Investigating the Fidelity of Classic Cardiovascular Metrics in the Context of a Failing and Mechanically Supported Heart

by

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Abstract

The advent of mechanical circulatory support devices (MCS) has ushered in a new era in the treatment of low cardiac output states. Proper titration of MCS is essential for optimal therapeutic outcomes and relies on monitoring metrics of cardiac state. However, innovation in clinically determining these metrics has lagged compared to treatment options. Consequently, many rely on assumptions about the cardiovascular environment that are invalidated by the use of MCS, raising concerns about their reliability.

This work used thermodilution, the gold standard method for measuring a patient's cardiac output, as well as a newly developed MCS-based method, to explore under what conditions traditional metrics are impacted by MCS. Data from porcine studies and clinical trials were used to examined how the validity of both measurement methods can be impacted by changes in a patient's cardiac state as well as commonly used medical interventions like mechanical ventilation and pharmacologic treatment, with and without MCS present. Ultimately, we found that thermodilution remains valid under conditions where beat-to-beat variability in flow is low, a limitation not present in the new MCS-based method.

Translation of this work to the clinic will help better inform physicians on when thermodilution measurements should and should not be used to titrate MCS support due to possible unreliability. What's more, understanding when and how traditional, "gold standard" metrics, such as thermodilution, fail is essential for validating newer, more reliable metrics like the MCS-based method. Both of these consequences will ultimately improving patient outcomes.

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Chapter 1 – Background and Significance

1.1 Introduction

The advent of mechanical circulatory support devices (MCS) has ushered in a new era in the treatment of common place diseases. However, to achieve optimal therapeutic outcomes with these devices, it is crucial to have reliable metrics for assessing cardiac state in order to effectively guide titration and weaning of support. Innovation in clinically determining these metrics has lagged compared to that of treatment, and thus many of the assumptions these metrics traditionally rely on are unreliable in many circumstances precisely because of the introduction of the device. In particular, this is a matter of scale where the classic metrics assume a steady state which the MCS necessarily disrupt. I will discuss the general context of these challenges as well as how emerging measurement methods will allow us to leverage the inherent interactions between these devices and the heart to overcome them.

In this chapter I will review the conditions that require the use of MCS, how these conditions are traditionally assessed and treated, and the particular MCS device used in this study. This chapter will conclude with a summary of future chapters.

1.2 Low Cardiac Output States

Cardiovascular disease (CVD) has remained the leading cause of death in the United States for the past few decades, accounting for approximately 695,000 fatalities per year [1]. Over half of these deaths are attributed to coronary artery disease (CAD), a condition that involves the narrowing or complete blockage of the coronary arteries, which are responsible for

supplying the cardiac muscle with oxygen-rich blood. This reduction in blood flow, known as ischemia, can result in various cardiac complications that transiently or permanently lower cardiac output, including myocardial infarction (MI), heart failure (HF), and cardiogenic shock (CS) [2, 3].

An MI occurs when the reduction in blood flow to the myocardium is severe and prolonged enough that the myocardium is deprived of necessary oxygen, leading to cell death. Additionally, if the section of myocardium impacted by the MI is large, it can lead to significant impairment to the heart's ability to pump blood, possibly resulting in more severe conditions, such as a low cardiac output disease like CS or certain cases of HF [4, 3].

Low output cardiac states represent a spectrum of conditions in which cardiac output (CO) is insufficient to meet the metabolic demands of the body. Besides HF and CS, other conditions that can reduced cardiac output include myocarditis, arrhythmias, and valvular disease. These states often arise from impaired cardiac contractility, reduced preload, increased afterload, or a combination of these factors. Consequently, there's inadequate blood flow to various organs and tissues, including the heart, leading to systemic and cardiac hypoperfusion. Prompt diagnosis and appropriate management are important to improve cardiac function, restore blood flow, and prevent further complications.

CS is often considered the most severe and life-threatening of low cardiac output states and is characterized by a significant decrease in CO. It's typically caused by a major MI, but can be the result of a variety of serious cardiac conditions that impact the heart's ability to function properly, such as myocarditis, valvular disease, surgical complications, or severe heart failure [2, 3, 4]. The impaired pumping ability of the heart leads to hypotension, reducing blood flow to

vital organs and tissues, including the heart itself. This can further exacerbate the ischemia and damage to the myocytes, ultimately creating a vicious cycle of worsening conditions. Without prompt treatment, CS can quickly result in multiple organ failure death [5, 6].

Immediate medical treatment for CS aims to hemodynamically stabilize the patient and restore adequate blood flow and oxygenation [7, 5, 8, 9, 6]. This may involve administering intravenous fluids, medications to support blood pressure, and inotropic medications to enhance heart contractility. Additional interventions such as angioplasty to open blocked coronary arteries, coronary artery bypass grafting (CABG), or mechanical circulatory support devices like intra-aortic balloon pump (IABP) or ventricular assist devices (VADs) may be required in certain cases [8, 9, 7].

1.2.1 Assessing Cardiac State

Hemodynamic monitoring plays a crucial role in the management of critically ill patients, such as those with CS [10, 11, 12]. It provides invaluable insight into the cardiovascular state and helps to guide therapeutics interventions. Traditionally, many of these measurements are obtained through a variety of invasive methods that characterize the pressure, flow, and oxygen delivery of the cardiovascular system in relation cardiovascular state. The most crucial hemodynamic metrics used to assess cardiac state include the left ventricular end diastolic pressure (LVEDP), left ventricular end systolic pressure (LVESP), stroke volume (SV), left ventricular ejection fraction (LVEF), and cardiac output (CO).

LVEDP informs clinicians on the preload of the heart [13]. Preload refers to the initial stretch of the cardiac muscle fibers immediately prior to contraction and is determined by the volume

of blood returning to the heart, called the venous return, as well as the compliance of the ventricles. Generally speaking, as preload increases, so does the force of contraction, resulting in a greater SV and CO. This is due to a physiological principle called the Frank-Starling mechanism that will be expanded on in the following chapter. The opposite can occur if preload decreases. An abnormal LVEDP is often indicative of cardiac disease, making LVEDP measurements a crucial metric for monitoring cardiac state.

LVESP is used as a surrogate to measure the afterload of the heart. Afterload is the resistance that the heart must overcome to eject blood from the left ventricle into the aorta and is proportional to the average aortic pressure [12]. As such, afterload is impacted by changes in systemic vascular resistance (SVR) as well as pathologies such as aortic stenosis that impede blood flow out of the ventricle. When afterload is increased, so too is the workload on the heart leading to a decrease in SV and CO. Conversely, a decrease in afterload, such as with vasodilation, leads to a decrease in SVR and an increase in SV and CO.

The SV and LVEF of the heart, along with heart rate (HR) determine CO, and thus are of high clinical interest. SV is defined as the volume of blood ejected by the left ventricle during systole, while HR is the is the number of times the heart beats per minute and is typically between 60-100 bpm [3] [14]. CO, therefore, can be calculated as the product of the SV and HR and is typically between 5-6 lpm [14]. LVEF represents the difference between the volume of blood in the left ventricle at the end of diastole and the volume remaining at the end of systole and is used to inform clinicians on the contractile state of the heart [2 [15]]. Simply stated, contractility is the force of the contraction generated by the cardiac muscle fibers and is directly controlled by the sympathetic nervous system but can also be influenced by circulating

catecholamines like adrenaline, certain medications, and increased preload. When contractility is enhanced, the ventricular contraction is more forceful, resulting in an increase SV, LVEF, and CO, with the opposite occurring when it's diminished. A normal range for LVEF is between 50-70%, with mild dysfunction at 40-49%, moderate dysfunction at 30-39%, and severe dysfunction is an LVEF lower than 30% [16].

CO can be measured clinically using specific method called thermodilution, which I will be discussing in further detail in the following chapter. However, briefly stated, the method involves injecting a small amount of cold saline into the bloodstream and measuring the resulting temperature change over time at a distal point in the cardiovascular system [17]. The resulting temperature variations are analyzed to determine the rate flow, which is equal to the CO.

1.2.2 Treatment

Mechanical circulatory support (MCS) has become increasingly popular as treatment option for low cardiac outflow conditions [9, 2, 8, 7]. MCS relies on use of mechanical devices to assist or replace the pumping function of the heart, increasing blood flow, improving cardiac function, and supporting end-organ perfusion in patients who are experiencing heart failure or other severe cardiovascular conditions. MCS devices can be temporary or long-term solutions depending on the patient's needs. Temporary MCS devices are used as a bridge to recovery, providing support until the patient's heart recovers its function or until a suitable donor heart becomes available for transplantation.

Ventricular assist devices (VADs) are implantable mechanical pumps that are surgically placed within the chest or abdomen to assist the weakened heart in pumping blood [18, 19, 20]. These devices can either partially support the heart's pumping function or completely take over the pumping function depending on the patient's needs. Percutaneous ventricular assist devices (pVADs) are a form of VAD that are increasingly being used to during acute cardiogenic events [21]. They are inserted into the heart through minimally invasive procedures, typically without the need for open-heart surgery, and are used to provide temporary circulatory support. They provide short-term support to the failing heart and can be used as a bridge to recovery or to stabilize patients in acute cardiac failure. The Impella (Abiomed, Inc., Danvers, MA) is one such pVAD, and is used as the paradigmatic model in this work due to its intrinsic ability to directly assess the local cardiac environment [21].

1.3 The Impella

Abiomed's Impella CP is a 9-Fr catheter-based axial flow pump that is inserted percutaneously into the femoral or axillary/subclavian artery and advanced through the aorta and across the aortic valve into the left ventricle (Fig 1.1). The device supports the heart by actively withdrawing blood from the left ventricle and pumping it into the ascending aorta, simultaneously unloading the left ventricle and augmenting cardiac output. The amount of support provided by the Impella is adjusted by varying the rpm of the pump which similarly alters the forward flow through the device. There are nine different operating speeds the Impella can be set to, ranging from the slowest at P1 to the fastest at P9. While higher levels will provide the greatest amount of support, higher support levels are more associated with

adverse, such as hemolysis or LV suction which occurs when the Impella's outflow surpasses the LV inflow. It's important to stress that the Impella is running in parallel with the heart. That is to say, the Impella generates a continuous flow of blood out of the LV that supplements the native, pulsatile output produced by the heart. Additionally, while clinicians can adjust the Impella's outflow from the LV, they have no control over that provided by the heart which is liable to change if the heart starts recovering or deteriorating. As such, the ratio of continuous to pulsatile flow is fundamentally variable.

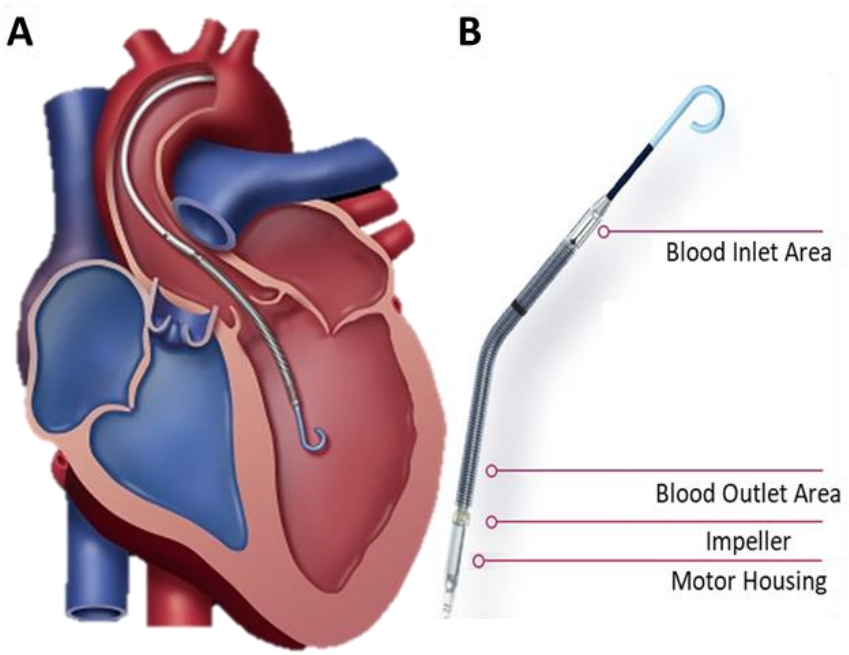

Figure 1.1: The Impella. *(A) Impella CP shown placed across the aortic valve into the LV of the heart via a femoral approach. The Impella vents the LV into the aorta continuously, operating parallel to the native heart to augment total CO. (B) The different components of the Impella are highlighted, and consist of a blood inlet and outlet area through which blood is carried from the LV into the aorta. The impeller and motor housing are responsible for generating the flow through the device.*

The Impella catheter can be broken down into four main elements (Fig 1B). The first is the inlet area of the catheter, which sits within the LV. It serves as the entry point through which blood is drawn out of the LV and into the device. Approximately 40 mm down from the inlet area, situated in the ascending aorta, is the outlet area of the catheter. It ensures the blood drawn into the catheter is returned to circulation. Adjacent to the outlet area is the impeller, a

small propeller-like rotor with blades designed to create a forward axial force on the blood as it rotates. Thus, as the impeller begins to rotate, it generates a local low-pressure zone which continuously draws blood from the LV through the inlet and propels it along the Impella's central axis. Once the blood reaches the outlet area of the catheter, it is ejected into the ascending aorta and back into systemic circulation. The motor housing is the final major component of the Impella catheter. It predominately contains the motor that powers in the impeller, however it also incorporates a pressure sensor that, when the Impella is correctly positioned, measures the aortic pressure.

The distal end of the Impella catheter is connected to an external control console, called the Automated Impella Controller (AIC) (Fig 1.2) which serves as the primary user interface for the Impella. Using the AIC, clinicians can modify the pumping speed of Impella by adjusting the P-level from P1 up to P9, the highest setting. Additionally, the AIC is also responsible for monitoring and maintaining the Impella's performance as well as displaying and recording real-time operating data for the system. During operation, the AIC will typically display two waveforms: the placement signal and the motor current.

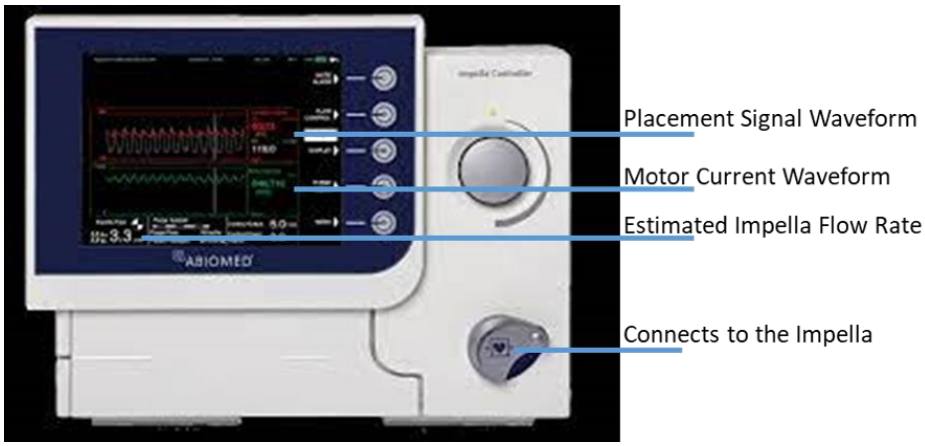

Figure 1.2: Impeller controller, called the AIC. *The AIC connects to the Impella and provides power and maintains the operating settings determined by the user. It also displays and records operational signals in real-time, such as the placement signal (aortic pressure), motor current, motor speed, and estimated flow rate.*

The placement signal waveform displays the pressure measurements taken from the sensor located in the motor housing. Therefore, when the Impella is properly positioned with its inlet in the LV and the outlet in the ascending aorta, the pressure measurements will resemble an aortic pressure waveform. Motor current is used as a measure of the amount of energy used by the Impella motor and is a function of the motor speed as well as the pressure difference between the inlet and outlet of the Impella. As the pressure differential across the LV and aorta varies during the cardiac cycle, so too will the energy need of the Impella, and consequently the motor current waveform will be pulsatile. Next to each waveform, the AIC displays the maximum, minimum, and average values along with the units of measurement and a time scale. At the bottom left of the display, the AIC gives the estimated flow rate through the Impella, as well as the maximum and minimum flows generated.

