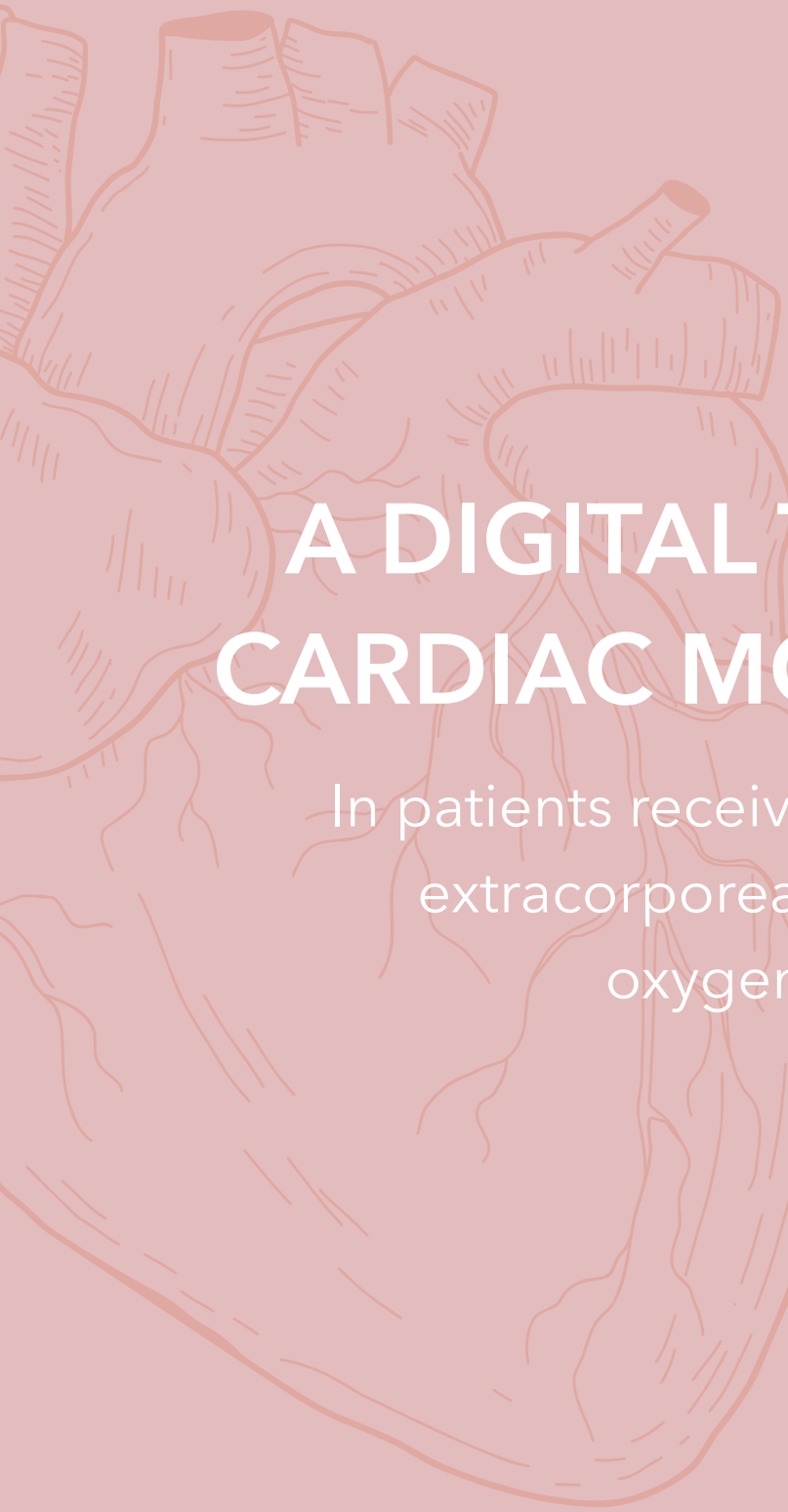
MASTER THESIS TECHNICAL MEDICINE



A DIGITAL TWIN FOR CARDIAC MONITORING

In patients receiving venoarterial extracorporeal membrane oxygenation

KIMMIA AZAMPANAH

A digital twin for cardiac monitoring

in patients receiving venoarterial extracorporeal membrane oxygenation

Master thesis

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Preface

Before you lies my master thesis, "A digital twin for cardiac monitoring in patients receiving venoarterial extracorporeal membrane oxygenation". This has been written to fulfill the graduation requirements of the master Technical Medicine, the track 'Medical Sensing and Stimulation', at the University of Twente, Enschede, The Netherlands. I have done my graduation internship and research at the Intensive Care Unit of the University Medical Centre Utrecht from October 2023 to July 2024.

I would like to take a short moment to thank **Dirk Donker** for, what I can only describe as, your pep-talks and the insights you gave me during them. I am grateful for the supervision of **Lex van Loon**, thank you for stepping in and helping me organise my thoughts, each meeting gave me little more confidence. I also want to thank **Jeannine Hermens** for your help in reaching my clinical goals and interpreting the clinical implications of my results to keep my focus on the patients and doctors, not just numbers. I want to thank **Elyse Walter** for your guidance regarding my personal and professional development throughout the last two years of my studies.

In addition I would like to thank **Libera Fresiello** for your technical supervision during the first few months of my research and **Marijn Mulder** for the endless number of simulation files you have sent me. I also want to thank **Carlotte Hekkert** for taking the time to design my front page.

Finally, I want express my immense gratitude to all my **friends** and **family** that have supported (and endured) me, kept me sane, and made me feel loved during, not just this final part, but all the phases of my studies.

To the reader, I hope you enjoy reading what is my greatest accomplishment yet.

Sincerely,

Kimmia Azampanah
Utrecht, July 2nd 2024

Abstract

Introduction: Cardiogenic shock occurs in 5-10% of patients with acute myocardial infarction and is associated with high mortality rates of up to 60%. Patients with refractory cardiogenic shock can benefit from venoarterial extracorporeal membrane oxygenation (VA ECMO), which offers temporary circulatory mechanical support. Despite its benefits, VA ECMO carries significant risks. The optimal timing for weaning remains challenging due to the complexity of extracorporeal support, the interaction it has with the patient's circulatory system and bedside monitoring, as well as a lack of evidence-based guidelines. This study therefore aims to develop a method for monitoring left ventricular contractile function in patients receiving VA ECMO support, using a digital twin to assist in daily clinical management and weaning of these patients.

Methods: Relevant clinical parameters were collected from patients receiving VA ECMO in the ICU in the University Medical Centre Utrecht. The patient data were used to estimate model parameters and perform baseline tuning of the patient with an elaborate cardiovascular computational physiological model (CPM). A digital twin was modelled by further tuned the CPM using both automatic and manual protocols. Tuning was considered successful when all model output varied less than 10% from patient data. Cardiac contractile function was estimated by determining the end systolic elastance (Ees) and ventriculo-arterial coupling (VA coupling) in the digital twins.

Results: Five patients were included in the study. The median RMSE of the automatically tuned digital twins was 0.181, with an interquartile range (IQR) of 0.151. The manual tuning protocol resulted in a median RMSE of 0.028 (IQR 0.0105).

Discussion: The automatically tuned digital twins had a high RMSE, and the estimated cardiac function did not correlate well with the clinical outcomes of the patients. The manual tuning protocol demonstrated the feasibility of tuning a digital twin with the cardiovascular CPM. The estimated cardiac function of manually tuned digital twins also correlated better with clinical outcomes,discrepancies still existed in several cases. With improvement and rigorous validation, a digital twin could ultimately become a clinical decision-making tool to support daily management and weaning strategies for patients on VA ECMO.

Keywords: *VA ECMO, digital twin, computational physiological model, cardiovascular simulator, contractility, VA coupling*

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Abbreviations

ABP	Arterial blood pressure
C_a	Aortic compliance
CO	Cardiac output
CPM	Computational physiological model
cSBP	Central systolic blood pressure
CVP	Central venous pressure
DBP	Diastolic blood pressure
dPAP	Diastolic pulmonary artery pressure
ECG	Electrocardiogram
ECMO rpm	ECMO revolutions per minute
Ees	End-systolic elastance
ESPVR	End-systolic pressure volume relation
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
IQR	Inter quartile range
KID	Renal
LL	Left leg
LV	Left ventricle
LVe	Left ventricular elastance
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
OHCA	Out of hospital cardiac arrest
pSBP	Peripheral systolic blood pressure
PV loop	Pressure-volume loop
Qecmo	ECMO flow
RL	Right leg
RtA	Arterial resistance
RMSE	Root mean square error
SBP	Systolic blood pressure
sPAP	Systolic pulmonary artery pressure
SPL	Splanchnic
TBV	TBV
UB	Upper body
VA coupling	Ventriclo-arterial coupling
VA ECMO	Venoarterial extracorporeal membrane oxygenation

1. Introduction

Cardiogenic shock is associated with mortality rates of up to 60% and is often caused by an acute myocardial infarction or decompensating heart failure. It is a state of end-organ hypoperfusion due to myocardial pump failure and is characterised by reduced cardiac output (CO). Left ventricular (LV) systolic failure is the primary reason for derangement of the entire circulatory system in most forms of cardiogenic shock [1–6]. Patients that suffer from refractory cardiogenic shock, despite pharmacological support, can benefit from temporary circulatory mechanical support like venoarterial extracorporeal membrane oxygenation (VA ECMO) as a rescue therapy [7–10].

The goal of VA ECMO is to restore an adequate systemic circulation and related tissue perfusion and oxygenation in the patient as fast as possible. Patients on VA ECMO are managed in the intensive care unit (ICU) as a bridge to either decision-making, recovery, long-term mechanical support, or transplantation. A VA ECMO circuit consists of a venous cannula, a pump, an oxygenator, a blood heater-cooler, and an arterial cannula. VA ECMO support is associated with daily accumulative risks of complications such as bleeding, infection, limb ischaemia, and thrombosis. The duration of VA ECMO therapy varies between one day and a few weeks. Between to 25-70% of the critically ill patients that require VA ECMO are able to wean successfully, half of these patients does not survive until hospital discharge [7–13].

VA ECMO is a complex modality that is difficult to manage on a daily basis and requires a lot of expert knowledge. Weaning of VA ECMO should be considered once a patient shows signs of myocardial recovery and more specific, LV contractile function. If a patient is weaned too early, the cardiac function might not have recovered sufficiently to resolve the cardiogenic shock, late weaning increases the risk of complications. Determining the optimal timing of weaning is challenging and physicians heavily rely on expert opinion and their pathophysiological, clinical reasoning at the bedside, in the absence of evidence-based guidelines. To assess LV contractile recovery during VA ECMO support, a weaning-trial can be performed. During a weaning trial, VA ECMO flow is reduced significantly (<0.5 L/min), thereby increasing native cardiac loading conditions. During this weaning trial, both hemodynamic and echocardiographic parameters are assessed (such as, for example, LV ejection fraction (LVEF) and CO) to evaluate cardiac contractility and recovery. Despite this thorough evaluation, durable cardiac recovery appears difficult to predict [7–10, 12, 14–16]. A method to continuously estimate LV contractile function under VA ECMO support, based on readily available clinical parameters, would be highly valuable for optimised clinical daily decision-making.

Such a method could be developed by using clinical parameters to tune an elaborate computational physiological model (CPM) as a virtual representation of the patient. A virtual representation of a patient is also known as a digital twin, which can be used to gain insights into human physiology that are challenging to obtain otherwise. By tuning a CPM as a digital twin, it could be used to estimate the LV contractile function of a patient on VA ECMO continuously. A digital twin can assist clinicians in daily decision-making, improving management and weaning strategies for patients on VA ECMO [17–20].

1.1 Study objective

The objective of this study is explore the feasibility of developing a method to continuously evaluate left ventricular contractile function in patients during VA ECMO support, by using a digital twin.

The research question is: Can a computational physiological model, tuned as a digital twin, aid in the evaluation of left ventricular contractile function of patients receiving VA ECMO?

Sub questions are:

1. How can a computational physiological model be tuned as a digital twin of a patient supported by VA ECMO?
2. Can a computational physiological model, tuned as a digital twin, be used to evaluate left ventricular contractile function of a patient receiving VA ECMO?

2. Background

2.1 Cardiac function

Currently, a multidisciplinary team of medical specialists is involved in the daily management of patients receiving VA ECMO. Decision-making regarding tapering of VA ECMO support and withdrawal is currently based on a combination of both hemodynamic and echocardiographic parameters. Although guidelines provide target values for each parameter, patient tailored support within daily clinical care remains extremely complex.

