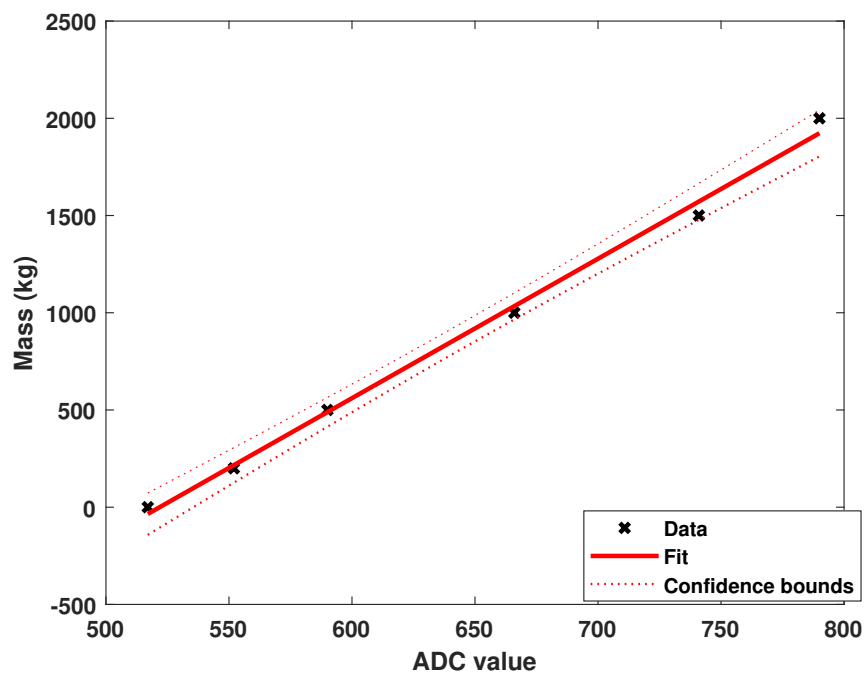


Figure 7.11: Hanging scale calibration curve.

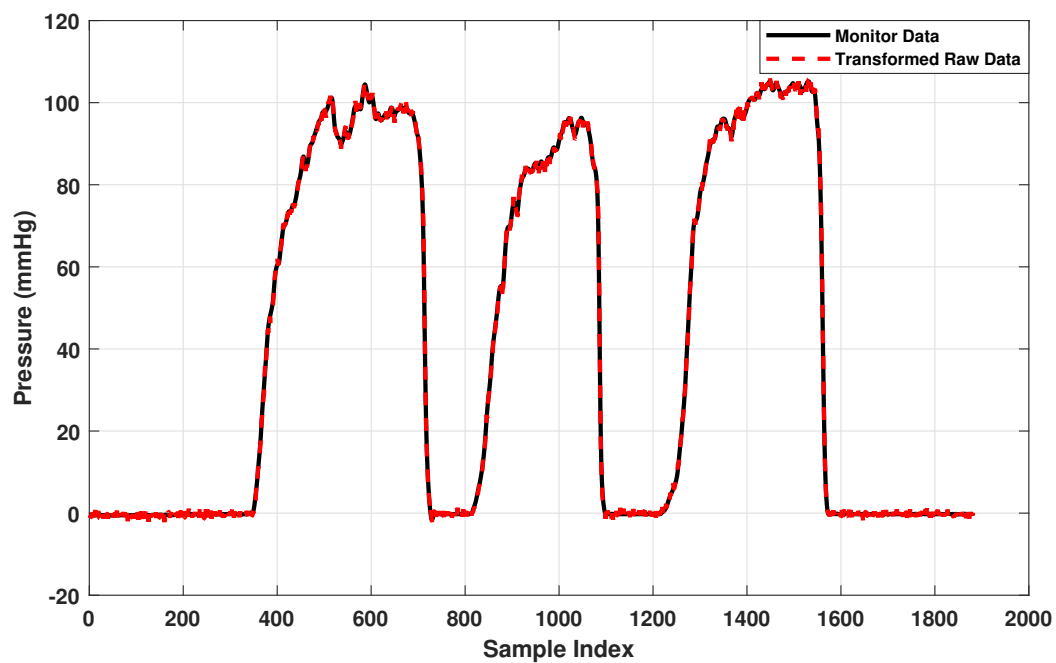


Figure 7.12: Monitor pressure data vs calibrated data from DAQ.

Once calibration values were found, 4 pressure recordings of 5 seconds were made from 4 different DAQ units. The syringe driver setup was repeated, and the results between the Philips monitor and DAQ units were compared. The recordings are shown in Figure 7.13.

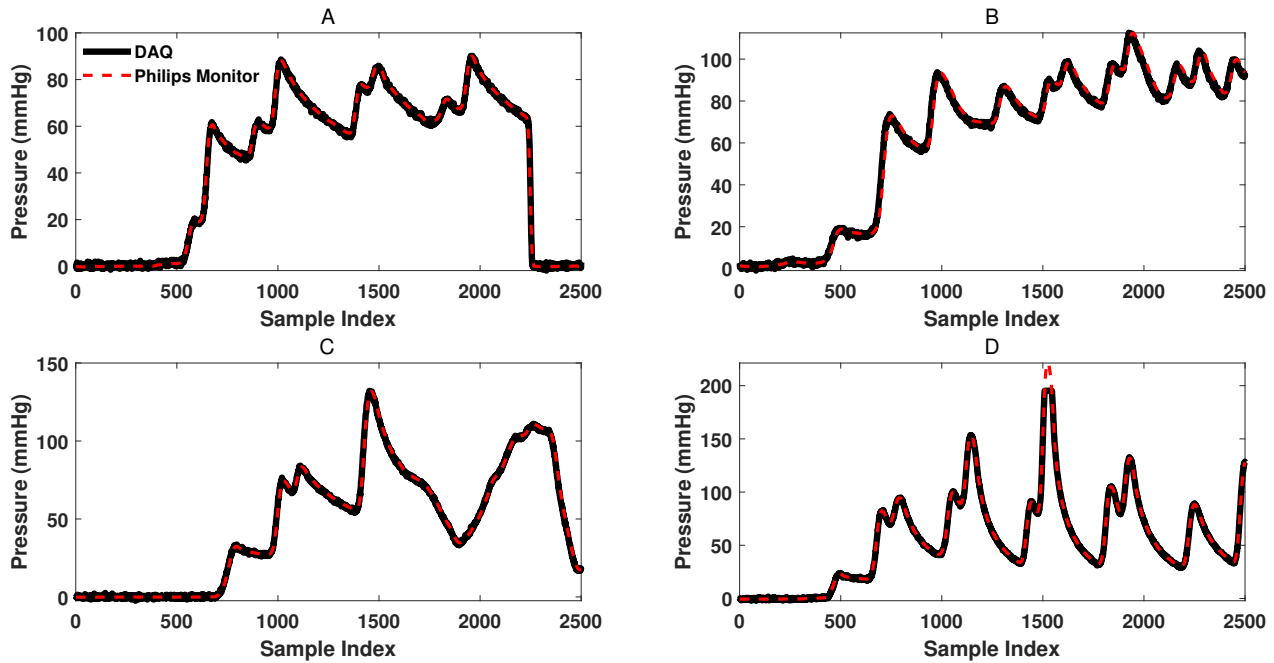


Figure 7.13: Pressure recordings from 4 separate DAQ units compared with simultaneous recording from Philips monitor. Subplots A, B, C and D were recorded by DAQ units 1, 2, 3 and 4 respectively.

A slight difference between recordings can be seen on the largest pressure peak in the fourth block of Figure 7.13. This is because the DAQ unit saturates at 200mmHg. While the recordings of the Philips device did not saturate at this level, the Philips monitors only display pressure up to 150mmHg. The RMS errors as well as the correlation coefficients for each of the recordings are shown in Table 7.1.

The RMS range from 1.17 to 4.37, this could be perceived as high, however, the DAQ data is noisy, and the Philips data is filtered, so a slight RMS is expected. Furthermore, the very strong correlation coefficients confirm the devices ability to

Table 7.1: RMS errors for pressure recordings

Recording	RMS	Correlation Coefficient
1	1.17	0.9997
2	4.37	0.9934
3	2.90	0.9978
4	2.53	0.9978

accurately capture pressure waveforms.

The hanging scales were verified by hanging a variety of known weights on 4 different scales, and ensuring that the GUI displayed the correct reading for each weight.

7.3.1.1 *In-use device calibration*

The pressure sensor calibration is expected to change based on the surrounding atmospheric pressure, which is subject to change depending on environmental conditions. This adds a potential offset error to the data. In order to combat this, the same technique which is used for the Philips bedside machines is used for calibration of the DAQ data. On the python GUI, there is a built in “zero” button, which resets the calibration offset to the current atmospheric conditions. To use it, the pressure sensor must first be exposed to atmospheric pressure, and then the zero button pushed. The pressure sensors have a built in chord, which when pulled, opens a valve and exposes the sensor to atmospheric pressure. This is the same process that clinicians and bedside nurses are accustomed to calibrating pressure sensors attached to the Philips bedside monitor. The process thus adds little to no complexity to the existing bedside calibration procedure. Figure 7.14 and 7.15 show the pressure sensor chord being pulled and the zero button on the python GUI respectively. Pressure sensors are expected to drift over long lifetimes. However, hospital pressure sensors are disposable and drift is not expected for single use.

Likewise, the loadcell offset is expected to change based on the weight of the apparatus used for hanging the fluid bag from it. This is addressed in a similar manner,

with a “zero” button added which can be pressed once the hanging apparatus has been installed.

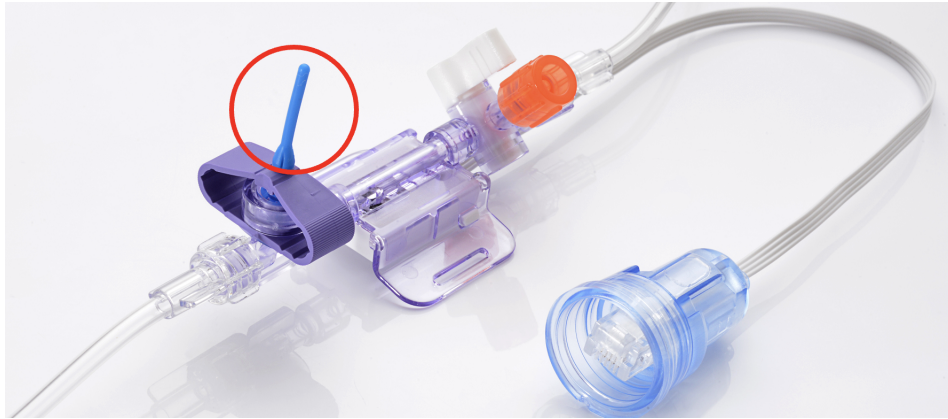


Figure 7.14: Pressure sensor with chord used for exposing sensor to atmospheric pressure circled in red.

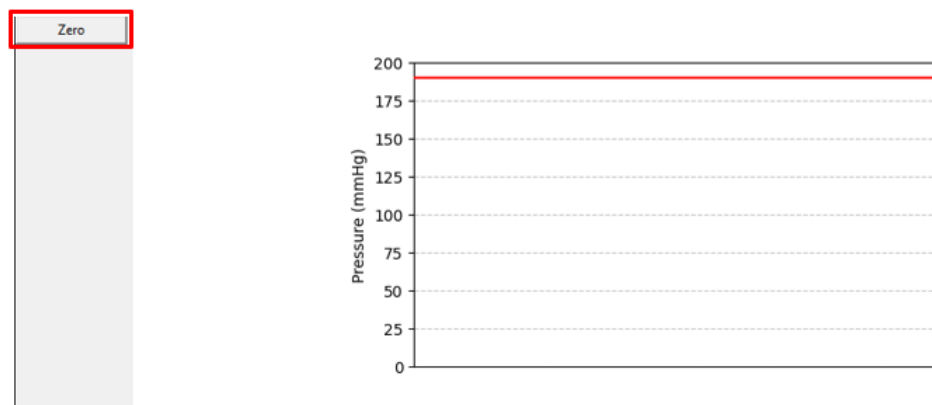


Figure 7.15: Zero button for resetting calibration offset. The zero button is boxed in red.

7.4 *Liege Hospital Trials*

Trials were performed at the University of Liege hospital. The ethics approval document is shown in Appendix A. The trial followed a simple protocol, using the

DAQ to continuously record the following measurements:

- Arterial pressure
- Venous pressure
- Bedside fluid bag weight

As well as the above mentioned measurements, an echocardiogram recording was also taken to capture cardiac volume information required by the 3 chamber model. The following measurements were obtained:

- Stroke volume
- End diastolic volume
- End systolic volume

7.4.1 Trial Protocol

Firstly, patients scheduled to undergo fluid therapy were chosen for the trial. Patients were chosen on this criteria so the full cardiovascular model could be validated retrospectively on its ability to predict fluid responsiveness.

Once a patient was identified, the system was installed in the ICU while the patient received a fluid infusion. The hanging scale was attached to the bedside apparatus, and the fluid bag was hung from the scale. The scale was then connected to port number 4 on the DAQ via an RJ-45 cable. The adaptors were then connected to the existing pressure lines, and the device was connected to the adaptors via RJ-45 cables. The DAQ was then connected to a laptop via USB cable. Once the device was securely connected, and powered on, the Python application was started.

Before recording, the devices, both pressure sensors and the hanging scale, were calibrated, as described in Section 7.3.1.1. Following calibration, data recording was initiated using the record button on the Python application.

Once the python application was recording, a single echo measurement was taken to measure all of the required cardiac volume information, and the information was recorded. The device was allowed 10 minutes to record the baseline cardiovascular state before fluids were administered. Thereafter, fluid infusion was initiated. The fluid infusion consisted of administering 500mL of a saline fluid to the patient. The device recorded for the duration of the infusion. Once the infusion was completed, a further echo measurement was taken to obtain post-fluid cardiac volume information, and the trial was then completed. The device was unplugged from the computer, and the hanging scale and pressure adaptors removed.

7.4.2 Trial Results

The device was used on a total of 3 patients at the University of Liege hospital. The device was setup as per the protocol described previously, and the data was recorded for all patients. Nurses forgot to connect the hanging scale for the second patient, and thus no fluid information was recorded for this patient. 10 second slices of pressure data are shown in Figures 7.16 - 7.18. The fluid data is shown in Figures 7.19 and 7.20.

Patient 1 exhibited atrial fibrillation, illustrated by the irregular beats seen in the arterial pressure wave in Figure 7.16. Patient 2 displayed some ectopic beats, but mostly exhibited a normal cardiac rhythm, and Patient 3 presented a standard cardiac rhythm. The cardiac volume information for the patients both pre and post fluids is summarised in Table 7.2.

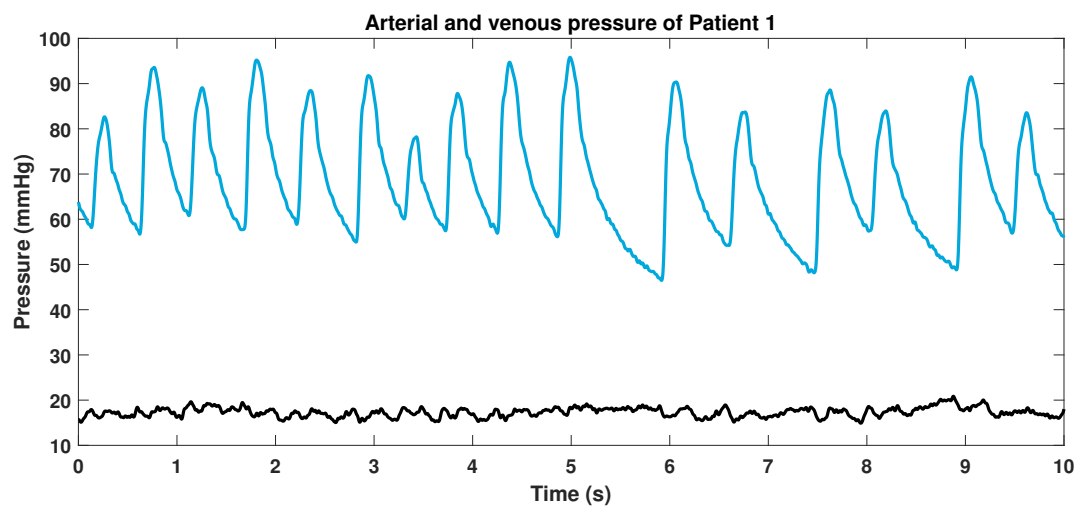


Figure 7.16: 10 second slice of arterial and venous pressure recording for Patient 1. Arterial pressure is shown in blue while venous pressure is shown in black.

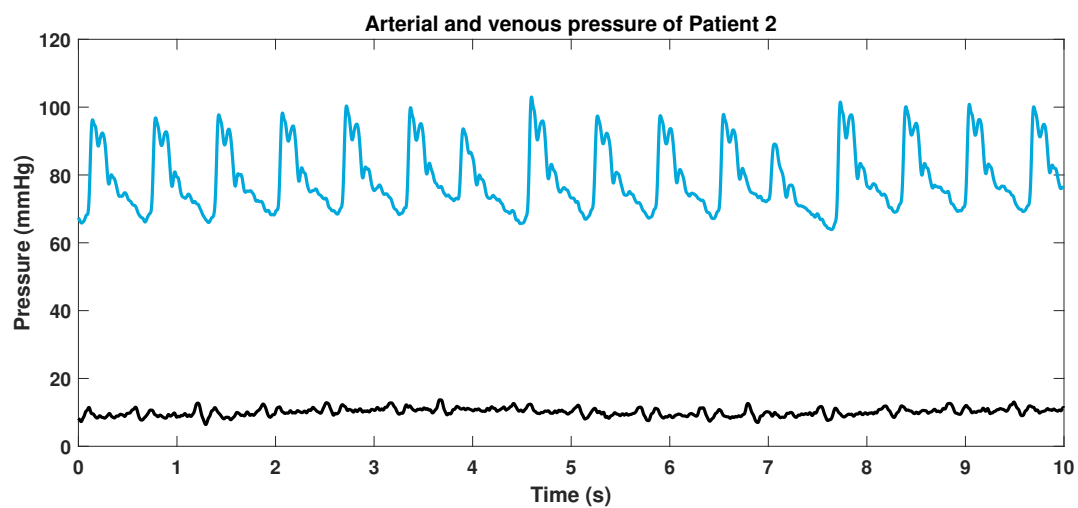


Figure 7.17: 10 second slice of arterial and venous pressure recording for Patient 2. Arterial pressure is shown in blue while venous pressure is shown in black.