1.3.1 Impella-Heart Interactions

The Impella maintains a constant motor speed during operation, determined by the P-level. The flow generated by the Impella is dependent on both the motor speed as well as the pressure difference between the inlet and outlet, called the pressure head. The exact nature of this relationship is unique to each Impella due to otherwise insignificant manufacturing variations. Therefore, each Impella is characterised by a series of empirically derived performance curves that illustrate the impact of pressure head on flow rate for each operating speed [22, 23, 24].

The AIC verifies the Impella's speed by analyzing the frequency of polarity changes occurring during each rotation of the pump's rotor. This is an important feature of the system because

while the motor speed is meant to remain constant, the power required by the pump to achieve this speed is not. This is due to the fact that the load felt by the pump is directly related to the pressure head, which for the Impella is the pressure difference between the LV and aorta. Throughout the cardiac cycle, this pressure differential constantly changes, and thus so does the Impella's power needs. In order to maintain the desired level of support, the AIC compensates for these changes by adjusting the current supplied to the pump's motor. Leveraging this intrinsic heart-device relationship it is possible to acquire valuable metrics for assessing cardiovascular state.

Recently, a novel method for measuring CO near-continuously using the Impella was developed [24]. It uses an algorithm that rapidly drops the Impella to its lowest speed setting, P-1, for two seconds before returning to the initial speed; crucially, the therapeutic function of the Impella is not impacted by this brief drop in support. During this pulse, the outflow from the Impella is momentarily reduced, resulting in a drop in mean arterial pressure, and an increase in preload and therefore SV. A two-element lumped parameter model of the vasculature is then used to determine CO using the measurements recorded by the AIC.

While this algorithm has shown promise for reliably calculating CO, before it can be adopted into clinical use, it must first be validated by comparing it to the gold standard for CO measurement: thermodilution. However, as I mentioned at the very start of this chapter, in many circumstances the reliability of classic metrics is impacted by MCS and there is a real possibility that in some cases thermodilution has greater variability than appreciated. Until this is understood, it will be difficult to validate new methods for measuring cardiovascular metrics.

In the following chapter I will be discussing the potential issues with thermodilution that can impact its reliability, especially in the context of MCS and specific patient populations.

1.4 Overview of Chapters

In the remainder of this thesis, I will explore under what conditions traditional metrics of cardiac state are impact by the MCS, using thermodilution as my paradigmatic metric. Specifically, I will be looking at how cardiac state can impact the validity of thermodilution measurements, either by increasing or decreasing the precision both with and without the MCS. This will be compared to CO values calculated using the novel AIC CO algorithm to determine the relative vulnerability of either method to different cardiac states. Additionally, I will be examining how common medical interventions used to treat cardiac patients requiring hemodynamic monitoring, such as mechanical ventilation and pharmacologic treatment, can also impact the validity of thermodilution measurements, both with and without MCS. Understanding under what conditions thermodilution accuracy is impacted will ensure that clinicians are properly informed of their patients need and able to treat them optimally. Additionally, understanding when and if the thermodilution, “gold standard” of CO measurement, fails is important for validating any new metrics, such as the AIC CO algorithm, which are not as vulnerable to these failure points.

Chapter 2 is a detailed discussion of thermodilution, specifically how it is measured and the assumptions underlying that measurement technique. Additionally, I will explore the theoretical limitations of thermodilution, especially in the context of critically ill patients

experiencing heart failure as well as those undergoing medical interventions such as MCS and mechanical ventilation.

Chapter 3 explores the impact of cardiac disease on the fidelity of thermodilution measurements. Specifically, I will be discussing the impact of changes in cardiac state on thermodilution fidelity compared to measurements performed using the AIC CO algorithm. I will present data from both patient and animal studies. The patient data is obtained from an anonymized retrospective study on treating patients with acute cardiogenic shock using the Impella. The animal data uses a porcine acute cardiogenic shock model and explores how cardiac state can impact thermodilution fidelity.

Chapter 4 explores the impact of medical intervention on the fidelity of thermodilution measurements. I will present data from the same patient and animal studies discussed in chapter 3 along with a second animal study using the same acute cardiogenic shock model. Here I investigate how medical interventions, including the Impella, mechanical ventilation, and drug delivery can affect the cardiovascular system and consequently the reliability of thermodilution measurements.

Chapter 5 discusses the overall implications of this work and future applications. The immediate results of this work will help elucidate under which conditions cardiac state will directly impact thermodilution accuracy. As CO is an important metric in assessing and titrating care for the critically ill, it is imperative that clinicians know when they can and cannot trust the given results. Additionally, in the long term, this work will help pave the way for newer metrics, such as the AIC CO algorithm to get regulatory clearance as a reliable alternative to the current gold standard of thermodilution. MCS is an effective and increasing popular treatment option

for patients suffering from acute cardiovascular diseases. However, they require constant guidance from clinicians in order to appropriately titrate the level of provided support. Clinicians commonly base these decisions on hemodynamic monitoring, using classic methods like thermodilution, but these measurements can only be taken intermittently and represent only a single snap-shot of the dynamic cardiac environment, making them difficult to rely on. Newer MCS-based metrics of cardiac state, that leverage real-time interactions between the heart and the device, can provide clinicians with an immediate characterisation of cardiac state. Thus, their approval will ensure that MCS can be appropriately titrated to match patient needs without delay, ultimately improving patient outcomes.

Chapter 2 – Thermodilution Overview

2.1 Introduction

As mentioned in Chapter 1, hemodynamic monitoring is a fundamental aspect in managing treatment for critically ill patients [25, 26, 27, 28]. One of the most critical metrics is the cardiac output (CO) of the patient. Since the 1970s the clinical standard for measuring CO has been the thermodilution technique [29, 30, 27, 31]. Most commonly and traditionally, this technique utilising a pulmonary artery or Swan–Ganz catheter to inject a 10 ml bolus of either cold or room temperature saline into the right atrium [32, 30, 33, 27, 31]. This results in a brief fluctuation in temperature of the blood circulating through the heart. This change in temperature is captured by a thermistor located at the distal end of the catheter, in the pulmonary artery and graphed as an inverted temperature-time curve, for ease of representation and called a thermodilution curve [30, 33]. An example of thermodilution curves at different CO flow rates is shown below in Figure 2.1. The initial sharp increase of the curves denotes the initial drop in blood temperature from the injection, with the gradual return to baseline values being due to blood diluting and washing away the cold indicator through the pulmonary circulation [34]. As such, the area under this thermodilution curve is inversely proportional to CO.

The exact shape and amplitude of thermodilution curves are directly impacted by CO [33, 35]. When CO is high, the injectate is quickly pumped out of the heart through the pulmonary circulation. As such, the curve will have a steep initial upstroke with a narrow peak and will quickly return to baseline [33]. When CO is within normal range the upstroke will be more

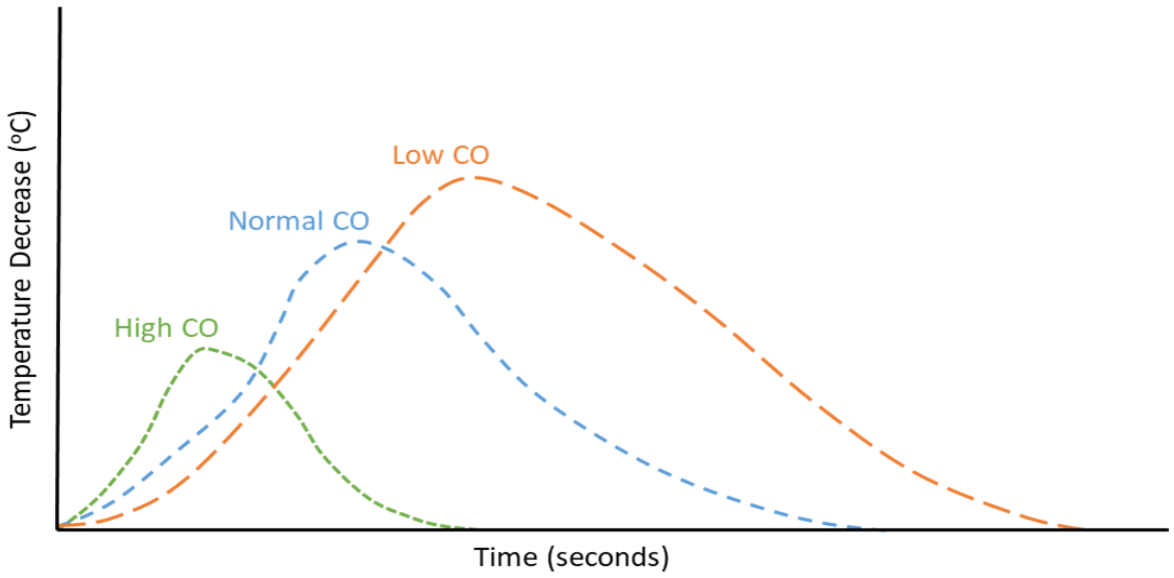

Figure 2.1: Examples of thermodilution curves for low, normal, and high CO. *Higher CO results in a curve with a steeper initial increase, narrower peak, and a quicker return to baseline temperature. A lower CO, conversely, produces a curve with a very gradual initial increase, very broad peak, and very gradual return to baseline. Additionally, the total magnitude of the curve is generally inversely related to CO; curves when CO is low will often be taller than curves when CO is higher.*

gradual with a broader peak and a more gradual return to baseline. In low CO settings, the injectate will be slow to leave the heart and travel through the pulmonary circulation. Consequently, the thermodilution curve will have a very gradual upstroke with a very broad peak and a very gradual return to baseline [33]. Additionally, the height of the thermodilution curve is often impacted by CO, with higher curves when CO decreases, and shorter curves when CO increases [33].

The area under the thermodilution curve is calculated using integration techniques [34, 35]. Specifically, the curve is divided into smaller time intervals and a single, averaged temperature value is calculated for each interval. Multiplying these values by the length of the time interval and summing them give an approximate value for the curve's area. The exact number of intervals used, and their length is proprietary and depends on the analysis software used, yet

knowing the length and number of these intervals is key to understanding the risk of error in a thermodilution [34]. For example, as shown in Fig 2.1, when CO is high, the curve is much shorter, meaning that integrating over the same number of time intervals will lead to less precise results as it's a smaller snapshot of the total blood flow [33]. Thus, when CO is high, thermodilution is likely to be less precise. However, when CO is low, the curve is much longer [33]. Consequently, this can result in greater error during integration as the time intervals will be further apart, increasing the odds of beat-to-beat variations in CO occur during the measurement process. As such when CO is low, you would expect more variability in thermodilutions.

Additionally, in some cases it may be necessary to extrapolate the thermodilution curve as it fails to return to baseline temperatures during the measuring time [32, 30, 33, 35]. This most frequently occurs when the injectate is poorly timed with the cardiac cycle, or when CO is either low or high. In these cases, the end of the thermodilution curve must be extrapolated so that it falls back down to baseline. The exact method used to do this is also proprietary, and depends on the specific analysis software used, but essentially involves fitting a mathematical model to the measured portion of the curve and then estimating the missing portion of the curve using this model. Since extrapolation relies on making assumptions on how the thermodilution curve should look, and therefore extrapolated curves are considered more prone to error than curves not requiring any modification.

The principle of obtaining CO from the thermodilution curve is based on the Stewart–Hamilton equation, which explains the relationship between blood flow, an indicator, and its blood concentration, as depicted in the equation below [36, 33, 27, 31]:

$$CO = \frac{Indicator}{\int_0^\infty \Delta C(t)dt}$$

It stems from the law of conservation of mass: when a known concentration of indicator is added into a moving liquid, the dilution rate of the indicator can be used to calculate flow. In the case of thermodilution, instead of measuring a change in concentration of an indicator, temperature changes are measured instead [26, 36, 33, 31]. Consequently, the specific heat and specific gravity of both the blood and indicator need to be taken into account. These factors are represented by a variable, k_1, referred to as the density constant. An additional variable, k_2, is also needed as a calibration constant to accounts for factors such as indicator warming during injection. The resulting modified Stewart-Hamilton equation is as follows [26, 32, 30, 27, 31, 35]:

$$CO = \frac{V(T_b - T_i)k_1k_2}{\int_{t_1}^{t_2} \Delta T dt}$$

V is the absolute volume of the injected indicator and for thermodilution it is directly dependent on the initial temperature difference between the blood (T_b) and the indicator (T_i) [30, 32, 26, 27, 31, 35]. The denominator of this equation characterises the change in temperature as blood flows, and is represented as the area under the thermodilution curve discussed above.

2.2 Known Limitations with Thermodilution

As thermodilution is based on the law conservation of mass, it therefore assumes ideal conditions [27]. The most salient assumptions being: (1) constant flow rate for both blood and indicator injection; (2) single inflow and outflow tracts; (3) no indicator recirculation; (4) complete mixing of indicator and blood; (5) no heat exchange between the indicator and the surrounding tissue [32]. None of these assumptions can be guaranteed to be satisfied during thermodilution, and as such, some error is always assumed [37, 38]. However, in practice, the error introduced by these failed assumptions can generally be offset by performing three thermodilutions in serial and averaging the calculated flow rates to determine the patient's true CO. If any of these triplicate values differ by more than $\pm$15%, the thermodilutions are repeated until three values are within this margin of error [34, 29, 28].

2.2.1 Procedural Errors

There are various sources of operator error that can violate the above assumptions to such an extent that the thermodilution measurements are no longer considered valid representations of the patient's CO [26, 32, 37, 30]. The most notable source of error is the manual nature of the injection, as it can be very difficult for the operator to ensure a consistent and repeatable injection rate.

During serial thermodilution measurements, it is essential that the cold indicator is injected at a constant rate [26, 32, 37, 30, 34]. An increase in injection rate will result in a faster clearance of the indicator, a smaller thermodilution curve, and therefore a higher calculated

CO. If the injection rate is decreased, the indicator will take longer to clear and the CO will be calculated as lower.

Additionally, it is important that thermodilution measurements are conducted starting at end-expiration [32, 30, 34]. During inhalation, there is a decrease in intrathoracic pressure which is directly felt by every structure within the thoracic cavity, including the heart. This results in a transient increase in venous return, a corresponding increase in preload, and ultimately a slightly higher CO will be recorded during inhalation. During exhalation the intrathoracic pressure increases, reducing venous return and preload, and thus CO will be measured as lower. By performing thermodilution measurement at end-expiration, error introduced by these potential variations can be reduced and serial thermodilution will have a greater agreement. [30, 34]

Catheter placement is also important for reducing error in thermodilutions, both in terms of location and position [26, 32, 37, 30]. The catheter needs to be located with West's Zone 3 of the lung to ensure that the thermistor is located in a region within the PA that will receive undisturbed blood flow. What's more, the catheter needs to be positioned such that the thermistor is not pressed up against the wall of the PA so that it is able to sense the cold indicator flowing through the blood rather than the temperature of the vessel wall.