In the clinical decision-making process during VA ECMO support, evaluating cardiac function and recovery is crucial. Ideally, clinicians would have a reliable, minimally invasive, and continuous method to evaluate the native LV contractility during VA ECMO at their disposal, however, this is challenging to perform in vivo [21, 22]. LV contractility is defined as the intrinsic ability of the ventricle to generate force, independent of preload or afterload conditions and can be pharmacologically increased using inotropic agents [23–25]. Contractility can be described using a pressure-volume (PV) loop, which represents the pressure volume relationship of one cardiac cycle (see figure 2.1) [23]. The slope of the end-systolic pressure volume relation (ESPVR) is considered equal to the end systolic elastance (Ees), a measure of ventricular contractility [26, 27]. In healthy adults, Ees is 2.3 $\pm$ 1 mmHg/mL [28].

In addition to LV contractility, ventriculo-arterial coupling (VA coupling) is a method that provides information about cardiovascular performance. It represents the relationship between the heart and the arterial system and is considered to be a powerful predictor of mortality [28, 29]. VA coupling is defined as the ratio between arterial elastance (Ea) and Ees. Ea represents arterial function and can be depicted as the slope between the end-systolic pressure (Pes) and the end-diastolic volume (see Figure 2.1). In healthy adults a normal Ea value is 2.2 $\pm$ 0.8 mmHg/mL and the mean value of VA coupling is 1 $\pm$ 0.36. In patients with heart failure VA coupling is increased [28–30].

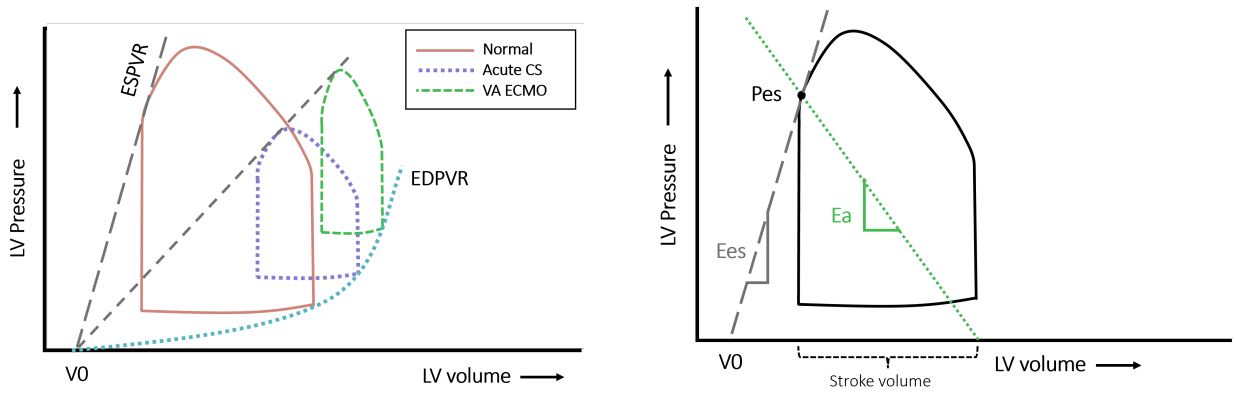

Figure 2.1: **Left:** *PV-loops in a healthy heart, a heart in cardiogenic shock, and a failing heart on VA ECMO support.* **Right:** *PV-loop with arterial elastance (Ea) and end-systolic elastance (Ees).*

2.2 Digital twin

A digital twin of a patient on VA ECMO would allow for the assessment of physiological parameters without requiring additional, possibly invasive, diagnostics. Additionally, a digital twin would enable the prediction of the patient's response to treatment options. This could aid in the daily clinical decision-making process [17, 19, 20].

To create a digital twin of a patient receiving VA ECMO, a cardiovascular computational physiological model (CPM) has to be tuned to virtually represent the patient. The CPM must meet several requirements in order to facilitate this. It should accurately model cardiovascular dynamics, including heart function, vascular properties, and blood flow dynamics. To tune the cardiovascular CPM in order to match a patient on VA ECMO, it is essential that an ECMO component is integrated into the CPM. The CPM must allow for independent variation of key parameters such as ventricular contractility, vascular resistance, and compliance. Additionally, the CPM's output should be translatable into clinically meaningful variables to facilitate interpretation and application in a clinical context.

The cardiovascular CPM developed by Fresiello et al. [31] is a lumped parameter model of the cardiovascular system, developed in LabVIEW (National Instruments, Austin, TX, USA). As required, the CPM offers a representation of atria, ventricles, and systemic and pulmonary circulation. The systemic circulation is split into: upper body (UB), renal (KID), splanchnic (SPL), and lower limbs (RL and LL for right an left leg respectively) circulatory subsystems. The ECMO is connected between the right atrium and the aorta of the cardiovascular CPM and it includes inflow and outflow tubing, a pump, and an oxygenator. Refer to Figure 2.2 for a schematic overview of the CPM.

Mathematically, the atria and ventricles are represented with time varying elastance models [32] and the circulation is modelled with windkessel models in series or in parallel [19]. The tubing of the ECMO is modelled with resistive and inertance elements and the hemodynamic behaviour of the pump is modelled as a relationship between pump pressure drop and flow. Lastly, the oxygenator is modelled as a linear resistance to the flow according to Poiseuille's law [31].

The main input parameters of the model are resistances and compliances. The main output variables of the model are pressure, flow, and volumes. These are, for example, presented as clinically meaningful pressure waveforms and pressure-volume loops. The CPM allows the adjustment of cardiovascular input parameters and ECMO settings to model a patient receiving (VA) ECMO therapy [19, 31].

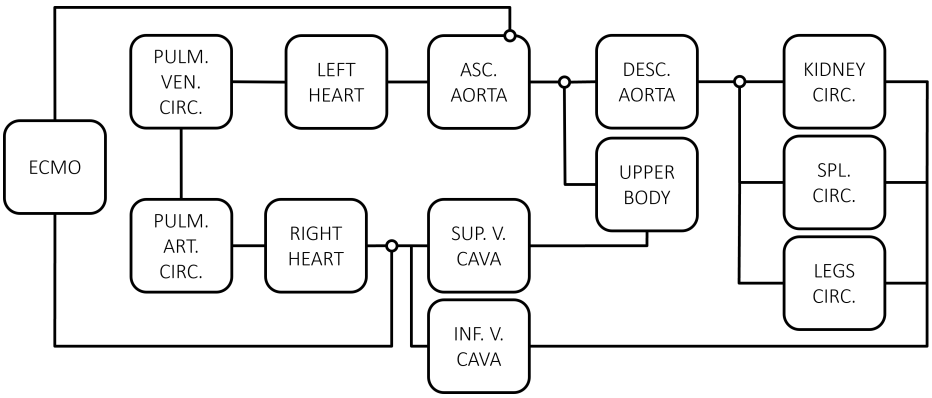

Figure 2.2: Schematic overview of all components of the cardiovascular CPM including an ECMO compartment, adapted from [31]

3. Methods

The aim of this study was to develop a method to monitor LV contractile function in patients supported with VA ECMO by using a digital twin. First, the cardiovascular CPM used to tune the digital twin was selected based on the requirements outlined in section 2.2 and its availability. The selected CPM was evaluated using a sensitiviity analysis. Then, a prospective study was conducted to collect readily available clinical parameters from patients on VA ECMO, to evaluate the feasibility of using the CPM as a digital twin to estimate LV contractile function in these patients. The clinical parameters were used to estimate model parameters and perform baseline tuning. Two methods were employed to tune the CPM into a digital twin: an automatic tuning method, and a manual tuning method. Finally, the cardiac function of the patients was estimated using the resulting digital twin (see Figure 3.1).

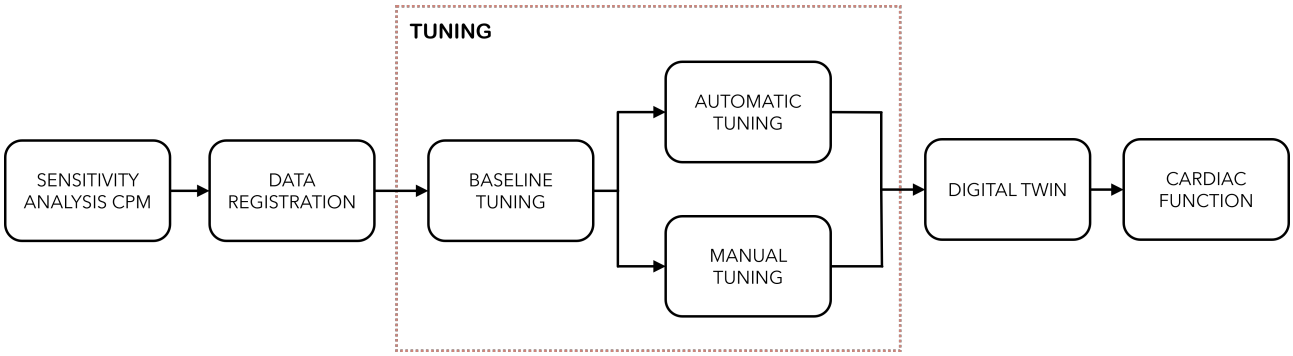

Figure 3.1: Flowchart of methods

3.1 Sensitivity analysis computational physiological model

Identifying how model parameters influence the output of the CPM is crucial to guide the tuning process. To gain this insight, a sensitivity analysis was performed. First a typical patient on VA ECMO was modelled. Data from a typical patient with a cardiac indication for VA ECMO, on the first day of the VA ECMO run, were selected from the 'PRECISE-ECLS' database of the UMCU (NCT05444764). Missing data were estimated using group data and clinical expertise. The CPM was first tuned to match the clinical parameters of the typical patient using a previously published tuning protocol for patients with VA ECMO turned off [19]. Additional tuning was performed by educated trail-and-error until the model output matched the target values of the patient with a maximum error of 15%.

Next, a one-at-the-time sensitivity analysis was performed by varying all model parameters one by one. The parameters were varied from -60% to +60% of their original values, in increments of 15%. The following model parameters were varied: systemic vascular resistance (SVR), LV elastance (LVe), right ventricular elastance (RVe), HR, total blood volume (TBV), ECMO rpm, aortic compliance (C_a), Venous compliance (C_v), and compliance of the right atrium (C_{RA}). The effect of a model parameter on an output variable was evaluated by calculating the normalised difference between the new output

and the default output of the variable, with respect to the range between the minimum and maximum values of the corresponding variable, as shown in Equation (3.1). The minimum and maximum values of the variables were established from the PRECISE-ECLS database,

$$Effect = \frac{X - X_{default}}{X_{max} - X_{min}} \cdot 100\%. \tag{3.1}$$

3.2 Data registration

Study population

Patients were included for this study if they received VA ECMO support in the ICU of the UMC Utrecht. Due to the explorative nature of this study, all indications for VA ECMO were included. Patients that received additional mechanical support by a ventriculo-aortic axial pump (Impella) or an intra-aortic balloon pump (IABP) that could not be turned off during registration were excluded as the additional support affects the arterial arterial blood pressure (ABP) waveform. Additionally, patients were excluded if their age was below 18 years or a general informed consent was not provided.

Data collection

Readily available clinical parameters were registered for all patients on three different days. Data were collected from the electronic medical record and/or from the ICU monitor at the bedside. When possible, additional bedside registrations were performed to extract the ABP waveform from the ICU monitor for at least 10 seconds. The ABP waveform was used to perform additional model parameter estimation. In patients with additional IABP support, the device was paused or adjusted to partial support (a 1:3 setting) during the bedside registration to extract the ABP waveform resulting from native ventricular function. If available, echocardiographic recordings were obtained to estimate CO. An overview of the collected clinical parameters is shown in Table 3.1.

Table 3.1: Overview of readily available clinical parameters that were registered.