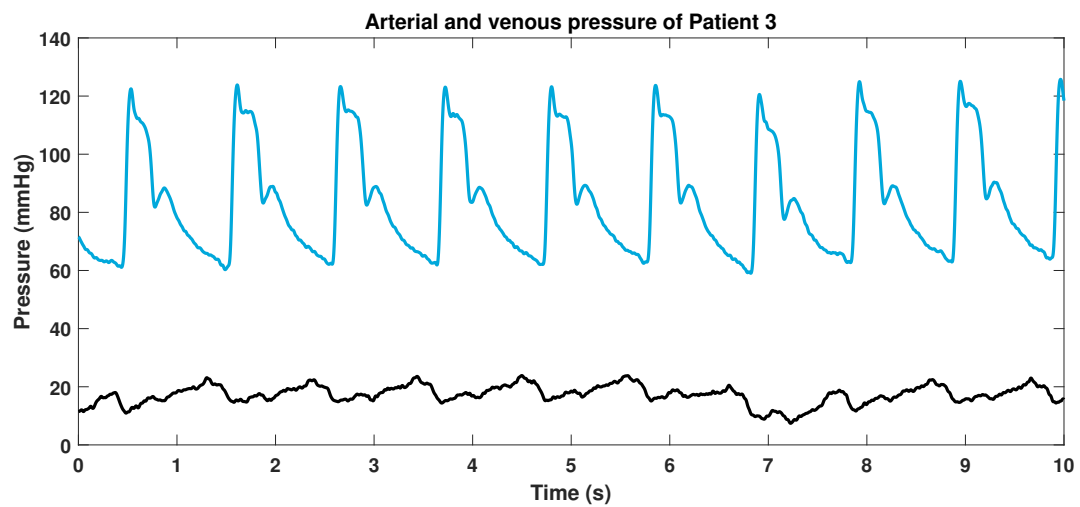


Figure 7.18: 10 second slice of arterial and venous pressure recording for Patient 3. Arterial pressure is shown in blue while venous pressure is shown in black.

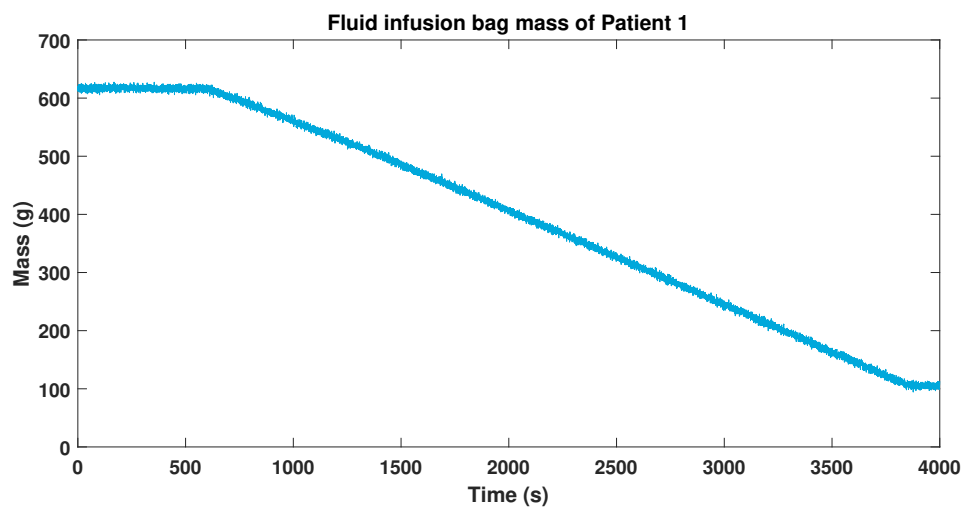


Figure 7.19: Fluid infusion bag mass for Patient 1 over full duration of fluid infusion.

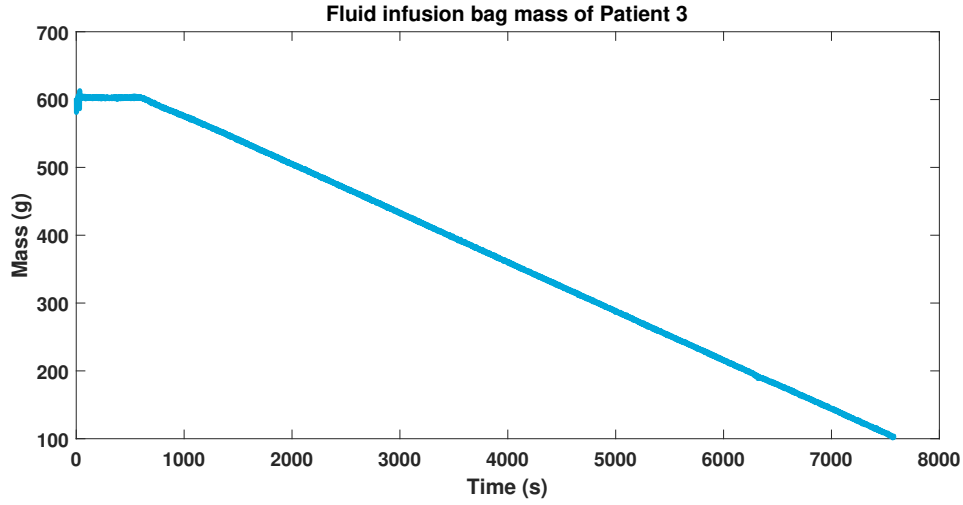


Figure 7.20: Fluid infusion bag mass for Patient 3 over full duration of fluid infusion.

Patient	Pre-Fluids		Post-Fluids	
	EDV (mL)	ESV (mL)	EDV (mL)	ESV (mL)
1	51	26	52	26
2	180	142	160	112
3	103	48	102	41

Stroke volume can be found from these measurements by subtracting ESV from EDV. Cardiac output was obtained by multiplying the SV by heart rate.

7.4.3 Discussion

The trials were executed successfully. Bed side nurses found the device easy to install, and had no complaints. Arterial and venous pressures were acquired for 3 patients undergoing a 500mL fluid infusion. The fluid infusion was also captured for Patients 1 and 3, however, the hanging scale for Patient 2 was not connected correctly and the fluid data was not recorded. Cardiac volume information was

recorded pre- and post-fluids, providing both end-diastolic and end-systolic volume, and thus also stroke volume and cardiac output.

7.5 Summary

This chapter presented a novel data capture system for use in the ICU. The device was able to simultaneously record 3 pressure inputs, and 1 input from a hanging scale used for measuring the weight of the fluids administered to a patient. The system was made up of a custom designed PCB controlled by an Arduino nano microcontroller, and a custom made adaptor which allowed the system to record pressure signals without the need for additional pressure sensors, or interfering with the bedside measurements. Data was displayed and recorded using a python desktop application. The device was used successfully in a clinical trial in Liege. The system was easy to install, and no problems were encountered in the recording of data. In total, the system was used to record data from 3 patients who underwent a fluid infusion.

Chapter VIII

The Secondary Systolic Shoulder

8.1 Introduction

The late systolic shoulder (SBP_2) is an important point in the cardiac cycle. It is used to define augmentation index (AIx), which is a key indicator of arterial stiffness and left ventricular afterload [118–122]. AIx has multiple definitions, but is most often defined as either the ratio of SBP_2 to the early systolic shoulder [121], or as the ratio of the difference of SBP_2 and the early systolic shoulder, and the pulse pressure, giving AIx as a percentage of pulse pressure [118].

SBP_2 and pulse augmentation are caused by wave reflections in the arterial system. Wave reflections are generated at any impedance mismatch site in the arterial system including arterial bifurcations, blood vessel tapering and the high resistant peripheral vascular bed. These reflections interfere with forward travelling waves, causing constructive interference in pressure waves, and destructive interference in flow waves. The timing of this interference determines the magnitude of SBP_2 and AIx.

In healthy, young individuals, the reflected wave tends to arrive later in the cardiac cycle, which results in a smaller SBP_2 , causing a smaller AIx. However, in patients with stiffer arteries, such as elderly patients, waves travel faster, and the reflected wave intercepts the forward wave earlier in the cycle. This results in a larger SBP_2 and AIx.

Further, SBP_2 is also an important input for cardiovascular modelling, specifically in the use of arterial transfer functions. Arterial transfer functions are used to recreate aortic pressure from peripheral pressure waveforms, since aortic pressure is not usually clinically available due to its highly invasive nature. SBP_2 is often used as an important input in the objective function of such transfer functions [123].

Aortic pressure is also a key indicator of overall cardiovascular health [124, 125]. It is thus crucial input to cardiovascular models used for identifying important cardiovascular parameters [1, 16, 41, 123]. Thus, overall, SBP_2 is a crucial point for reliable identification of important cardiovascular parameters.

Despite its clinical importance and usefulness, SBP_2 is not very clearly defined. SBP_2 is generally taken to mean the late peak in the aortic pressure, as shown in Figure 8.1. In some cases, there are two obvious peaks, making SBP_2 easy to identify, both visually and mathematically. However, in many cases, the peaks are far less obvious, and are often indistinguishable, both visually and by mathematical methods, as depicted in Figure 8.2. SBP_2 is also a highly patient specific point, and identifying it by mathematical means is highly challenging.

Takazawa *et. al.* posed a method for identifying SBP_2 using the fourth derivative of aortic pressure [126], which has since been widely adopted in the literature [32]. However, this method is a generalisation, and several cases of erroneous results have been reported [127–129]. These studies all reported AIx measures of over 50%, which should not be possible [32]. There are also devices available which use proprietary algorithms for locating SBP_2 , such as SphygmoCor. However, even with these clinically approved devices, studies have encountered cases where SBP_2 was indeterminable [130].

This study uses the data presented in Chapter 3 to evaluate previous algorithms posed for identifying SBP_2 , as well as separating invasive aortic blood pressure measurements waves into their constituent components to identify the determinants of SBP_2 and provide a clearer understanding of what exactly SBP_2 is.

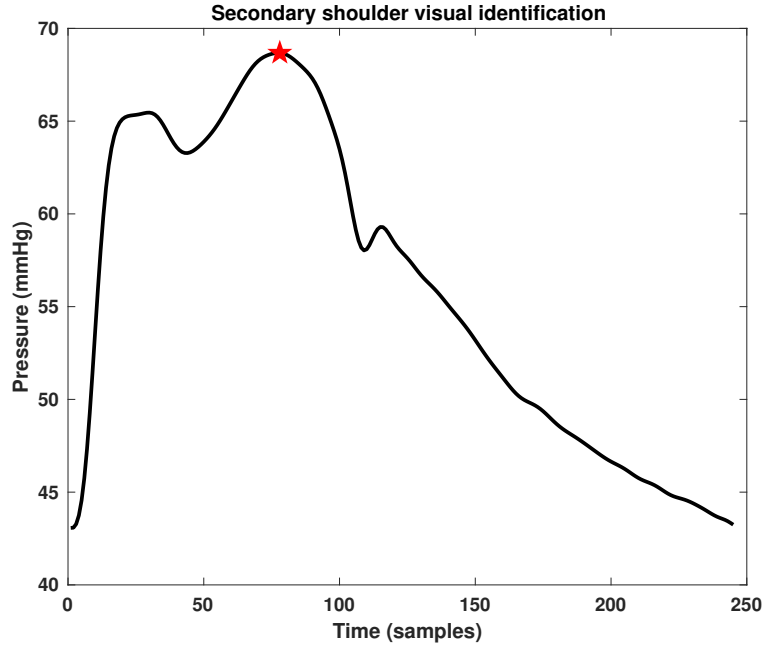


Figure 8.1: Visual identification of SBP_2 . SBP_2 can be visually identified as the second peak occurring during systole, marked by the red star.

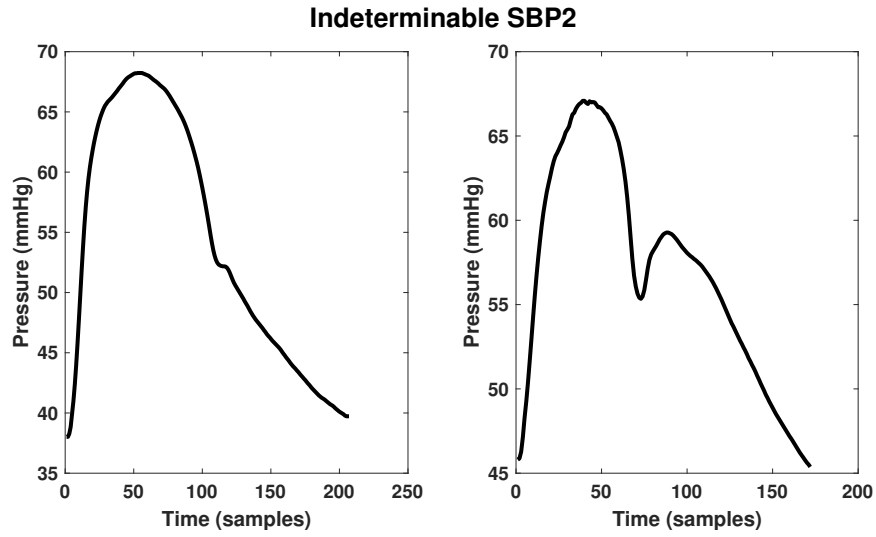


Figure 8.2: Aortic pressure waves displaying different types of indeterminable SBP_2 points. The first wave has a reflected wave which arrives very early in systole, and the second wave has very late arriving reflected wave.

8.2 Waveform Decomposition

The aortic pressure wave can be decomposed into its forward and reflected waves using the reflection coefficient:

$$\Gamma = \frac{Z_{in} - Z_c}{Z_{in} + Z_c} \quad (8.1)$$

$$P_f = \frac{P_{ao}}{1 + \Gamma} \quad (8.2)$$

$$P_b = \Gamma P_f \quad (8.3)$$

where P_{ao} , P_f , and P_b are the aortic, forward and reflected pressure waves respectively, Γ is the reflection coefficient, and Z_{in} and Z_c are the input and characteristic impedance of the aorta respectively.

Input impedance can be found using the Fourier series approximations of aortic pressure and flow:

$$Z_{in}(j\omega) = \frac{P_{ao}(j\omega)}{Q_{ao}(j\omega)} \quad (8.4)$$

where $Z_{in}(j\omega)$ is the input impedance Fourier series, $P_{ao}(j\omega)$ is the aortic pressure Fourier series and $Q_{ao}(j\omega)$ is the aortic flow Fourier series. Matlab's fft algorithm was used to transform aortic pressure and flow into their Fourier series equivalents.

Characteristic impedance can be approximated by taking the mean of the upper harmonics of input impedance. Varying harmonic intervals have been used throughout the literature. This work chose to use harmonics 4 - 10, which was in line with other works [131, 132].

The characteristic and input impedance were used to calculate the reflection coefficient using Eq. 8.1. Thereafter, the forward and reflected waves were calculated using Eq. 8.2 and Eq. 8.3 respectively. The forward and reflected waves were then

converted back into the time domain using Matlabs ifft algorithm.

8.3 Determining of SBP_2

Takazawa *et. al.* used the fourth derivative of the aortic pressure wave with respect to time (d^4P_{ao}) is used to determine SBP_2 [126]. If the gradient of d^4P_{ao} corresponding to aortic peak pressure is positive, this point is used as SBP_2 . If the slope of d^4P_{ao} corresponding to peak aortic pressure is negative, the third zero crossing from below to above is used to determine SBP_2 .

8.4 Analyses

Once all forward and reflected waves and SBP_2 points were calculated, forward and reflected waves were verified by matching the peak of the forward wave to the peak of aortic flow, since the peak of the forward wave should coincide with the peak of flow [122]. The SBP_2 points were verified by visually identifying SBP_2 in 100 beats per pig and comparing it to computed SBP_2 values. Beats were chosen if they showed a prominent secondary peak which could be easily visually identified. An example of a visually identified SBP_2 is shown in Figure 8.1.

The percentage of correctly identified points was recorded. For incorrectly calculated points, the average error (in samples) between correct and incorrect points was recorded. To better understand SBP_2 , and any potential determinants, the relationship between SBP_2 and the forward and reflected waves was examined, specifically looking at the shapes of the forward and reflected waves compared to the location of SBP_2 .

8.5 Results

8.5.1 Waveform Decomposition

Waveform decomposition was verified by ensuring the peaks of the forward pressure wave and the aortic flow wave matched. From the 4 pigs, a total of 8691 beats were decomposed. The error between the forward wave peak and peak flow was calculated as a percentage of the total beat length. The overall error across all beats for all pigs was $4.29 \pm 2.87\%$. The error for each pig is shown in Table 8.1. It should be noted that flow waveforms are very noisy, and noise present may cause a slight shift in perceived peaks, which causes peak values to slightly vary from beat to beat. Despite this, the small errors show the peaks of flow and forward waves align, demonstrating the forward wave has been correctly identified. A decomposition from each pig is shown in Figure 8.3.

Table 8.1: Flow and forward wave peak errors

Pig	Error (%)
1	4.93 ± 2.14
2	2.39 ± 1.81
3	5.81 ± 3.23
4	3.92 ± 1.55

8.5.2 SBP_2

SBP_2 was calculated using the method proposed by [126]. The location of SBP_2 was verified by means of visual inspection, by inspecting 100 beats from each pig. The location of the secondary shoulder was taken as any visible late systolic peak. The secondary shoulder was deemed to have been correctly identified if it fell within a 10 sample window of the visually identified SBP_2 . The percentage of correctly identified secondary systolic shoulder points is shown in Table 8.2.

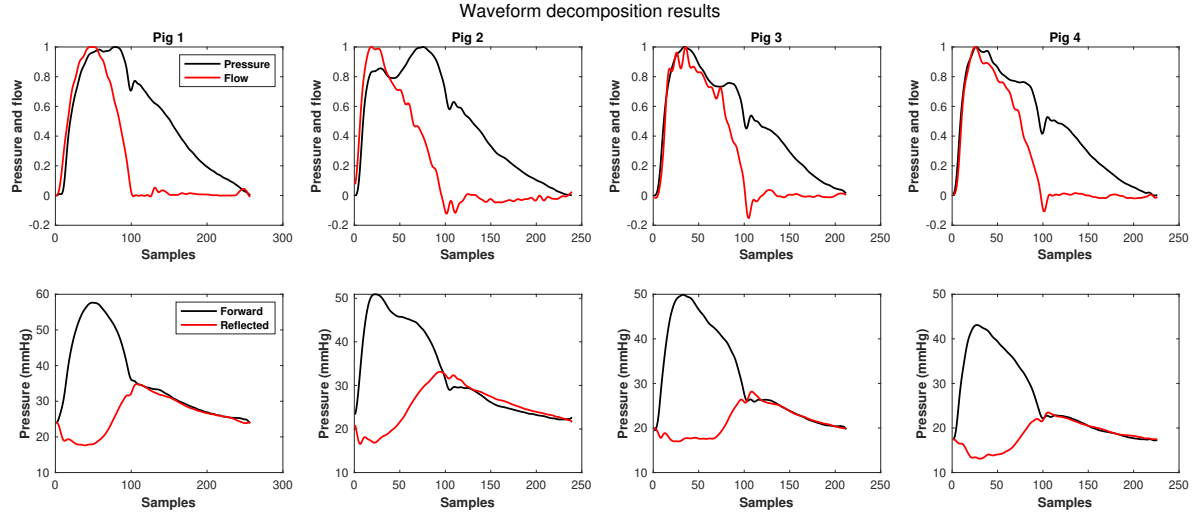


Figure 8.3: Pressure decomposition of a beat from each pig. The top row shows the aortic flow and pressure wave for each pig, normalised to a peak flow and pressure of 1, and the lower row shows the corresponding decomposed forward and reflected pressure waves.