2.2.2 Errors Due to Patient Physiology

On top of inaccuracies caused by operator error, thermodilution is known to be impacted by various anatomical defects and different disease states [26, 32, 36].

Thermodilution on a patient with severe tricuspid regurgitation results in an underestimation of the patient's CO [26, 32, 36, 30]. During systole, instead of ejecting out of the right ventricle towards the thermistor, a portion of the cold indicator is instead directed back into the right atrium. This ultimately elongates the thermodilution curve as it takes significantly longer for all the cold indicator to pass out of the right ventricle, thus appearing like the flow rate is lower than it actually is [30].

An intracardiac shunt will also impact the reliability of thermodilution [26, 32, 36, 30]. In the case of a left-to-right shunt, the cold indicator is recirculated back to the right heart, creating a new peak on the thermodilution curve. This increases the area underneath the thermodilution curve, leading to an underestimation of the patient's CO [30]. In the case of a right-to-left shunt, the cold indicator escapes to the left heart, bypassing the thermistor and thus decreasing the area underneath the curve leading to an overestimation in CO [30].

When CO is low, the reduced circulation allows for greater temperature loss from the indicator to surrounding the tissue [30]. This results in a reduction to the area under the thermodilution curve and ultimately an overestimation of the patient's CO [32].

Changes in patient physiology not directly impacting the heart can also interfere with the accuracy of thermodilution measurements. As mentioned above, thermodilution measurements are performed at end-expiration since CO is vulnerable to the pressure changes that occur during respiration. However, if a patient has an erratic respiratory pattern this will result in a randomly varying venous preload and equally unpredictable momentary changes in CO that will introduces variability in serial thermodilutions that can't be negated through timing the procedure to end-expiration [34]. Additionally, if the patient has an unexpected

haematocrit, such as with anemia or erythrocytosis, the specific heat and specific gravity of their blood will be different [36, 30, 34]. This will create an error with the k_1 variable in the modified Stewart-Hamilton equation thermodilution is dependent on.

2.3 Theoretical Limitations with Thermodilution

As mentioned above thermodilution is based on the law of conservation of mass and therefore it assumes the patient's CO has a constant flow rate. Each thermodilution takes approximately 30 seconds to perform, and in order to ensure the accuracy and consistency of the measurements, thermodilutions are performed in triplicate and the results averaged [29, 34, 28]. In general, cardiac state is unlikely to change much during the time needed to perform all three measurements, and so any error caused by random variations in CO during the procedure is considered sufficiently eliminated by taking the average. However, it's important to understand, that just because it was traditionally considered unlikely for cardiac state to change that quickly, it doesn't mean it can't [28].

Specifically, there are many physiological factors that can impact CO and many of them can be varied at much higher frequencies than the 30 seconds needed for a thermodilution. For example, average HR varies from 60 to 100 bpm, but can increase to 160+ bpm, especially when dealing with critically ill patients. Additionally, the average respiration rate (RR) is 12 to 18 breaths per minute, but as with HR, it can be much higher in critically ill patients. Figure 2.2 compares the normal frequencies of HR and RR to the time needed to perform one thermodilution. Both of these factors are able to vary during the thermodilution measurement,

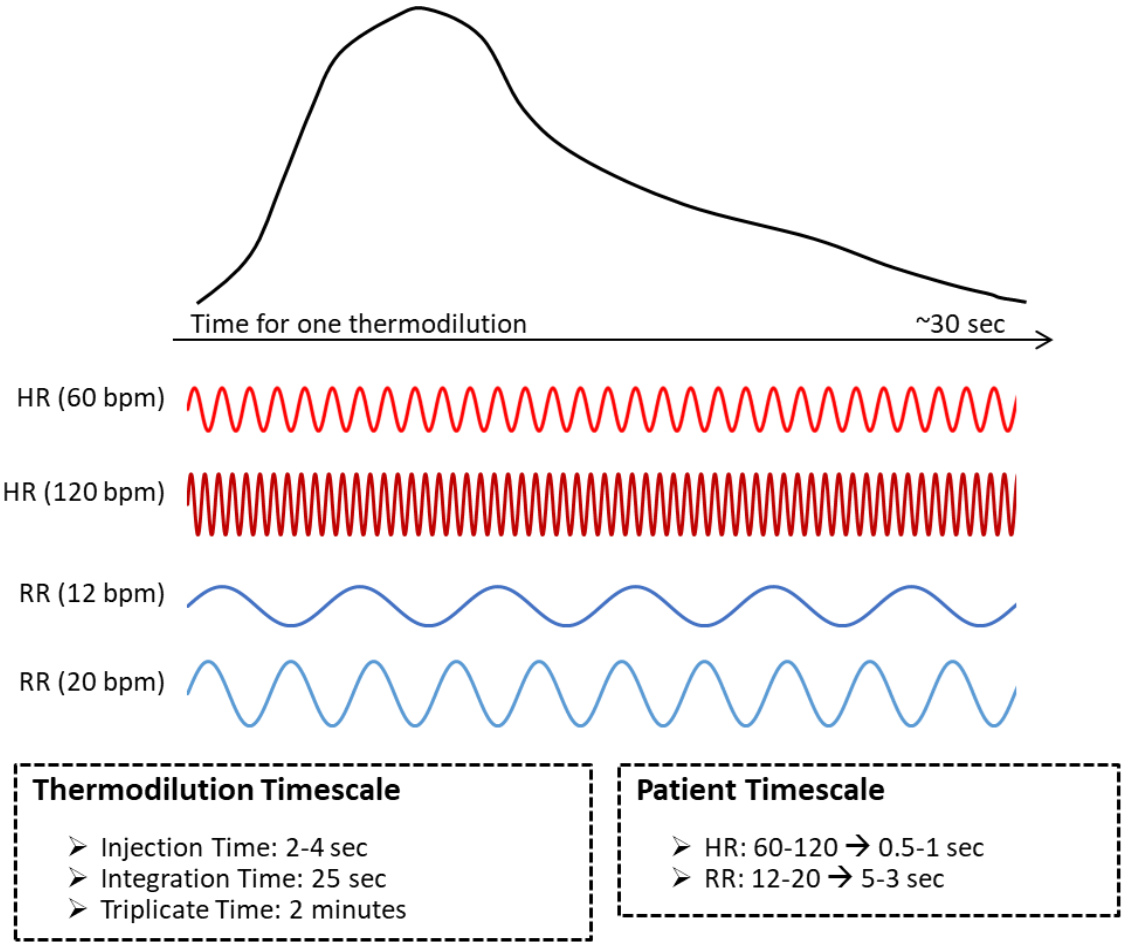

Figure 2.2: Understanding the timescales of thermodilution. *Comparing the time taken for one thermodilution measurement to the relatively much higher frequencies at which a patient's physiologic state is liable to vary.*

and both are known to impact CO, either directly or indirectly [29, 32, 33, 34]. As such, it's important to understand, when cardiovascular state changes more rapidly than the measurement time, what happens to the validity of classic cardiovascular metrics that rely on a steady state, such as thermodilution. Below I will be discussing how various scenarios might theoretically influence the validity of thermodilutions.

2.3.1 In the Context of Heart Failure

In healthy physiology, in order to meet the immediate global metabolic needs of an individual, CO is varied by manipulating stroke volume (SV) and heart rate (HR). Exactly how the cardiac system is impacted by perturbations throughout the day is a function of both cardiac state as well as blood flow. As the cardiac state of a patient undergoing heart failure is incredibly different from a healthy individual, it stands to reason that their cardiac systems would react differently to the same perturbations, and in fact this can be seen in practice, such as with the Frank-Starling mechanism.

The Frank-Starling mechanism describes the phenomenon by which the force of contraction, and therefore the SV, of the heart varies in response to changes in venous return [39, 40]. An increase in venous return results in an increase in ventricular filling during diastole, and consequently preload increases too. As described in chapter 1, preload is the amount of stretch experienced by the cardiac myocytes immediately prior to contraction. As the myocytes are increasingly stretched, the amount of force they are able to generate likewise increases, enabling the heart to eject this additional venous return [40]. Thus, the Frank-Starling mechanism intrinsically allows the heart to modify SV in order to immediately match venous return without depending on external regulation [39]. That being said, while the mechanism is not reliant on extrinsic regulation, it can be heavily impacted by cardiovascular state, demonstrated by the Frank-Starling (F-S) curves in Figure 2.3. These curves illustrate the relationship between the left ventricular end-diastolic pressure (LVEDP) and the SV under different cardiovascular conditions. When inotropy increases or afterload decreases, the curve becomes steeper and shifts upwards and to the left [39]. Physiologically, this translates to an

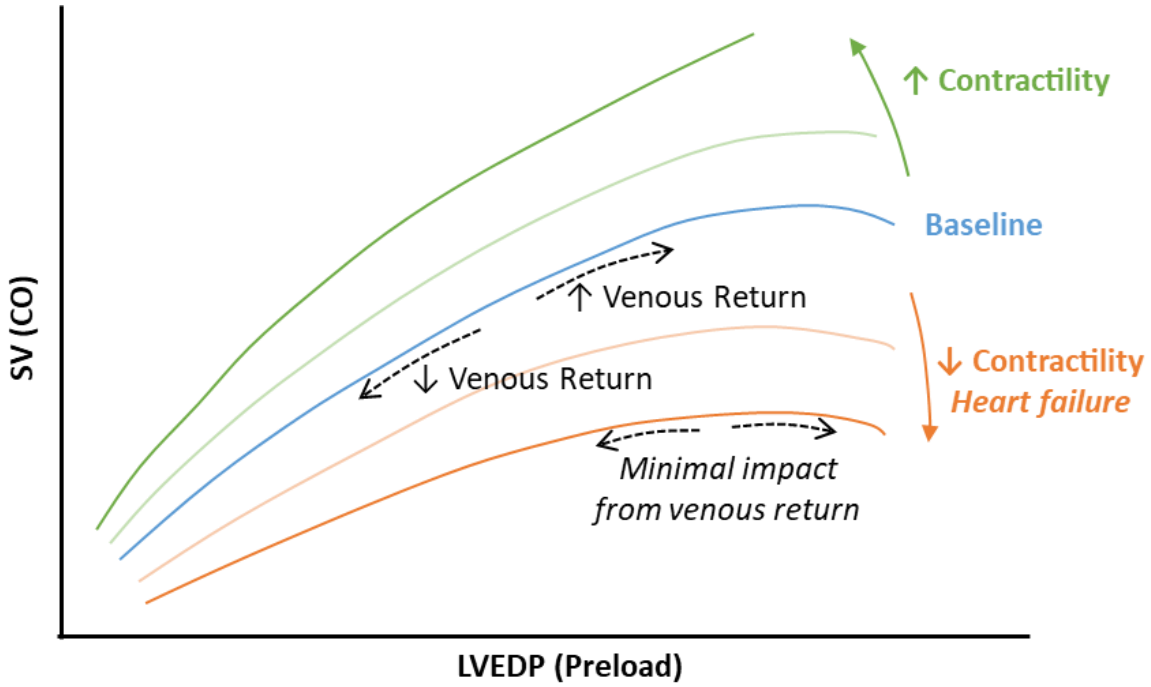

Figure 2.3: Examples of Frank-Starling curves showing the impact of cardiac state on the relationship between stroke volume and LVEDP. *When contractility is increased, the curve shifts up and left, meaning that the same LVEDP will result in a much greater SV. Conversely, when contractility decreases, the curve shifts left and down, indicating that at the same LVEDP, SV will be much lower. As LVEDP is directly related to venous return, a decrease in venous return results in moving down the curve while an increase in venous return moves back up the curve, increasing SV. However, this relationship is almost non-existent when contractility is very low.*

increase in SV for a given LVEDP and also makes SV more vulnerable to variations in LVEDP. The opposite occurs when inotropy decreases or afterload increases; under these conditions there is a decrease in SV for a given LVEDP and SV becomes less vulnerable to variation in LVEDP [39].

In heart failure, cardiac contractility is reduced, resulting in a F-S curve that is shifted right and blunted, similar to the orange curve from Fig. 2 [39]. As a result, it will take a greater pressure change in order to see the same change in SV that would occur in healthy physiology. Additionally, the curve flattens out at a much lower value, meaning SV is much more limited and at a lower LVEDP. In theory, both of these elements make SV much less vulnerable to manipulation and therefore limit the possibility of beat-to-beat differences in CO. Thus,

compared to a healthy individual, thermodilutions performed on heart failure patients are, in theory, less likely to be impacted by transient changes in CO and there will consequently be an increase in accordance between triplicate measurements.

What's more, heart failure can be classified as having either a reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF) [41]. HFrEF, or systolic heart failure, occurs when the cardiac muscle becomes too weak to effectively pump blood. Accordingly, a much smaller portion of blood from the ventricles is expelled during systole, decreasing the ejection fraction (EF) of the heart to 40% or lower [41]. HFpEF, or diastolic heart failure, on the other hand, occurs when the heart is unable to relax properly during diastole. As a result, blood flow to the ventricles is reduced enough that despite having a normal EF, CO is sufficiently impaired to cause disease [41].

While HFpEF is not primarily the result of poor cardiac contractility, many patients may have underlying myocardial dysfunction or comorbidities that still result in some reduced contractility compared to healthy physiology [42, 40]. That being said, contractility is not expected to be as impaired as in patients with HFrEF. Hence, patients with HFrEF have a much flatter F-S curve compared to those with HFpEF, leading to a much greater limitation in SV and reduction in beat-to-beat variability in CO. Thus, by similar logic as above, it can further be supposed that thermodilution triplicates performed on patients with HFrEF will be in greater agreement than those performed on patients with HFpEF.

2.3.2 In the Context of MCS

Patients with severe heart failure or other low output conditions often require mechanical circulatory support (MCS) to augment or even replace the function of their heart [43]. Left ventricular assist devices (LVADs) are a commonly used form of MCS that help improve end-organ perfusion by pumping blood from the left ventricle of the heart into the aorta [43]. Most LVADs used today are designed for continuous flow, compared to the normal pulsatile flow of blood. Additionally, LVADs are known to alter the normal physiology of the cardiovascular system, leading to changes in the relationship between preload, afterload, and stroke volume [43]. As a result, it's important to understand if and how these alterations impact the accuracy of traditional hemodynamic monitoring methods such as thermodilution.

LVADs directly lead to an increase in total SV because now the amount of blood ejected during systole is comprised of that from the native heart, as well as what's being pumped by the LVAD. The impact of LVADs on preload is more varied and depends on both the pump settings as well as the patient state [44]. In general, LVADs are expected to decrease preload as the continuous pumping of blood out of the ventricle even during diastole results in a decrease in blood volume and subsequently pressure at the end of diastole. While this decrease in preload can result in a decrease in SV from the native heart due to the F-S mechanism discussed earlier, total CO is not diminished due to the additional blood flow provided by the LVAD. However, in some cases LVADs can actually increase preload by improving blood flow and reducing pulmonary congestion [44]. In this case, the heart is able to generate a greater SV, and coupled with the additional flow support of the LVAD, CO would be expected to increase

even more. Similarly, LVADs can have a varied impact on afterload, either increasing or decreasing depending on pump settings and patient state in a manner difficult to predict [44].