Clinical parameters	**Abbreviation**	**Source**	**Sample frequency**
Heart rate	HR	ECG electrodes	min^{-1}
Systolic blood pressure	SBP	ABP catheter	min^{-1}
Diastolic blood pressure	DBP	ABP catheter	min^{-1}
Mean arterial pressure	MAP	ABP catheter	min^{-1}
Systolic pulmonary artery pressure	sPAP	SG catheter	min^{-1}
Diastolic pulmonary artery pressure	dPAP	SG catheter	min^{-1}
Central venous pressure	CVP	SG catheter	min^{-1}
Cardiac output	CO	SG catheter, Echo	min^{-1}
ECMO flow	Qecmo	ECMO device	$hour^{-1}$
ECMO revolutions per minutre	ECMO rpm	ECMO device	$hour^{-1}$
Arterial blood pressure wave	ABP wave	ABP catheter	1000 sec^{-1}

Note that the cardiovascular CPM models a central systolic blood pressure (cABP), while peripheral arterial blood pressure (pABP) is usually measured in patients. MAP and DBP are typically similar in both cABP and pABP, the cSBP tends to be higher than peripheral SBP (pSBP) [33–35]. Therefore, Equation (3.2) was used to estimate the cSBP [36]

$$cSBP = \frac{MAP^2}{DBP}. \tag{3.2}$$

3.3 Tuning

The performance of a model was evaluated by scoring the difference between the CPM's output and the patient's data. The differences were normalised in the same manner as in Section 3.1. The Root Mean Square Error (RMSE) of the normalised difference, as described in Equation (3.3), was determined to score the models,

$$RMSE = \sqrt{\frac{1}{n}\sum(\frac{X_{patient} - X_{CPM}}{X_{max} - X_{min}})^2}. \tag{3.3}$$

Baseline tuning

The first step to match the output of the cardiovascular CPM to the patient's data was to perform baseline tuning. Initially, fixed model parameters, such as HR and ECMO rpm were set based on the collected data. Next, model parameters that could be estimated from patient data, such as SVR and TBV, were adjusted accordingly. All remaining model parameters were set to their default values (see Appendix A). This provided a baseline model that served as the starting point for further tuning.

The following model parameters were estimated based on gathered clinical parameters:

- **Total blood volume (TBV):** Estimated according to the 'normal' ratio of blood volume to weight, which is 75 cm^3/kg [19]
- **Venous compliance (C_i):** Estimated based on the patient's weight at ICU admission compared to a reference patient [19] using Equation (3.4)

  $$Ci = Ci_{ref} \cdot BodyWeight/BodyWeight_{ref}. \tag{3.4}$$

  C_i was calculated for each circulatory subsystem, refer to Appendix C for the default compliance of each subsystem.
- **The arterial resistance (RtA):** Can be calculated using the systemic vascular resistance (SVR), which was estimated using Equation (3.5). RtA is calculated using Equation (3.6), where t represents the tissue area of the circulatory subsystems (UB, KID, SPL, RL, and LL). The systemic vascular resistance (SVR) was estimated using Equation (3.5),

  $$SVR = (MAP - CVP)/CO, \tag{3.5}$$

  $$RtA = \frac{100\%}{Qt[\%]}SVR - RtV, \tag{3.6}$$

  with Q_{UB} = 23%, Q_{KID} = 22%, Q_{SPL} = 30%, Q_{RL}= Q_{LL}= 12.5%.
- **The aortic compliance (C_a):** Can be estimated using the time-decay method applied on the diastolic part of the ABP waveform, see Equation (3.7), the method is based on the two-element Windkessel model [37, 38],

  $$P(t) = P_1 e^{\frac{-(t-t_1)}{SVR \cdot C_a}}. \tag{3.7}$$

  The time decay method assumes zero flow during diastole, but since ECMO flow is continuous, the method was adapted for patients on VA ECMO, see equation (3.8) [39] ,

  $$P(t) = (P_1 - SVR \cdot Q_{ecmo})e^{\frac{-(t-t_1)}{SVR \cdot C_a}} + SVR \cdot Q_{ecmo}, \tag{3.8}$$

  where P(t) the calculated pressure over time, P_1 the pressure at t_1 of the diastolic part of the ABP wave, and Q_{ecmo} the ECMO flow. P(t) was calculated for a range of values of C_a between

0.01 and 10 mL/mmHg with increments of 0.01 mL/mmHg. For each C_a the root mean square error (RMSE) between the resulting $P(t)$ and the diastolic phase of the ABP was calculated. The C_a that provided the lowest RMSE was chosen as the estimated value for C_a. This method was applied to each consecutive heartbeat.

The time-decay method and the adapted time-decay method were validated with modelled ABP waveforms for a range of C_a. The methods were also validated on ABP waveforms from the included patients. The diastolic part of the ABP wave was defined as the location of the dicrotic notch. The CPM does not model a dicrotic notch (Figure 3.2), the start of the diastolic part of the wave was defined as one third of the time between two systolic peaks. In patient data, continuously estimated C_a was filtered by removing outliers that were more than three scaled median absolute deviations from the median, followed by a moving average filter of 15 heartbeats. The estimated C_a were tested for significant difference between flows, using the nonparametric Kruskal-Willis test, a $p<0.01$ was considered statistically significant.

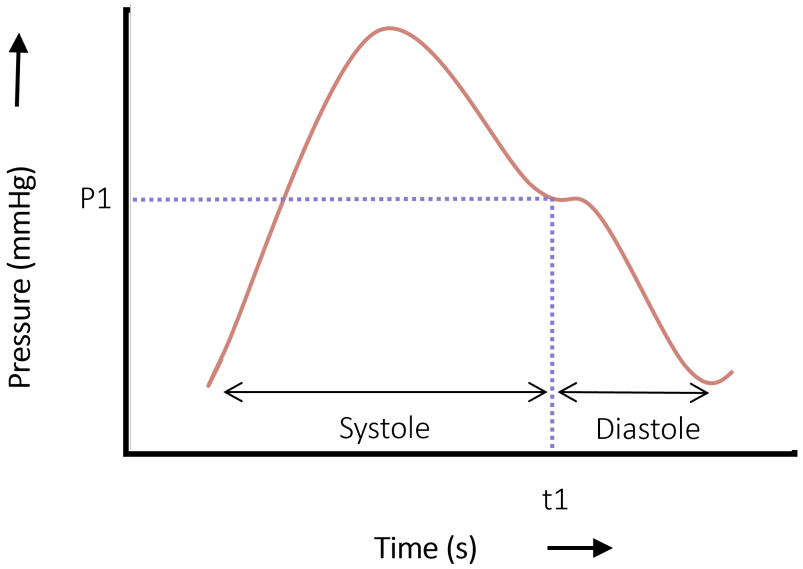

Figure 3.2: Arterial blood pressure waveform with systolic and diastolic phase. t1 is the time at the start of diastolic phase, P1 is the pressure at t1.

Automatic tuning

Automatic tuning was performed by using a grid search method to find the optimal model parameter values that minimised the RMSE. Starting from the baseline tuned patient, the first parameter for grid search was SVR, as it is one of the key parameters that can adapt quickly to changing physiological conditions. The grid ranged from -80% to +80% of the original SVR value, in increments of 10%. The second parameter subjected to grid search was LVe, as this parameter is equal to Ees, which is used to evaluate the cardiac function. The grid for LVe ranged from 0.2 to 1.8 mmHg/mL in increments of 0.1 mmHg/mL.

Manual tuning

Manual tuning was performed by adjusting model parameters manually until all normalised output errors were less than 10%. The starting point was baseline tuning, after which manual adjustment to model parameters were performed. Adjustments were guided by the results of the sensitivity analysis performed on the typical patient on VA ECMO. The following steps were taken to tune the CPM manually:

1. Perform baseline tuning:
    - Change HR and ECMO rpm to exact values
    - Estimate TBV, C_v, and RtA using patient data
2. Change SVR until arterial pressures are just above their target values
3. Change pulmonary resistance (Rpolm) and compliance of the pulmonary artery (cap) so the pulmonary pressures match their target values
4. Change LVe and C_{RA} until arterial pressures, CO, and Q_{ecmo} match their targets
5. Adjust C_v to adjust CVP
6. Adjust C_a to improve pulse pressure
7. Use the results from the sensitivity analysis to perform additional tuning until all output variables match their targets

3.4 Cardiac evaluation

Cardiac contractile function was evaluated for each modelled digital twin. This was done by determining Ees, which is equal to the model parameter LVe. Additionally, cardiovascular performance was evaluated by VA coupling, which is defined as the ratio between Ea and Ees. Ea is calculated by dividing the end systolic pressure (P_{es}) by the stroke volume (SV) (see figure 2.1. The resulting Ees and VA coupling values were compared to the outcome of the patients, which were deducted from the electronic medical record.

4. Results

4.1 Sensitivity analysis computational physiological model

To gain insight into the effect of model parameters on the output of the cardiovascular CPM, a one-at-the time sensitivity analysis was performed on a modelled typical patient receiving VA ECMO. The selected patient data for the typical VA ECMO patient are displayed in Table 4.1. The settings used to simulate this patient can be found in appendix A. The modelled typical patient achieved an RMSE of 0.152.

Table 4.1: Patient characteristics of a typical VA ECMO patient with a cardiac indication. See list of abbreviations for the meaning of all used abbreviations.

Typical VA ECMO patient	**Value**	**Unit**
HR	83	BPM
SBP/DBP/MAP	87/60/68	mmHg
sPAP/dPAP	28/18	mmHg
CVP	12	mmHg
PCWP	13	mmHg
CO	3.2	L/min
ECMO rpm	3000	RPM
Q_{ecmo}	3.3	L/min

A summary of the results from the sensitivity analysis of the typical patient is shown in Figure 4.1. For a full overview of the results, refer to appendix B. Figure 4.1 features a heatmap that displays the calculated error for each variable as a result of a 30% increase in the corresponding model parameter. This heatmap can be used to predict model behaviour. For instance, if one were to increase SVR, CO and Q_{ecmo} would likely decrease, while the DBP and MAP would likely increase the most.

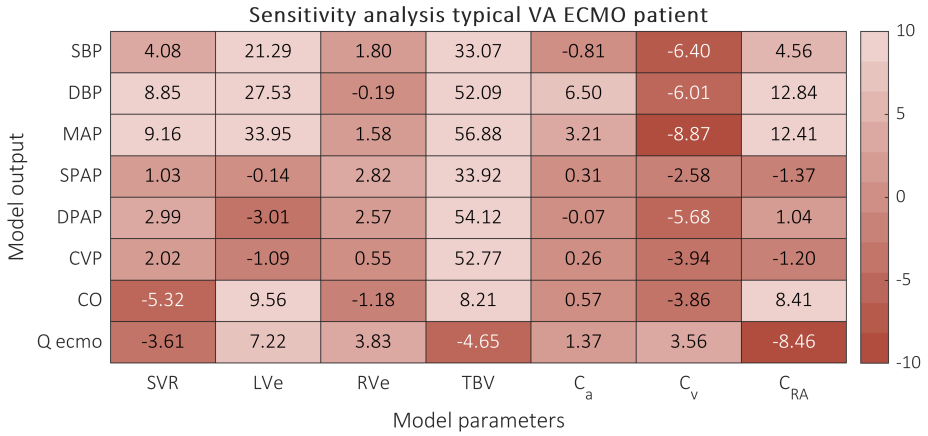

Figure 4.1: Heatmap with summary of results of the sensitivity analysis conducted for the typical patient on VA ECMO. See list of abbreviations for the meaning of all used abbreviations.

4.2 Data registration

Population

In total, data were registered from eight patients on VA ECMO in the ICU. Three patients were excluded from the analysis due to missing variables, resulting in five included patients (Table 4.2). See Appendix A for all collected data.

Table 4.2: Characteristics of included patients.

Characteristic	**n = 5**	**Patient no.**
Female (n, %)	1 (20%)	-
Age (median years, IQR)	53.3 (10)	-
BMI (median, IQR)	24.9 (9.3)	-
Duration VA ECMO run (median hours, IQR)	102 (129)	-
Died before hospital discharge (n, %)	1 (20%)	3
Indication		
OHCA	2 (40%)	1, 5
Aortic dissection	1 (20%)	2
ARDS	1 (20%)	3
Post lung transplant	1 (20%)	4
Additional mechanical support		
IABP (n, %)	1 (20%)	5
Pacemaker (n,%)	1 (20%)	2

OHCA: out of hospital cardiac arrest, ARDS: acute respiratory distress syndrome, IABP: intra-aortic baloon pump.

4.3 Baseline tuning

The RMSE resulting from baseline tuning for each registered day and patient are presented in Table 4.3. The median RMSE was 0.455 with an inter quartile range (IQR) of 0.1235.