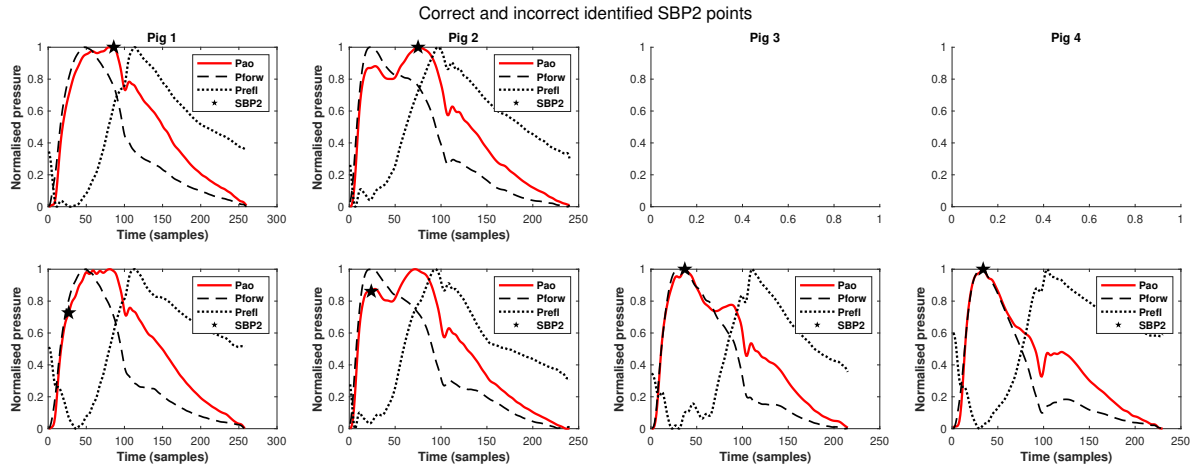


Figure 8.4: Identified SBP_2 for all pigs. The upper row of plots represent correctly located points, while the lower row represents incorrectly located points. Aortic pressure, the forward wave, and the reflected wave are represented by the red, black dashed and black dotted lines respectively. SBP_2 is represented by the star. Note Pig's 3 and 4 had no correctly identified SBP_2 points.

For incorrect beats, the average error (in samples) is also recorded in Table 8.2. Examples of a correct and incorrect identification of SBP_2 for each pig is shown in Figure 8.4. Pig's 3 and 4 displayed a 0% success. This failure was because the peak of the aortic pressure wave always coincided with the primary shoulder, and the third zero crossing from above to below of the 4th derivative always occurred before this peak. The algorithm was thus not capable of finding SBP_2 for these pigs.

Table 8.2: Secondary shoulder errors.

Pig	Correctly identified (%)	Error(samples)
1	58	38.09 ± 18.57
2	71	51.37 ± 3.17
3	0	54.32 ± 6.79
4	0	51.42 ± 3.70

8.5.3 SBP_2 and the forward and reflected wave

The reflected wave was plotted alongside the aortic pressure and SBP_2 to gain further insight into the relationship between SBP_2 and the reflected wave. Figure 8.5 shows a reflected and aortic waves and SBP_2 for each pig. Unsurprisingly, SBP_2 occurs near the peak of the reflected wave, and the inflection point occurring in the aortic pressure wave preceding SBP_2 can be seen to occur just after the foot of the reflected wave. The same 100 beats were analysed, and the distance between the visually identified SBP_2 and the peak of the reflected wave was recorded. The gap between the peak of the reflected wave and SBP_2 remained relatively constant, and the results are shown in Table 8.3.

Table 8.3: Distance between reflected wave peak and SBP_2

Pig	Distance (samples)
1	30.42 ± 2.47
2	22.45 ± 5.46
3	23.8 ± 5.46
4	22.18 ± 1.01

Figure 8.6 shows SBP_2 plotted on top of the forward wave. As can be seen from the figure, the forward may also possess a shoulder where SBP_2 is located. This shows the exact location of SBP_2 is not only dependent on the timing of the reflected wave, but also on the shape of the forward travelling wave.

8.6 Discussion

8.6.1 Calculated SBP_2

The proposed method from [126] did not perform well on this data. For 2 of the pigs, it could not correctly identify SBP_2 in any beats. The other 2 pigs showed a 58% and 71% success rate. This result is indicative of the highly variable nature of the secondary systolic shoulder and a simple count of fourth derivative features is insufficient to identify it.

The poor performance of the algorithm is due to several factors. First, while it is likely the algorithm developed by [126] best suited their data and provided good results, it is a generalisation, and does not adapt well to other data. Second, even if the method was patient specific, it uses 4th derivatives for the identification of SBP_2 and is thus highly susceptible to noise. Even small amounts of noise in the original waveform can result in large oscillations in the 4th derivative. The data used in this study is considered to be much higher fidelity than data from bedside machines. However, the noise present still posed a large problem, and rendered the zero crossing method highly inaccurate. It is possible to heavily filter the original

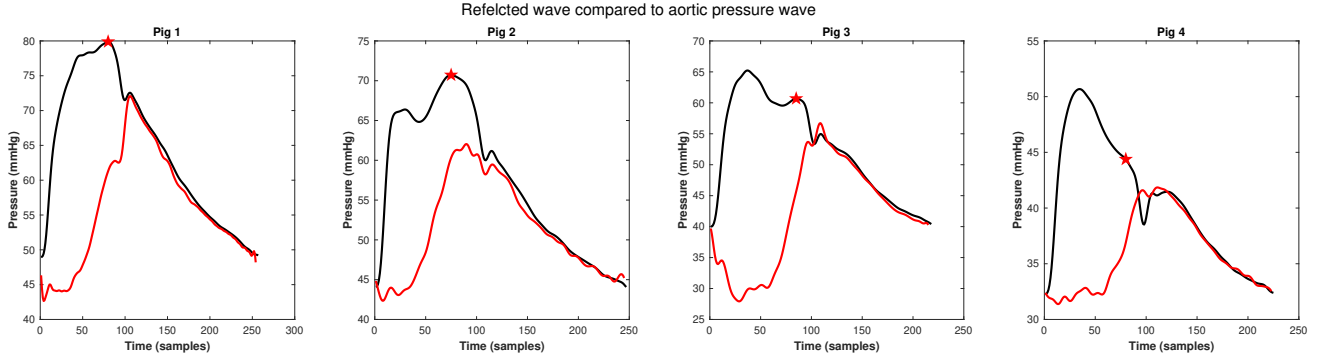


Figure 8.5: Reflected wave compared to aortic pressure wave and SBP_2 . The reflected wave is plotted in red, the aortic wave in black and SBP_2 is the red star. The magnitude of the reflected wave has been doubled for better visual comparison.

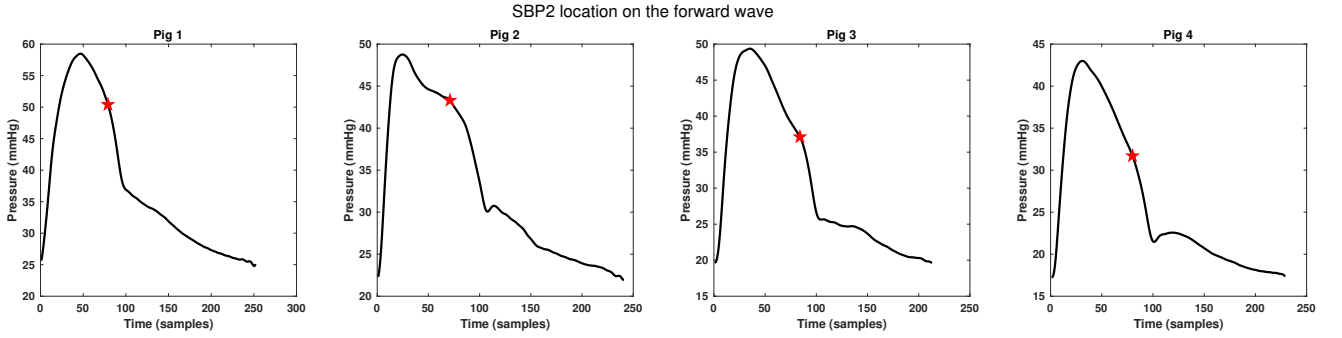


Figure 8.6: SBP_2 plotted on the forward wave for all pigs. The forward wave is plotted in black and SBP_2 is represented by the red star.

waveform. Equally, heavy filtering causes information loss from the waveform, and important features in the 4th derivative may be lost, which may also yield incorrect results.

8.6.2 SBP_2 and the forward and reflected waves

The above-mentioned flaws of the algorithm are not the only problems when attempting to identify SBP_2 . It is also the blurry definition of SBP_2 itself. Usually, SBP_2 is taken to mean the late peak in systole caused by wave reflections. However, there is often no distinguishable second peak. Indeed, as shown in Figure

8.2, SBP_2 is indistinguishable. SBP_2 is largely dependent on 3 major factors: timing; magnitude; and shape of the reflected wave. Figure 8.2 depicts two cases: 1) the reflected wave arrives early enough in systole for it to create one large peak, where neither the early or late shoulders are identifiable; and 2) the reflected wave arrives late enough for there to be little to no visible effect in systole and SBP_2 is not determinable. Therefore, it is insufficient to design an algorithm which just searches for a second peak or inflection point during systole.

A more appropriate definition of the secondary shoulder would be the point of maximum interaction between the forward and reflected wave. This point usually occurs close to the peak of the reflected wave. However, it also occurs very near to the shoulder of the forward wave, showing SBP_2 is also dependent on the shape of the forward wave.

On some forward travelling waves, there is a clear shoulder in late systole. The shoulder on the forward wave could be caused by late atrial ejection during systole. It could also be due to a reflected wave reaching the terminal of the aorta and then re-reflected, becoming a forward travelling wave again. Since this waveform decomposition can only decompose the aortic waveform into a net forward and net reflected wave, it is not possible to tell if this issue could be the cause.

Important timing locations on the reflected wave, such as the foot and peak, and any potential identifiable shoulders on the forward wave may assist in locating SBP_2 . However, in a clinical setting, there is no access to the flow wave, and waveform decomposition would not be possible. [133] performed waveform decomposition using aortic pressure alone. Since only peripheral arterial pressure is available in an ICU setting, this approach could be performed on peripheral arteries as well. However, the flow waveform in peripheral arteries is more complex than aortic flow, and, to the authors knowledge, there is little to no information on simple modelling of a peripheral flow waveform from peripheral pressure in the literature. The inverse relationship may also apply between SBP_2 and the reflected waves. SBP_2 gives important timing information as to the whereabouts of the reflected wave, and may be used to estimate reflected wave timings in absence of a flow waveform.

8.7 Summary

This work investigated an established method for determining SBP_2 , as well as investigating the determinants of SBP_2 and its relationship with the forward and backward waves. Ultimately, the method posed by [126] for finding SBP_2 did not perform well, and was unable to locate SBP_2 in any beats for 2 of the 4 pigs. The poor performance of this algorithm is likely due to the fact this algorithm relies on the fourth derivative of pressure, which is highly sensitive to noise. However, the method is also a generalisation, and while it may have fitted the original data set well, it does not appear to adapt well to other data. Given the patient specificity of SBP_2 , it seems clear any generalised algorithm used for identifying SBP_2 would likely be susceptible to similar issues, and any works using such algorithms should apply caution in doing so.

SBP_2 functions as an important point for determining clinical metric such as AI_x , as well as a model input for identifying central pressure from peripheral pressures. Accurate identification of SBP_2 could prove crucial for cardiovascular assessment, as well as model based clinical care. Given its patient specific nature, a patient specific algorithm is required to accurately and reliably identify SBP_2 . Waveform decomposition is a simple method which can be used to assist identifying in SBP_2 . Currently, given flow waveforms are not usually available clinically, waveform decomposition may not be possible in a clinical setting. However, as shown by [133], this issue could be overcome by simple modelling of the flow waveform.

Chapter IX

Clinically Feasible 3 Chamber Model

9.1 Introduction

Given its proximity to the heart, the aortic pressure wave contains a large amount of information pertaining to the overall cardiovascular status of a patient, and potential future cardiac events [104, 125, 134–136]. Furthermore, major organs of the body are subjected to central pressure, rather than peripheral pressures [137]. However, given its highly invasive nature, aortic pressure measurements are generally not clinically available.

In Chapter 4, the 3 chamber model was introduced and validated on a reduced measurement set, where both P_{lv} and V_{lv} were estimated from the aortic pressure wave. The method was able to reliably capture fundamental system dynamics and identify important haemodynamic parameters. However, as aortic pressure is not usually clinically available, an aortic pressure surrogate must also be found to use the model clinically.

Models of the arterial system are used to extract information about central pressure from readily available peripheral pressure measurements [1, 102–104, 123, 138–140]. These models range in complexity from simple lumped parameter models to complex high dimensional 3D models. For a model to be clinically feasible, it must rely on clinically available measurements. Thus, high dimensional models would not be suitable due to their complexity, lack of identifiability, and high computational costs [141].

Arterial transfer function have been used to estimate aortic pressure from downstream arterial pressure measurements [104, 123, 142–147]. Arterial transfer functions have been commonly implemented using population based relations to create a generalised transfer function (GTF). A GTF is obtained using a database of recordings from patients, where both central and peripheral pressure are known. Population based functional relations are derived from the ratio of amplitude and phase of waveform harmonics obtained via Fourier analysis of the pressure waveforms [148].

The GTF is then obtained by averaging these relations over a population experiencing a range of different haemodynamic states. The GTF is then applied to new patients to estimate central pressure from peripheral pressure measurements. Other studies have expanded on the harmonic ratios of pressure waves, using autoregressive exogenous models to identify model parameters relating central and peripheral pressures and then creating a population based average of model parameters [149]. However, the limitations of the GTF are clear.

Most importantly, any generalised solution will not provide an optimal solution to individual-specific problems. Such transfer functions are thus poorly suited to clinical scenarios where both inter- and intra- patient variability are present and significant.

One form of modelling the arterial system to identify central pressure from peripheral pressure is the arterial transfer function (TF). The TF uses a simple tube-load (TL) model to describe the propagation path from central arterial pressure to peripheral sites. A simple TL model assumes uniform, lossless tubes where the arterial pulse wave propagates to terminal sites without distortion, where they are reflected by the reflection coefficient, determined by the impedance mismatch between the load and the tube, described in Equation 9.8. Figure 9.1 depicts a simple tube load model. The arterial system contains many parallel branches, and thus, would be represented by many tubes and reflections sites. However, in contrast, generally, only 1 arterial line is clinically available.

This chapter presents a previously validated, simple arterial transfer function, used in conjunction with the 3 chamber cardiovascular model, yielding a clinically

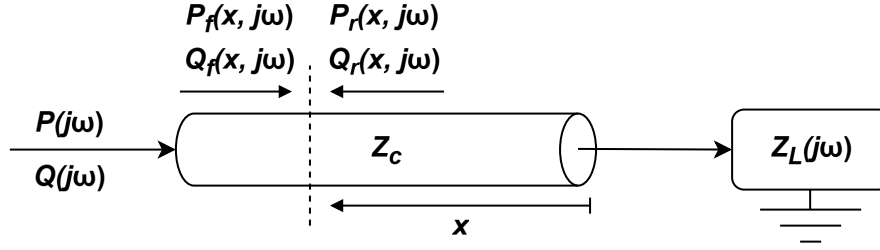


Figure 9.1: Tube-load model representing pulse propagation through the arterial system.

feasible model capable of identifying SBV from clinically available datasets. This clinically feasible model and approach is validated using the experimental pig data from the University of Liege, where model outputs and identified parameters are compared to those obtained from the full measurement set in Chapter 4.

9.2 Arterial Transfer Functions

Pressure and flow at any point along a tube is defined by the combination of forward and reflected waves:

$$P(x, j\omega) = P_f(x, j\omega) + P_r(x, j\omega) \quad (9.1)$$

$$Q(x, j\omega) = Q_f(x, j\omega) + Q_r(x, j\omega) \quad (9.2)$$

where $P(x, j\omega)$ and $Q(x, j\omega)$ are the pressure and flow at a point x along the tube, and P_f and P_r , and Q_f and Q_r represent the forward and reflected components of the pressure and flow waves.

The relationship between pressure and flow for forward and reflected waves is defined by the characteristic impedance of the tube (Z_c):

$$Q_f(x, j\omega) = \frac{P_f(x, j\omega)}{Z_c} \quad (9.3)$$

$$Q_r(x, j\omega) = -\frac{P_r(x, j\omega)}{Z_c} \quad (9.4)$$

The forward and reflected waves at any point x along the tube can be represented by the distal forward and reflected waves shifted by a time constant:

$$P_f(x, j\omega) = P_f(0, j\omega)e^{j\omega T} \quad (9.5)$$

$$P_r(x, j\omega) = P_r(0, j\omega)e^{-j\omega T} \quad (9.6)$$

where $P_f(0, j\omega)$ and $P_r(0, j\omega)$ are the forward and reflected waves at the distal end of the tube, and the distal end of the tube is represented by $x = 0$.

The time constant, T is dependent on the length of the tube, d , the point x of the tube, and the time it takes for a pulse to travel down the tube, known as the pulse transit time (PTT):

$$T = \frac{x}{d}PTT \quad (9.7)$$

As shown in Section 2.2, the reflection coefficient is defined by the impedance mismatch between a tube and its terminal impedance:

$$\Gamma(j\omega) = \frac{Z(j\omega) - Z_c}{Z(j\omega) + Z_c} \quad (9.8)$$

Where $Z(j\omega)$ is the frequency dependent load impedance and Z_c is the characteristic impedance of the tube.

Using the reflection coefficient, the reflected wave is then calculated:

$$P_r(j\omega) = P_f(j\omega) \cdot \Gamma(j\omega) \quad (9.9)$$

Substituting Equation 9.9 into Equation 9.6, and summing with Equation 9.5 gives the resulting peripheral pressure at point x along the tube:

$$P_p(x, j\omega) = P_f(0, j\omega)[e^{j\omega T} + \Gamma(j\omega)e^{-j\omega T}] \quad (9.10)$$

where $P_p(x, j\omega)$ is the peripheral pressure.