The level of support provided by LVADs can be modified based on needs of the patient, one of the reasons why hemodynamic monitoring is so important for this patient population. The Impella, discussed in detail in the previous chapter, is a type of percutaneous LVAD that operates by ejecting blood from the ventricle at a constant flow rate set by the operator. As such, patients with an Impella have two types of outflows from their heart: a pulsatile component generated by the native heart, and the continuous flow from the Impella. The proportion of the total CO that is pulsatile compared to continuous is dependent on both cardiac state and the Impella settings. At a higher Impella setting a greater proportion of the flow will be continuous and set to a fixed flow rate, leading to a more constant CO. Similarly, if the heart starts to further deteriorate, the native, pulsatile component of the blood flow will be reduced, also leading to a more constant CO. However, if the Impella settings are either reduced or the heart improves its functionality, the proportion of pulsatile flow will increase, and CO will be more variable. It stands to reason that as CO becomes more variable, measurements that take a longer period to conduct, and rely on averaging measurements taken minutes apart, become less reflective of the actual CO of the patient. It is likely in these cases that there will be significantly less concordance between triplicate measurements than otherwise.

2.3.3 In the Context of Mechanical Ventilation

Respiration and CO are highly interrelated, and it's possible for changes in respiration to have a significant impact on CO. This is primarily due to the fact that both organs are housed

within the thoracic chamber allowing the heart to directly experience the changes in pressure that occur during respiration.

During inspiration, the diaphragm contracts downwards, decreasing the intrathoracic pressure, and air into the lungs via the newly created pressure gradient [45]. At the same time, this decrease in pressure is translated to the heart, increasing venous return in the same way which directly leads to an increase in CO via the F-S mechanism discussed above. Conversely, during expiration, the diaphragm relaxes, moving up, and increasing the intrathoracic pressure, expelling air from the lungs. Again, this change in pressure is translated to the heart, leading to an increase in right atrial pressure, and impeding venous return to the heart and decreasing CO [45].

As the heart and lungs are closely interconnected, respiratory issues are common in patients with cardiac disease. In certain cases, these issues can be severe enough to require mechanical ventilation, often referred to as positive-pressure ventilation (PPV). PPV is a method of breathing where pressurized air is delivered into the lungs through a mechanical ventilator [45]. As such, while PPV is effective at ventilating the lungs, it leads to drastic alterations in heart-lung interactions [35, 45].

During PPV, the air being pushed into the lungs causes an increase in intrathoracic pressure. Contrary to with natural breathing, intrathoracic pressure is greater during inspiration than expiration when using PPV resulting in almost opposing heart-lung interactions [45]. Additionally, to ensure the airway stays properly open during PPV, a positive end-expiratory pressure (PEEP) is applied at the end of expiration, meaning that for the entirety of the respiratory cycle the intrathoracic pressure is higher than would naturally occur [45]. This in

turn increases the pressure within the right atrium, which can lead to decreasing venous return and consequently cardiac output [45].

Changes in respiratory rate and depth can alter the degree of intrathoracic pressure changes during respiration, which in turn affects venous return and thus CO [35, 45]. Additionally, PPV leads to very different relationship between the heart lungs compared to natural breathing [35, 45]. On one hand, in PPV preload is decreased as venous return is hindered which generally decreases SV and thus CO [45]. However, at the same time, depending on both the ventilator settings and cardiac state of the patient, PPV can also either increase or decrease afterload, further impacting CO [45]. That being said, as respiratory rate and depth are tightly regulated in PPV, any variations in CO from ventilation will remain consistent and should be easily negated through timing the procedure to end-expiration. By timing the procedure to end-expiration these errors can be largely negated.

2.4 Discussion

Recalling the modified Steward-Hamilton equation used to calculate CO from a thermodilution, the only non-constant variable is the denominator, which represents the area underneath the thermodilution curve. Thus, any sources of error within and between thermodilution measurements will be due to errors in generating this curve. As mentioned earlier in this chapter, thermodilution relies on five key assumptions: (1) constant flow rate for both blood and indicator injection; (2) single inflow and outflow tracts; (3) no indicator recirculation; (4) complete mixing of indicator and blood; (5) no heat exchange between the indicator and the surrounding tissue. Of these five, the first is by far the most likely to be

violated, especially considering that the pulsatile nature of CO ensures that the flow is not constant. However, on top of this, many factors can lead to transient alterations in CO, as explained above. If these occur during a thermodilution measurement it can lead to either an underestimation or overestimation of a patient's CO. If they occur between triplicate thermodilutions it can lead to an increased discordance between measurements. Therefore, it's necessary to understand to what extent CO can change during and between thermodilutions and how this might in turn impact the thermodilution curve, especially in the patient populations most in need of precise hemodynamic monitoring.

CO is the product of the SV and HR, thus any changes in CO are due to changes in at least one of these parameters. Thermodilutions take between 20-30 seconds to complete and physiologically it's incredibly unlikely that a HR could increase significantly in that time frame. However, that is enough time for beat-to-beat variability in SV to occur. Consequently, any variation in SV during a thermodilution measurement will likely result in an underestimation or overestimation of CO, directly related to the magnitude and direction of the SV change. The time needed to complete the triplicate thermodilution measurements is long enough for significant changes in HR to occur between thermodilution measurements. As a result, it's possible for either SV or HR, or both to vary between serial thermodilutions, leading to a greater disparity between measurements. This disparity is directly related to the product of the errors associated with the increased variability of SV and HR. Understanding this, it should be possible to predict what situations are likely to exaggerate beat-to-beat variability in SV and HR and consequently increase the error of thermodilution measurements, and which situations might diminish this variability, decreases measurement errors.

Many critically ill patients, often experience increased stroke volume variability as a result of changes in preload, afterload, and contractility as well as the possible presence of arrhythmias. Arrhythmias in particular can result in extreme fluctuations in SV as the irregular heart rhythm leads to disordered filling and emptying of the heart chambers. As a result, you would expect these patient populations to have a higher error associated with thermodilutions due to this increased SV variability.

That being said, referring to the F-S curves in Fig. 2 discussed earlier, as contractility is so frequently impaired in heart failure, these patients often have a limited SV. Therefore, the reliability of thermodilution is not just a function of SV variability but also the heart's contractility. As contractility is much lower in HFrEF compared HFpEF, you would expect errors in thermodilutions to be reduced in those patients, with greater agreement in serial measurements.

As explained above, patients with severe heart failure or other low output conditions often require MCS to augment or even replace the function of their heart. One such type of MCS used is the Impella, which supports the failing heart by continuously pumping blood out of the heart at a constant flow rate. This flow rate is adjusted to match the needs of the heart, which are accessed using traditional methods of hemodynamic monitoring, such as thermodilution. As such, it's incredibly important that these measurements be accurate. However, as the Impella, like other MCS devices, alter the normal physiology of the cardiovascular system it's imperative to determine if and how these alterations impact the validity of these measurements.

The main modification to the cardiovascular system by the Impella is the introduction of a second type of outflow from the heart. CO is divided into two components: pulsatile flow from

the heart and continuous flow from the Impella. While the flow generated by the heart can vary beat-to-beat, the flow from the Impella is constant unless modified by the operator. Therefore, in situations where the Impella provides a greater fraction of the total flow, you would expect CO to be much less variable as the impact of any variability in the patient's SV or HR will have much less of an impact on the total flow. Specifically, when Impella support is high or the heart further deteriorates, you would expect thermodilutions to more accurately represent the CO and there to be greater harmony between the serial measurements. However, when Impella support is low, or cardiac state has improved, a greater fraction of the flow will derive from the native heart. Consequently, the total CO is likely to be more vulnerable to changes in the patient's SV or HR resulting in a more variable CO. Thus, in these situations it's probable that there will be a higher error associated with thermodilutions, with greater conflict between the serial measurements.

Many critically ill patients requiring hemodynamic monitoring experience respiratory distress and this can have a significant impact on CO by altering the balance between oxygen supply and demand in the body. Respiratory distress can manifest itself as rapid or shallow breathing, wheezing, coughing and often leads to hypoxemia. This in turn signals for the heart to increase CO in order to increase oxygen delivery. At the same time, respiratory distress can also lead to extreme variations in the magnitude of intrathoracic pressure changes during breathing, as well as the RR. As explained above, SV is highly vulnerable to changes in intrathoracic pressure, but this error can usually be negated through timing the procedure to end-expiration. However, when intrathoracic pressure changes become more irregular so do the subsequent changes in SV, and timing the procedure to end-expiration is less effective in accounting for this possible

variability. Consequently, the error associated with thermodilution is likely to be higher in patients experiencing respiratory distress than those with normal breathing patterns.

When respiratory distress becomes too severe, PPV might be necessary. A main consequence of PPV is an overall increase in intrathoracic pressure, resulting in a decrease in venous return, or preload, that directly reduces SV. That being said, it also decreases LV afterload, which ultimately increases SV. Thus, the overall impact of PPV on SV will be dependent on each patient's volume status and fluid responsiveness, which is defined as the ability of the LV to increase SV in response to the administration of fluid [46]. A patient with a higher volume or that's fluid responsive can generate a greater SV due to the F-S mechanism than a patient with less volume or who isn't fluid responsive. Thus, the SV of these patients is likely to increase with PPV, where as patients with low volume status will see their SV decrease. Additionally, PPV tightly regulated the respiratory parameters, ensuring a constant RR and consistent intrathoracic pressure changes during the respiratory cycle. This would actually make timing thermodilutions to end-expiration even easier and more effective compared to non-ventilated individual. As a result of both the decreased SV and tighter regulation of respiratory parameters, the error associated with thermodilution is likely to be lower in ventilated patients with a low volume status than it is for unventilated patients, even those not in respiratory distress. For patients with a higher volume status, or who are fluid responsive, the impact on SV is less clear, making thermodilution variability more difficult to predict.

Chapter 3 - The Impact of Cardiac State on Thermodilution Fidelity

3.1 Introduction

As explained in the previous chapter thermodilution is considered the gold standard for measuring a patient's CO, however, there are many known limitations associated with this method. This is likely due to the fact that thermodilution measurements assume steady and stable conditions and there is little concern for how long each measurement took. Additionally, as thermodilution determination requires at least three separate measurements, the entire procedure can take several minutes. However, despite assuming steady flow, the cardiovascular environment that thermodilution samples is far from steady. In fact, it's constantly regulating CO in order to meet physiological needs, by modulating both SV and HR.

Thus, we hypothesize that when cardiovascular state changes more rapidly than the necessary measurement time, thermodilution becomes less reproducible and therefore less reliable. These small-scale changes occur as beat-to-beat variations in either of the cardiac factors: SV or HR. That being said, we would expect beat-to-beat variation in SV to be more impactful on thermodilution measurements than variations in HR. This is due to the fact that there is an inherent limit to how quickly the heart's rate of contraction can increase or decrease but there is a much wider range of possible SV adjustment in the normal heart. Thus, changes in SV would have a greater impact on thermodilution reproducibility than changes in HR.

Recalling the Frank-Starling curves discussed in chapter 2, when LVEF is low, such as with heart failure, SV variance is limited. As such, the compensatory mechanism induced by changes

in LVEDP will have little impact on SV and its value will be more stable. Consequently, we would expect more reproducible thermodilution measurements for patients with low LVEFs compared to those with greater LVEFs.

This set of studies aimed to investigate why and under what conditions classic thermodilution fails to reproducibly measure CO using a combination of both patient and animal data. Additionally, this chapter will compare the reproducibility of CO measurements conducted using thermodilution and using the AIC CO algorithm mentioned in chapter 1. Unlike thermodilution this method doesn't assume steady and stable flow, and instead was developed to operate under a highly dynamic cardiac flow environment. Therefore, it is expected that in cardiac states with greater beat-to-beat variations, especially in SV, the AIC CO algorithm will result in more reproducible measurements than thermodilution.

3.2 Materials and Methods

3.2.1 Patient Study

Anonymized retrospective patient data was used to analyze the impact of various cardiac metrics on the reproducibility of both thermodilution and the AIC CO algorithm. In this study, 10 patients with an Impella had their CO measured in triplicate using both thermodilution and the AIC CO algorithm at four different speeds: P-2, P-4, P-6, and P-8. The data set consists of the initial LVEF of these patients, the measured COs, and all information collected by the Impella system. Of note, one patient from this study was considered to be a significant outlier and in many cases was removed from the figures within this document so as to better illustrate the overall trends of the data.

3.2.2 Animal Study

We used a specifically designed porcine model of acute cardiogenic shock (CS) developed in our lab. This model serves as a valuable tool for conducting research aimed at evaluating the impact of mechanical circulatory support (MCS) devices on shock physiology. As such, it provides an ideal opportunity for studying and improving techniques for monitoring physiological changes in cardiac state when undergoing MCS treatment.

In this chapter, we will explore the findings from a cardiogenic shock model animal study to examine the influence of changes in cardiac state brought on by pathophysiologic conditions on the repeatability of thermodilution.

3.2.2.1 Porcine Cardiogenic Shock Model

~70 kg young adult male Yorkshire swine were used in all studies due to their similarities in both behaviour and size of their cardiovascular system to that of humans. All experimental procedures and protocols ensured animals were maintained in accordance with Nation Institute of Health (NIH) and institutional guidelines regarding humane care and use of laboratory animals.

Animals were initially sedated via an intramuscular injection of Telazol (4-6 mg/kg) and anesthesia was sustained using isoflurane. Throughout the duration of the studies, the animals were continuously monitored via oxygen saturation, core body temperature, and electrocardiogram. Animals were subsequently intubated, placed in dorsal recumbency, and draped for all procedures. Vascular access was established through the left and right femoral

arteries and veins, jugular vein, and right carotid artery. Catheters were introduced in order to use hemodynamic measurements to continually assess the cardiac state of the animals. After completing this setup, a series of initial measurements was conducted to serve as baseline values for calibration and quantification of physiological changes that occur once the animal enters a CS state.

CS was achieved by inducing permanent localized ischemia primarily in the left region of the heart. This was accomplished by inserting a Judkins guide catheter into the left anterior descending (LAD) coronary artery via the left femoral artery. Small boluses of Hydropearl microbeads (45-105 um in diameter) were prepared by mixing 0.25 ml of microspheres with 10 ml of isotonic saline and 10 ml of contrast. Following each bolus injection, the animal's cardiac function was reassessed and microbead injection ceased once the LVEDP exceeded 16 mmHg and one of the following conditions were met: (a) mean arterial pressure (MAP) dropped below 50 mmHg, (b) mixed venous oxygen saturation fell below 55%, (c) thermodilution measurements indicated a CO below 50 ml/kg/min, or (d) clear evidence of LV decoupling was observed. At this stage, a new experimental baseline was established for each animal.

3.2.2.2 Impella Support

An Impella CP device was inserted into the left ventricle through the right femoral artery. The correct positioning of the device and the competency of the aortic valve were monitored using fluoroscopy. Each condition was evaluated at four different Impella speeds: P-2, P-4, P-6, and P-8. Once the desired level of support was achieved, continuous real-time monitoring ensured hemodynamic stability and data collection in the newly established steady state. After

reaching a hemodynamically stable state, consecutive two-minute intervals of data were recorded and appropriately labeled for subsequent retrospective analysis.

3.3 Results

3.3.1 Patient Data

To first analyze the reliability of the AIC CO algorithm compared to the current gold standard of thermodilution, we compared them via a Bland-Altman plot and linear regression (Fig 1). These graphs show that on average CO measured via thermodilution is roughly 0.91 L/min lower than measurements conducted using the AIC method. Additionally, the difference between these methods increases with CO. Finally, while CO measured using the AIC was generally greater than measurements made using thermodilution, there were a few times that thermodilution yielded greater values. When this happened, thermodilution measurements were much greater than the average value and the difference between the two methods was much larger.