Table 4.3: Root mean square error of baseline tuned CPMs

Patient	**Day of ECMO run**	**RMSE**
Patient 1	2	0.505
	3	0.408
	4	0.496
Patient 2	2	0.709
	3	0.793
	4	0.602
Patient 3	4	0.363
	5	0.340
	6	0.414
Patient 4	2	0.397
	3	0.545
	4	0.455
Patient 5	2	0.515
	3	0.405
	6	0.409

Validation adapted time-decay method

To ensure proper estimation of C_a, the adapted time-decay method was validated. The estimated C_a, using both methods applied on modelled data for a range of C_a values, is shown in Figure 4.2. The time-decay method had a median error of 0.273 mL/mmHg with an IQR of 0.168 mL/mmHg. The median error of the adapted time-decay method was 0.855 mL/mmHg with an IQR of 0.994 mL/mmHg.

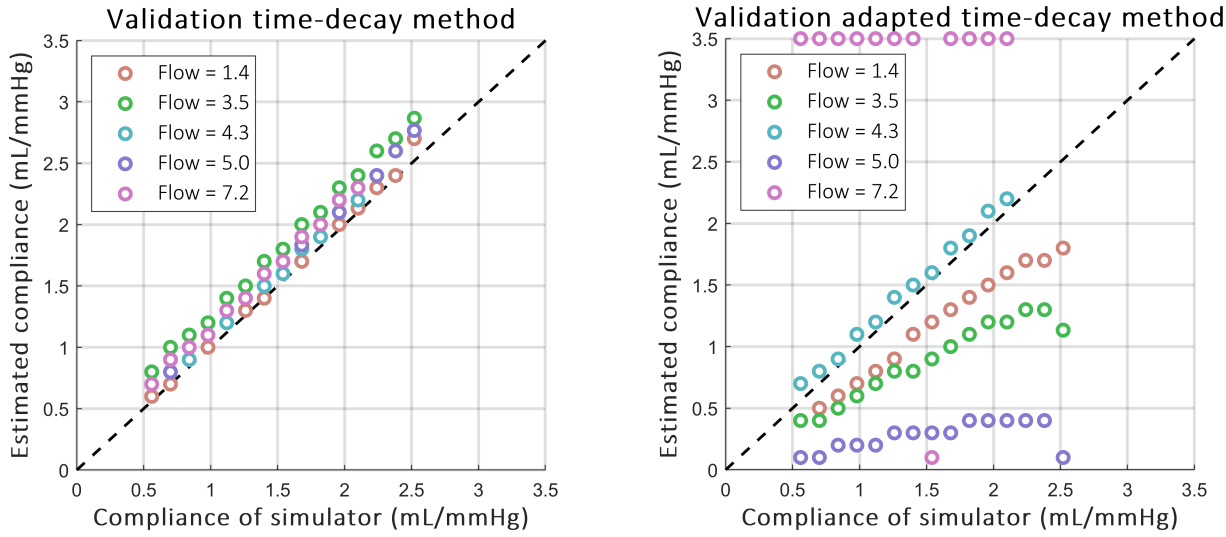

Figure 4.2: **Left:** *Validation of estimated C_a using the time-decay method for different Q_{ecmo}.* **Right:** *Validation of estimated C_a using the adapted time-decay method for different Q_{ecmo}.*

The continuously estimated C_a using both methods for patient 1 during a weaning trial is shown in Figure 4.3. The time-decay method estimated a median C_a of 0.328 mL/mmHg with an IQR of 0.0081 mL/mmHg, with no significant difference in estimated C_a during the different flows. The adapted time-decay method, however, estimated an undesired significant increase in C_a for decreasing flow, with a median C_a of 0.174 (IQR 0.0044) mL/mmHg at 2 L/min, 0.212 (IQR 0.0053) mL/mmHg at 1.5 L/min, and 2.49 (IQR 0.0062) mL/mmHg at 1 L/min. Significance was confirmed with $p<0.001$.

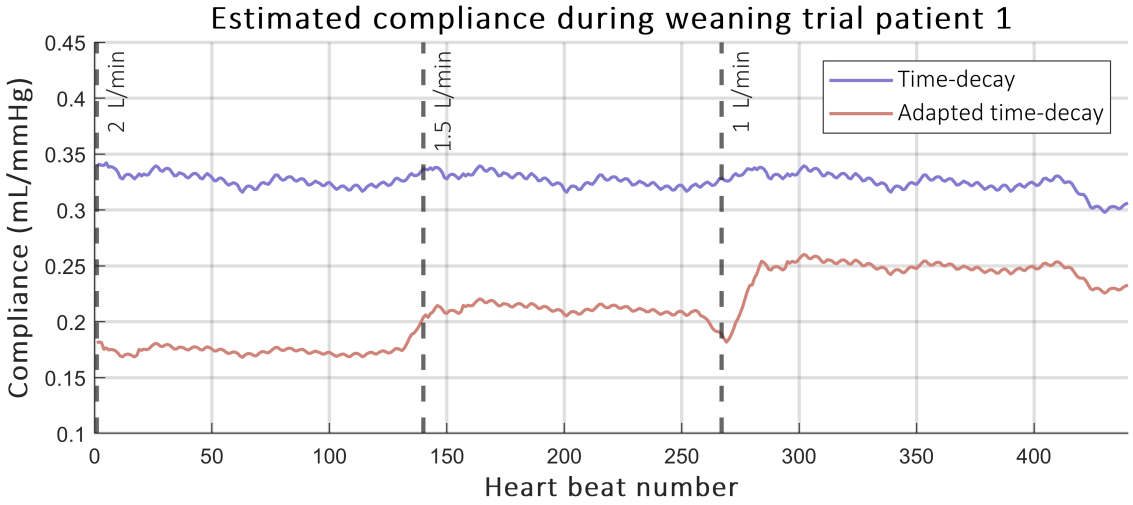

Figure 4.3: Estimated arterial compliance in patient 1 during weaning trial using the time-decay method and the adapted-time decay method. The vertical dotted lines indicate a change in Q_{ecmo}.

The compliance estimated in patients using the ABP waveforms can be found in Table 4.4 and is visualised in Figure 4.4. The results show that the adapted time-decay method estimates a lower compliance than the time-decay method in all patients on all days.

Table 4.4: Estimated median compliance and IQR (inter quartile range) of patient data, using both the time-decay and the adapted time-decay method. The dashes indicate that no adequate ABP waveform was registered.

Patient	**Day ECMO run**	**Time-decay**		**Adapted time-decay**	
		Median	*IQR*	*Median*	*IQR*
Patient 1	2	1.04	0.02	0.47	0.02
	3	0.67	0.05	0.41	0.01
	4	0.33	0.01	0.17	0.004
Patient 2	2	-	-	-	-
	3	-	-	-	-
	4	-	-	-	-
Patient 3	4	-	-	-	-
	5	-	-	-	-
	6	2.59	0.02	0.43	0.01
Patient 4	2	-	-	-	-
	3	-	-	-	-
	4	1.82	0.02	0.97	0.01
Patient 5	2	6.22	1.41	3.00	0.73
	3	1.19	0.04	0.75	0.02
	6	5.25	1.17	3.84	0.83

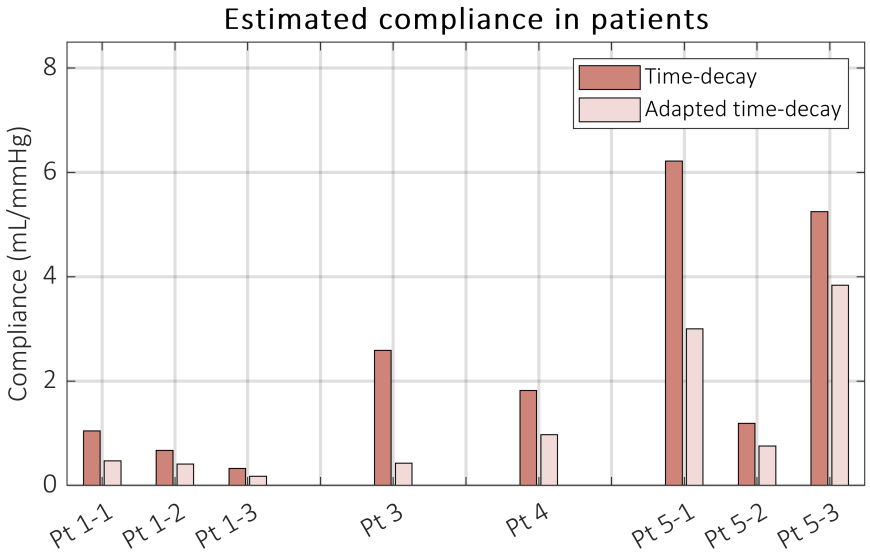

Figure 4.4: Estimated compliance in patients using the time-decay method and the adapted time-decay method.

4.4 Automatic tuning

Table 4.5 contains the estimated Ees and the corresponding RMSE of the automatically tuned CPMs. The median RMSE of all automatically tuned CPMs was 0.181 (IQR 0.151). Figure 4.5 visualises the estimated Ees for all patients. Ees increased in patient 1, 3, and 4, while it decreased in patient 2 and 5. VA coupling decreased in patient 1, 4, and 5, increased in patient 2, and remained somewhat stable in patient 3.

Table 4.5: Results from automatic tuning.

Patient	Day of ECMO run	Selected SVR	RMSE	Selected Ees	RMSE	VA coupling
Patient 1	2	0.4	0.222	0.5	0.190	3.26
	3	0.5	0.376	0.2	0.315	2.53
	4	0.4	0.181	0.7	0.149	2.86
Patient 2	2	0.2	0.169	0.8	0.168	2.67
	3	0.2	0.145	0.5	0.111	2.45
	4	0.4	0.165	0.5	0.083	3.35
Patient 3	4	0.5	0.250	0.5	0.237	2.66
	5	0.6	0.213	0.5	0.213	2.90
	6	0.5	0.243	0.6	0.216	2.82
Patient 4	2	0.5	0.256	0.3	0.181	2.67
	3	0.4	0.283	0.4	0.172	2.79
	4	0.4	0.248	0.6	0.234	2.37
Patient 5	2	0.4	0.303	0.4	0.193	2.40
	3	0.5	0.189	0.6	0.178	3.05
	6	0.4	0.258	0.3	0.179	1.93

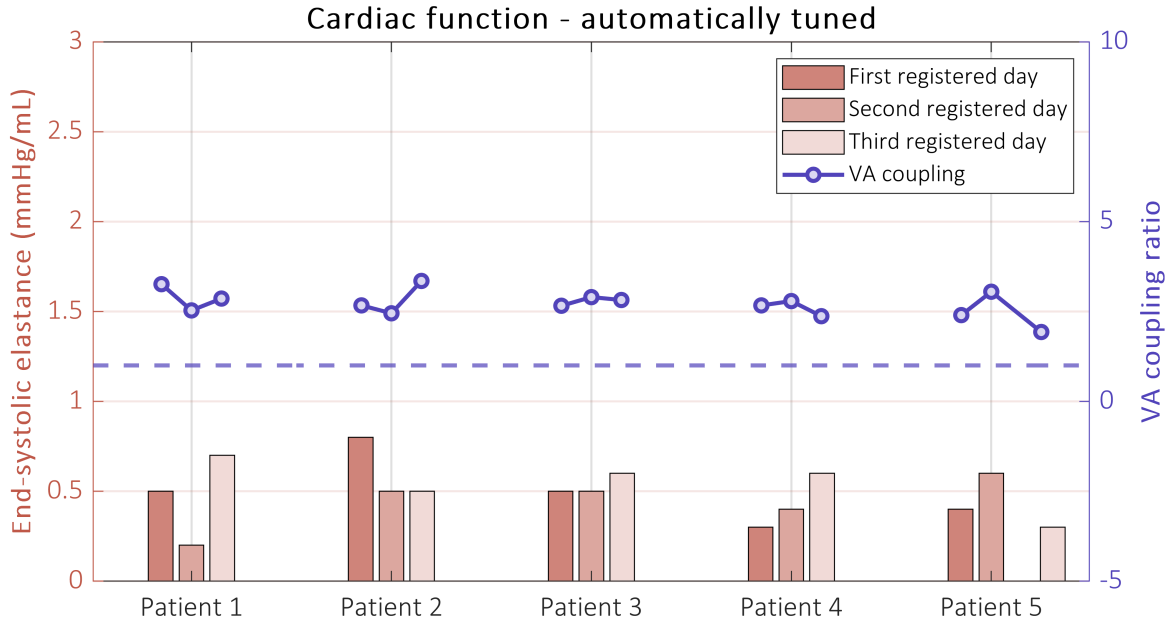

Figure 4.5: Results of automatic tuning. The estimated end-systolic elastance (Ees) on the left y-axis. Estimated VA coupling on the right y-axis, the dashed line indicates VA coupling = 1

4.5 Manual tuning

Manual tuning was performed by applying the findings from section 3.1 to model a digital twin. The median RMSE of all manually tuned CPMs, including the hourly analysis, was 0.028 (IQR 0.0105). The cardiac function of the digital twins is shown in table 4.6 and Figure 4.6. Ees increased over time for all patients. VA coupling ratio decreased for all patients over time.