Using Equations 9.3 and 9.4, the equation can be used to derive the corresponding flow waveform:

$$Q_p(x, j\omega) = \frac{P_f(0, j\omega)[e^{j\omega T} - \Gamma(j\omega)e^{-j\omega T}]}{Z_c} \quad (9.11)$$

The arterial transfer function defines the relationship between central and peripheral arterial pressure, where peripheral pressure is pressure at $x = 0$ in the tube, and central pressure is the input pressure to the tube at $x = d$, where d is the length of the tube. Substituting $x = 0$ and $x = d$ into the time constant, the transfer function is thus defined:

$$\frac{P_p(j\omega)}{P_c(j\omega)} = \frac{P_f(0, j\omega)[1 + \Gamma(j\omega)]}{P_f(0, j\omega)[e^{j\omega PTT} + \Gamma(j\omega)e^{-j\omega PTT}]} \quad (9.12)$$

The corresponding transfer function for central flow is derived using Equations 9.3 and 9.4, yielding:

$$\frac{Q_c(j\omega)}{P_p(j\omega)} = \frac{e^{j\omega PTT} - \Gamma(j\omega)e^{-j\omega PTT}}{Z_c(1 + \Gamma(j\omega))} \quad (9.13)$$

Equations 9.12 and 9.13 are used by many models for deriving central pressure from peripheral pressure [123, 142–147, 150]. These models differ in how they define the load used to describe the terminal impedance. This work uses a simplistic pole-zero load, defined:

$$Z_L(\omega) = \frac{Z_c(j\omega + B)}{j\omega + A} \quad (9.14)$$

where A and B characterise the capacitance and resistance of the tube and are bounded by $0 < A < B$.

Substituting Equation. 9.14 into Equation 9.8, the resulting reflection coefficient is substituted into Equation 9.12, yielding:

$$\frac{P_c(j\omega)}{P_p(j\omega)} = \frac{(\frac{B+A}{2} + j\omega)e^{j\omega PTT} + \frac{B-A}{2}e^{-j\omega PTT}}{B + j\omega} \quad (9.15)$$

$$\frac{Q_c(j\omega)}{P_p(j\omega)} = \frac{(\frac{B+A}{2} + j\omega)e^{j\omega PTT} - \frac{B-A}{2}e^{-j\omega PTT}}{Z_c(B + j\omega)} \quad (9.16)$$

These relationships can then be converted into their discrete time difference equations by converting the functions from the Fourier domain into their z-domain transfer functions, and finally converting from z-domain into a discrete time difference equation [151], yielding:

$$p_c[n] = \alpha p_c[n-1] + \beta p_p[n+ptt] - \alpha p_p[n+ptt-1] + (1-\beta)p_p[n-ptt] \quad (9.17)$$

$$q_c[n] = \frac{\alpha p_c[n-1]}{Z_c} + \beta p_p[n+ptt] - \alpha p_p[n+ptt-1] - (1-\beta)p_p[n-ptt] \quad (9.18)$$

where n is the discrete time step, ptt is the discrete time representation (in samples) of PTT , and where:

$$\alpha = \frac{f_s}{B + f_s} \quad (9.19)$$

$$\beta = \frac{\frac{B+A}{2} + f_s}{B + f_s} \quad (9.20)$$

where α and β are bounded by $0 < \alpha < \beta < 1$.

9.3 Parameter Identification

The greatest challenge of the TF is the lack of direct measurements to use for an objective function. Since neither aortic pressure or flow are available in a clinical setting, the objective function is made from physiological assumptions relating peripheral pressure to central pressure.

Both peripheral and central pressure are largely determined by wave reflection dynamics, and the interaction between P_f and P_r , which pass through both sites. Thus, identifying specific features relating to these component waveforms on the peripheral pressure wave can yield information relating to central pressure, which can be used for the objective function. These identified features can be combined with simple physiological assumptions about wave propagation to construct initial estimates of aortic pressure and flow, $P_{ao,est}$ and $Q_{ao,est}$ [123]. These waveform estimates can then be used in the TF objective function to constrain the optimisation problem.

9.3.1 Estimating Aortic Pressure

Estimated aortic pressure can be defined using 5 characteristic features, maximum positive gradient (MPG), the timing of the central primary and secondary systolic shoulders (t_{SBP_1} and t_{SBP_2}), the magnitude of the peripheral secondary systolic shoulder ($pSBP_2$), and the timing of end-systole (t_{es}).

As previously mentioned, $pSBP_2$ is highly challenging to identify, given its unclear definition, and generic methods for identification should be avoided. Thus, $pSBP_2$ should be identified on a case by case basis. The method used by Murphy *et.*

al. is employed in this work for identification of $pSBP_2$ [123]. Pressure waves are classified into 2 separate types, dependant on the arrival time of the reflected wave, where the reflected wave is classified as either early or late arriving. Following waveform classification, a combination of features from both the second and fourth derivative are used to identify $pSBP_2$.

Once $pSBP_2$ is identified, t_{SBP_2} can be assumed to occur at some point after $pSBP_2$ and before t_{es} , given the reflected wave arrives later to central sites than it does at peripheral sites. This point is set at the minimum of the second derivate of the peripheral pressure waveform between $pSBP_2$ and t_{es} [123]. Thereafter, t_{SBP_1} is simply set to 30% of the ejection duration [133], and the magnitude at both t_{SBP_1} and t_{SBP_2} is set to the magnitude of $pSBP_2$.

9.3.2 Estimating Aortic Flow

Determining actual flow values from pressure is not possible without knowledge of the impedances of the tube. However, the contour of the flow waveform can be inferred from the previously identified characteristic points. The flow estimation makes use of a quadrangle estimation approach, rather than the classic triangular approach [133], which allows for capture of the deceleration effects caused by the arrival of the reflected wave [123].

The flow wave rises from zero to a peak flow. Peak flow is assumed to occur simultaneously with peak peripheral pressure, as the peak of pressure and flow are largely determined by the peak of the forward wave. However, unlike the pressure amplification experienced due to the arrival of the reflected wave, the flow wave experiences a deceleration due to the reflected wave travelling in the opposite direction to the forward wave.

To address this point, an inverse augmentation index is created to quantify flow deceleration. The augmentation index (AI) is a measure of pulse pressure amplification. The pulse pressure from the previously identified $P_{ao,est}$ is used to determine *AI*:

$$AI = \frac{PP_{peri}}{PP_{ao,est}} \quad (9.21)$$

Where PP_{peri} and $PP_{ao,est}$ are the pulse pressures of the measured peripheral pressure wave and the estimated aortic pressure wave respectively.

The resulting flow drop (Q_{drop}) is then found using the following relationship:

$$Q_{drop} = 1 - \frac{1}{AI} \quad (9.22)$$

Q_{drop} is used to quantify the drop from max flow (Q_{max}) to the flow at t_{pSBP_2} . The remainder of the systolic portion of the flow pulse then drops to zero from t_{pSBP_2} to t_{es} . The diastolic portion of the flow wave is then assumed to be zero, since the presence of the aortic valve prevents the possibility of backflow during diastole.

Once $P_{ao,est}$ and $Q_{ao,est}$ are found, they are used for the objective function, where the RMSE is calculated between the TF identified pressure and flow and $P_{ao,est}$ and $Q_{ao,est}$.

9.3.3 Exclusion of Pig 6

As previously mentioned in Section 3.1.1, Pig 6 experienced an issue with its femoral pressure catheter, where mean femoral pressure was always greater than aortic pressure, which is physiologically impossible. While this issue is less important when using the full measurement set 3 chamber model, the clinically feasible model used in this chapter relies on accurate peripheral pressure measurements as an input to the arterial transfer function. Without femoral pressure, a clinically feasible 3 chamber model is not possible. Thus, Pig 6 was excluded from the analysis in this chapter.

9.4 Analysis

The clinically feasible results are compared to results obtained from the full measurement set in Chapter 4. Initially, TF output pressures are inspected and compared to the actual measured aortic pressures to validate the performance of the TF. Mean and pulse pressures over the course of the PR are also compared for further validation. Finally, SBV identified from the clinically available dataset is compared to SBV identified from the full measurement dataset to quantify the model's ability to reliably identify SBV in a clinical setting compared to the most ideal baseline case.

9.5 Results and Discussion

Transfer function results for a single beat for each pig are shown in Figure 9.2. The results clearly show the ability of the TF to recreate central pressure, as output pressure closely matches measured aortic pressure. However, the TF is limited by both the contour and mean pressure of the peripheral pressure used for waveform reconstruction.

As is seen for Pig's 2, 4, 5 and 7, the maximum gradient of the upstroke of the output pressure is significantly less steep than the measured aortic equivalent. This difference is expected, as the maximum gradient of the TF output pressure is limited to the maximum gradient of the peripheral input pressure [104]. As a pressure pulse moves through the arterial tree, the upstroke becomes less steep as due to the natural decay of the pulse wave. This effect results in a less steep maximum gradient in peripheral pressure measurements relative to central pressure.

Figure 9.3 shows the mean and pulse pressures of the measured and TF output aortic pressures over the duration of the PR. The mean TF pressure is always lower than the measured aortic pressure. This difference occurs because mean TF output pressure is highly dependent on peripheral input pressure, which is always lower than mean central pressure [9, 123]. Despite the small difference in mean pressure, the TF is able to track both mean and pulse pressure very well, even over

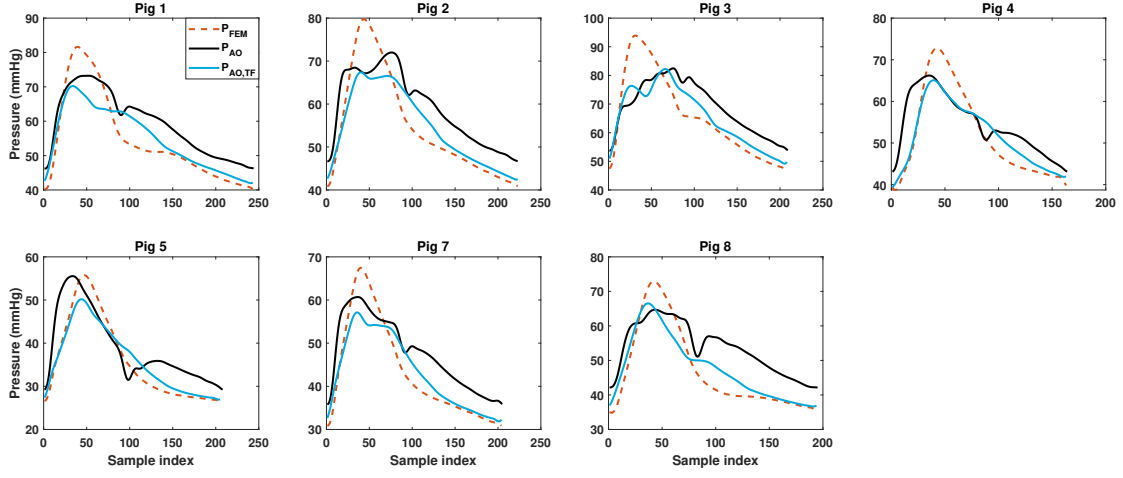


Figure 9.2: Results of the arterial transfer function for each pig. The original aortic wave is shown in black, the transfer function output is shown in blue, and the femoral pressure wave is shown by the dashed orange line.

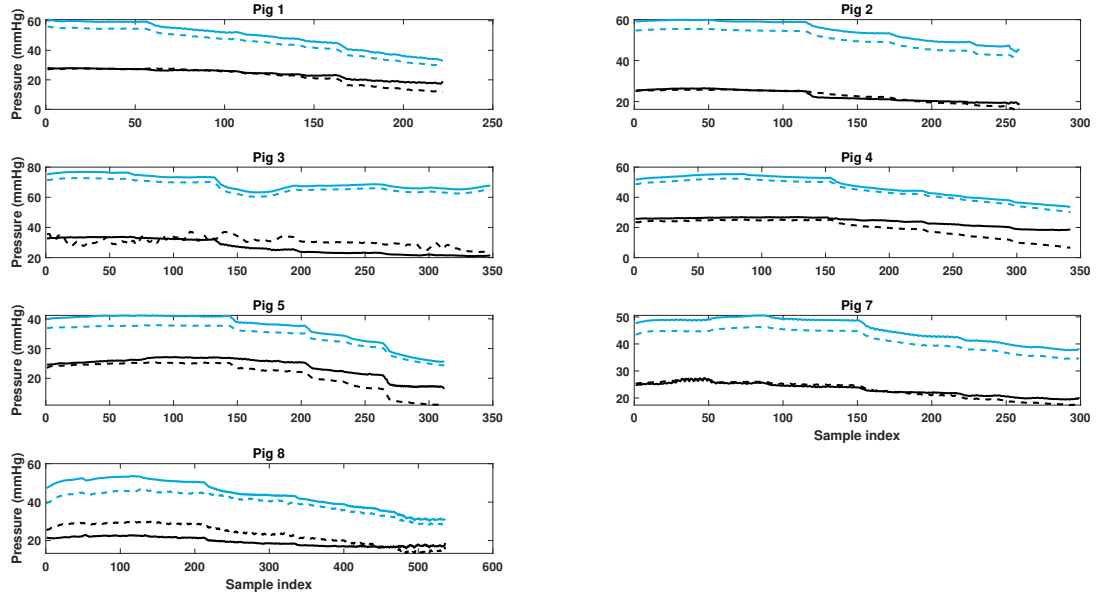


Figure 9.3: Mean and pulse pressures for measured aortic and TF output pressure. Solid and dashed blue lines indicate mean aortic and TF pressure, respectively, while solid and dashed black lines represent aortic and TF pulse pressure respectively.

the course of a PR where mean and pulse pressures are changing significantly more rapidly than would otherwise be observed. This latter point on trend accuracy is critical as trends are a major part of clinical decision making.

Figure 9.4 shows the model errors from parameter identification of the 3 chamber model for all pigs over the course of the PR. Some pigs display small, single-beat instances where model error momentarily jumps. However, the error largely remains very small, once again displaying the simple 3 chamber models ability to reliably accurately identify haemodynamic parameters. This accuracy is further emphasized by the average over the course of the PR, shown in Table 9.1. Note the error has no units, as the model error is obtained from the norm of the error vector, which is composed from multiple measurements of differing units.

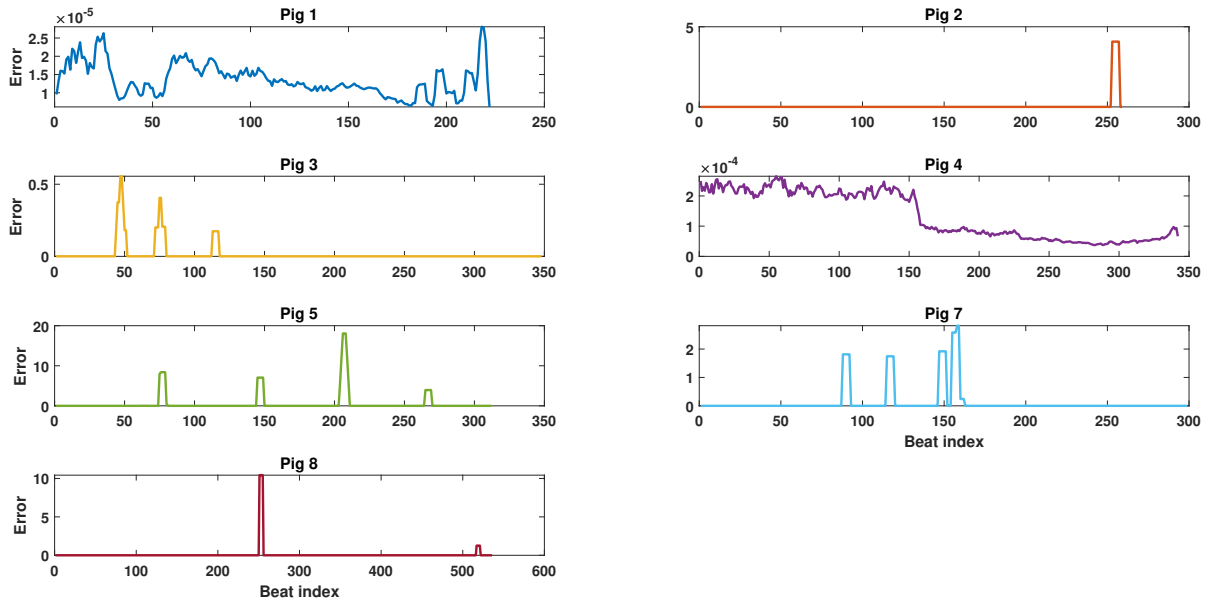


Figure 9.4: Model errors for all pigs over the course of the PR.

Table 9.1: Model errors.

Pig	MAE
1	0.00
2	0.08
3	0.01
4	0.00
5	0.60
7	0.13
8	0.10

Figure 9.5 shows identified SBV over the course of the PR. SBV identified from both the full measurement set, as well as the value identified from the clinically available measurement set, is shown. Dotted lines show results obtained from the full measurement set, while solid lines show SBV identified from the clinically available measurement set.

For all pigs, with the exception of the final section of Pig 4, the clinically feasible model was able to successfully track SBV, closely following the identified SBV produced by the full measurement set. This accuracy demonstrates the ability of the TF to successfully identify aortic pressure, as well as the 3 chamber model’s ability to reliably identify haemodynamic parameters, even from limited but clinically feasible datasets.

Identified SBV for Pig 4 diverged towards the end of the PR under high PEEP conditions. It was discovered at high levels of PEEP, the femoral pressure of Pig 4 significantly diminished compared to aortic pressure. Figure 9.6 shows both the aortic and femoral pressure waveforms of Pig 4 over the interval where the highest PEEP level (20mmHg) was applied.