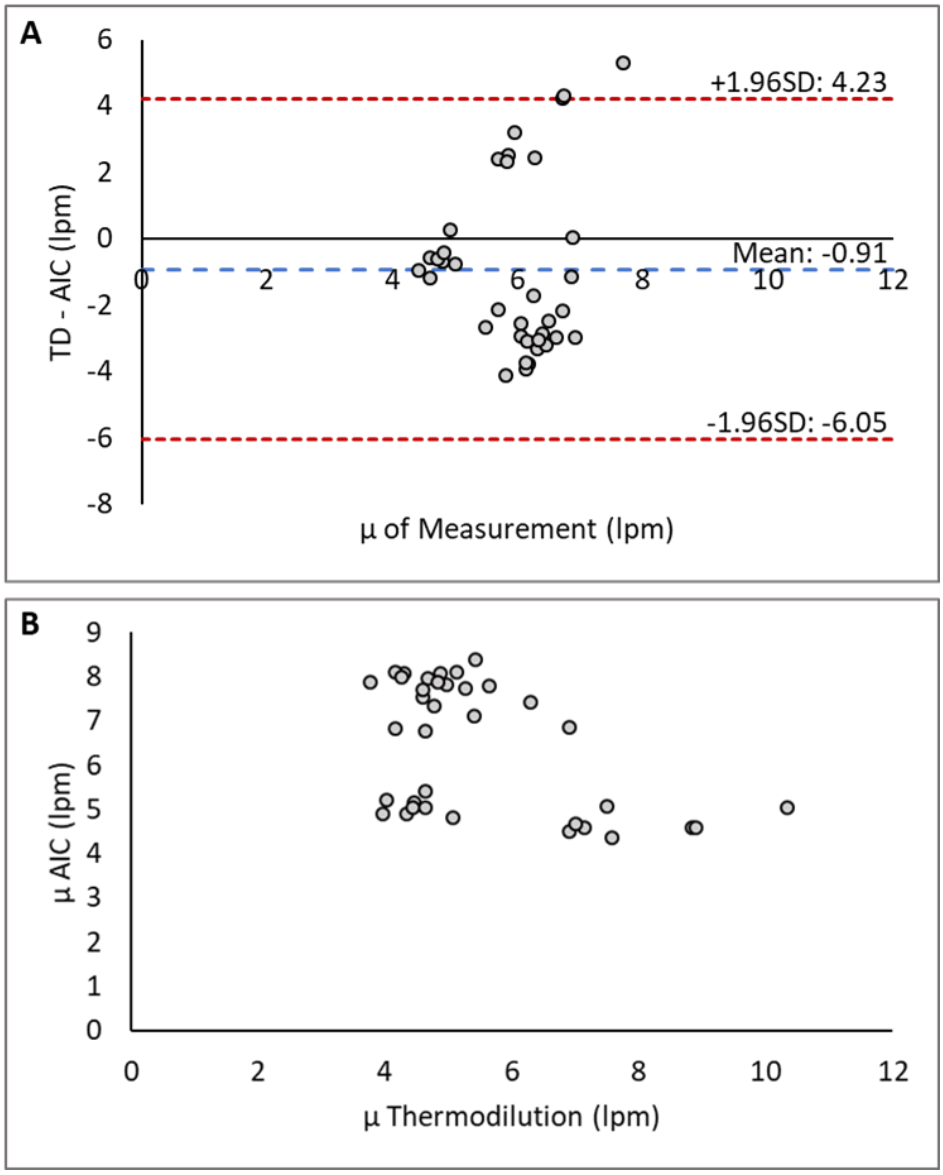

Figure 3.1: Comparing CO measured using the AIC algorithm to the gold standard of thermodilution. *(A) Bland-Altman Plot and (B) linear regression comparing CO measured using the AIC algorithm compared to the gold standard of thermodilution. In general, thermodilution measurements were 0.91 lpm lower than measurements using the AIC algorithm, with the difference between measurements increasing with the average CO. While thermodilution measurements were typically lower than their AIC-derived counterparts, there are occasions when thermodilution measurements are much greater than typical values.*

To quantify the degree of reproducibility of measuring CO using both thermodilution and the AIC CO algorithm, the standard deviation of triplicate measurements taken at each setting was

used. Thus, the higher the standard deviation between triplicate CO measurements, the less likely subsequent CO measurements will be congruent. For all patients, CO measurements taken using the AIC exhibited a significantly higher level of concordance amongst themselves compared to measurements taken via thermodilution, illustrated in Figure 3.2. Specifically, triplicate thermodilution measurements had an average standard deviation of 0.9 L/min with the highest being 3.97 L/min. Using the AIC CO algorithm however, the standard deviation of triplicate CO measurements was only 0.15 L/min, with the highest being only 0.49 L/min, well below the average seen with thermodilution. To understand the reasons for these differences in reproducibility, we next examined how these measurement methods can be impacted by cardiac state, focussing on LVEF, HR, PP, and LVEDP.

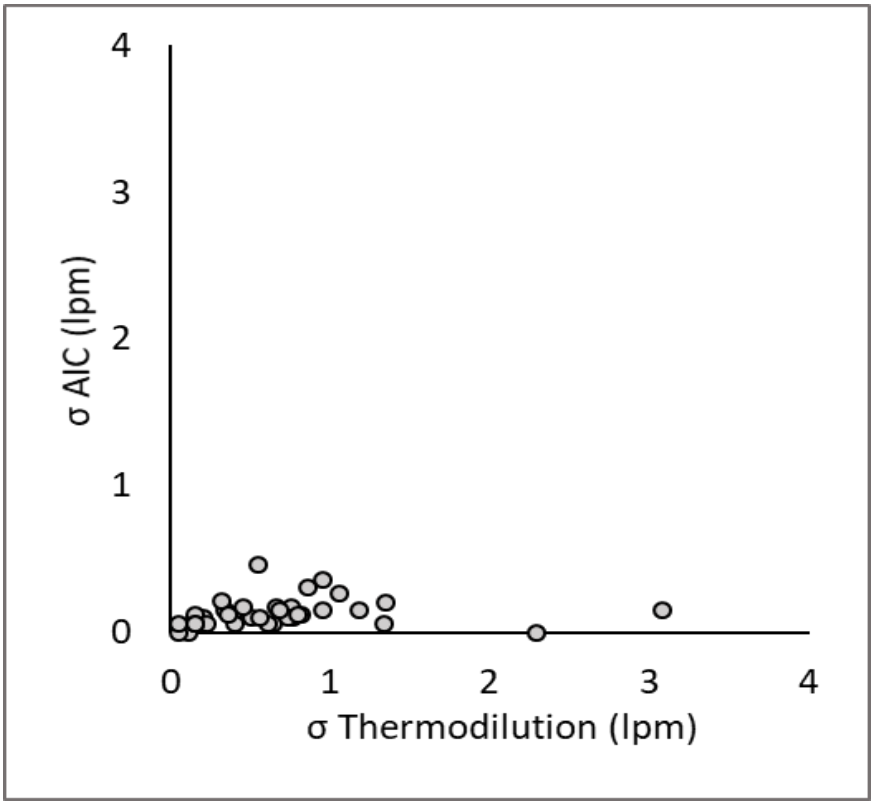

Figure 3.2: Comparing the standard deviation of triplicate CO measurements using the AIC algorithm vs the gold standard of thermodilution. *Of note, the axes are the same length, highlighting the much greater variability seen using thermodilution compared to the AIC algorithm.*

To investigate whether LVEF can impact CO measurements, we compared the standard deviations of each set of triplicate CO measurements averaged across all P-levels for each

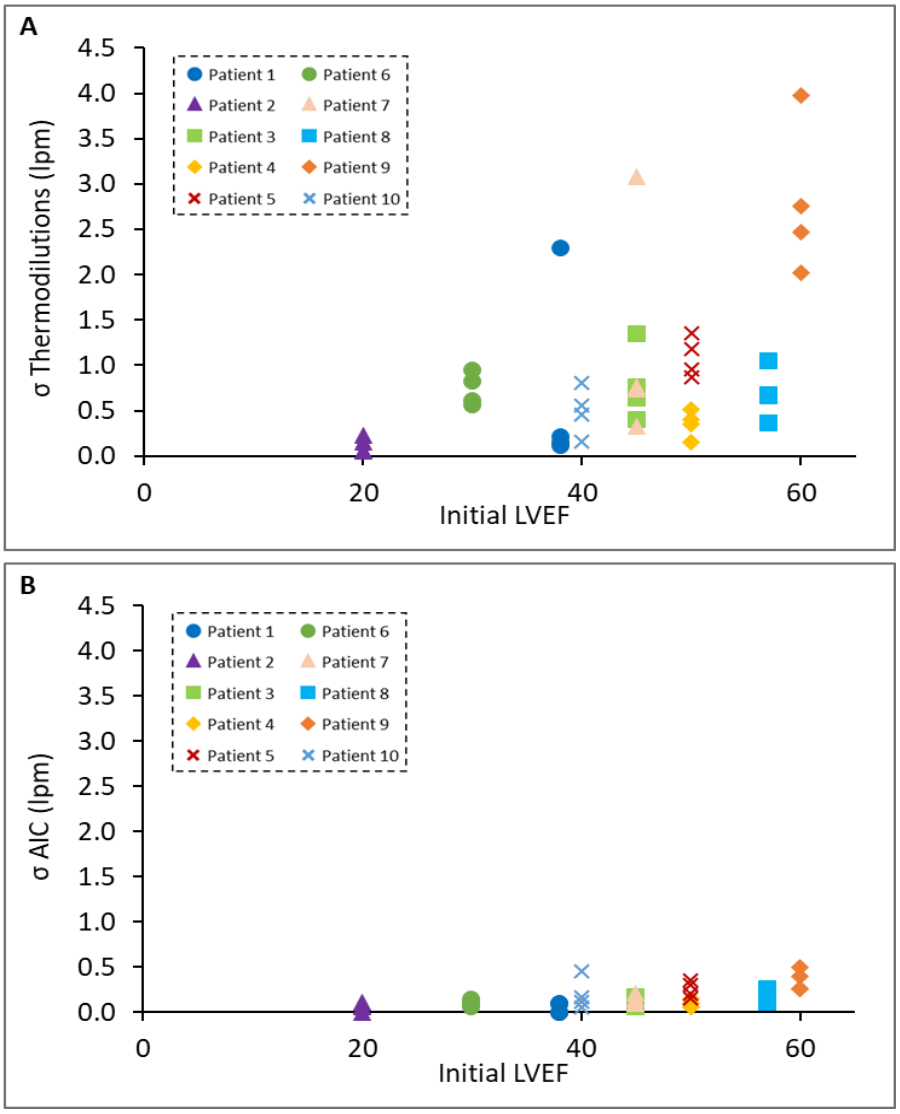

Figure 3.3: Graphs depicting the relationship between the reproducibility of triplicate CO measurements using (A) thermodilution and (B) the AIC CO algorithm versus the patients LVEF. *Each data point represents the standard deviation of triplicate CO measurements for each patient enrolled in the study at each P-level used during the trials. Measurements taken using thermodilution appear much more unreliable, showing more discordance between serial measurements and a greater vulnerability to variations in Impella support. Additionally, as LVEF increases, thermodilution measurements appear to become increasingly inconsistent. While this trend appears to also impact the measurements taken using the AIC CO algorithm, the scale is much smaller making the resulting discordance between measurements trivial.*

patient to their initial LVEF upon admittance to the hospital (Fig 3.3). In these graphs, the increased fidelity achieved measuring CO using the AIC CO algorithm compared to thermodilution is readily evident. Triplicate CO measurements taken using the AIC CO algorithm

were substantially more reproducible than those taken using the thermodilution method, with less disagreement between triplicate measurements as well as less variability between measurements taken under different levels of Impella support.

What's more, there is a clear trend evident that suggests that thermodilution reproducibility is inversely related to the patient's LVEF. Meaning that thermodilutions performed on patients with a low LVEF were in much higher accordance with each other than those performed on patients with an LVEF in the normal range. While this trend appears to impact the AIC CO algorithm measurement too, it occurs at a much smaller scale making the impact of LVEF on these measurements largely insignificant.

Next, we aimed to understand how the dynamic cardiovascular environment can impact thermodilution measurements. Specifically, we examined how the variability in a patient's LVEDP, PP, and HR influences the reproducibility of thermodilution measurements (Fig 3.4).

The first graph shows the impact of LVEDP on thermodilution variability. Here we are specifically looking at LVEDP when the Impella is at the lowest setting (P-2), meaning it's influence on LVEDP is minimized, and comparing it to the average standard deviation of thermodilution measurements across all P-levels. Ultimately the graph shows no obvious trend or impact of LVEDP on thermodilution. The second graph demonstrates the impact of PP, a surrogate for SV, on thermodilution. For each patient, the standard deviation of their PP during each triplicate measurement was averaged across all P-levels and compared to the standard deviation of thermodilution measurements averaged across all P-levels. The final graph illustrates the impact of HR on thermodilution in the same manner as with PP. Unlike the first

graph, these last two figures indicate that that thermodilution fidelity decreases as the variability of PP and HR increases

3.3.2 Animal Data

The impact of shock on HR and PP is displayed in Fig 3.5. The x-axis represents the average standard deviation of PP, the y-axis is the standard deviation in HR, and each data point represents an average of four different animals. Three different experimental time points are displayed on the graph. The first, represented by the blue triangle, is the baseline PP and HR. Next, once the Impella was inserted into the animals, but before shock was simulated, new baseline measurements were

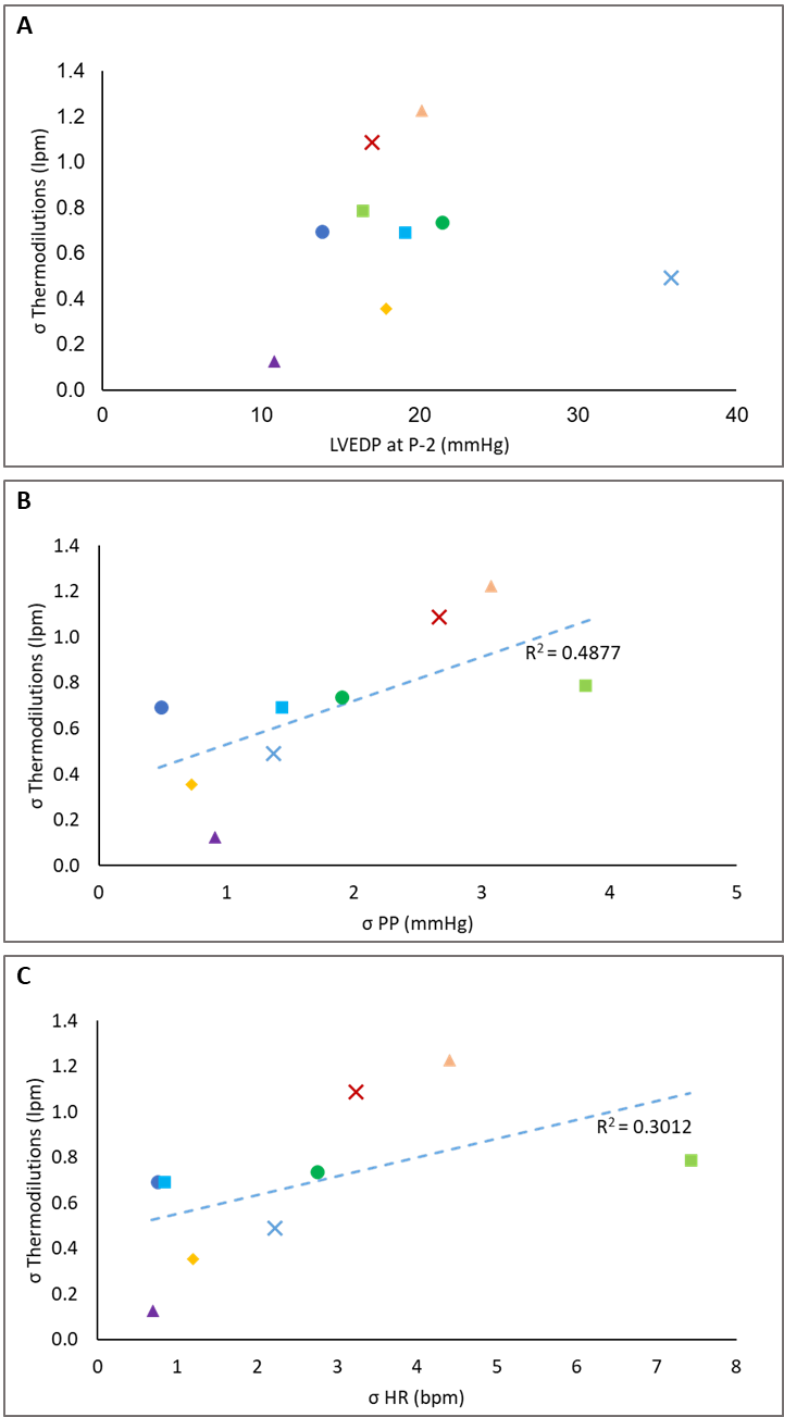

Figure 3.4: Investigating the impact of various factors of cardiac state on thermodilution fidelity. *The graphs show the impact of (A) LVEDP at P-2; (B) PP range; and (C) HR range on thermodilution variability. Each data point represents the standard dev*

taking at four different P-levels: P-2, P-4, P-6, and P-8. This is represented in the graph below by the green data points. Finally, another set of measurements were taken at the same P-levels once the animals were in shock, represented in orange on the graph.