Table 4.6: Estimated cardiac function of all manually tuned digital twins.

	Day of ECMO run	RMSE	Ees	VA coupling
Patient 1	2	0.041	0.85	2.68
	3	0.034	1.00	1.70
	4	0.036	2.30	1.17
Patient 2	2	0.025	0.42	8.47
	3	0.039	0.40	6.77
	4	0.015	0.44	6.97
Patient 3	4	0.035	0.75	2.04
	5	0.039	0.63	2.19
	6	0.039	0.99	1.64
Patient 4	2	0.031	0.83	1.89
	3	0.029	0.90	1.91
	4	0.036	2.10	0.77
Patient 5	2	0.049	0.72	2.03
	3	0.043	1.10	1.67
	6	0.040	1.40	0.82

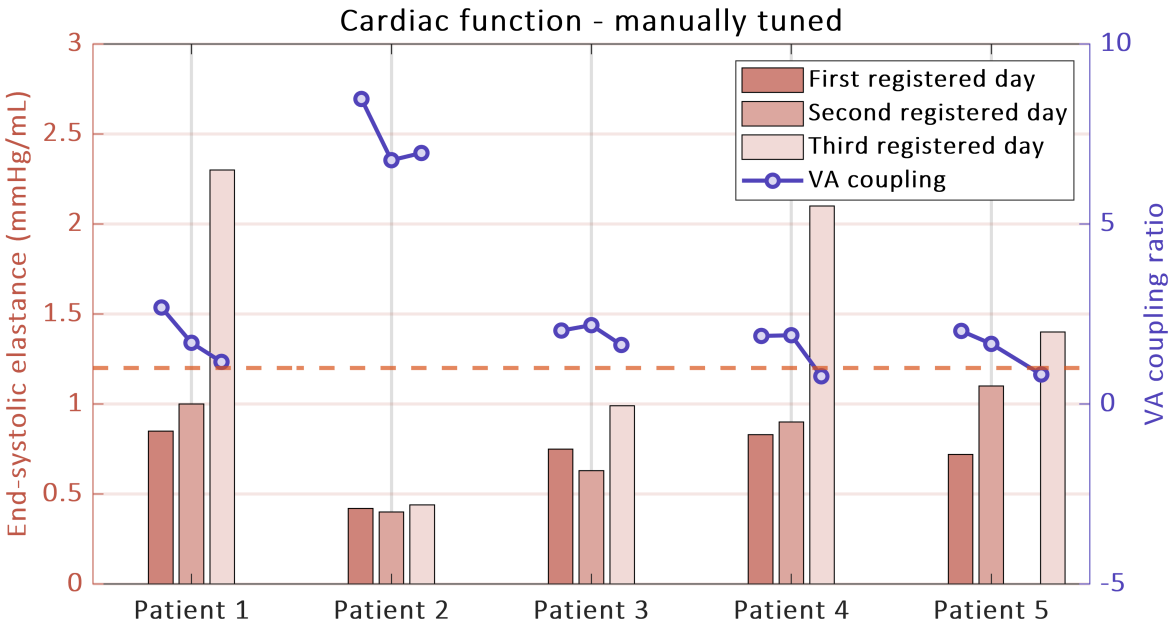

Figure 4.6: Results of manual tuning. The estimated end-systolic elastance (Ees) on the left y-axis. Estimated VA coupling on the right y-axis, the dashed line indicates VA coupling = 1.

Hourly analysis

An hourly analysis was performed on patient 2, for 41 consecutive hours. Figure 4.7 shows the trends of estimated Ees and VA coupling. In addition to the cardiac parameters, changes in pharmacological dosage of Noradrenaline and Milrinon are shown. Noradrenaline ranged between 6 and 25 mL/h and Milrinon ranged between 0 to 4 mL/h. The patient also received Amiodarone at 4.2 mL/h and Dobutamine at 4 mL/h for all 41 hours. Between the hours 16 and 20, CVP varied more than 10% from the target value.

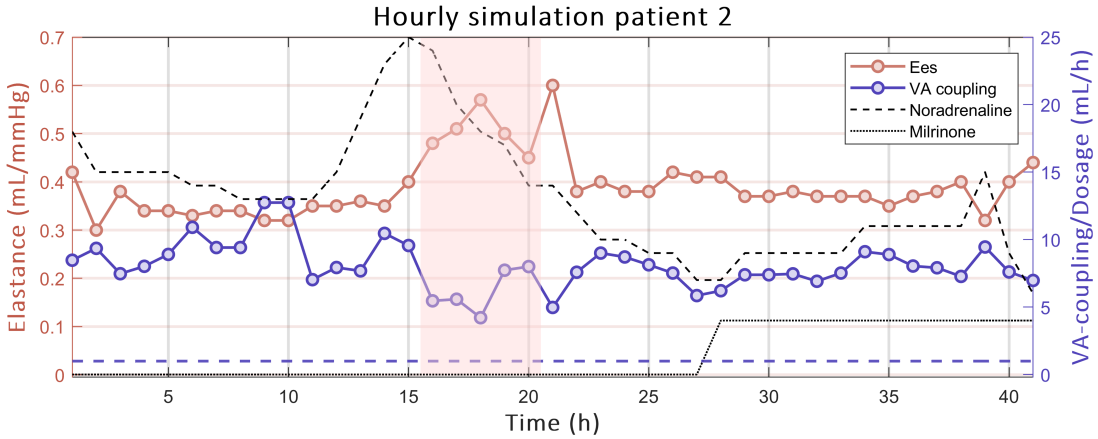

Figure 4.7: Hourly manual digital twin of patient 2. The estimated left ventricular elastance on the left y-axis. Estimated VA coupling on the right y-axis, the dashed line indicates VA coupling = 1. Dotted lines represent dosage change of milrinone and noradrenaline. The marked area from hour 16 to 20 represents the hours in which CVP varied more than 10% from the target value.

Arterial blood pressure

The ABP waveform of patient 5 on day 2 of the VA ECMO run is shown in Figure 4.8. The modelled ABP waveforms after tuning are plotted to show the effect of baseline, automatic, and manual tuning on the ABP waveform. Note that the SBP of the patient is peripherally measured while the CPM models cSBP (see Section 3.2).

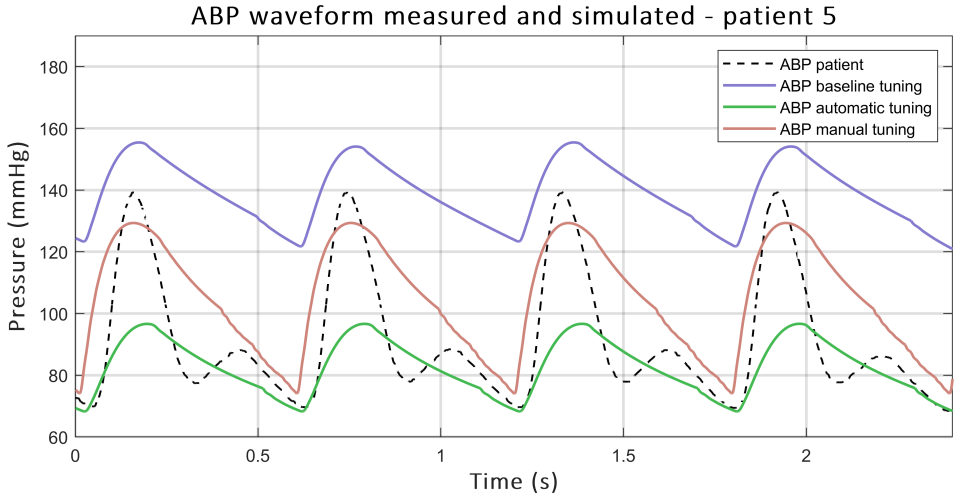

Figure 4.8: The ABP waveforms of patient 5 on day 2 of the VA ECMO run, measured in the patient and after baseline, automatic, and manual tuning.

5. Discussion

In this study, a novel method to monitor LV contractile function in patients on VA ECMO by using a digital twin, was explored. Patient data were collected and utilised to estimate model parameters. A method for estimating aortic compliance was validated using the ABP waveform. In addition two methods for tuning the cardiovascular CPM to individual patients were proposed: an automatic tuning method and a manual tuning method. Cardiac function of the resulting digital twins was estimated and compared with the patients' clinical outcome.

The results indicate that the time-decay method surpasses the adapted time-decay method in estimating aortic compliance for VA ECMO supported patients. The sensitivity analysis of the cardiovascular CPM yielded clinically realistic outcomes that are generally consistent with existing literature. While the automatic tuning protocol showed promise, it exhibited a high RMSE and failed to consistently estimate a reliable cardiac function in alignment with clinical outcomes. Manual tuning did achieve the desired RMSE and provided better correlation with clinical outcomes, yet it occasionally fell short in accurately estimating cardiac function.

5.1 Interpretation of results

Sensitivity analysis computational physiological model

The aim of this analysis was to create an overview of the effect of that parameters have on output variables. Figure 4.1 provides this comprehensive overview. The general outcome of the sensitivity analysis aligns with existing literature [40–44]. However, changes in hemodynamics during VA ECMO support are complex and vary among patients due to multiple clinical variables.

A notable finding is that an increase in TBV lead to a decrease in Q_{ecmo}. Given the increased volume available to be pumped by the ECMO device, an increase in Q_{ecmo} was expected [42, 44]. One explanation might be the increase in SBP, suggesting high afterload which the ECMO device must overcome. If the device cannot manage this, Q_{ecmo} could decrease [45] .

Another remarkable outcome is an increase in TBV lead to an increase in CVP, despite absence of significant right ventricular failure in the patient. If the right ventricle functions adequately, it would be expected to pump away the excess volume, preventing a rise in CVP [41]. A possible explanation is that the patient is decompensating due to poor LV function, which can lead to pulmonary hypertension and increased CVP.

The results of this analysis can be used to better tune the cardiovascular CPM, providing general insights into how the CPM's output responds to changes in model parameters. However, the smaller effects are too complex to predict, much like the variability seen in patients on VA ECMO. For more detailed results of the sensitivity analysis, once can consult the extensive results in Appendix B.

Estimation aortic compliance

In simulated data, the time-decay method consistently outperforms the adapted time-decay method, especially in cases of unrealistically high Q_{ecmo} values. As Q_{ecmo} increases, the adapted time-decay method estimates a lower C_a. When (Q_{ecmo}· SVR) surpasses P1, the method then takes the maximum C_a within the grid and ceases to function completely (refer to Appendix D for details). This effect of Q_{ecmo} on the adapted time-decay method is also evident in the studied patient data, where it consistently estimates a lower C_a than the time-decay method. During the weaning trial of patient 1, the adapted time-decay method showed a significant influence of Q_{ecmo} on C_a. As C_a is an intrinsic property of the aorta and does not typically change within seconds, these estimates are unlikely to be accurate [46]. The errors of the time-decay method were similar to the values found by Stergiopolus et al. [37], using a non-linear computer model of the systemic arterial tree to test the time-decay method without VA ECMO.

In healthy adults aged 25 to 56, aortic compliance ranges between 0.230 and 2.719 mL/mmHg [47]. The unrealistically high C_a in patient 5 on day 2 and 6 is likely caused by the IABP. The device was paused for only a few heartbeats, which was not sufficient for the ABP waveform to stabilise [48]. These findings suggest that an IABP should be paused for sufficient time.

Patient 1's unusual ABP waveform during the weaning trial may have affected the accuracy of the methods, as the start of the diastolic phase could not be be determined in a straightforward manner (refer to Appendix D).

While the adapted time-decay method should be more comprehensive for patients on VA ECMO, it performs poorly in modelled data and gives unlikely results when applied to patient data. For model parameter estimation to create a digital twin, a rough estimate suffices, which implies that the time-decay method is suitable for this purpose.