Pig 4 had the most severe reaction to the infused endotoxin, resulting in rapid onset of septic shock. It has been shown during severe forms of cardiovascular shock, central and peripheral arteries can become decoupled, producing atypical pressure waveforms [103, 152, 153]. It is likely the high level of PEEP exacerbated the

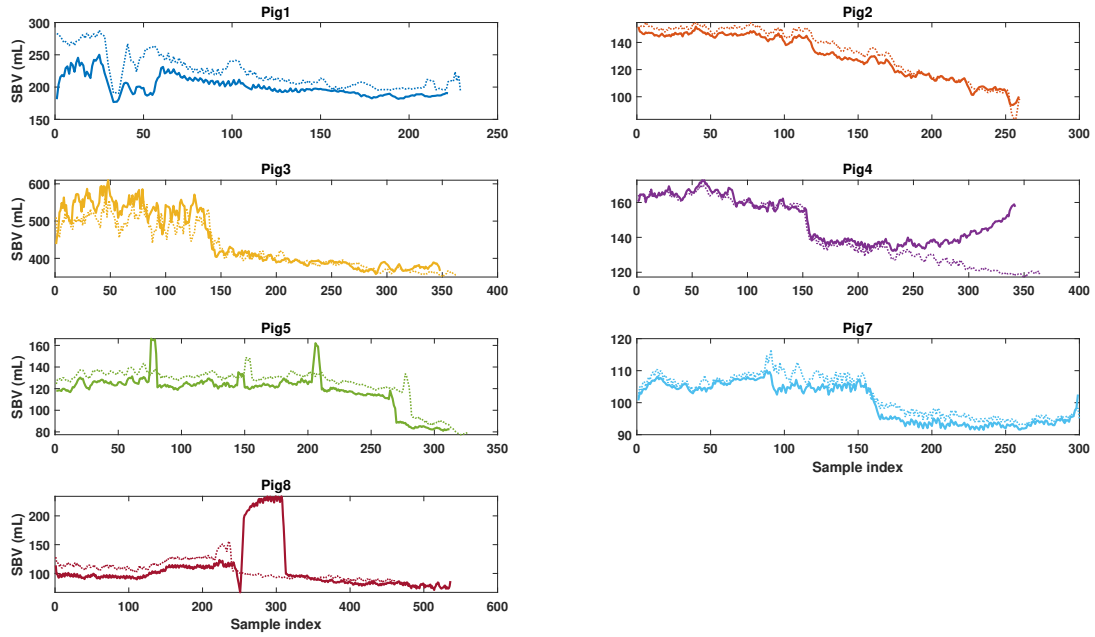


Figure 9.5: SBV for all pigs over the duration of the PR. The dotted lines represent results from the 3 chamber model using the full measurement set, and solid lines represent results where the TF was used.

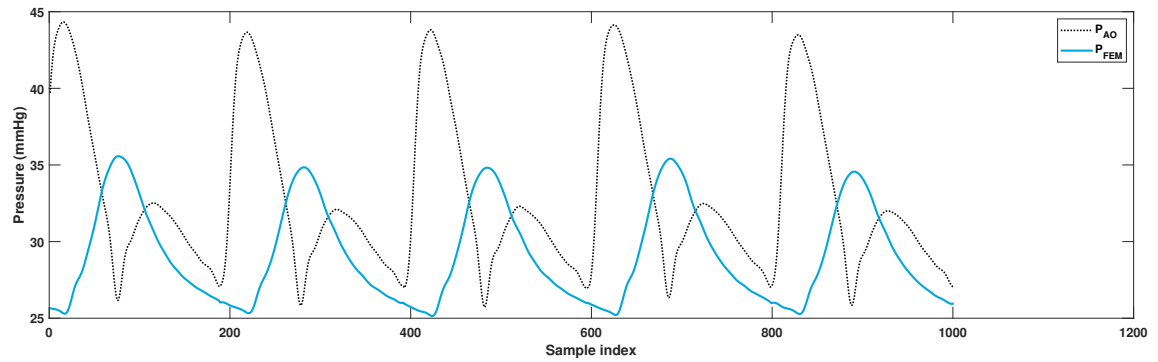


Figure 9.6: Femoral and aortic pressure from Pig 4. Femoral pressure (blue solid) can be seen to be significantly diminished compared to aortic pressure (black dotted).

effects of the vascular decoupling, causing a significant diminishing of the femoral pulse.

9.6 Limitations

The output of the TF is heavily dependent on input peripheral pressure. While some peripheral pressures more closely match aortic pressure, some pressures, such as femoral pressure, display highly different contours to the aortic pressure wave due to high pulse pressure amplification. Further, as the pressure pulse travels down the arterial tree, it decays, and mean pressure slowly drops. The resulting TF mean pressure is highly dependent on the mean peripheral pressure. As such, it will always be slightly lower than actual mean central pressure.

Moreover, the maximum gradient of the TF output pressure is also heavily dependent on the maximum gradient of input peripheral pressure. The decay of the pressure pulse also dampens the initial upstroke of the pulse. Given the maximum gradient is used as part of the objective function, this issue will cause slight alteration to the final identified haemodynamic parameters. Despite these limitations of peripheral pressure, the TF was still able to accurately reproduce central pressure, and was also able to track clinically relevant trends in both mean and pulse pressure over the course of the PRM, where pressures change more rapidly than usual.

Finally, for Fig 4, at high PEEP levels where arterial decoupling was observed, the transfer function was unable to successfully recreate central pressure, and SBV identified from the clinically available dataset diverged from the full measurement set identified SBV. This issue and resulting error are an inherent limitation of the TF, as it relies on the coupling between arteries to recreate central pressure. However, at severe stages of cardiovascular shock, there is little diagnostic loss, as there would have already been many available signs of severe critical condition.

9.7 Summary

This chapter presented a clinically feasible 3 chamber cardiovascular model using an arterial transfer function to identify central pressure from peripheral pressure measurements. The TF was successful in accurately recreating central pressure, and the model was able to successfully identify SBV from a clinically feasible measurement set, further validating it as a potential candidate for use as a bedside assistance tool.

Chapter X

Real Time Simulation of the 3 Chamber Model

10.1 Introduction

Preceding chapters posed several potentially clinically feasible cardiovascular and cardiopulmonary models. Ultimately, the 3 chamber model proved the most reliable, and clinically relevant, and thus the most promising for real-time use as a diagnostic tool in the ICU. However, the current implementation of the 3 chamber model does not take a real-time approach, and has, thus far, only been used on retrospective data.

The main difficulty in implementing the model in ICU is data accessibility, as well as the ability to stream data in real-time. Chapter 7 introduced a simple data capture system enabling real-time capture of arterial and venous pressure, as well as fluid infusion rate. With access to this real-time data, the model can be tested in real-time. However, the model must first be altered to accept and process data in real time over a serial connection.

Though the 3 chamber model has been widely clinically validated [15, 16, 102, 103, 138], it has never been implemented as a real-time application. For this model to serve any purpose as a diagnostic tool to doctors and bedside clinicians, it is crucial the model be able to run and reliably identify parameters in real-time. The constraints on such a system depend heavily on how rapidly outputs are required. The speed the algorithm can produce identified parameters will heavily influence its real-time capabilities. However, since the cardiovascular system is a relatively

slowly evolving system, the model does not need to return identified parameters on every beat, and a semi-real-time, or “clinically relevant real-time”, solution can be achieved.

This chapter presents a real-time simulation of the clinically feasible 3 chamber model, designed to simulate the model receiving data from the DAQ presented in Chapter 7. The simulation uses a Python application to simulate the DAQ, streaming measurement data over serial in real-time, and a real-time implementation of the 3 chamber model in MATLAB, used to receive the data and feed it into the 3 chamber model as inputs. The real-time simulation is performed using the human data recorded by the DAQ at the University of Liege hospital (CHU de Liege), thus performing the first ever real-time identification of SBV from clinically obtained data.

10.2 Data Streaming System

To simulate the model in real time, systems must be developed to both stream and receive data over serial connection. Furthermore, as the simulation will be run on a single computer, the separate applications require virtual serial ports to communicate over, since they do not use any physical hardware ports. Both the streaming and receiving application are designed to send and receive data in the same format as data sent from the DAQ, ensuring simple future integration with physical hardware.

10.2.1 Data Streaming

To simulate the DAQ, data is streamed over serial from a simple Python application. Retrospective data is converted from Matlab arrays to NumPy arrays, ensuring data is usable by the Python application. Since the DAQ streams data at 500Hz, waveforms are first interpolated from their original sample rate to 500Hz. Data from the NumPy arrays is then packaged in the same format used by the DAQ, and sent over serial connection at 500Hz.

Before data can be streamed by the Python application, a virtual COM port must be opened on the local machine running the application. Since the Python applications sending and receiving data are run on the same machine, they do not communicate using physical serial ports. Thus, virtual ports must be opened. For this task, an application called Virtual Serial Port Tools was used. The free tier of this application allows for a virtual serial port bridge to be established, which opens and connects 2 ports using a software bridge. To create a bridge, 2 COM ports are chosen, e.g. COM1 and COM2, and the software establishes the connection. Any data sent through these ports is then handled by the software, and is sent and received over the software bridge between the ports.

10.2.2 Real-Time Processing

Data streamed by the streaming application is sent to a MATLAB application responsible for receiving and processing the data, and then feeding it as an input to the 3 chamber model. Once data is received, it must be split into beats before being fed into the 3 chamber model. The same beat identification algorithm presented in Section 3.2 is used for beat separation.

To read data from the Python application, the MATLAB ‘serialport’ tool is used. A serial device is created in MATLAB to connect to the other open serial port connected to the previously created software bridge. Data is then received in real-time from the Python application, and is automatically accepted by MATLAB into a buffer on the serial device. Data can be read from the buffer using the MATLAB ‘read’ command, passing in the created serial device, size of data to read, and data type as parameters.

The size of the data to be read from the serial device buffer is dependent on the speed the application can process the received data. To avoid lagging behind the streamed data, the application processing the data must be able to process data as fast as it can receive it. For the clinically feasible cardiovascular model, this requirement would mean the application must be able to sort data into beats, obtain central pressure using the TF, and then perform parameter identification.

Given the computational intensity of the optimisation processes used for both the TF and 3 chamber model, it is highly likely the time taken to process data will far exceed the time taken to receive the same data.

Thus, to prevent the processing application lagging behind live data, a single beat can only be processed every T seconds. The parameter T is highly dependent on 2 main factors, computing power and sampling frequency. Higher computing power results in faster processing time, while a higher sampling frequency results in slower processing time, as each beat contains more data to process.

To determine T for this simulation, the average time taken to process a single beat, in seconds, was determined by running the model for a section of 100 beats before the real-time simulation. The sampling rate used for the simulation was 500Hz, the same rate used by the DAQ. Once the average processing time of a beat was determined, the size of the data to be read from the serial buffer, N , was then calculated:

$$N = 2 * 500 \times T \quad (10.1)$$

To allow for time taken by computational overheads and variation in the optimisation process, the size of data to be read is multiplied by 2. Given a single beat takes approximately 1s, or 500 samples, this requirement equates to a single beat being processed for approximately every $2N$ beats received. Given the cardiovascular system is a relatively slowly evolving system, this semi-real-time solution of processing every N^{th} beat is adequate for use in a clinical setting, providing N is not very large. Clinically, every 20^{th} or 30^{th} beat might be more than enough for regularly monitoring of CVS dynamics which evolve in 2-5 minute or larger intervals.

Since only a single beat from a large chunk of data is selected for optimisation, a validation process is implemented to ensure the selected beat has not been incorrectly identified by the beat identification algorithm. Following the beat identification process, the median of the absolute deviation from the median (MAD)

length is used to remove outliers from an identified sequence of beats:

$$MAD = \text{median}_{i=1\dots n}(|x_i - \tilde{X}|) \quad (10.2)$$

where $\tilde{X}$ is the median length of the of the identified beats. Beats are then removed as outliers if the deviation from the median of the beat lies outside of the product of the MAD and a constant:

$$x_i - \tilde{X} < k \cdot MAD \quad (10.3)$$

where x_i is the candidate beat, and k is a constant, usually chosen as 2, 2.5 or 3 in the literature [154], with 2 being the most aggressive and 3 the least aggressive constant for elimination.

Generally, correctly identified beats will have very similar beat lengths, and incorrectly identified beats vary significantly in beat length. Thus, the more aggressive constant, $k = 2$, is chosen for this work. Once outliers are eliminated, the average length of remaining beats is taken, and the beat most closely matching the average is selected.

Once a candidate beat is selected, it is used as an input for the TF, and then the 3 chamber cardiovascular model, where haemodynamic parameters are identified. The full program flow for the real-time application is shown in Figure 10.1. Note, serial communication is handled concurrently to data processing, and is represented as a separate program thread constantly receiving data from the serial connection.

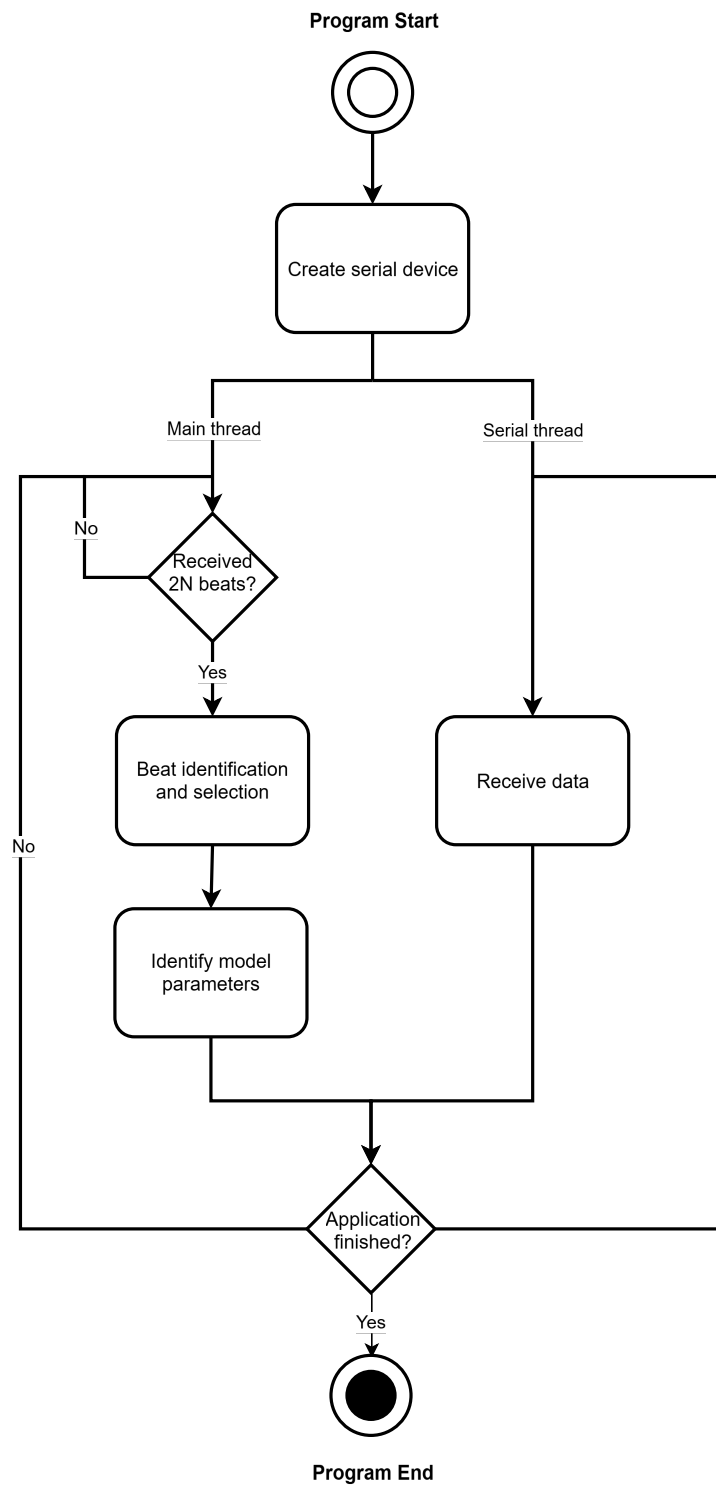


Figure 10.1: Program flow for real time CVS model

10.3 Analysis

10.3.1 Real-time Performance Analysis

Depending on the diagnostic needs of the bedside guidance tool, the real-time performance needs of an application may vary. Some systems may need to produce data at a faster pace than others, particularly when patient condition is critical and deterioration can happen rapidly. Thus, the performance of the real-time system is analysed, and potential measures for improvement identified.

The performance was analysed by inspecting the distribution of the time taken by the optimisation processes of both the TF and 3 chamber model, as well as modifying key parameters of the optimisation algorithm to assess the trade off between speed-up and performance. Finally, the effect of sample rate was also analysed on application performance.

10.4 Results and Discussion

10.4.1 Real-time Performance

The real-time performance of the application is dependent on the speed it can identify and process beats with. To determine this, the application was run over a period of ≈ 2000 beats for each patient, and the time taken for both the TF and model parameter identification process recorded. Figures 10.2 and 10.3 show the distribution of the times taken for the TF and model identification respectively, and 10.4 shows the combined time taken.

From Figure 10.4, the average time taken per beat is approximately $2s$, and the maximum time is just under $3s$. Using Equation 10.1, the amount of time to process a single beat would be taken as twice the average processing time. Thus, a time interval of $4s$ is used. Hence, the full parameter identification process can be performed on a single beat every $4s$, which is every 4^{th} (60bpm) to 8^{th} (120bpm)

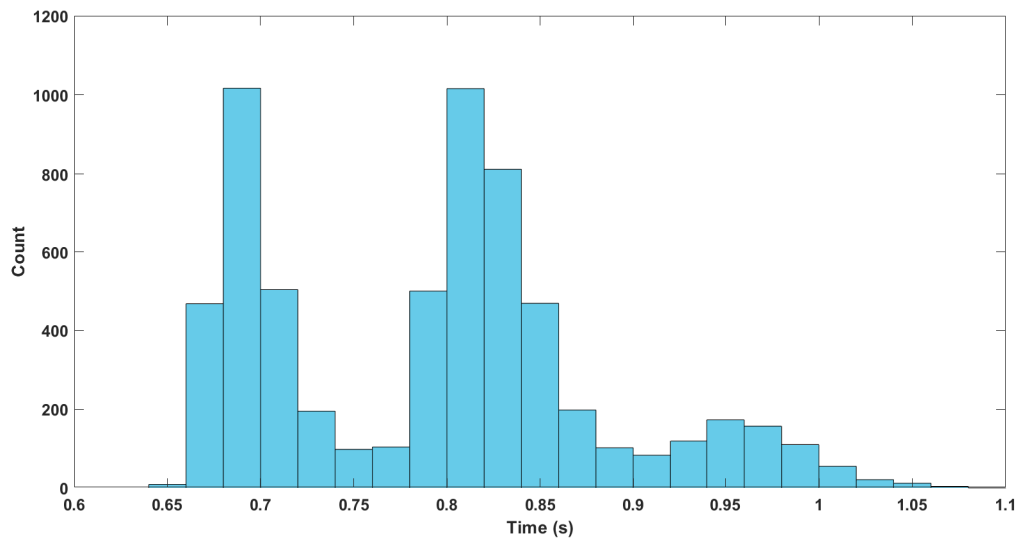


Figure 10.2: Distribution of times taken for the arterial transfer function.