Interestingly, there is a profound change in cardiovascular behaviour in the shock compared to baseline. Specifically, at baseline there is minimal change in HR compared to SV, while this trend is reversed in the shock condition.

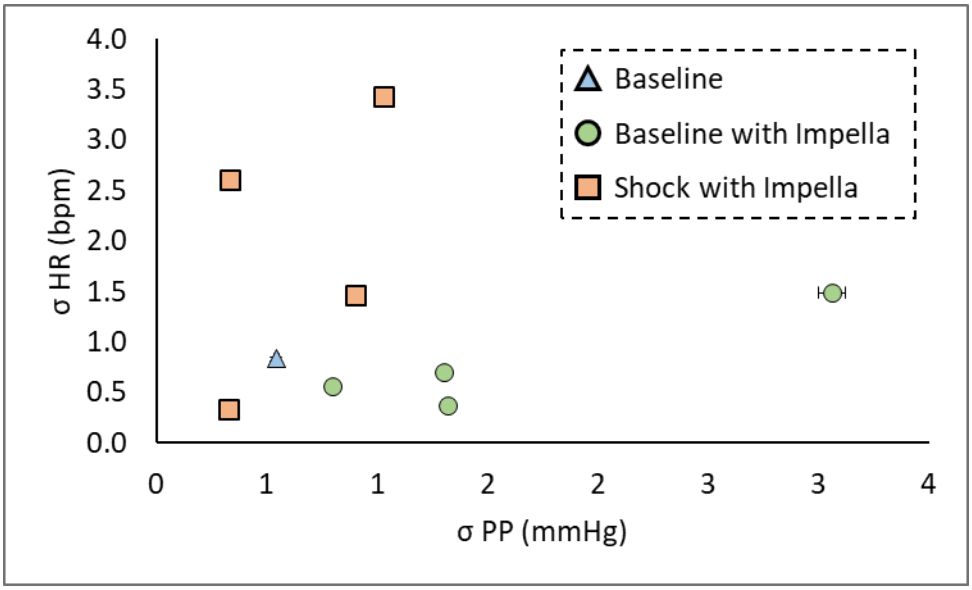

Figure 3.5: The impact of shock on cardiovascular function. *The blue triangle represents the baseline PP and HR variability averaged across all four animals. The green circles represent the average PP and HR variability with the Impella at health while the orange squares represent the average variability with the Impella once shock has been induced.*

3.4 Discussion

Broadly speaking, this chapter explores the impact of cardiac state on two different CO measurement methods using both patient and animal data. From the data it can be easily noted that CO measured using the AIC CO algorithm was significantly more reproducible than thermodilution. What's more, thermodilution was sensitive to any forces on cardiac dynamics such as LVEDP, HR, and surrogates of SV like PP and its reproducibility inversely related to LVEF.

To understand the impact of LVEF on thermodilution, consider the cardiovascular implications of an extremely high and low ejection fraction. Recalling the previously described Frank-Starling relationship, when LVEF is within the physiologic range small beat-to-beat changes in filling pressure, or LVEDP, can result in large changes in SV and therefore CO. However, when LVEF is low, SV is limited, meaning that even very large changes in LVEDP will result in little variations in SV and therefore CO. Thus, when LVEF is high, CO is primarily regulated by SV, however when LVEF is low it is primarily controlled by HR.

The animal data appear to directly validate this theory. Under baseline Impella conditions, there is much greater variations in PP, a proxy for SV, than HR as the Impella support was adjusted. However, once in shock, this relationship reverses itself: HR became much more variable than PP as Impella support varied. This suggests that in healthy or physiologic states cardiovascular behaviour is primarily a function of SV, however in shock or pathologic condition cardiovascular behaviour becomes a function of HR.

Comparing the reproducibility of thermodilution to the AIC CO algorithm the differences are likely due to the timescale of measurements. Thermodilution gives an accurate snapshot of cardiac flow during 30 seconds, however this accuracy is called into question if there are any significant variation in cardiac flow during this period. Additionally, it can take a few minutes to conduct the triplicate thermodilution needed. Changes in cardiac flow between these measurements will also increase in greater disagreement between measurements. The AIC however is able to detect changes in cardiac state in real-time, thus is able to measure CO at the same time scale in which these changes occur. Consequently, measurements taken with this method will more accurately represent cardiac flow.

Chapter 4 – The Impact of Cardiac State on Thermodilution Fidelity

4.1 Introduction

In the previous chapter, we established that thermodilution reproducibility is inversely related to LVEF and that thermodilution fidelity decreases as variability in HR, PP, and LVEDP increased. We also discovered that in healthy physiology, cardiovascular function is largely controlled by SV, but in shock physiology cardiovascular function is primarily driven by HR. Ultimately, we concluded that thermodilution variability is directly related to beat-to-beat variability in cardiac state, primarily through SV irregularity, but also HR to a lesser extent.

Thermodilution, as a method for CO measurement, was derived in the 1970s, and as such it predates the majority of modern medical treatment options for patients in cardiac distress. Because of this, it was developed with little concern for how treatments that have influences on a beat-to-beat basis might impact their fidelity. Successful treatment for acute cardiovascular disease often includes MCS, PPV, and a variety of different drug therapies and they all can modulate cardiac state, either directly, or indirectly, in extremely short time. Additionally, as we showed in the previous chapter, cardiac state has a measurable impact on fidelity of thermodilution. This raises the obvious question of whether these medical interventions alter cardiac state quickly enough to impact measurements such as thermodilution.

In this chapter, we explore the influence of medical interventions such as MCS, mechanical ventilation, and drug therapy on the cardiovascular system and their implications for the precision of thermodilution measurements. The examination encompasses data from the trials

discussed earlier in Chapter 3, as well as insights from an additional animal study that specifically investigates pharmacological effects during shock. These investigations unveiled the varied impact of Impella support on the cardiac state, depending on the patient's current condition. Moreover, they provided a deeper understanding that shock substantially diminishes beat-to-beat variability in cardiac behavior, resulting in more consistent thermodilution measurements.

4.2 Materials and Methods

4.2.1 Patient Study

The same anonymized retrospective patient data used in these studies as was used in chapter 3.

4.2.2 Animal Studies

In this chapter, I will consolidate findings from various sets of studies to examine how mechanical and pharmaceutical interventions, along with different pathophysiologic states, impact the accuracy of thermodilution. All studies begin with an acute CS porcine model, but subsequent interventions differ. These studies all use same porcine shock model as discussed in chapter 3.

4.2.2.1 Impella Support

The Impella was deployed as described in chapter 3. The main difference is that in one of these studies, each condition was assessed at four Impella speeds: P-2, P-4, P-6, and P-8. In the second study each condition was assessed at only two Impella speeds: P3 and P-6.

4.2.2.2 Pharmacological Interventions

A range of inotropic and vascular states were studied in one set of experiments, achieved by pharmacological interventions. These interventions consisted of drugs commonly used for CS with the end goal of hemodynamics stabilization, with or without MCS. These drugs and their primary effect are: (1) Nitroprusside: a vasodilator; (2) Phenylephrine: a vasoconstrictor; (3) Dobutamine: increases inotropy; (4) Esmolol: a beta blocker.

Pharmacological interventions were injected via the femoral venous sheath, after three different conditions were confirmed to have approached a steady state: baseline, shock, and shock with Impella. The Impella condition consisted of two different levels of support (P-3 and P-6), and the impact of both low and high doses of the drugs were examined. Proper washout was ensured between different drug boluses by waiting the appropriate half-life, and through hemodynamically monitoring to ensure a new baseline was properly established for each section.

4.3 Results

4.3.1 Patient Data

As discussed in the previous chapter, there is a clear trend that the reliability of thermodilution measurements decreases as the patient's LVEF increases and when LVEDP range widens. The LVEF values were obtained prior to Impella insertion, and are therefore unimpacted by the device. The LVEDP range, however, represents the maximum difference in each patient's LVEDP values as the Impella was cycled through all four power levels. LVEDP range followed a sharp

parabolic relationship with initial LVEF (Fig 4.1) peaking at ~ 45% and falling off below or above these values in a steep manner. As will be discussed further below, it therefore seems that LVEDP variability is minimized when a patient is least capable of mobilizing SV (infraphysiologic domain) or already doing so (supraphysiologic domain), and variability is maximized closer to the physiologic range when SV regulation can be recruited in order to modulate CO.

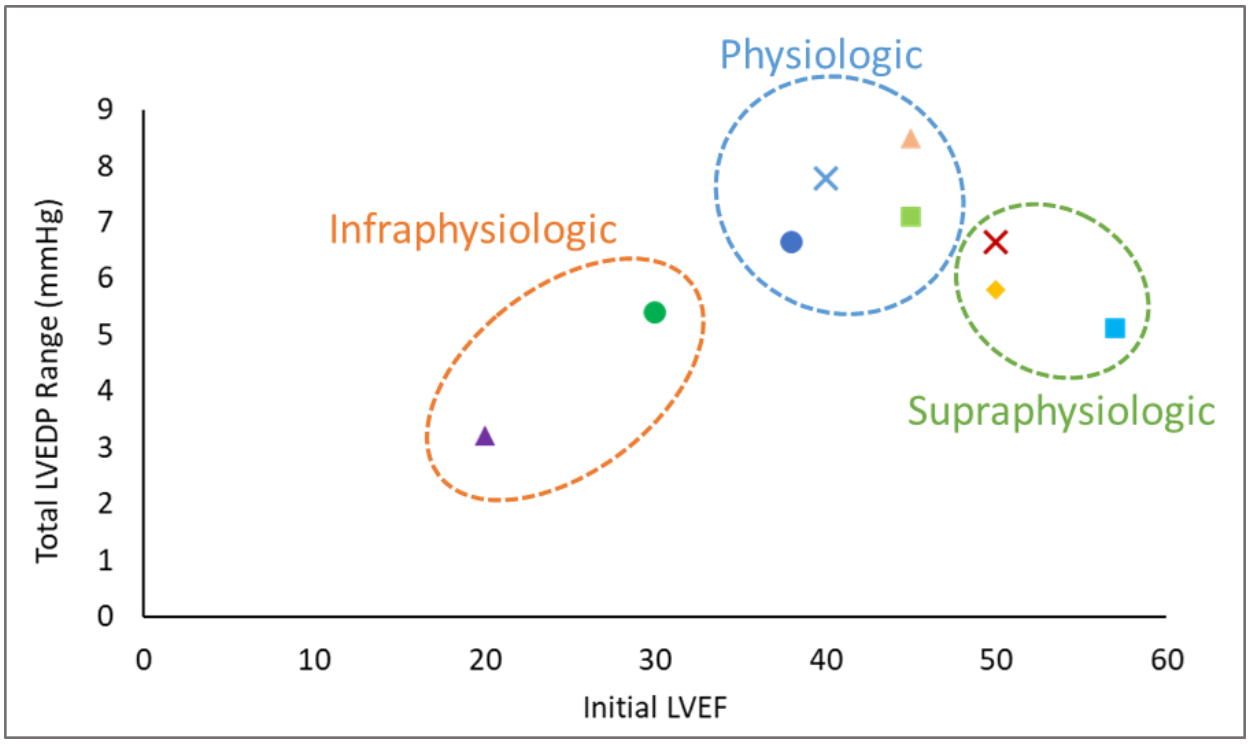

Figure 4.1: Investigating the impact of the Impella on cardiac state. *The graph plots the patients initial LVEF against the total LVEDP range experienced as the Impella varied between the different P-levels. In the physiologic domain, the Impella is able to most effectively unload the heart, indicated by the much wider LVEDP range obtained as the P-levels varied. In the infra/supraphysiologic domains the Impella is less impactful at unloading the heart, resulting a lower total LVEDP range.*

4.3.2 Animal Data

Data from two different animal studies helped determine how MCS such as the Impella, and other medical interventions, such as ventilation and medication, impact cardiac behaviour and therefore might further affect thermodilution measurement fidelity.

4.3.2.1 Shock Study Data

As in chapter 3 thermodilution reliability is impacted by PP variability, and the more stable the PP, the more reliable thermodilution. Revisiting the data from the shock animal study, we next investigated how MCS impacts the average mean aortic pressure (MAP), both in healthy physiology and under shock conditions. MAP is a proxy measurement for PP or SV as they are highly related by aortic distensibility. The following data will refer to the average MAP and the standard deviation of MAP, and these are calculated based off direct measurements of the aortic pressure during each thermodilution measurement. Meaning they represent the average MAP and standard deviation of MAP for all triplicate thermodilution measurements combined.

Figure 4.2 plots the average MAP against the standard deviation of MAP, with each point representing the average value across all four animals. There are three different experimental time points displayed on the graph, with the first, the blue triangle, representing baseline conditions. The green circles indicate data for healthy physiology with the Impella inserted and the orange square indicate data for shock physiology with the Impella.

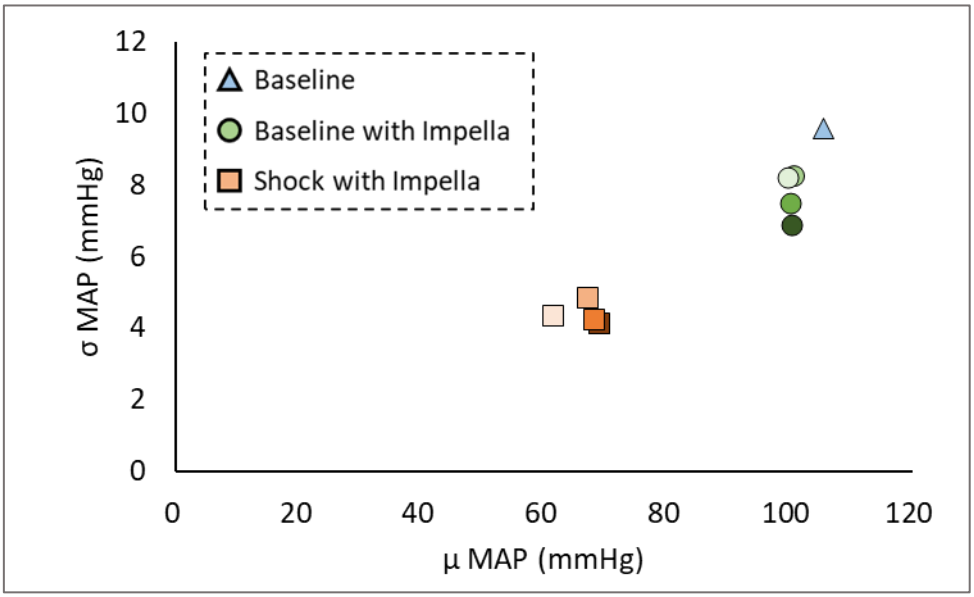

Figure 4.2: Impact of MCS and CS on MAP. *This graph shows the average MAP during thermodilution at each P-level compared to the MAP's standard deviation, averaged across the animals. MCS and CS both result in a decrease in the average MAP and its variability.*

For both Impella conditions, the different shades of each colour differentiate the four different Impella P-levels used (P-2, P-4, P-6, and P-8), with the darker colours indicating the higher levels and the lighter colours the lower levels. From this graph a few things become immediately apparent. First of all, it validates that the Impella is operating as it should – namely that it is providing support during CS and that it's acting in tandem with the native heart.