Patient-specific interpretation

Patient 1 experienced an OHCA and successfully weaned from VA ECMO due to cardiac recovery. It was expected that Ees would increase and VA coupling would decrease over the days. The estimated cardiac function based on the automatic tuning protocol shows an overall improvement in Ees, however, on day 3, there is a decrease in Ees, which is clinically unlikely. VA coupling did improve. The manual tuning provided more realistic estimates, showing consistent improvement in both Ees and VA coupling each day.

Patient 2 required VA ECMO support for acute post-cardiotomy biventricular failure after an aortic dissection. Successful weaning was achieved after biventricular recovery. It was expected that Ees and VA coupling would improve over time. However, the automatic tuning initially estimated a decreased Ees and VA coupling, followed by stable Ees and an increased VA coupling, which does not match with clinical observations. Manual tuning indicated stable Ees and improved VA coupling. Strikingly, VA coupling was estimated to be extremely high, likely due to low SVR and low venous compliance, which is probable given the patient's age (70-79). The low SVR might have been intentional to reduce pressure on the fragile post-operative aorta [49].

Patient 3 initially received venovenous-ECMO for ARDS, which was later upgraded to VA-V ECMO support because of secondary evolving septic cardiomyopathy. This patient was included during VA-V ECMO support. Cardiac function improved during the VAV ECMO run. Ees increased in both automatic and manual tuning over three consecutive days. Both the slight increase in VA coupling in

the automatic tuning and the dip in Ees in the manual tuning are unlikely. Further cardiac recovery was observed after day 5, leading to the removal of the arterial cannula. Despite this, life sustaining support was withdrawn a few days later due to developing multi-organ failure.

Patient 4, who underwent a bilateral lung transplantation was supported posttransplant with extended VA ECMO to prevent pulmonary hypertension and was successfully weaned after 4 days. As this patient had no history of cardiac failure, no significant cardiac improvement was expected during ECMO support. However, both tuning methods suggested cardiac improvement. This might be due to an 'overuse' of inotropes supporting the right ventricle, creating a 'hyperdynamic cidculatory state', rather than actual cardiac function improvement [50, 51].

Patient 5, admitted due to OHCA, was successfully weaned, suggesting cardiac improvement. The automatic tuning protocol, however, showed a deterioration of cardiac function between days 3 and 6, which did not align with clinical expectations. The manual tuning provided estimates that are consistent with the expected cardiac improvement.

Automatic tuning

The goal of creating an automatic tuning protocol was to provide an objective method to estimate cardiac function and progression using the CPM. However, the current protocol does not produce estimates that align well with clinical outcomes. The simplicity of the protocol does not account for the extreme complexity of a patient on VA ECMO. Although the RMSE decreases somewhat in the second step of the protocol, it remains high. Developing a more sophisticated automatic tuning protocol, that encompasses more parameters, could potentially lower the RMSE and improve the accuracy of cardiac function estimations.

Manual tuning

The results from manual tuning demonstrate that it is feasible to match the CPM to a patient with a low RMSE, in accordance to previous findings [31]. In most cases, it was possible to tune the CPM so that all errors were even 5% or less, which generally resulted in an RMSE value below 0.04. Once a patient was matched, the estimated cardiac function somewhat correlated with clinical expectations, especially for the patients with OHCA as indication for VA ECMO. Due to the small and heterogeneous group of patients, it is not yet possible to determine whether manual tuning can be used to estimate cardiac function definitively. However, the low RMSE and estimated cardiac functions are promising.

The hourly analysis of patient 2 illustrates the trends of Ees and VA coupling over time over timedemonstrating the feasibility of tuning a digital twin semi-continuously. The results show a noticeable response of end-systolic elastance (Ees) to noradrenaline, which possesses inotropic qualities [52]. Milrinone was initiated around hour 26 at a dosage of 0.89 mcg/kg/min, likely aimed at preparing the ventricles for weaning [53], which was accomplished shortly after hour 41. However, it is unexpected that Ees does not appear to react to the introduction of milrinone.

The manual tuning protocol presented in section 3.3 is grounded in best practices and is an effective method to tune the CPM to the desired values for a patient on VA ECMO. The required data for manual tuning includes HR, ECMO RPM, Arterial pressures (DBP, MAP), Pulmonary pressures (SPAP, DPAP), CVP, CO, Q ecmo. Optional data includes PCWP (to estimate Rpolm and tune the CPM more accurately), ABP waveform (to estimate arterial compliance, possibly other features), and ECG (to consult if registered data seems illogical).

A remarkable outcome is that the SVR used in both automatic and manual tuning is much lower than the estimated SVR using MAP, CVP, CO (see section 3.3) in all patients. This is noteworthy as SVR is typically elevated in most cases of cardiogenic shock. A low SVR may signify end-stage cardiogenic shock, resulting from inappropriate vasodilation and inflammatory processes [54, 55]. Additionally, the estimated Ees was very low in most patients, even for the patients without a cardiac indication for VA ECMO. Currently the estimated Ees cannot be used to compare cardiac function between patients, but using the digital twin to follow trends in cardiac function within a single patient appears feasible.

5.2 Strengths and limitations

A key strength of this study lies in the utilisation of a validated cardiovascular CPM, enabling detailed modeling of patient-specific hemodynamics [19, 31]. Despite the time-consuming nature of the manual tuning protocol, it achieved low RMSE values, signifying a robust alignment between the CPM and patient data.

However, several limitations of this study should be acknowledged. The study's small and heterogeneous patient sample restricts the generalisability of the findings to a VA ECMO patient population. Developing an automatic tuning protocol for the CPM proved nearly impossible due to the current configuration, lacking the capability for automatic adjustment of crucial parameters. Furthermore, running simulations is time-consuming, and output data is not directly accessible. The time investment for manual tuning, coupled with the need for specific patient data such as CO [56] and detailed ABP waveforms, currently poses challenges for clinical implementation. Additionally, the CPM's setup does not accommodate pressures below 1 mmHg, which can be troublesome when CVP decreases below 0 mmHg [55].

5.3 Future perspective

This thesis explored the application of a digital twin for cardiac monitoring in patients undergoing VA ECMO support. The future of such personalised cardiovascular simulations appears to be promising [57], however, implementing a digital twin in a clinical setting requires extensive research and development. Ideally, a digital twin should possess the capability to semi-automatically tune itself to match individual patient characteristics [58].

To enhance trust in the digital twin, it could provide confidence intervals for its estimates. If the confidence interval is too broad, the digital twin should indicate which patient information is needed to improve precision. Alternatively, the digital twin could explain how they arrive at their conclusions, which is a focus in the field of artificial intelligence to enhance trust in the digital twin [57].

The digital twin should function as an adjacent to current clinical practice, updating regularly and ideally even in real-time. Importantly, the information provided must be readily interpretable by healthcare professionals, not just technical personnel. While this thesis primarily focuses on estimating cardiac function, a digital twin that accurately responds to medical interventions could serve as a valuable clinical decision-making tool.

5.4 Recommendations

The current manual tuning protocol, serves as the most effective method for tuning a digital twin with the CPM used in this study. However, its validation across a broader spectrum of patients is crucial. The introduction of standard continuous CO monitoring with a pulmonary artery catheter with a thermal filament, streamlines data collection from electronic medical records. This reduces the time required for patient inclusion for future research.

Nevertheless, relying on manual tuning for all patients in a clinical setting is impractical. Hence, there is a pressing need to devise an automated tuning method. One approach could involve refining the automated tuning protocol proposed in this study. Alternatively, once a sufficient volume of patient data is available, a data-driven model could be used for parameter estimation [59], as attempted by Kwok et al. [60].

The cardiovascular CPM utilised in this study was originally developed for educational purposes. To transition towards a clinical decision-making tool, several adaptations are necessary. Firstly, the model and its output should be readily accessible to users. Secondly, automating the adjustment of all model parameters, preferably through a range of values, should be straightforward. Lastly, enhancing user control by enabling the selection of specific data for upload could significantly reduce file sizes.

5.5 Conclusion

This thesis demonstrates the feasibility of tuning a cardiovascular CPM as a digital twin of patients supported with VA ECMO, providing a clinically realistic assessment and evaluation of cardiac contractile function and recovery. Further research is needed to validate and automate tuning protocols for broader clinical application. With continued development, a digital twin has the potential to facilitate continuous monitoring of LV function, thereby acting as a clinical-decision tool to assist daily management and weaning strategies for patients supported with VA ECMO.

Bibliography

1. Samsky, M. D. *et al.* Cardiogenic Shock After Acute Myocardial Infarction: A Review. *JAMA* **326,** 1840–1850. ISSN: 1538-3598 (Nov. 2021).
2. Goldberg, R. J., Spencer, F. A., Gore, J. M., Lessard, D. & Yarzebski, J. Thirty-Year Trends (1975 to 2005) in the Magnitude of, Management of, and Hospital Death Rates Associated With Cardiogenic Shock in Patients With Acute Myocardial Infarction. *Circulation* **119,** 1211–1219. ISSN: 0009-7322 (Mar. 2009).
3. Jentzer, J. C. & Baran, D. A. The changing face of cardiogenic shock: definitions, epidemiology, and severity assessment. *Current Opinion in Critical Care* **29,** 363–370. ISSN: 1070-5295 (Aug. 2023).
4. Baran, D. A. *et al.* SCAI clinical expert consensus statement on the classification of cardiogenic shock. *Catheterization and Cardiovascular Interventions* **94,** 29–37. ISSN: 1522-1946 (July 2019).
5. Rubin, E. & Reisner, H. M. *Essentials of Rubin's pathology* 6th ed., 426–427. ISBN: 978-1-4511-1023-4 (Lippincott Williams & Wilkins, a Wolters Kluwer business., 2014).
6. Reynolds, H. R. & Hochman, J. S. Cardiogenic Shock. *Circulation* **117,** 686–697. ISSN: 0009-7322 (Feb. 2008).
7. Rao, P., Khalpey, Z., Smith, R., Burkhoff, D. & Kociol, R. D. Venoarterial Extracorporeal Membrane Oxygenation for Cardiogenic Shock and Cardiac Arrest. *Circulation: Heart Failure* **11.** ISSN: 1941-3289 (Sept. 2018).
8. Pineton de Chambrun, M., Bréchot, N. & Combes, A. Venoarterial extracorporeal membrane oxygenation in cardiogenic shock: indications, mode of operation, and current evidence. *Current Opinion in Critical Care* **25,** 397–402. ISSN: 1070-5295 (Aug. 2019).
9. Meuwese, C. L. *et al.* Extracorporeal life support in cardiogenic shock: indications and management in current practice. *Netherlands Heart Journal* **26,** 58–66. ISSN: 1568-5888 (Feb. 2018).
10. Koziol, K. J. *et al.* Extracorporeal Membrane Oxygenation (VA-ECMO) in Management of Cardiogenic Shock. *Journal of Clinical Medicine* **12,** 5576. ISSN: 2077-0383 (Aug. 2023).
11. Rajsic, S. *et al.* Extracorporeal membrane oxygenation for cardiogenic shock: a meta-analysis of mortality and complications. *Annals of Intensive Care* **12,** 93. ISSN: 2110-5820 (Oct. 2022).
12. Hermens, J. A. *et al.* Patient-centered weaning from venoarterial extracorporeal membrane oxygenation: "A practice-oriented narrative review of literature". *Perfusion* **38,** 1349–1359. ISSN: 0267-6591 (Oct. 2023).
13. Extracorporeal Life Support Organization (ELSO). *ECLS International Summary of Statistics* Oct. 2023. `https://www.elso.org/registry/internationalsummaryandreports/internationalsummary.aspx`.
14. Lorusso, R. *et al.* ELSO Interim Guidelines for Venoarterial Extracorporeal Membrane Oxygenation in Adult Cardiac Patients. *ASAIO Journal* **67,** 827–844. ISSN: 1058-2916 (Aug. 2021).
15. Bishop, M. A. & Moore, A. *Extracorporeal Membrane Oxygenation Weaning* (2023).

16. Habran, S., Desaive, T., Morimont, P., Lambermont, B. & Dauby, P. C. Model-Based Weaning Tests for VA-ECLS Therapy. *Computational and Mathematical Methods in Medicine* **2020,** 1–15. ISSN: 1748-670X (Apr. 2020).

17. Pladet, L. *et al.* Clinical decision support for ExtraCorporeal Membrane Oxygenation: Will we fly by wire? *Perfusion* **38,** 68–81. ISSN: 0267-6591 (May 2023).