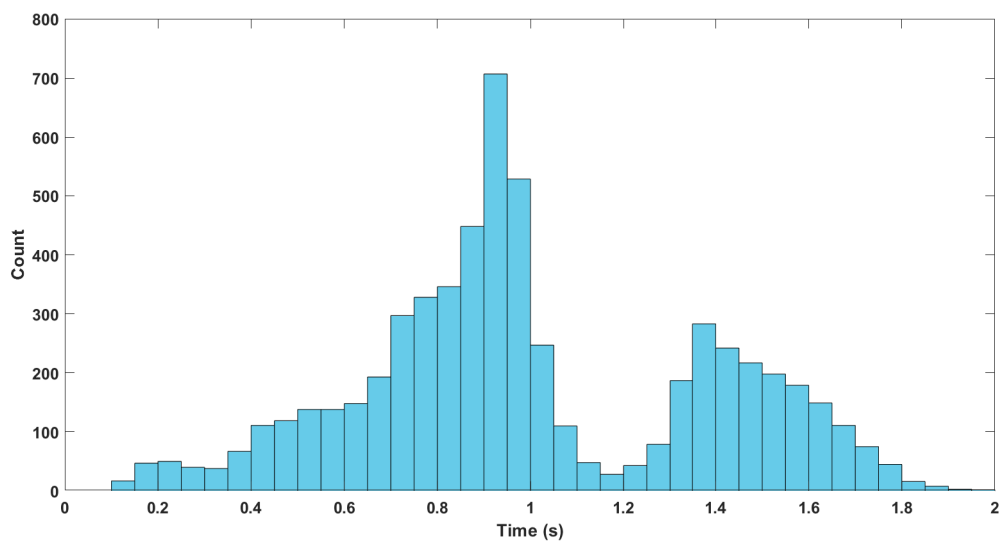


Figure 10.3: Distribution of times taken for parameter identification of the 3 chamber model.

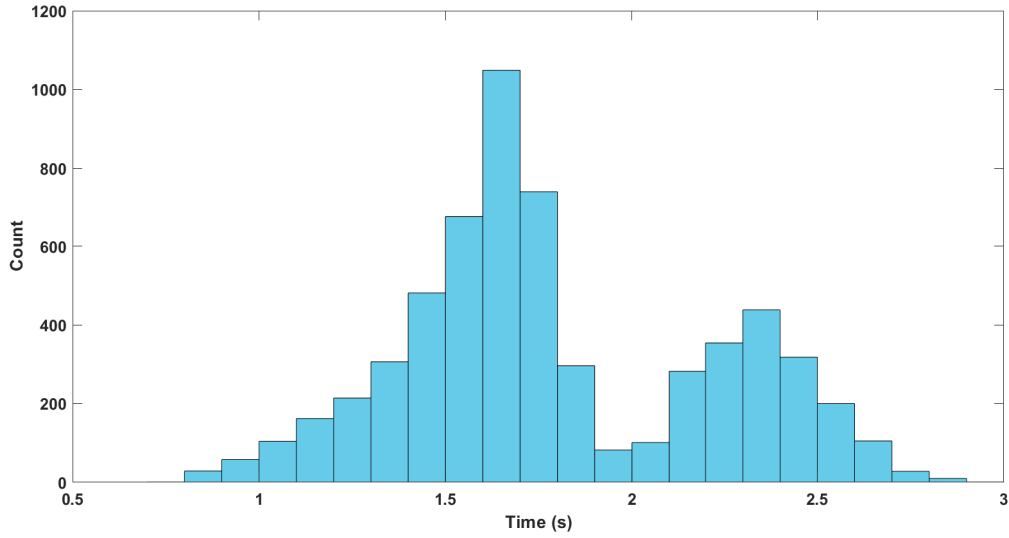


Figure 10.4: Distribution of combined time taken of transfer function and model parameter identification.

beat.

However, these are results obtained using a powerful computer capable of running MATLAB, which is highly optimised for intense computational algorithms such as optimisation problems. A dedicated device to be used in an ICU would likely have less computing power, and would likely not have access to MATLAB due to both operating system restrictions and licensing costs.

Likely the most important variable in the program execution time is the sampling frequency used for haemodynamic waveforms. While a frequency of $500Hz$ provides rich waveform data, it also results in much heavier computation required. Thus, to explore the relationship between the sampling frequency and program execution time, waveforms were downsampled and the parameter identification process repeated. Figure 10.5 shows the distributions of time taken for parameter identification of ≈ 2000 beats from a single patient using sampling frequencies of $100Hz$, $200Hz$ and $300Hz$.

The mean times taken for the sampling frequencies of $100Hz$, $200Hz$ and $300Hz$

were $0.076s$, $0.313s$ and $0.820s$ respectively. The mean time taken using $F_s = 500Hz$ for the same patient was $2.295s$. Thus, the lowest sampling frequency of $100Hz$ showed a speed up of 30 times compared to the time taken using the original $500Hz$. This difference would allow for real-time operation using even a lower powered, embedded CPU.

Given almost no frequency content significant to blood flow exists above $20Hz$ [32], even a sampling frequency of $100Hz$ should be sufficient for capturing arterial pressure waves. However, for problems involving complex pressure gradient analysis and higher order derivatives, higher sampling rates are generally required as noise is amplified when deriving waveforms. Since the TF uses higher order derivatives for determining important haemodynamic markers, higher sampling frequencies may be required for more accurate results.

10.4.2 Real-time Simulation Results

The MATLAB application running the parameter identification process received data in real-time over serial connection. After receiving $4s$ worth of data, the chunk of data was split into beats, and central pressure of a single beat was identified using the arterial transfer function. Figure 10.6 shows the results of TF output pressure for a single beat for each of the patients.

The TF was successfully able to reliably reproduce aortic pressure waveforms. As previously stated, the contour of $P_{ao,TF}$ is highly dependent on the shape of the input pressure, and some features seen in peripheral pressure waveforms are also visible in identified central pressure. This outcome is particularly evident for Patient 2, who displayed a particularly bumpy pressure waveform contour. However, the contour of the output pressure is not highly important, given only mean and pulse pressures are used for the parameter ID objective function.

Following identification of central pressure from peripheral pressure, the parameter identification was performed on the identified beat. Figures 10.7 - 10.9 show the identified SBV for the 3 patients over the course of the experiment. Note, Patient

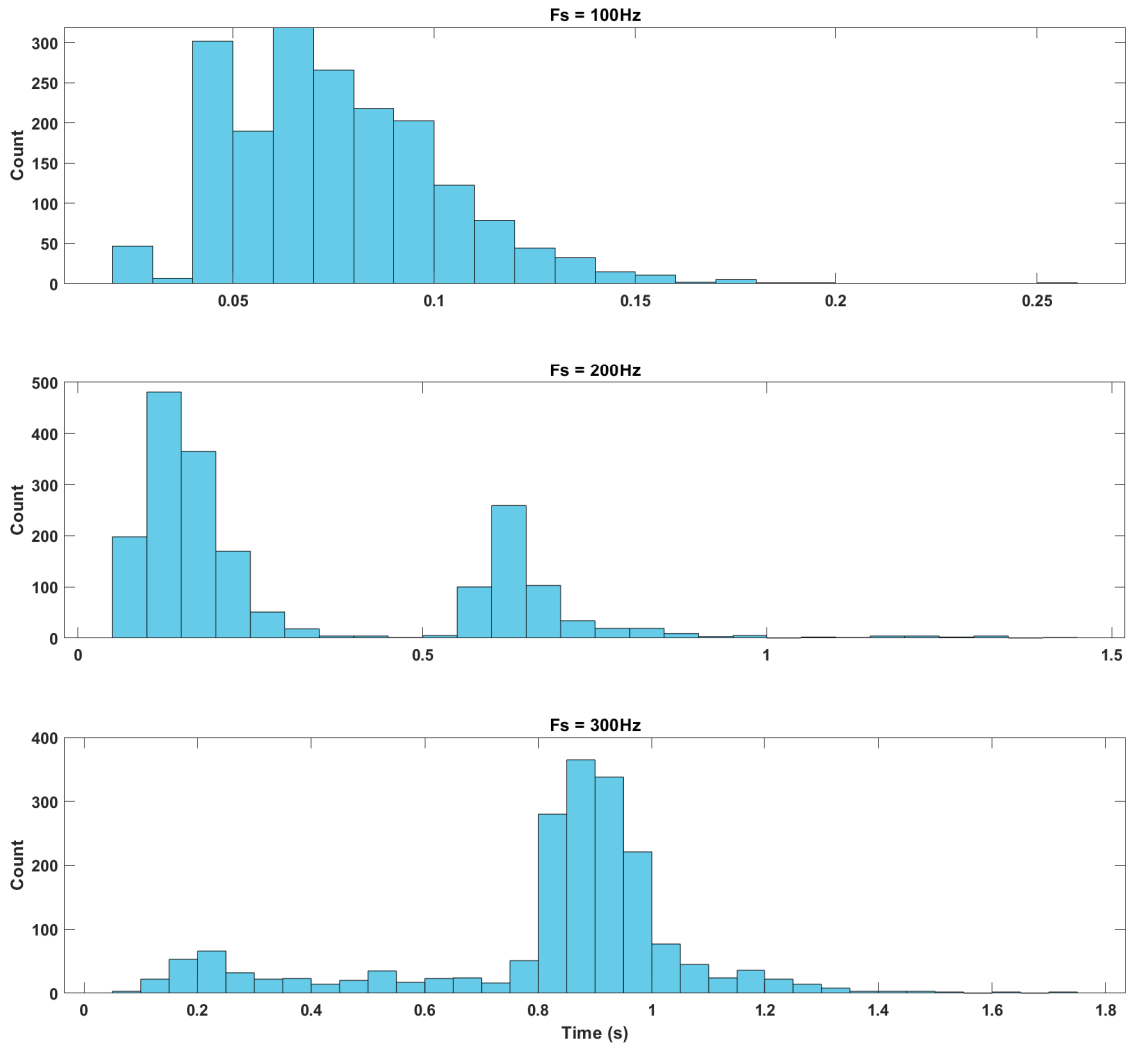


Figure 10.5: Distributions of combined time taken of transfer function and model parameter identification when using different sampling frequencies. The top, middle and bottom charts used 100Hz, 200Hz and 300Hz respectively.

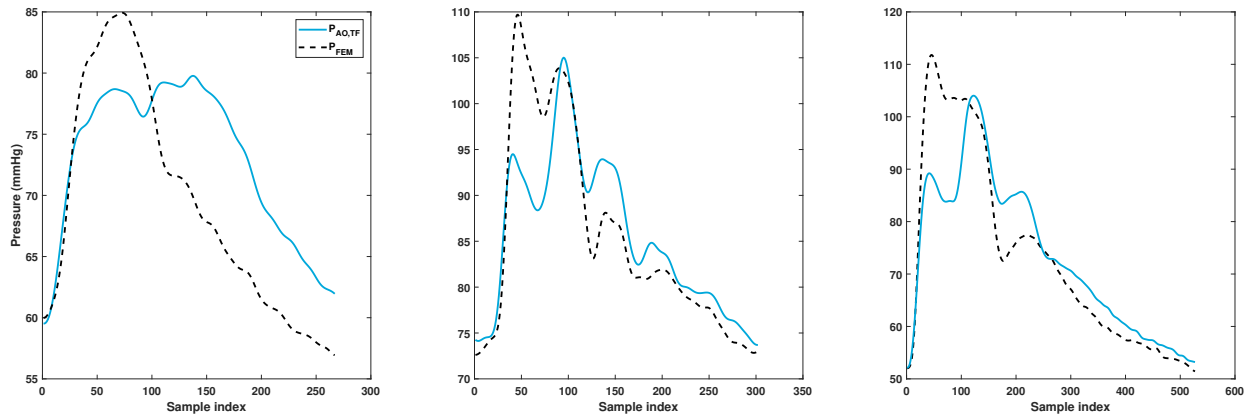


Figure 10.6: Transfer function pressure outputs for each patient. Pressure waveforms for Patients 1,2 and 3 are shown on the left, centre and right respectively.

3 has almost double the identified beats than both Patient's 1 and 2. This discrepancy is due to Patient 2 undergoing a shorter measurement period (≈ 30 min rather than 60min), and Patient 1 having a large section of unusually elevated venous pressure which was unusable and thus discarded.

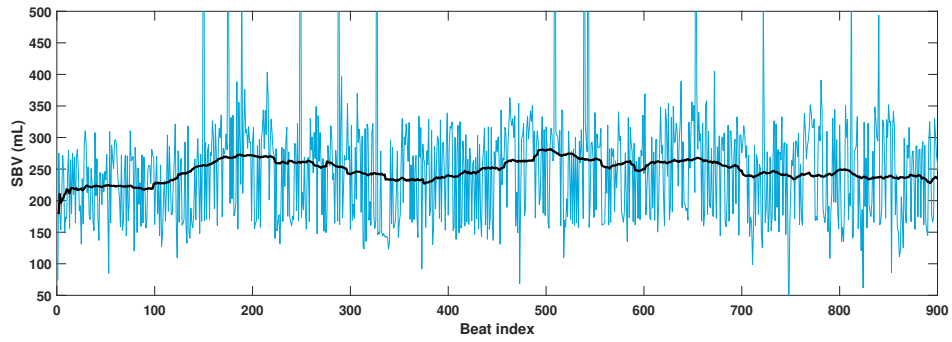


Figure 10.7: Real-time identified SBV for Patient 1 over the course of the trial data.

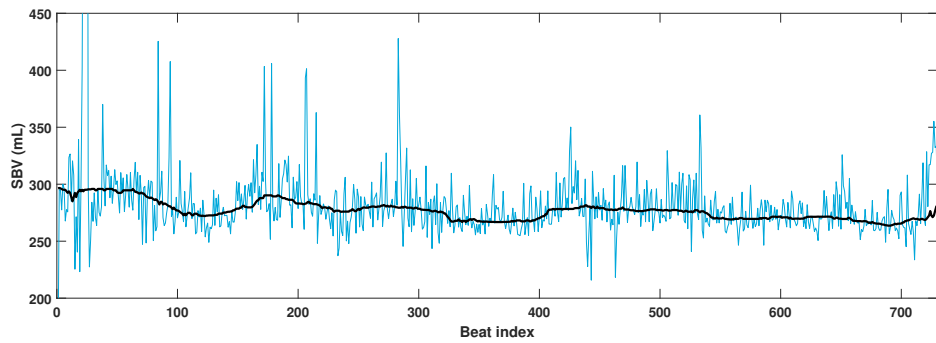


Figure 10.8: Real-time identified SBV for Patient 2 over the course of the trial data.

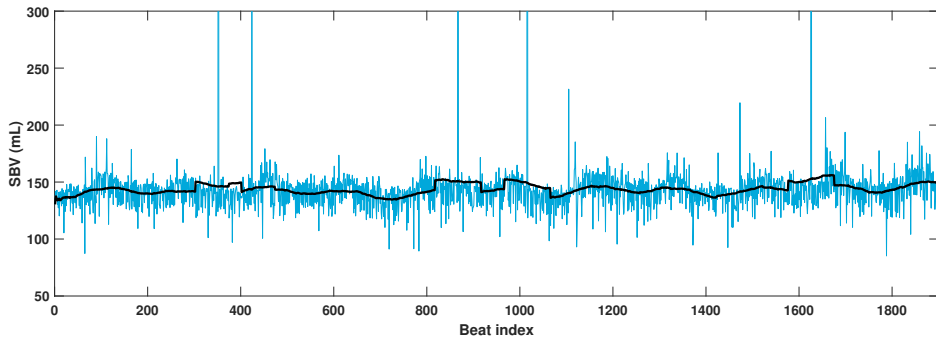


Figure 10.9: Real-time identified SBV for Patient 3 over the course of the trial data.

Figure 10.10 shows the venous pressure measurement for Patient 1 over the course of the experiment. The identified SBV for Patient 1 is thus comprised of the

sections of data before and after the discarded section.

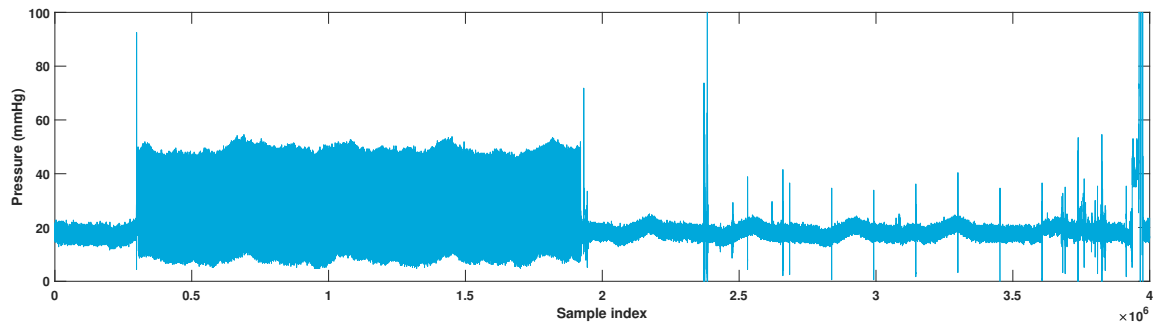


Figure 10.10: Measured vena cava pressure of Patient 1. An unusual augmentation of pressure occurs shortly after the start of data recording, rendering the data unusable.

Furthermore, Patient 1 displays the noisiest identified SBV. This result is due to the patient presenting with atrial fibrillation, shown in Figure 10.11. The large variation in pulse pressure of each beat causes large discrepancies in SBV. However, despite the noisy nature of the waveform, the identified SBV is still able to produce reliable trends, which are more important than absolute values for clinical decision making.

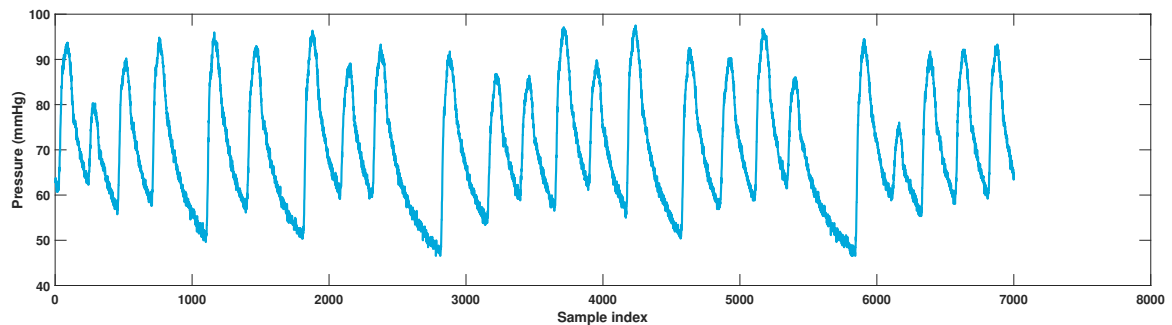


Figure 10.11: Measured arterial pressure of Patient 1, displaying highly variable beats due to atrial fibrillation.

10.5 Limitations

This work used MATLAB to receive the real-time data from the Python application simulating the DAQ. MATLAB is a very powerful computing tool, highly optimised for running powerful algorithms quickly. However, MATLAB requires the use of a computer. For this real-time system to be implemented in the ICU for long-term use, it is unlikely a computer would be feasible, and a smaller, dedicated system would likely be required.

Such a system would likely have less computing power, which would likely affect real-time performance. However, this can be easily compensated for by lowering the sampling frequency of recorded waveforms if necessary. Equally, applications programmed on dedicated embedded systems are usually coded in C or C++, which are compiled, low-level languages. These languages are highly efficient, and would also enable for faster execution than MATLAB, by factors of up to 10x or more.