In health, the average MAP remained constant regardless of the Impella P-level. This is as expected, because in health the MAP was already adequate, so as Impella support varies, the heart adapts appropriately so that MAP does not change. Therefore, as Impella support increases, the amount of CO supplied by the native heart necessarily decreases in order to maintain the MAP. Consequently, the proportion of CO supplied by the continuously pumping Impella is greater at higher Impella levels, while the proportion supplied by the pulsatile native heart will be lower. This is reflected by the fact that the standard deviation of MAP increases as Impella support decreases and the proportion of the total CO supplied by the pulsatile native heart increases. It is also notable that the average MAP and standard deviation of MAP are slightly lower once the Impella is inserted compared to baseline.

In shock, it is readily apparent that both the average MAP and its variability is muted compared to in health. This makes inherent sense as once CS is induced, the animal was expected to fall within the infraphysiologic domain, leading to a limit in SV and SV variability which is correlated to MAP as explained above. Unlike in health, in shock the average MAP increases with Impella support. Again, this aligns with expectations. In shock, MAP is significantly lower than required, so as Impella support increases, unlike in health, the native heart doesn't lower its contribution to the CO. Thus, since the amount of support provided by

the native heart doesn't change, MAP is expected to increase with the level of support provided by the Impella. Like in health, there is also a decrease in MAP variability as Impella support increases, for the same reasons discussed. However, the impact on variability seems more muted compared to health. This is possibly due to the fact that since there is no decrease in native flow in shock as the Impella P-level increases unlike in health. Thus, in health, as Impella support increases, native pulsatile flow decreases and continuous flow increases leading to an increase in MAP stability with each P-level. Whereas in shock, as Impella support increases only the continuous flow increases, resulting in less of an increase in MAP stability with each P-level.

In general, PP and MAP variability is dominated by native heart function which often dwarfs other factors. As just shown, the Impella progressively reduces this impact, creating the possibility for other influences to emerge. One of the more significant of these factors is respiratory variation, which as discussed earlier is known to impact the cardiovascular system, and therefore we next decided to investigate the impact of respiratory variation via PPV on MAP.

As we've seen, thermodilution reliability is worsened when PP is more variable, which is to say when MAP becomes less stable. To understand how PPV and shock can impact MAP variability, we examined MAP pressure tracings of each animal. These tracings were timed such that they represent the MAP during each thermodilution measurement. Fig 4.3 consists of representative MAP tracings. The first set of tracings represent the MAP measurements obtained during the triplicate thermodilutions at baseline conditions with the Impella at P-2. The second set shows the tracings of the same animal during the triplicate thermodilutions conducted once shock was induced, again with the Impella set to P-2. The impact of inspiration

and expiration on aortic pressure, designated by a periodic drop than rise, is highlighted on all tracings in which the phenomenon is readily apparent.

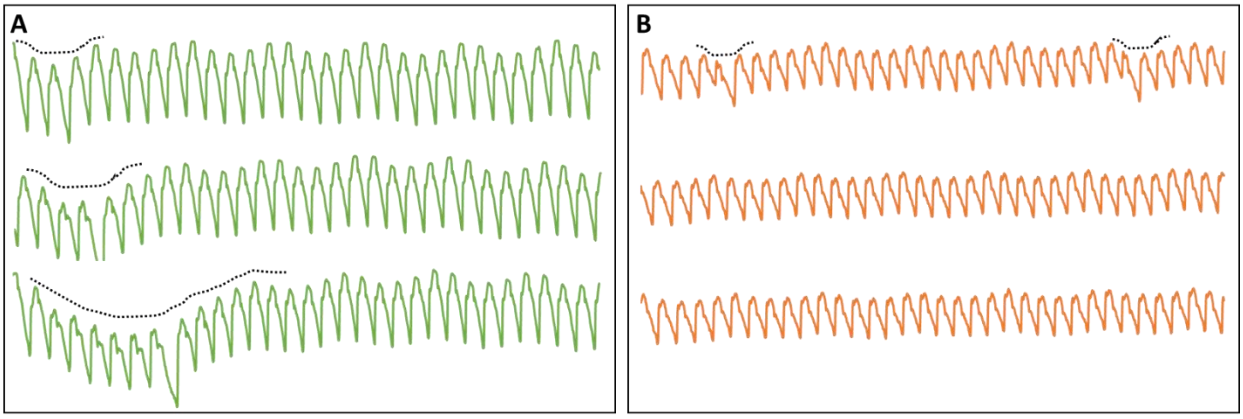

Figure 4.3: Impact of PPV on MAP. *(A) Pressure tracing samples under baseline conditions at P-2. (B) Pressure tracing samples of same animal once CS was induced at P-2. In both figures, the dotted lines trace where the effects of PPV is detected. Note how the impact of PPV is substantially lessened in shock compared to at baseline conditions, as well as the overall variability.*

Notable from these graphs, the tracings under shock have a much smaller amplitude than at baseline conditions. This agrees with our previous data showing that the standard deviation of MAP decreases with shock compared to baseline. What's more, qualitatively, the impact of PPV on MAP is much more apparently under baseline conditions than shock. Looking at how ventilation effects MAP values it's apparent that PPV has much less of an impact on MAP during shock than at health. While respiratory deviations in MAP are apparent, at least to some degree, in all three pressure tracings at baseline conditions that isn't true for the shock condition. Only one tracing showed signs of respiratory deviations and these deviations were much smaller than at health, implying that in shock the impact of respiration on MAP is less evident.

Up to now we had shown that PPV, MCS in the form of an Impella, and shock all impact MAP, with the latter two specifically decreasing the overall MAP variability. We have assumed, due to the interconnectivity between MAP and PP, that MAP variability would impact thermodilution reliability similarly to PP. Thus, to ensure that this is the case we proceeded to compare the standard deviation of MAP during triplicate thermodilution to the standard deviation of these three measurements for each Impella level and averaged across all animals (Fig 4.4).

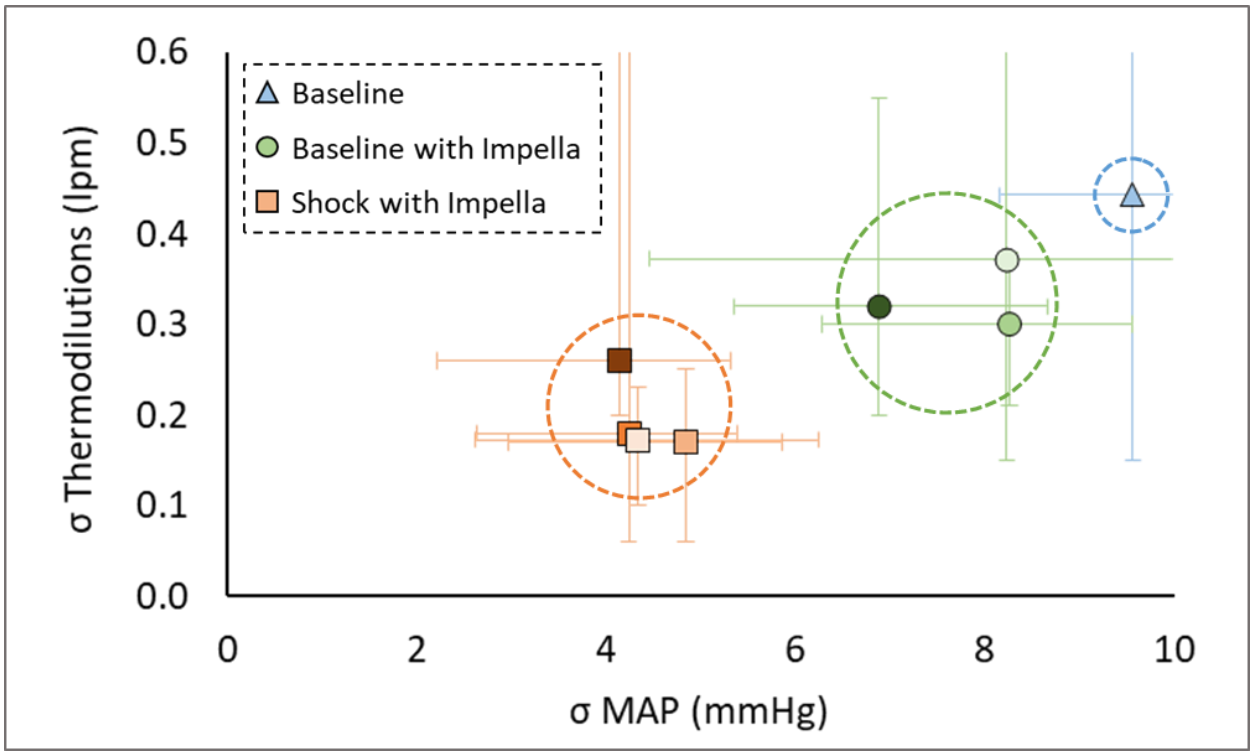

Figure 4.4: The impact of MAP variability on thermodilution reproducibility. *Overall, thermodilution variability increases with MAP variability. Comparing the baseline condition (blue) to when the Impella is inserted in health (green) and once CS is induced (orange) shows that variability in MAP and thermodilution decreases with the introduction of MCS and the induction of CS.*

In this graph, the blue marker is the average variability of MAP and thermodilution after triplicate measurements at baseline. The green markers represent baseline conditions with the Impella inserted, while the orange markers represent the shock condition with the Impella

inserted. Each green and orange marker illustrations data from one of the four power levels used (P2, P4, P6, and P8) averaged across all animals. As earlier, the darker the colour of the marker, the greater the associated P-level. The data for baseline with the Impella at P-6 was considered a significant outlier, so was omitted from the figure so as to better illustrate the overall trends.

From the data it is apparent that variation in MAP is correlated with variations in thermodilution measurements, meaning that as MAP variability so does the variability between serial thermodilution measurements. Additionally, it shows MCS in the form of the Impella decreases MAP variability, and that inducing CS further decreases this variability.

4.3.2.1 Pharmacological Study Data

We next delved into the data from the pharmacological study in order to see how altercations in cardiac state brought on by drug therapy impact thermodilution repeatability, both with and without MCS. The results of these studies are shown in Table 4.1 below. Here we

Table 4.1: The impact of pharmacologically induced alterations in cardiac state on thermodilution repeatability. *The table below shows how different pharmacological interventions impact thermodilution fidelity compared to baseline. Nitroprusside and esmolol increase thermodilution variability while phenylephrine decreases variability. The impact of dobutamine is variable, increasing variability at lower P-levels and decreasing it at higher P-levels.*

		Changes in σ CO from baseline – averaged across all animals			
		Nitroprusside	**Phenylephrine**	**Dobutamine**	**Esmolol**
	Primary Impact	↓ afterload	↑ afterload ↑ HR	↑ contractility ↑ HR	↓ contractility ↓ HR
Low Dose	**P3**	1.53	1.08	1.53	2.61
	P6	2.06	0.94	0.92	2.80
High Dose	**P3**	1.87	0.83	1.86	
	P6	2.05	0.61	0.70	

show the change in standard deviation of CO from baseline for each drug in both the low and high dose conditions at each of the two Impella speeds used for this study.

Nitroprusside enhances cardiac function by reducing afterload, while phenylephrine decreases cardiac function by increasing afterload and also increases HR and these effects appear to directly impact thermodilution fidelity. Specifically, when afterload decreases, such as with Nitroprusside, thermodilution fidelity decreases, and then is further decreased as Impella support increases. However, when afterload increases, as is the case with Phenylephrine, thermodilution fidelity generally increases, especially as the dose increases and Impella support increases. Dobutamine has a varied effect on cardiac function as it increases contractility which improves CO, but increases HR which can result in a decrease in venous return and therefore CO. Consequently, dobutamine appears to have a mixed effect on thermodilution fidelity: at both low and high doses, when Impella support is low, thermodilution fidelity decreases, but at greater Impella support, thermodilution fidelity increases from baseline. Finally, esmolol should decrease cardiac function by decreasing contractility and HR. While there is no data for the high dose condition, at low doses this decrease in cardiac function results in large decrease in thermodilution fidelity compared to baseline, with fidelity being further lessened as Impella support increased.

4.4 Discussion

In this chapter we delved into how medical interventions, including MCS, mechanical ventilation, and drug therapy, can influence the cardiovascular system, thereby affecting the accuracy of thermodilution measurements. The analysis incorporates data from the trials

previously discussed in Chapter 3, as well as findings from an additional animal study focusing on pharmacological effects during shock. These studies revealed that the impact of Impella support on cardiac state is diverse, contingent on the patient current state. Furthermore, they further elucidated the fact that shock significantly reduces beat-to-beat variability in cardiac behaviour, which leads itself to more stable thermodilution measurements.

From examining the patient data, we were able to establish that the impact the Impella is able to have on cardiac state is dependent on the initial patient state. That is to say, under low LVEF conditions, the Impella become more effective at unloading the heart as LVEF increases towards normal values. This is likely due to the fact that when LVEF is low, SV is limited and more of the total cardiac output originates from "MCS flow", increasing the continuous component of outflow from the heart. Therefore, at very low LVEF most of the forward blood flow is continuously derived from the Impella and not the native heart. This ultimately decouples flow from the cardiac cycle, decreasing its impact on pressure within the ventricle, leading to a more stable, less variable LVEDP.

Under normal and high LVEF condition, SV is no longer limited, and, due to the Frank-Starling mechanism a change in LVEDP corresponds to a change in SV. Additionally, in this scenario, native, pulsatile cardiac flow will make up the bulk of flow out of the heart. However, at very high LVEF values, there is so much forward flow being generated by the heart already that it comparatively dwarfs the flow generated by the Impella. Consequently, the impact of the Impella on the total outflow is lower and therefore it's ability to impact the cardiac state is lower, resulting in a less variable LVEDP.

Re-examining the shock study specifically looking at how cardiac state, represented by MAP, is impacted by various medical interventions led us to conclude that while the Impella doesn't impact MAP, it does decrease the variability in MAP as Impella support increases. Additionally, we noted that the impact of ventilation on MAP is almost undetectable in shock compared to baseline conditions. Taken together this implies that both shock and PPV lead to less beat-to-beat variability in cardiac state and therefore more consistent thermodilution measurements.