18. Rasheed, A., San, O. & Kvamsdal, T. Digital Twin: Values, Challenges and Enablers From a Modeling Perspective. *IEEE Access* **8,** 21980–22012. ISSN: 2169-3536 (2020).

19. Fresiello, L. *et al.* A cardiovascular simulator tailored for training and clinical uses. *Journal of biomedical informatics* **57,** 100–12. ISSN: 1532-0480 (Oct. 2015).

20. Broomé, M. & Donker, D. W. Individualized real-time clinical decision support to monitor cardiac loading during venoarterial ECMO. *Journal of Translational Medicine* **14,** 4. ISSN: 1479-5876 (Dec. 2016).

21. Tibby, S. M. Monitoring cardiac function in intensive care. *Archives of Disease in Childhood* **88,** 46–52. ISSN: 00039888 (Jan. 2003).

22. Abbasi, A. *et al.* in *Encyclopedia of Intensive Care Medicine* 460–462 (Springer Berlin Heidelberg, Berlin, Heidelberg, 2012).

23. Solaro, R. J. Regulation of Cardiac Contractility. *Regulation of Cardiac Contractility.* `https://www.ncbi.nlm.nih.gov/books/NBK54078/` (2011).

24. Kaddoura, R. *et al.* The Effectiveness of Levosimendan on Veno-Arterial Extracorporeal Membrane Oxygenation Management and Outcome: A Systematic Review and Meta-Analysis. *Journal of Cardiothoracic and Vascular Anesthesia* **35,** 2483–2495. ISSN: 10530770 (Aug. 2021).

25. VanValkinburgh, D., Kerndt, C. C. & Hashmi, M. F. *Inotropes and Vasopressors* (2023).

26. *Cardiopulmonary Monitoring* (eds Magder, S., Malhotra, A., Hibbert, K. A. & Hardin, C. C.) 49–60. ISBN: 978-3-030-73386-5 (Springer International Publishing, Cham, 2021).

27. Walley, K. R. Left ventricular function: time-varying elastance and left ventricular aortic coupling. *Critical Care* **20,** 270. ISSN: 1364-8535 (Dec. 2016).

28. Guinot, P.-G., Andrei, S. & Longrois, D. Ventriculo-arterial coupling: from physiological concept to clinical application in peri-operative care and ICUs. *European Journal of Anaesthesiology Intensive Care* **1,** e004. ISSN: 2767-7206 (2022).

29. Andrei, S. *et al.* Ventriculo-Arterial Coupling Is Associated With Oxygen Consumption and Tissue Perfusion in Acute Circulatory Failure. *Frontiers in Cardiovascular Medicine* **9.** ISSN: 2297-055X (Feb. 2022).

30. Monge García, M. I. & Santos, A. Understanding ventriculo-arterial coupling. *Annals of Translational Medicine* **8,** 795–795. ISSN: 23055839 (June 2020).

31. Colasanti, S. *et al.* Development of a computational simulator of the extracorporeal membrane oxygenation and its validation with in vitro measurements. *Artificial Organs* **45,** 399–410. ISSN: 0160-564X (Apr. 2021).

32. Sagawa, K., Suga, H., Shoukas, A. A. & Bakalar, K. M. End-systolic pressure/volume ratio: A new index of ventricular contractility. *The American Journal of Cardiology* **40,** 748–753. ISSN: 00029149 (Nov. 1977).

33. KROEKER, E. J. & WOOD, E. H. Comparison of Simultaneously Recorded Central and Peripheral Arterial Pressure Pulses During Rest, Exercise and Tilted Position in Man. *Circulation Research* **3,** 623–632. ISSN: 0009-7330 (Nov. 1955).

34. Pauca, A. L., O'Rourke, M. F. & Kon, N. D. Prospective Evaluation of a Method for Estimating Ascending Aortic Pressure From the Radial Artery Pressure Waveform. *Hypertension* **38,** 932–937. ISSN: 0194-911X (Oct. 2001).

35. Jankowski, P. *et al.* Twenty-four-Hour Profile of Central Blood Pressure and Central-to-Peripheral Systolic Pressure Amplification. *American Journal of Hypertension* **26,** 27–33. ISSN: 0895-7061 (Jan. 2013).

36. Chemla, D. *et al.* New Method to Estimate Central Systolic Blood Pressure From Peripheral Pressure: A Proof of Concept and Validation Study. *Frontiers in Cardiovascular Medicine* **8.** ISSN: 2297-055X (Dec. 2021).

37. Stergiopulos, N., Meister, J. J. & Westerhof, N. Evaluation of methods for estimation of total arterial compliance. *American Journal of Physiology-Heart and Circulatory Physiology* **268,** H1540–H1548. ISSN: 0363-6135 (Apr. 1995).

38. Westerhof, N., Lankhaar, J.-W. & Westerhof, B. E. The arterial Windkessel. *Medical & Biological Engineering & Computing* **47,** 131–141. ISSN: 0140-0118 (Feb. 2009).

39. Wösten, M. *Cardiac function monitoring during venoarterial extracorporeal membrane oxygenation in the intensive care unit* PhD thesis (University Medical Center Utrecht, Utrecht, Nov. 2023).

40. DeMers, D. & Wachs, D. *Physiology, Mean Arterial Pressure* (2024).

41. Su, Y. *et al.* Hemodynamic monitoring in patients with venoarterial extracorporeal membrane oxygenation. *Annals of Translational Medicine* **8,** 792–792. ISSN: 23055839 (June 2020).

42. Moller, P. W. *et al.* The Effects of Vasoconstriction And Volume Expansion on Veno-Arterial ECMO Flow. *Shock* **51,** 650–658. ISSN: 1073-2322 (May 2019).

43. Laurent, S. & Boutouyrie, P. Arterial Stiffness and Hypertension in the Elderly. *Frontiers in cardiovascular medicine* **7,** 544302. ISSN: 2297-055X (2020).

44. Fresiello, L., Hermens, J. A., Pladet, L., Meuwese, C. L. & Donker, D. W. The physiology of venoarterial extracorporeal membrane oxygenation - A comprehensive clinical perspective. *Perfusion* **39,** 5S–12S. ISSN: 0267-6591 (Apr. 2024).

45. Scaravilli, V., Zanella, A., Sangalli, F. & Patroniti, N. in *ECMO-Extracorporeal Life Support in Adults* 19–36 (Springer Milan, Milano, 2014).

46. Mohiaddin, R. H. in *Cardiovascular Magnetic Resonance* 352–364 (Elsevier, 2019).

47. Liu, Z. R., Ting, C. T., Zhu, S. X. & Yin, F. C. Aortic compliance in human hypertension. *Hypertension* **14,** 129–136. ISSN: 0194-911X (Aug. 1989).

48. Quaal, S. J. Interpreting the Arterial Pressure Waveform in the Intra-Aortic Balloon-Pumped Patient. *Progress in Cardiovascular Nursing* **16,** 116–125. ISSN: 0889-7204 (June 2001).

49. Fletcher, A. J., Syed, M. B., Aitman, T. J., Newby, D. E. & Walker, N. L. Inherited Thoracic Aortic Disease. *Circulation* **141,** 1570–1587. ISSN: 0009-7322 (May 2020).

50. Nazarnia, S. & Subramaniam, K. Pro: Veno-arterial Extracorporeal Membrane Oxygenation (ECMO) Should Be Used Routinely for Bilateral Lung Transplantation. *Journal of Cardiothoracic and Vascular Anesthesia* **31,** 1505–1508. ISSN: 10530770 (Aug. 2017).

51. Thunberg, C. A. *et al.* Pulmonary Hypertension in Patients Undergoing Cardiac Surgery: Pathophysiology, Perioperative Management, and Outcomes. *Journal of Cardiothoracic and Vascular Anesthesia* **27,** 551–572. ISSN: 10530770 (June 2013).

52. Sandilands, A. J., O'Shaughnessy, K. M. & Brown, M. J. Greater inotropic and cyclic AMP responses evoked by noradrenaline through Arg389 β ₁ -adrenoceptors versus Gly389 β ₁ -adrenoceptors in isolated human atrial myocardium. *British Journal of Pharmacology* **138,** 386–392. ISSN: 0007-1188 (Jan. 2003).

53. Cavarocchi, N. C. *et al.* Weaning of extracorporeal membrane oxygenation using continuous hemodynamic transesophageal echocardiography. *The Journal of Thoracic and Cardiovascular Surgery* **146,** 1474–1479. ISSN: 00225223 (Dec. 2013).

54. Furer, A., Wessler, J. & Burkhoff, D. Hemodynamics of Cardiogenic Shock. *Interventional Cardiology Clinics* **6,** 359–371. ISSN: 22117458 (July 2017).

55. *Advanced Hemodynamic Monitoring: Basics and New Horizons* (eds Kirov, M. Y., Kuzkov, V. V. & Saugel, B.) ISBN: 978-3-030-71751-3 (Springer International Publishing, Cham, 2021).

56. Monnet, X. & Teboul, J.-L. Transpulmonary thermodilution: advantages and limits. *Critical care (London, England)* **21,** 147. ISSN: 1466-609X (June 2017).

57. Garber, L., Khodaei, S. & Keshavarz-Motamed, Z. The Critical Role of Lumped Parameter Models in Patient-Specific Cardiovascular Simulations. *Archives of Computational Methods in Engineering* **29,** 2977–3000. ISSN: 1134-3060 (Aug. 2022).

58. Coorey, G. *et al.* The health digital twin to tackle cardiovascular disease—a review of an emerging interdisciplinary field. *npj Digital Medicine* **5,** 126. ISSN: 2398-6352 (Aug. 2022).

59. Warnaar, R. S. P. *et al.* Computational physiological models for individualised mechanical ventilation: a systematic literature review focussing on quality, availability, and clinical readiness. *Critical Care* **27,** 268. ISSN: 1364-8535 (July 2023).

60. Kwok, H., Linkens, D., Mahfouf, M. & Mills, G. Adaptive ventilator FiO2 advisor: use of non-invasive estimations of shunt. *Artificial Intelligence in Medicine* **32,** 157–169. ISSN: 09333657 (Nov. 2004).

61. Schipperheijn, J. in *Vademecum permanente nascholing huisartsen* 63–64 (Bohn Stafleu van Loghum, Houten, 2006).

A. Data registration

Clinical parameters patients

All patient variables that were collected can be found in table A.1. These were collected at one point in time.

Patient	1			2			3			4			5		
ECMO day	**2**	**3**	**4**	2	**3**	4	**4**	**5**	6	2	3	**4**	**2**	**3**	**6**
HR	**110**	**120**	**80**	75	**80**	93	**101**	**93**	92	100	85	**80**	**85**	**101**	**80**
cSBP	**110**	**91**	**111**	96	**76**	82	**93**	**91**	102	73	78	**97**	**82**	**117**	**78**
DBP	**64**	**45**	**73**	67	**57**	65	**56**	**60**	63	48	59	**66**	**63**	**69**	**51**
MAP	**84**	**64**	**90**	80	**66**	73	**72**	**74**	80	59	68	**80**	**72**	**90**	**63**
sPAP	**21**	**22**	**34**	32	**21**	24	**40**	**35**	33	67	55	**55**	**13**	**41**	**36**
dPAP	**16**	**16**	**22**	16	**8**	14	**21**	**19**	19	25	23	**24**	**11**	**8**	**22**
CVP	**10**	**10**	**14**	9	**-3**	8	**16**	**14**	19	8	8	**14**	**21**	**10**	**13**
Q_{ecmo}	**5.6**	**6.3**	**3.7**	1.8	**1.9**	2.6	**6.4**	**6.5**	6	5	4	**4.4**	**5.2**	**7**	**5.9**
ECMO rpm	**3.4**	**2.5**	**2**	2.2	**2.2**	2.5	**5.2**	**5.2**	5.2	3.3	3.6	**2.3**	**3.5**	**2.5**	**2**

Table A.1: Overview of registered data. The registrations that are bold were performed bed-side.

Typical patient on VA ECMO

The default values of the model parameters in the cardiovascular simulator that were used for tuning are shown in table A.2. Other parameters that were used in tuning, such as TBV and arterial resistances are estimated in section 3.3. Compliance was estimated in relation to the default values. All remaining parameters were not used during tuning and can be found in [31].