For Patient 1, identified SBV had much higher beat to beat variation than the other patients. This result is largely due to the patient presenting with atrial fibrillation, resulting in highly varying input pressure waveforms. However, despite the highly varying pressure and identified SBV, the identified SBV was still clearly able to produce trends over time. This point is highly important, since trends, rather than absolute values, are a major part of clinical decision making in the ICU.

10.6 Summary

This chapter presented a simple system for simulating the clinically feasible model as a real-time application. The real-time performance of the system was analysed before performing the full real-time simulation. Once the speed at which parameter identification could be performed per beat, the real-time simulation was run on patient data obtained from the clinical trial detailed in Chapter 7. The system was able to identify SBV in real-time from clinically available datasets, obtained from a trial performed at the University of Liege. This is the first instance SBV

has been successfully identified from real-time, clinically available data, and is a crucial step towards model-based fluid therapy in the ICU. The next chapter presents a validation of the real-time, clinically identified SBV as an indicator of fluid responsiveness.

Chapter XI

SBV as an Index of Fluid Responsiveness

11.1 Introduction

Thus far, the main aim of this work has been developing a real-time system capable of measuring clinically available haemodynamic waveforms, and using these measurements for identifying haemodynamic parameters in clinically-relevant real-time. Real-time simulations of the system have showed it is possible to run the system in clinically-relevant real-time. However, the main goal of the cardiovascular system model is to identify SBV, and use it as an indicator of a patient's fluid responsiveness. Thus far, all components of the real-time system have been developed, but, real-time identified SBV has yet to be examined as an indicator of fluid responsiveness.

SBV has been thoroughly validated as an index of fluid responsiveness on retrospective sets of experimental data [15, 16, 102]. These validations clearly demonstrate the ability of SBV as a model-based index for prediction of fluid responsiveness. However, no validation has been performed on SBV identified in real time from a clinically available dataset.

This chapter introduces an analysis of SBV as an index of fluid responsiveness from the real-time simulation of the hospital trial data. While the analysis is retrospective, it is performed on data obtained in real-time simulation, and can thus be considered as a validation of real-time identified SBV as an index of fluid responsiveness in the ICU.

11.2 Clinical Data

Data from 3 patients obtained from the trial performed at CHU de Liege, detailed in Section 7.4, was used to perform a real-time simulation of the clinically feasible 3 chamber model, as described in Chapter 10. The real-time simulation was able to identify SBV for approximately every fourth beat, which is a clinically relevant time frame ($\approx 2 - 4s$) with respect to monitoring and decision making.

11.3 Analysis

The average SBV from the first and last 5 minutes of each of the experiment was calculated for all patients. Both SBV, and SBV normalised to mass (SBV_m), are investigated as potential determinants of the patients fluid responsiveness. These metrics are then compared to the more conventionally used dynamic index of fluid responsiveness, PPV.

11.4 Indices of Fluid Responsiveness

Figure 11.1 shows the initial and final model identified SBV vs CO measured by echocardiogram. Initial values of SBV are taken as the average identified SBV over the first 5 minutes of the experiment, and the final value is taken as the final 5 minutes of the experiment. The initial and final CO values are from readings performed by an echocardiogram at the beginning and end of the experiment for each patient.

Patient 1 displays very little change in CO despite a significant ($\approx 10\%$) increase in SBV. Patient 2 displays a massive increase in CO, despite a significant decrease in SBV. Finally, Patient 3 displays a significant increase in CO corresponding to a significant increase in SBV. Figure 11.2 displays the the initial and final SBV normalised to each patients mass (SBV/kg). The relationships follow the same trends seen in Figure 11.1.

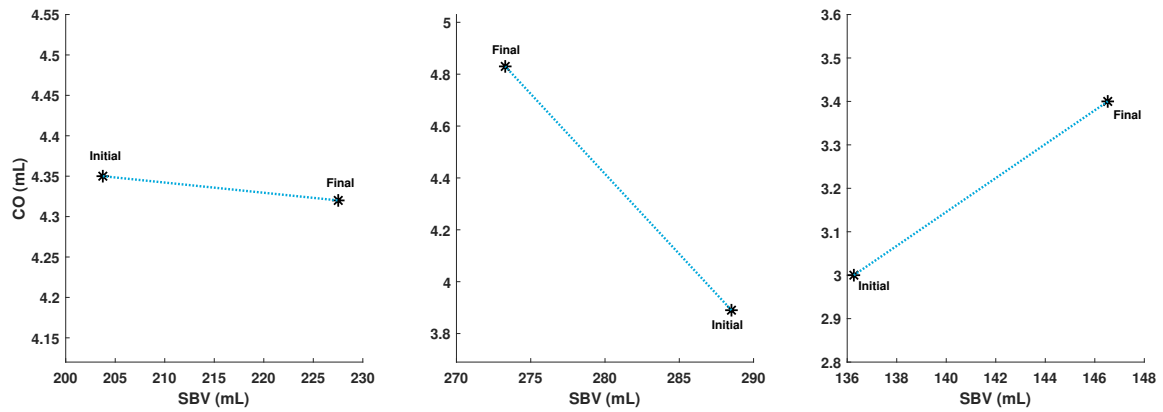


Figure 11.1: SBV vs CO for the initial and final 5 minutes of the experiment.

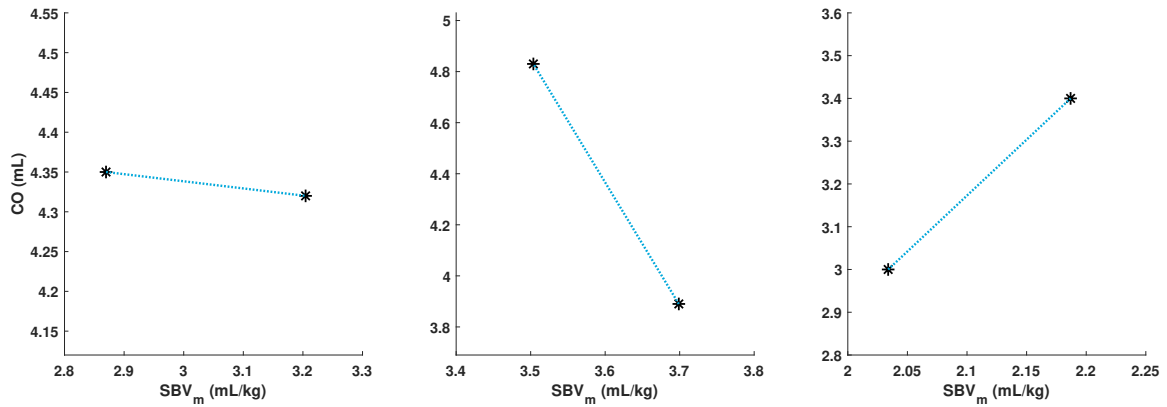


Figure 11.2: SBV_m vs CO for the initial and final 5 minutes of the experiment.

Figure 11.3 shows the initial and final PPV vs CO measured by echocardiogram. PPV is calculated as the variation in peak arterial pressure over a section of 4 beats. The initial value of PPV is calculated as the mean PPV for the first 5 minutes of the experiment, and the final value is taken as the average PPV from the final 5 minutes of the experiment. Similar to the SBV relationship with CO, Patient 1 displays very little change in CO despite a significant increase in PPV. Patient 2 displays a markedly large decrease in PPV for the increase in CO. Finally, Patient 3 displays almost no change in PPV despite the increase in CO.

The left plot from Figure 11.4 shows the relationship between SBV normalised to

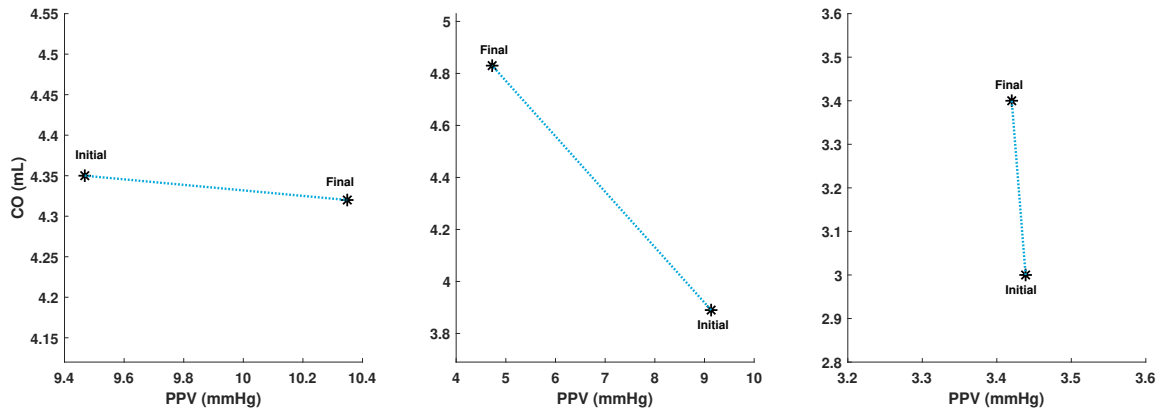


Figure 11.3: PPV vs CO for the initial and final 5 minutes of the experiment.

mass (SBV/kg) and CO, using a linear model to fit the data. The coefficient of determination (r^2) was 0.602 and the p-value 0.0695. While the quantity of data is small, limiting the significance of trend extrapolation from results, the results still show a strong relationship, which provides strong justification for further investigation into real-time identified SBV as an index of fluid responsiveness.

In a clinical setting, model identified SBV would be used to guide fluid therapy. Thus, SBV values obtained before fluids should show some predictive power for change in CO. The right side of Figure 11.2 shows the initial SBV_m vs the percentage change in CO. Generally, SBV and change in CO should display a negative correlation, as a higher SBV would indicate a more sufficiently perfused patient, and a lower change in CO would be expected. However, as is shown in the figure, the overall trend line shows a positive correlation. However, the trend line does not accurately represent the data, with a poor r^2 of 0.187 and p-value of 0.715. This result is not unexpected, since statistically significant results are not realistically achievable from such small datasets.

Furthermore, the result is also skewed by the outlying data of Patient 2, who experienced a significant increase in CO, despite having both higher values of SBV_m and an overall decrease in SBV despite the increase in CO. While having only 3 data points does not allow for strong interpretation of the data, it still highlights the difficulties faced in a clinical setting, where uncertainties in data

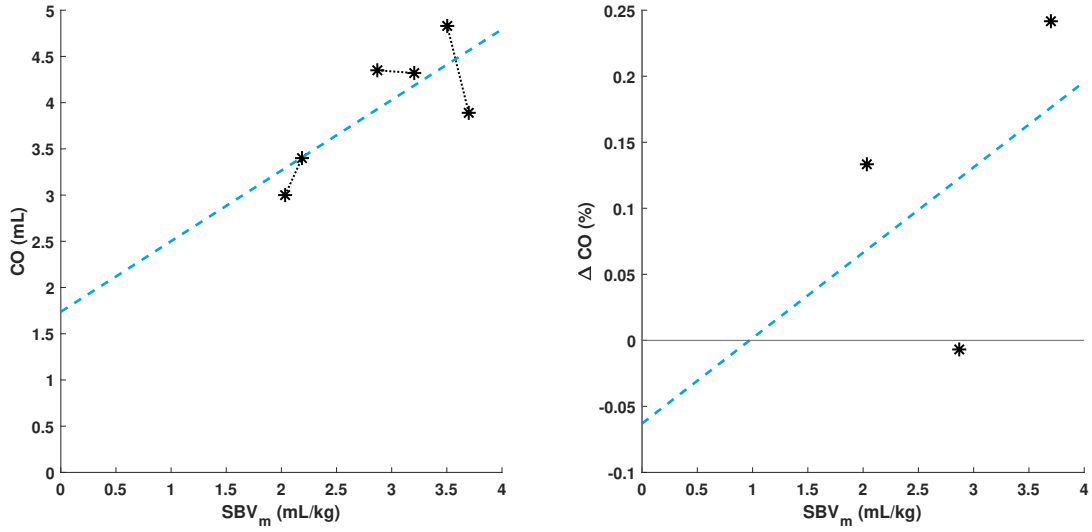


Figure 11.4: SBV_m vs CO for the initial and final 5 minutes of the experiment for all patients (left) and Δ CO vs initial SBV_m (right) with calculated linear fits (blue dashed line).

make crucial decision making a highly challenging task for bedside clinicians.

The left plot from Figure 11.5 shows the relationship between PPV and CO, using a linear model to fit the data. The coefficient of determination (r^2) was 0.252 and the p-value 0.311. It is clearly a weaker fit than was shown for SBV. However, as was previously mentioned, the small sample size limits the significance of any trends produced by the data.

The right side of Figure 11.5 shows the initial PPV vs the percentage change in CO. Generally, a larger PPV is considered an indicator of a patient being on a favourable section of the Frank Starling curve, indicative of a lower preload. Thus, PPV and CO should display a positive correlation. However, the computed linear fit displays a slightly negative correlation, though the fit was also very poor with $r^2 = 0.015$ and a p-value of 0.921. As for SBV, the computed linear fit for this data carries little statistical significance due to the small sample size.

Furthermore, as previously mentioned Patient 1 presented with atrial fibrillation. As a result, Patient 1 presented with the largest PPV of all patients. However,

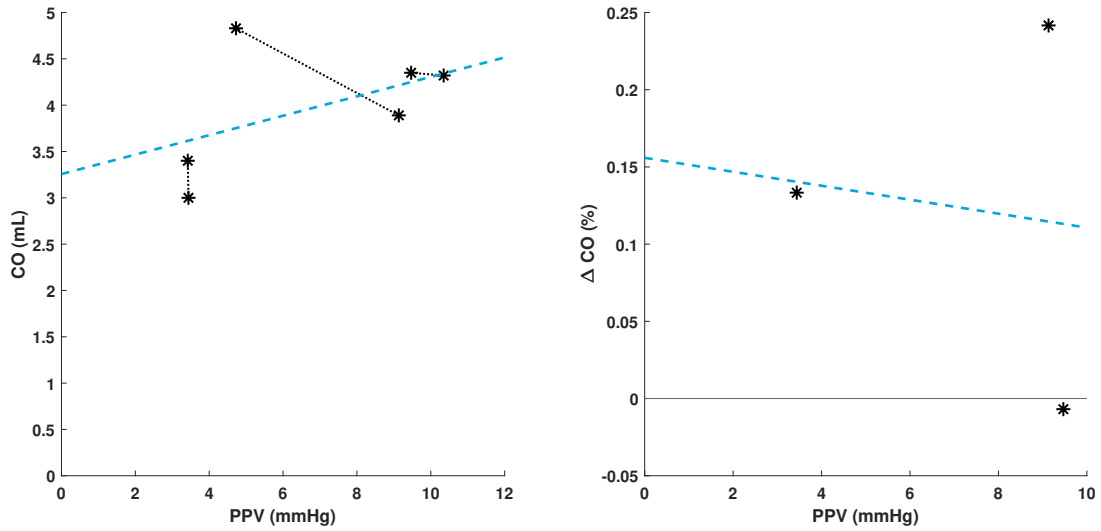


Figure 11.5: PPV vs CO for the initial and final 5 minutes of the experiment for all patients (left) and Δ CO vs initial PPV (right) with calculated linear fits (blue dashed line).

despite presenting with the largest PPV, which would usually be taken as a strong indicator of fluid responsiveness, Patient 1 displayed the smallest change in CO, clearly indicating one of the limitations of using PPV to guide fluid therapy.

11.5 Limitations

Fluid therapy is often not conducted in isolation within the ICU. A variety of drugs are often used for patient treatment. These drugs, often combinations of norepinephrine, adrenaline and vasopressors, have drastic effects on a patient's haemodynamic state, as well as how a patient responds to fluids. Accordingly, these drugs will also highly influence a patient's SBV in ways that the CVS model cannot necessarily predict. However, these global changes will affect haemodynamic measurements. Though the model does not have the potential to predict changes from these drugs, it can still identify resulting parameter changes from changing haemodynamic measurements.

The analysis of real-time identified SBV as an indicator of fluid responsiveness was highly limited due to the small sample size of 3 patients to date in an ongoing trial. Furthermore, data from each of the patients was only recorded for ≈ 1 hour, encompassing only a single fluid infusion of 500mL. The clinical trial performed also did not allow for a significant amount of time to pass following the fluid infusion. As a result, the cardiovascular state may not have been allowed sufficient time to settle following fluid infusion. Despite the inconclusive result, as the first real-time trial of SBV, this result is considered to be a large step towards the goal of real-time model-based bedside fluid therapy.

11.6 Summary

This chapter performed a first ever validation of real-time identified SBV as an index of fluid responsiveness, presenting a large step forward toward the ultimate goal of real-time model-based fluid therapy in the ICU. An analysis was performed on trial data obtained from 3 patients from the University of Liege hospital. Both PPV and SBV were analysed as predictors of fluid responsiveness, and the limitations of PPV were clearly shown in the case where a patient presented with atrial fibrillation. Ultimately, the sample size was too small to draw conclusions on real-time identified SBV as an indicator of fluid responsiveness, however, it has presented strong justification for further studies and trials to investigate its potential.

Chapter XII

Conclusions

Unguided fluid therapies in the ICU result in an increase in CO in only 50% of patients. Numerous studies have also established a strong correlation between fluid overload and mortality in critically ill patients. As patient condition is constantly changing, naturally or at times drastically due to deterioration of condition, fluid responsiveness too is constantly evolving. Thus, fluid responsiveness prediction is a continuous process which should be applied throughout the course of patient stay, versus today's very intermittent monitoring and metrics.

This work aimed to provide a clinically feasible, real-time, model-based solution to predict fluid responsiveness in the ICU. Several models were explored including multiple cardiopulmonary models, the clinically validated 3 chamber cardiovascular model and finally the real-time clinically feasible 3 chamber model, which also incorporated an arterial transfer function used to identify central pressure. A novel data capture system was also developed with the ability to measure haemodynamic waveforms and fluid infusion rates, and send them to an external device using serial communication, where captured data was displayed to bedside clinicians. Together, these create the fundamental system elements necessary for continuous, automated, model-based assessment.

Ultimately, the cardiopulmonary model proved to be too unreliable for clinical use. This outcome was likely due to the overly simplistic coupling mechanism used for the pulmonary and cardiovascular systems. The systems were linked through an identified P_{th} , where P_{th} was treated as an external pressure acting on intrathoracic chambers, thus reducing the transmural pressure of the chambers. Though this coupling process is physiologically accurate, it was shown to be highly exaggerated

for both the vena cava and the left ventricle.

To reduce the exaggerated effect of applied P_{th} , the cardiopulmonary model was modified with a new parameter, α . The new parameter attempted to reduce the exaggerated effects of thoracic pressure on the vena cava and left ventricle chambers by modulating the percentage of thoracic pressure applied to the intrathoracic chambers. The α parameter was partially successful, and was able to reduce the exaggerated effects of thoracic pressure. However, α proved highly computationally costly, requiring a grid search to find an optimal value, increasing computing times by an order of magnitude compared to the original 3 chamber and cardiopulmonary models.