Looking at the data from the pharmacological study further supports the conclusions we have previous drawn. Nitroprusside is a vasodilator and as such it primarily used to lower afterload. The cardiovascular implications of this are an increase in possible SV ranges and consequently greater beat-to-beat variability. This great beat-to-beat variability directly leads to the increase in thermodilution variability seen with nitroprusside administration. Phenylephrine is a vasoconstrictor and thus it works to increase afterload. Accordingly, this results in a decrease in possible SV range and therefore less beat-to-beat variability. This decrease in SV variability should directly translate to a decrease in thermodilution variability, which is what we see in the data. Additionally, Impella support appears to exaggerate the response of both of these drugs, with thermodilution fidelity decreasing with Impella support when nitroprusside is administered, yet increasing with Impella support when phenylephrine is given.

The impact of Dobutamine appears to be a function of both the dose and level of Impella support provided. Dobutamine increases contractility, directly resulting in an increase in SV range and therefore beat-to-beat variability. However, another effect of Dobutamine is an increase in HR which can result in a decrease in venous return and therefore LVEDP. Thus, as

per the Frank-Starling mechanism, this generally causes a decrease in SV range and thus beat-to-beat variability. Hence there are two effects of Dobutamine simultaneously encouraging an increase and decrease in SV and depending on the level of Impella support thermodilution variability may increase or decrease. The Impella supports the heart by helping to unload it, with the end result of lowering LVEDP which will decrease the SV. As such, it makes sense that at lower levels of Impella support, when it is less effective at unloading the heart, the combined effects results in an overall increase in SV range and shown by the increase in thermodilution variability. When Impella support is higher and it can more effectively unload the heart, the combined effects of the medical interventions are a decrease in SV, indicated by the decrease in thermodilution variability.

Finally, the impact of Esmolol also supports our previous results. Esmolol is a beta block and one of its main effects on the cardiovascular system is to decrease contractility and HR, although it is primarily HR that is impacted. This decrease in HR results in an increase in venous return, resulting in a higher LVEDP and therefore increases SV range. Consequently beat-to-beat variability is increased which is responsible for the increased thermodilution variability seen in the data. Additionally, the lower HR is likely to exacerbate timescale effects on thermodilution, increasing the overall variability between measurements. Interestingly, while a decrease in contractility would be expected to result in a decrease in beat-to-beat variability and therefore increase in thermodilution variability, this is not seen with esmolol. This indicates that the impact of esmolol on contractility is dwarfed by its impact on HR, which is as expected based on clinical use.

Chapter 5 – Conclusion and Future Directions

5.1 Overview and Challenges

The advent of MCS has revolutionized the treatment landscape for common diseases resulting in low output flow states. However, achieving optimal therapeutic outcomes with these devices requires dependable metrics to assess cardiac state effectively, enabling accurate guidance for clinicians to appropriately titrate support. Unfortunately, the development of clinically robust metrics has not kept pace with treatment innovations, and recently their reliability has been called into question, especially when used alongside newer treatment options such as MCS. We believed that this is largely an issue of scale, as traditional metrics assume a steady state, which is inevitably disrupted by the MCS.

The work presented in this dissertation draws from many different fields and studies in order to investigate the reliability of classic metrics of cardiac state. Specifically, we examined under which conditions thermodilution reliability is impacted, focusing primarily on the impact of (a) cardiac state, (b) MCS, and (c) other medical interventions. Determining when thermodilution measurements might not be reliable will help clinicians make the best decisions for their patients. Additionally, this work will provide insight to help pave the way to validate new metrics of CO, such the AIC CO algorithm, which prove to be more reliable than thermodilution under certain conditions.

In Chapter 2 we performed a thorough exploration of thermodilution, encompassing its measurement techniques and underlying assumptions. Moreover, this chapter delved into the

theoretical limitation of thermodilution, particularly concerning procedural errors, patient physiology, and theoretical limitations. Various factors like arrhythmias, heart failure, mechanical circulatory support (MCS), and mechanical ventilation can affect the accuracy of thermodilution measurements. The discussion emphasizes how beat-to-beat variations in SV and HR during the procedure and between repeated measurements can lead to errors in determining cardiac output, especially in critically ill patients with varying cardiovascular states. Overall, we provided an in-depth discussion on thermodilution as a hemodynamic monitoring technique while highlighting its potential limitations in specific clinical scenarios.

In Chapter 3 we used patient and animal data to investigate the influence of cardiac disease on the accuracy of thermodilution measurements, compared to the accuracy of measurements obtained through the new AIC CO algorithm and to determine how changes in cardiac state impact thermodilution accuracy. We discovered that thermodilution reproducibility is inversely related to LVEF and that thermodilution fidelity decreases as variability in HR, PP, and LVEDP increased. We also concluded that in healthy physiology, cardiovascular function is largely controlled by SV, but in shock physiology cardiovascular function is primarily driven by HR.

In Chapter 4 we investigated the impact of medical interventions, such as MSC, mechanical ventilation, and drug delivery, on the cardiovascular system, and consequently the reliability of thermodilution measurements. We used data from the same trials discussed in Chapter 3, along with a second animal study on pharmacological effects in shock. Here we concluded that Impella support has a varied impact on LVEDP depending on the patients LVEF. We also discovered that shock greatly impacts MAP, both lowering it and decreasing it's beat-to-beat variability.

Examining the impact of cardiovascular state on thermodilution reproducibility provided valuable insight on cardiovascular behaviour. Namely that in healthy physiology, cardiovascular function, and thus CO, is largely a function of SV, where as in shock physiology it becomes a function of HR. This is compounded by the fact that when LVEF is low, as is often the case with heart failure, SV is limited and is unlikely to be modified by changes in LVEDP. However, at higher LVEF, SV is readily varied by changes in LVEDP, creating the potential for larger beat-to-beat variations in CO. Thus, thermodilution variability is likely directly related to beat-to-beat variations in CO. When SV and HR variability increases, so does thermodilution variability. In shock conditions, when SV is limited and there are fewer beat-to-beat variations, thermodilution tends to be more consistent.

Investigating how medical interventions impact the reproducibility of thermodilution also added important context for understanding the accuracy of thermodilution measurements. Certain medical interventions, such as intubation or anesthesia, will decrease the variability in the cardiovascular system, which in turn directly increases the reproducibility of thermodilutions. The impact of other interventions, such as MCS can be more diverse.

As MCS directly impacts cardiac dynamics, it stands to reason that it will in turn impact thermodilution measurements. As shown in this thesis, thermodilution variability was also shown to be positively correlated both with LVEF. Additionally, while the Impella is expected to directly impacts the LVEDP, the degree to which depends on the patient's LVEF. When LVEF is in the physiologic domain, natural SV modulation is possible, and thus the Impella is more effective at unloading the heart, resulting in an increased LVEDP range. However, in the infraphysiologic domain, when LVEF is low and SV is limited, most of the outflow is MCS-derived

even at lower P-levels, resulting in little change in LVEDP as the power levels are varied. In the supraphysiologic domain, when LVEF is high, a greater potion of the flow is from the native heart, thus varying the Impella's P-levels have less impact on LVEDP. Consequently, when in the infraphysiologic and supraphysiologic domains the Impella is less effective at unloading the heart. Thus, the impact that MCS can have on LVEDP range is variable and therefore so is its potential impact on thermodilution.

All together, this dissertation explores the relationship between classic cardiac metrics like thermodilution, cardiac state, and medical interventions and suggests situations under which thermodilution reproducibility may be impacted. It also shows that these limitations are not present in the new generation of measurements methods, such as the AIC CO algorithm.

However, it's important to note that these findings were limited by the relatively small sample sizes with both with the patient data and animal studies. Additionally, with the patient studies were not well characterized and it's possible that there are additional factors or comorbidities that impacted the results. The animal studies also suffered very low numbers, increasing the likelihood of inter-subject variability affecting the results. What's more, in the vector study it's impossible to know where baseline between interventions was truly achieved, thus the results could be confused by the residual impact of the previous interventions.

5.2 Future Applications

Further studies and clinical data evaluation should be conducted to validate and expand on the findings presented in this thesis. Once fully validated, these insights can be leveraged to understand how classic metrics can be impacted by the introduction of new medical

interventions. In so doing, clinicians will know when certain measurements, like thermodilution, are likely to be valid and when they likely won't be representative of the true cardiovascular state.

Additionally, continued development and validation of the above findings will pave the way for regulatory approval of new metrics that don't face the same challenges as the classic gold standards. These newer metrics have the potential to better inform clinicians on patient needs and improve outcome. Additionally, it's a necessary step for the development of MCS incorporating diagnostic tools, such as the Impella and the AIC CO algorithm. Ultimately, these devices would have the capacity to automatically modulate support based on patient needs, with the end goal of in improving patient outcomes.

Appendix

Appendix 1 – Patient CO Data (Thermodilution and AIC)

Patient	P-level	Thermo CO (lpm)			*CO stdev*	*CO Avg*
		A	B	C		
1	8	4.20	3.90	4.00	*0.15*	*4.03*
	6	3.90	4.10	3.90	*0.12*	*3.97*
	4	7.70	3.50	4.00	*2.29*	*5.07*
	2	4.40	4.50	4.10	*0.21*	*4.33*
2	8	4.70	4.60	4.60	*0.06*	*4.63*
	6	4.60	4.30	4.50	*0.15*	*4.47*
	4	4.30	4.30	4.70	*0.23*	*4.43*
	2	4.70	4.60	4.60	*0.06*	*4.63*
3	8	6.50	5.30	5.10	*0.76*	*5.63*
	6	4.60	4.20	5.00	*0.40*	*4.60*
	4	4.30	4.50	5.50	*0.64*	*4.77*
	2	6.80	4.30	4.70	*1.34*	*5.27*
4	8	4.70	4.80	4.50	*0.15*	*4.67*
	6	5.30	4.80	4.50	*0.40*	*4.87*
	4	4.70	5.70	5.00	*0.51*	*5.13*
	2	4.70	4.10	4.10	*0.35*	*4.30*
5	8	6.20	8.50	7.80	*1.18*	*7.50*
	6	10.50	11.10	9.40	*0.86*	*10.33*
	4	9.80	8.80	7.90	*0.95*	*8.83*
	2	9.00	10.20	7.50	*1.35*	*8.90*
6	8	7.10	7.60	6.00	*0.82*	*6.90*
	6	4.70	3.50	4.30	*0.61*	*4.17*
	4	5.60	3.70	4.60	*0.95*	*4.63*
	2	4.90	6.00	5.30	*0.56*	*5.40*
7	8	2.90	8.90	7.10	*3.08*	*6.30*
	6	5.00	4.00	3.50	*0.76*	*4.17*
	4	4.00	3.40	3.90	*0.32*	*3.77*
	2	5.10	3.70	4.00	*0.74*	*4.27*
8	8	6.40	7.30	7.70	*0.67*	*7.13*
	6	7.90	7.00	5.80	*1.05*	*6.90*
	4	7.30	6.60	7.10	*0.36*	*7.00*
	2	8.10	6.80	7.80	*0.68*	*7.57*
9	8	10.60	13.00	16.10	*2.76*	*13.23*
	6	10.60	12.60	15.50	*2.46*	*12.90*
	4	8.10	15.70	13.90	*3.97*	*12.57*
	2	12.40	16.40	13.90	*2.02*	*14.23*
10	8	4.20	5.80	4.90	*0.80*	*4.97*
	6	5.00	4.10	4.70	*0.46*	*4.60*
	4	4.80	4.70	5.00	*0.15*	*4.83*
	2	5.40	4.90	6.00	*0.55*	*5.43*

Patient	P-level	Thermo CO (lpm)			*CO stdev*	*CO Avg*
		A	B	C		
1	8	5.20	5.30	5.10	*0.10*	*5.20*
	6	4.90	4.90	4.90	*0.00*	*4.90*
	4	4.80	4.80	4.80	*0.00*	*4.80*
	2	4.90	5.00	4.80	*0.10*	*4.90*
2	8	5.40	5.40	5.40	*0.00*	*5.40*
	6	5.10	5.30	5.10	*0.12*	*5.17*
	4	5.00	5.10	5.00	*0.06*	*5.03*
	2	5.00	5.10	5.00	*0.06*	*5.03*
3	8	8.00	7.70	7.70	*0.17*	*7.80*
	6	7.60	7.60	7.40	*0.12*	*7.53*
	4	7.30	7.40	7.30	*0.06*	*7.33*
	2	7.70	7.70	7.80	*0.06*	*7.73*
4	8	7.90	8.00	8.00	*0.06*	*7.97*
	6	8.10	8.10	8.00	*0.06*	*8.07*
	4	8.00	8.20	8.10	*0.10*	*8.10*
	2	7.90	8.20	8.10	*0.15*	*8.07*
5	8	5.20	4.90	5.10	*0.15*	*5.07*
	6	5.10	5.30	4.70	*0.31*	*5.03*
	4	4.70	4.20	4.90	*0.36*	*4.60*
	2	4.60	4.80	4.40	*0.20*	*4.60*
6	8	6.80	7.00	6.80	*0.12*	*6.87*
	6	6.80	6.90	6.80	*0.06*	*6.83*
	4	6.60	6.80	6.90	*0.15*	*6.77*
	2	7.10	7.20	7.00	*0.10*	*7.10*
7	8	7.30	7.40	7.60	*0.15*	*7.43*
	6	8.00	8.10	8.20	*0.10*	*8.10*
	4	7.80	7.70	8.10	*0.21*	*7.87*
	2	7.90	8.10	8.00	*0.10*	*8.00*
8	8	4.70	4.70	4.40	*0.17*	*4.60*
	6	4.80	4.30	4.40	*0.26*	*4.50*
	4	4.80	4.60	4.60	*0.12*	*4.67*
	2	4.50	4.40	4.20	*0.15*	*4.37*
9	8	7.60	7.50	8.00	*0.26*	*7.70*
	6	8.00	8.90	8.10	*0.49*	*8.33*
	4	7.70	8.20	8.50	*0.40*	*8.13*
	2	7.80	8.30	7.90	*0.26*	*8.00*
10	8	7.90	7.70	7.90	*0.12*	*7.83*
	6	7.60	7.90	7.60	*0.17*	*7.70*
	4	7.80	7.90	7.90	*0.06*	*7.87*
	2	8.30	8.00	8.90	*0.46*	*8.40*

Appendix 2 – Patient LVEF, LVEDP, PP, HR Data

Patient	LVEF	P-level	LVEDP	σ HR	σ PP
1	38	8	7.22	0.32	1.01
		6	10.66	1.22	0.19
		4	13.57	0.39	0.69
		2	13.88	1.12	0.08
2	20	8	8.27	0.45	1.22
		6	7.6	0.40	0.49
		4	10.03	0.63	0.65
		2	10.82	1.30	1.29
3	45	8	10.66	1.04	1.75
		6	9.33	10.69	4.49
		4	12.01	13.26	6.75
		2	16.42	4.74	2.25
4	50	8	13.93	1.18	0.69
		6	12.08	0.61	0.54
		4	12.75	2.60	1.06
		2	17.89	0.41	0.62
5	50	8	10.33	5.85	2.72
		6	13.46	0.91	3.77
		4	13.11	1.33	3.08
		2	16.98	4.87	1.09
6	30	8	16.07		
		6	17.78	1.14	3.01
		4	18.37	1.63	0.13
		2	21.46	5.50	2.58
7	45	8	11.63	8.47	4.30
		6	15.84	4.16	3.93
		4	18.96	2.51	1.31
		2	20.12	2.49	2.76
8	57	8	18.02	1.07	2.09
		6	15.19	0.33	1.25
		4	20.3	0.95	1.11
		2	19.1	1.03	1.30
9	60	8	15.75	0.86	2.14
		6	17.88	1.60	1.55
		4	18.3	1.58	2.92
		2	20.2	3.64	3.26
10	40	8	33.29	2.29	0.79
		6	41.07	1.94	2.46
		4	34.55	4.13	1.34
		2	35.85	0.52	0.88

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