Model parameter	**Value**	**Model parameter**	**Value**
LVe	1	CubV	8
Ca1	0.8	CkidV	15
Ca2	0.6	CsplV	55
RVe	0.5	ClegsV	9.5
RA compl	5	CsupVCint	15
Cap	4	CinfVCext	25
Rpolm	0.018	CinfVCint	2

Table A.2: Default values of simulator

B. Sensitivity analysis typical patient

The heatmaps resulting from the sensitivity analysis on an average VA ECMO patient. The values in the heatmap represent the effect on the output according to Equation (3.1).

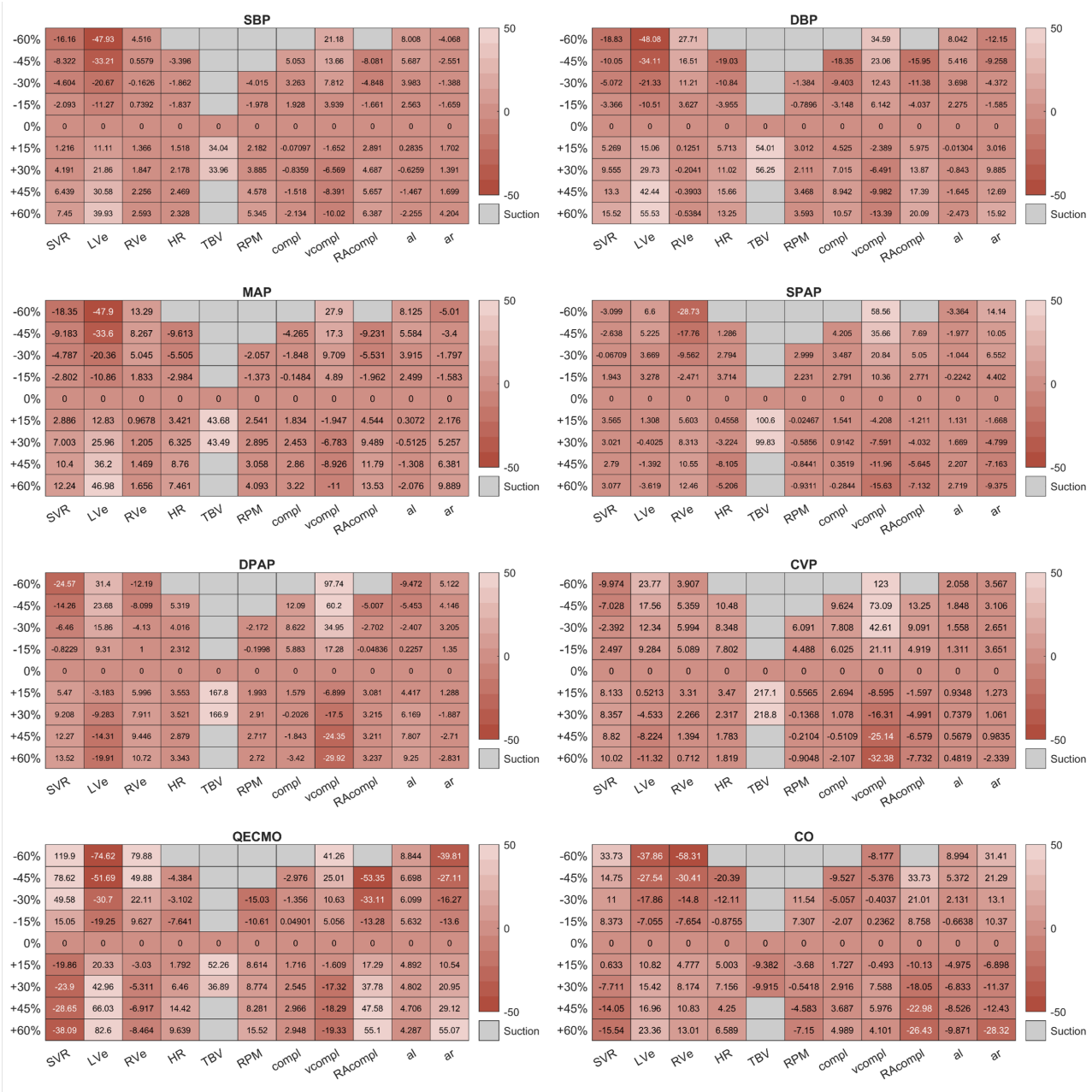

Figure B.1: The y-axis is the percentage change in the model parameter from the x-axis.

C. Settings CPM

Table A.1: Overview of settings CPM for different models. C.v is the factor of the original estimate of the value.

Patient	SVR	Rpolm	LVe	AI	RVe	Ar	Cap	C. RA.	Ca1	Ca2	C. v	TBV
Default	0.8	0.018	1	0.33	0.5	0.05	4	5	0.8	0.6	1	5600
Typical	0.84	0.074	0.45	0.35	0.4	0.5	-	2.5	0.56	0.42	0.5*	5500
1-1	0.50	0.08	0.85	-	0.27	-	-	2.3	0.4	0.3	0.9	6750
1-2	0.25	0.07	1	-	0.2	-	-	1.9	0.48	0.36	0.8	6750
1-3	0.74	0.38	2.3	-	0.2	-	2	1.1	0.4	0.3	0.9	6750
2-1	0.95	0.30	0.42	-	-	-	2	8	0.8	0.36	0.7	5625
2-2	0.72	0.18	0.4	-	-	-	1.5	8.5	-	-	1.4	5625
2-3	0.68	0.14	0.44	-	0.18	-	1.8	-	0.72	0.54	0.7	5625
3-1	0.23	0.13	0.75	-	0.3	-	2	1.6	0.72	0.54	0.6	6000
3-2	0.25	0.10	0.63	-	-	-	2	2.5	0.88	0.66	0.65	6000
3-3	0.24	0.10	0.2	-	-	-	1.5	1.1	1.56	0.42	0.6	6000
4-1	0.30	0.45	0.83	-	-	-	0.7	1.8	-	-	1.0	6825
4-2	0.36	0.45	0.90	-	0.35	-	1	1.7	0.96	0.72	1.0	6825
4-3	0.45	0.30	2.1	-	0.3	-	1.3	1.1	-	-	0.8	6825
5-1	0.29	0.00	0.72	-	0.06	-	0.0	1.1	1.2	0.9	0.7	8000
5-2	0.45	0.1	1.1	-	0.38	-	0.4	1.8	0.48	0.36	1.0	8000
5-3	0.31	0.15	1.4	-	0.2	-	-	0.9	1.2	0.9	0.85	8000

*SVR: systemic vascular resistance, Rpolm: pulmonary resistance, LVe: left ventricular elastance, RVe: right ventricular elastance, Cap: compliance pulmonary artery, C. RA: compliance right atrium, Ca1: compliance ascending aorta, Ca2: compliance descending aorta, C. v: compliance venous system, TBV: total blood volume, *: this is compared to the default value of the CPM, -: default value was used.*

D. Compliance estimation

Adapted time-decay

Figure D.1 displayes what happens with the adapted time decay method when Q_{ecmo} increases.

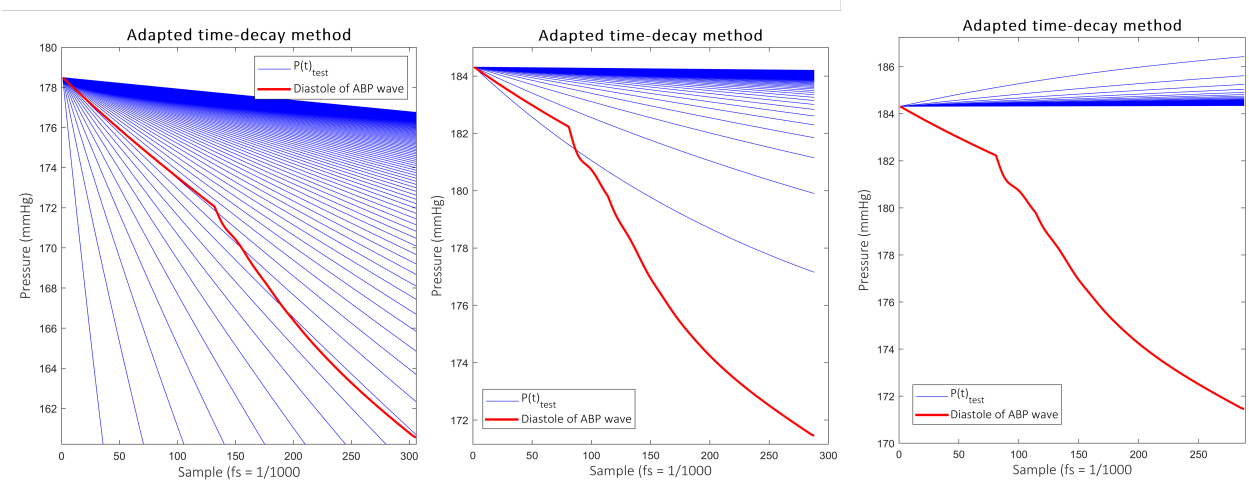

Figure D.1: Visualisation of adapted time decay method, in red the diastolic part of a ABP waveform, in blue the calculated P(t). **Left:** *Well functioning P(t) estimations* **Middle:** *Flow of ecmo is increased, and P(t) does not reach the lower pressures of the diastolic phase, which results in an extremely low estimation of C_a.* **Right:** *$(Q_{ecmo} \cdot SVR) > P1$, which causes the P(t) range to 'flip', the method does always takes the largest possible C_a as its estimate.*

Pulsus alternans

Figure D.2 shows the unusual ABP waveform of patient 1 during the registered weaning trial. The unusual extra activity between systolic peaks could be a pulsus alternans [61], where the variation of SBP is more than 20 mmHg between beats. The diastolic part of this ABP waveform was defined in the coloured parts of the waveform.

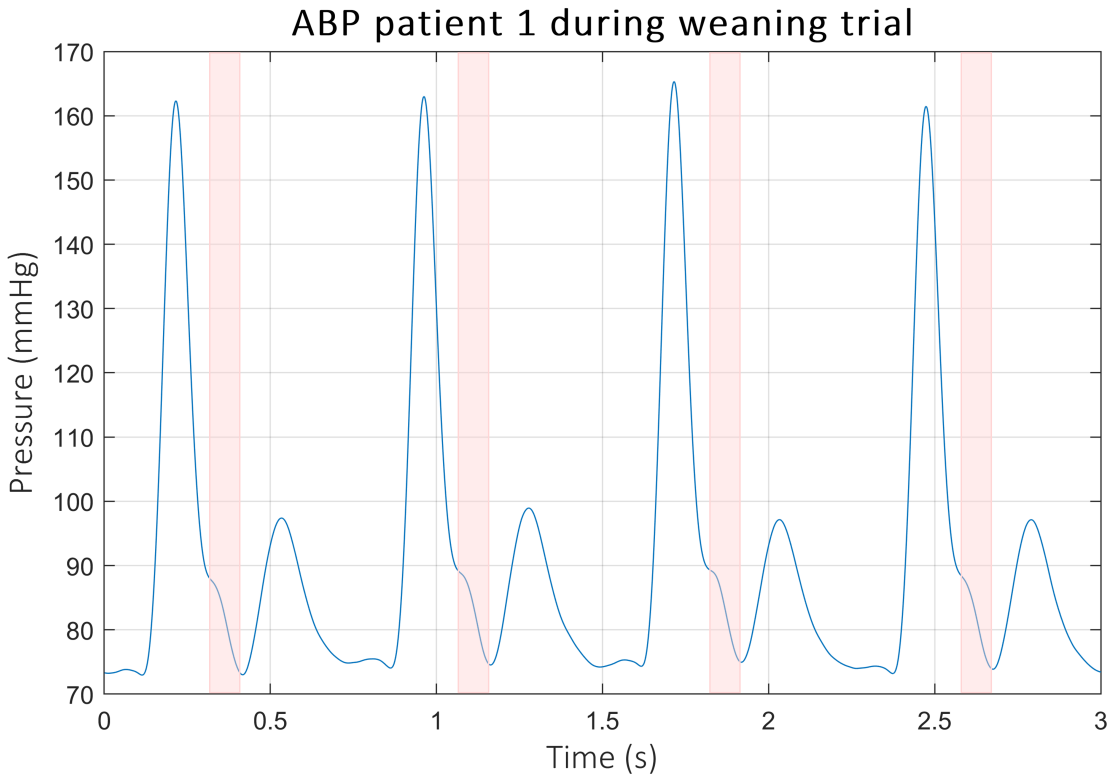

Figure D.2: ABP of patient 1 during their weaning trial.