Despite being an improvement on the original cardiopulmonary model, the alpha model proved far less reliable than the original 3 chamber model. It is highly probable the coupling used between the pulmonary and cardiovascular system models is too simplistic to fully incorporate the highly complex interactions of these two systems. By omitting the right circulation from the CVS model, and the alveoli from the pulmonary system model, crucial dynamics of cardiopulmonary interactions cannot be accounted for. However, such complex models would be infeasible for use in the ICU, as the highly limited, but clinically available, data is insufficient for identifiability of such complex models. Thus, this work provides a relatively complete scan of the trade offs between clinical relevance and utility, physiological relevance, and computational effort and identifiability.

Hence, the 3 chamber model thus remains the strongest candidate for prediction of fluid responsiveness in the ICU. In combination with the arterial transfer function, the 3 chamber model proved highly successful in identifying haemodynamic parameters from clinically available measurements. Most importantly, it was able to reliably identify SBV. The ability to identify SBV from clinically available metrics within the ICU is a crucial step towards model-based fluid prediction.

A novel data capture system was developed to ensure haemodynamic measurements could be made available as inputs to the 3 chamber model in real-time. The device used a simple Arduino based system in conjunction with custom made adaptors to read pressure measurements directly from existing pressure sensors in

the ICU. The device was used in a trial CHU de Liege. The device was trialled on 3 patients and successfully captured both arterial and venous pressure for all patients, as well as fluid infusion rates for 2 of the patients. The device ultimately proved to be highly successful for cardiovascular research based work in the ICU. It has been published open-source to aid future research and application.

The previously validated clinically feasible 3 chamber model was simulated to run in real-time using the retrospective data from the clinical trials. A simple Python application was developed to simulate the DAQ, by streaming the data obtained from the clinical trial in real-time over serial. A virtual serial port was created so the applications running on the same machine could communicate over a software serial bridge, removing the need for physical hardware to establish a serial connection.

The MATLAB application running the clinically feasible 3 chamber model was modified to run in real-time, by accepting data via serial communication and then processing it into beats and performing model parameter identification. The program was successfully able to identify SBV in real-time from the clinically available data, and was able to identify haemodynamic parameters at a rate of 1 beat every 4 seconds, which is more than adequate for providing real-time diagnostic information in the ICU at clinically relevant time frames or (much) more frequently.

However, given long term solutions would likely run MATLAB in the ICU, a dedicated device using custom software and/or on-board/cloud-based computing would be used, which may impact computing time depending on the system. Thus, an investigation into real-time performance explored how sampling frequency effected computing time. Higher sampling frequencies were found to increase computing time significantly. A sampling frequency of 100Hz was found to produce a 30 times speed up, compared to the 500Hz used by the DAQ. Despite providing lower quality information, a sampling frequency of 100Hz is still approximately equal to the sampling frequency of current bedside machines (120Hz), and is more than adequate to capture the highest frequency information present within haemodynamic measurements, approximately 15-20Hz.

Finally, the use of SBV as an index of fluid responsiveness was evaluated. SBV

has already been extensively validated as a potentially useful index of fluid responsiveness. However, thus far, no evaluation has been performed on real-time data obtained from an ICU. The real-time analysis of SBV, though limited by sample size, is a proof of concept serving to show real-time model based fluid therapy in the ICU is certainly possible.

This work performed a validation of multiple lumped parameter cardiovascular models, and ultimately performed the first ever validation of real-time identified SBV from a clinically obtained dataset, providing a strong justification for continued exploration into the use of SBV as index of fluid therapy in the ICU. The challenges faced for implementing such a system in the ICU have been clearly highlighted. With no access to real-time data, large barriers to model-based care exist, preventing any form of tangible, non-research based advancements. This work has provided an open-source device which provides access to real-time data in the ICU. Though the device is limited to haemodynamic measurements, and is currently a research based tool, it acts as a stepping stone which others can use to further the current standard of data accessibility and model-based care in the ICU.

Chapter XIII

Future Work

This work has presented several candidate cardiovascular and cardiopulmonary models, a custom data capture device for obtaining haemodynamic waveforms in the ICU, as well as a clinically feasible model that was validated through a real-time simulation using retrospective data obtained during a trial performed at the University of Liege. Though much of the work was successful, there are many potential avenues left to explore. This section presents the potential future work to be done, exploring some of these potential avenues and unresolved limitations of this thesis.

13.1 Cardiopulmonary Model

Several cardiopulmonary models were presented in this thesis, all of which seemed promising candidates for use in the ICU. However, it was clear the mechanism linking the cardiovascular and pulmonary system was overly simplistic and resulted in high model errors, and ultimately unreliability under high PEEP conditions. In reality, the mechanisms linking these two systems is far more complex than just the intrathoracic pressure exerted on intrathoracic chambers and vessels.

Furthermore, the right circulation is a crucial part of cardiopulmonary interactions. Though potentially infeasible for clinical use, exploring a more complex cardiopulmonary model using the 6 chamber model, and including simple alveoli models, may provide greater insights into potential modelling mechanisms for cardiopulmonary interactions. Better understanding of modelling these complex effects may lead to more accurate simplifications of cardiopulmonary interactions,

potentially allowing for a more reliable, clinically feasible model.

13.2 Transfer Function

The transfer function used in this work was able to successfully estimate central pressure from peripheral pressure. The transfer function does this by shifting and scaling a forward and reflected wave using the parameters α , β , and PTT . However, the transfer function is limited in that both the forward and reflected waves assume the contour of the peripheral arterial wave, and thus, the contour of the aortic pressure wave can not be accurately identified, reducing the overall capabilities of the TF.

This problem could be improved if peripheral arterial flow was known. If the flow was known, waveform decomposition could be used to identify forward and reflected waves, and these could be used in the transfer function, rather than the contour of the peripheral pressure measurement. Though no invasive flow measurements currently exist in the ICU, echocardiography can be used to identify flow contours. Though extracting the flow contours from the echo machine into the model-running application would be a challenging task.

Equally, the use of model based peripheral flow estimates has not been explored in this work. A simple model-based estimate of flow would allow for waveform decomposition. To the best of the author's current knowledge, a simple, clinically identifiable model for peripheral flow estimation has not yet been explored in the literature. Peripheral arterial flow is more complicated than aortic flow, as it can experience back flow, and is highly patient specific. A simple generic contour estimation from the pressure wave is infeasible. Thus, research towards this model has the potential to greatly improve the reliability and performance of the TF.

13.3 Future Trials

Though successful trials were performed at the University of Liege hospital, validating the data acquisition device as a useful tool for data collection in the ICU, this work was unable to implement a real-time SBV trial in the ICU. Future work for the DAQ system could incorporate the clinically feasible 3 chamber model into the Python GUI application used for displaying live haemodynamic measurements. A separate dashboard would be able to display live model identified parameters, and ultimately a patient's fluid responsiveness determined from SBV.

Further, the adaptors designed for the electrical connection, while highly successful for this research based project, would not be suitable for a final system to be used in the ICU. Given each hospital uses its own proprietary connector for pressure sensors, a new design would be required for every new hospital the device is trialled in. Furthermore, it is unlikely any proprietary company would take kindly to external devices being used to sniff data from their devices. Thus, a potentially implementable system should be fully self-contained, relying on its own measurements rather than data sniffed from external machines. This may impact the ease of installation of the system, as it is likely separate pressure sensors would be required, adding complexity to installation process. Though this process can easily be optimised through successive trials.

13.4 Data Sets

This work was able to demonstrate the ability of the 3 chamber CVS model in identifying SBV, both retrospectively, using the full measurement set from Chapter 3 and the clinically available measurement set from 7, as well as a real-time simulation on the clinically available dataset. Despite the successful validation of the model on these datasets, the datasets were highly limited in quantity, with only 8 pigs from the experimental dataset, and 3 humans from the trials at the University of Liege.

Moreover, the validation of real-time identified SBV was only performed on the 3

human subjects over the course of a single infusion. While this real-time simulation is the first of its kind, the sample size is certainly too small to be considered a full validation of SBV as an index of fluid responsiveness. Future trials will be able to collect more data from patients with varying conditions in the ICU, from which a more complete validation can be performed.

13.5 Real-time System

This work developed Python applications for both real-time display of haemodynamic data obtained during the clinical trials, as well a simulation for real-time SBV identification from the retrospective trial data. While these applications were highly successful, the Python applications do not allow much room for expansion, given the inherent limits of the language. Being a high-level, interpreted language, Python is much slower than other lower level, compiled languages, such as C or C++. The systems would heavily benefit from languages which are optimised for real-time computing.

Furthermore, Python is also not optimised for creating very clean user interfaces, making them potentially unpleasant and harder to use for bedside nurses and clinicians. This would be particularly limiting if the device were to be developed as a solution for hospital use as a bedside guidance tool. Using languages and frameworks that are more optimised for data display would highly increase the usability of the system, and potentially its ability to display data efficiently to bedside staff.

Finally, the system could be integrated into a single device, omitting the need for an external computer in the ICU, which is cumbersome for bedside nurses and clinicians, making it an infeasible solution for long-term use. A single, integrated system would require dedicated hardware, including a screen and a higher performance embedded system than the currently employed Arduino based system. To be used reliably in the ICU, the system would also ultimately require its own pressure sensors, rather than branching off the existing infrastructure in the ICU. Such a system would require a far more complex design and testing process, and

would likely cost significantly more than the current implementation. However, the system has the potential to be highly scalable and customisable, and could be extended to more physiological systems, such as mechanical ventilation data, as well as physiological models which could provide highly valuable data for bedside diagnostics. This would ultimately be a large step towards achieving a “digital twin”, a digital system where drugs and therapies can be trialled on a virtual version of a patient to produce a prediction of possible outcomes.

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Appendix A

Ethics Approval Document

Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège (707)



Sart Tilman, le 26/07/2024

Monsieur le **Prof. B. LAMBERMONT**
Monsieur le **Prof. Ph. MORIMONT**
Service de **SOINS INTENSIFS**
CHU B35

Cher Collègue,

Vous trouverez ci-joint l'avis d'approbation de l'étude :

"Numerical assessment of stressed blood volume to optimize cardiovascular performance in circulatory shock patients."

Protocole : v1

Dans le cadre des responsabilités qui lui sont imposées par la loi du 07 mai 2004, Le Comité d'Ethique souhaite vous faire part des recommandations suivantes :

- aucun patient ne peut être inclus dans l'étude avant la réception de la lettre d'approbation;
- nous souhaitons être informés de la date de début effectif de l'étude dans votre site (date d'inclusion du 1^{er} patient);
- nous attachons une grande importance à la protection de la vie privée des patients/volontaires sains et nous comptons sur vous pour :
 - assurer un archivage sûr des documents sources (conservation sous clefs),
 - assurer la protection par mot de passe des bases de données éventuellement créées pour la gestion de vos résultats, refuser, si ces données doivent être transmises à un tiers, de transmettre non seulement des données directement identifiantes (attention à l'anonymisation des copies d'examens ou protocoles d'examens) mais également toute association de données qui pourraient permettre la ré-identification du patient (attention à l'association initiales, date de naissance et sexe encore trop souvent retrouvée dans les CRF).
- nous devons impérativement être informés :
 - de tout événement indésirable grave, suspect et inattendu (SUSAR) survenu chez l'un de vos patients ou volontaire sain,
 - du renouvellement de l'assurance (request in progress: attestation to be furnished before starting the study) quand celle-ci arrive à échéance,
 - du déroulement de l'étude, et ce annuellement,
 - de la clôture de l'étude avec rapport des résultats obtenus.
- aucun changement ne peut être apporté au protocole sans l'obtention d'un avis favorable du Comité d'Ethique;
- qu'il relève de votre responsabilité de veiller à ce que tout dommage, lié de manière directe ou indirecte à l'expérimentation, encouru par un patient inclus par vos soins soit pris en charge financièrement par le promoteur soit directement, soit via le recours à l'assurance "étude";
- tout courrier/courriel de suivi que vous nous transmettez doit bien évidemment reprendre les références de l'étude et sera accompagné de votre évaluation actuelle de la balance risques/bénéfices si ce courrier est en rapport avec la sécurité du patient (amendement, nouvelle brochure d'investigateur, déviation de protocole, nouvelle information pouvant affecter la sécurité du sujet, SAE, etc....).

C.H.U. de LIEGE – Site du Sart Tilman – Avenue de l'Hôpital, 1 – 4000 LIEGE

Président : Professeur D. LEDOUX

Vice-Présidents : Docteur E. BAUDOUX, Docteur G. DAENEN, Professeur P. FIRKET

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Infos disponibles sur: <http://www.chuliege.be/orggen.html#ceh>

Comité d'Ethique Hospitalo-Facultaire Universitaire de Liège (707)



Sart Tilman, le 26/07/2024

Monsieur le **Prof. B. LAMBERMONT**
Monsieur le **Prof. Ph. MORIMONT**
Service de **SOINS INTENSIFS**
CHU B35

Concerne: Votre demande d'avis au Comité d'Ethique
Nr EudraCT ou Nr belge : B7072022000022 ; Notre réf: 2022/185

Cher Collègue,

J'ai le plaisir de vous informer que le Comité d'Ethique a donné une réponse favorable à votre demande d'avis intitulée :

"Numerical assessment of stressed blood volume to optimize cardiovascular performance in circulatory shock patients. "

Protocole : v1

Vous trouverez, sous ce pli, le formulaire de réponse reprenant, en français et en anglais, les différents éléments examinés et approuvés et la composition du Comité d'Ethique.

Je vous prie d'agréer, Cher Collègue, l'expression de mes sentiments les meilleurs,

Prof. D. LEDOUX
Président du Comité d'Ethique

Copie à la Direction de l'AFMPS

C.H.U. de LIEGE – Site du Sart Tilman – Avenue de l'Hôpital, 1 – 4000 LIEGE

Président : Professeur D. LEDOUX

Vice-Présidents : Docteur E. BAUDOUX, Docteur G. DAENEN, Professeur P. FIRKET

Secrétariat administratif: 04/323.21.58 – Coordination scientifique: 04/323.22.65

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Infos disponibles sur: <http://www.chuliege.be/orggen.html#ceh>

Notre Dossier nr : *Our File nr* : 2022 / 185
Nr EudraCT : B7072022000022

COMITE D'ETHIQUE HOSPITALO-FACULTAIRE UNIVERSITAIRE DE LIEGE
(707)

Approbation d'une demande d'étude clinique
Approval form for a clinical trial

Après examen des éléments suivants : *Having considered the following data* :

1. Protocole, Titre, *Title*

Numerical assessment of stressed blood volume to optimize cardiovascular performance in circulatory shock patients.

Numéro d'étude, *Study Number* : v1

Nr EudraCT ou Nr belge: B7072022000022

Promoteur, *Promoter*:

PROF. PH. MORIMONT

Date du protocole, *Protocol date* : 26/07/2024

Amendem. numéro et date, *Amend. Numb. and date*

	Date	Oui/Yes	Non/No
2. Brochure pour l'investigateur, <i>Investigator's brochure</i>		☐	☐
3. Information et consentement (en Français) <i>Subject information and consent sheet (in French)</i>	26/07/2024	☒	☐
4. Dossier clinique individuel <i>Case report form</i>		☐	☐
5. Déclaration d'assurance <i>Insurance declaration</i>	05/07/2024	☒	☐

Notre Dossier nr : *Our File nr* : 2022 / 185

Approbation d'une demande d'étude clinique (suite)
Approval form for a clinical trial (following page)

Protocole

Numerical assessment of stressed blood volume to optimize cardiovascular performance in circulatory shock patients.

Service de :
Clinical unit

SOINS INTENSIFS GENERAUX

Chef de Service :
Director of the clinical unit

Prof. B. LAMBERMONT

Expérimentateur principal :
Principal investigator

Prof. Ph. MORIMONT

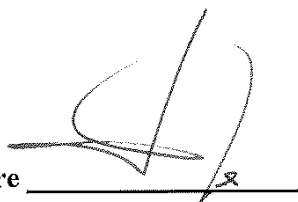
Par décision collégiale, le Comité d'Ethique (voir liste des membres en annexe) :
By collegial decision, the Ethics Committee (see enclosed list of the members) :

Oui/Yes Non/No

■ **estime que l'étude peut être réalisée**
has accepted the performance of the study



Signature
Signature



Nom : Prof. D. LEDOUX Président
Printed name :

Date, Date :

26/07/2024

The Ethics Committee states that it is organized and operates according to the ICH/GCP guidelines, the applicable laws and regulations, and their own written operating procedures

Cette approbation ne signifie pas que le comité prend la responsabilité de l'étude.
This approval does not mean that the Ethics Committee takes the responsibility of the study

MEMBRES DU COMITE D'ETHIQUE MEDICALE
HOSPITALO-FACULTAIRE UNIVERSITAIRE DE LIEGE

Monsieur le Professeur Didier LEDOUX Intensiviste, CHU	Président
Monsieur le Docteur Etienne BAUDOUX Expert en Thérapie Cellulaire, CHU	Vice-Président
Monsieur le Docteur Guy DAENEN Honoraire, Gastro-entérologue, membre extérieur au CHU	Vice-Président
Monsieur le Professeur Pierre FIRKET Généraliste, membre extérieur au CHU	Vice-Président
Monsieur Resmi AGIRMAN Représentant des volontaires sains, membre extérieur au CHU	
Madame Viviane DESSOUROUX / Monsieur Pascal GRILLI (suppléant) Représentant (e) des patients, membres extérieurs au CHU	
Madame Régine HARDY / Madame la Professeure Adélaïde BLAVIER (suppléante) Psychologue, CHU Psychologue, membre extérieure au CHU	
Madame Isabelle HERMANS Assistante sociale, CHU	
Monsieur le Professeur Maurice LAMY Honoraire, Anesthésiste-Réanimateur, membre extérieur au CHU	
Madame la Docteure Marie-Paule LECART Rhumato-gériatre, CHU	
Madame Marie LIEBEN Philosophe, membre extérieure au CHU	
Madame Patricia MODANESE Infirmière cheffe d'unité, CHU	
Madame la Professeure Anne-Simone PARENT Pédiatre, CHU	
Monsieur le Professeur Marc RADERMECKER Chirurgien, CHU	
Monsieur Stéphane ROBIDA Juriste, membre extérieur au CHU	
Madame Isabelle ROLAND / Monsieur le Professeur Vincent SEUTIN (suppléant) Pharmacien, CHU Pharmacologue, ULiège	
Madame la Docteure Liliya ROSTOMYAN Endocrinologue, membre extérieure au CHU	
Madame la Docteure Isabelle RUTTEN Radiothérapeute, membre extérieure au CHU	
Madame Cécile THIRION Infirmière cheffe d'unité, CHU	